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CADTH Therapeutic Review Report

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Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness

Supporting Informed Decisions

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Note Regarding Changes to the Report Following Stakeholder Feedback:
Following feedback received in response to the previous draft of this report, modifications were made to the text and data tables. These modifications did not alter the results of the main analyses or the conclusions of the report.

In the clinical review, changes were made mainly in the discussion section to include a summary of three combination therapy trials (COMPASS-2, AMBITION, and PACES-1). The results of the first two trials were recently made public, while the last one was excluded from the review because the sildenafil dose in the trial did not meet the Health Canada–approved dose. Clinical context of the results from the short-term trials and the lack of long-term controlled data on efficacy and safety of many pulmonary arterial hypertension (PAH) therapies, including sildenafil 20 mg three times daily, were also added in the discussion. In the critical appraisal section, limitations regarding differences in clinical trials with respect to study and patient characteristics were further clarified.

In the pharmacoeconomic analyses, the most notable changes include two additional deterministic sensitivity analyses: the incorporation of unadjusted values for relative risk of improvement and worsening in functional class with PAH therapies obtained from the CADTH network meta-analysis, instead of the values adjusted for baseline functional class status, and incorporation of survival estimates from the National Institutes of Health registry instead of the Pulmonary Hypertension Connection registry.

Canadian Agency for Drugs and Technologies in Health

Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness

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ABBREVIATIONS AND GLOSSARY

6MWD	six-minute walk distance
6MWT	six-minute walk test
AE	adverse event
APAH	associated pulmonary arterial hypertension
BDI	Borg dyspnea index
b.i.d.	twice a day
CBA	cost-benefit analysis
CDEC	Canadian Drug Expert Committee
CEA	cost-effectiveness analysis
CI	confidence interval
CMA	cost-minimization analysis
CrI	credible interval
CUA	cost-utility analysis
CVC	central venous catheter
DB	double-blind
EQ-5D	EuroQol 5-Dimensions Questionnaire
ERA	endothelin receptor antagonist
FC	functional class
FPAH	familial pulmonary arterial hypertension
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IM	intramuscular
INR	international normalized ratio
IPAH	idiopathic pulmonary arterial hypertension
ITT	intention-to-treat
i.v.	intravenous
MCID	minimal clinically important difference
mPAP	mean pulmonary arterial pressure
MTC	mixed treatment comparison
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NMA	network meta-analysis
NYHA	New York Heart Association
OCCI	Ontario Case Costing Initiative

OHIP	Ontario Health Insurance Program
OR	odds ratio
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCH	pulmonary capillary hemangiomatosis
PCWP	pulmonary capillary wedge pressure
PDE-5	phosphodiesterase type 5
PH	pulmonary hypertension
PPH	primary pulmonary hypertension
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
QALY	quality-adjusted life-year
q.d.	once a day
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
s.c.	subcutaneous
SD	standard deviation
SF-36	Short-Form (36-Item) Health Survey
sGC	soluble guanylate cyclase
t.i.d.	three times a day
WHO	World Health Organization

The glossary was adapted from Chen et al.[1]

6MWT/6MWD — six-minute walk test/distance: The 6MWT/6MWD measures the distance that a patient can walk unencouraged on a flat, hard surface in a time of six minutes.

Borg dyspnea index: A measure of perceived breathlessness on a scale of 0 to 10, where 0 is no breathlessness and 10 is maximal breathlessness. It was initially designed to measure exertion.

Cardiac index: Volume of blood pumped by the heart in a unit of time (cardiac output) per unit of body surface area. Cardiac index = (stroke volume x heart rate) / body surface area; expressed in L/min/m^2.

Functional class (FC): A classification of functional capacity initially developed by the New York Heart Association (NYHA) for patients with heart failure, based on clinical severity and prognosis. It was later adapted specifically for patients with pulmonary hypertension. Patients are classified into one of the following four categories: FC I (asymptomatic), FC II (mild), FC III (moderate), and FC IV (severe).

Pulmonary arterial hypertension (PAH): In this report, PAH refers to Group 1 (excluding Group 1' and subgroup 1.5) of the Dana Point 2008 classification for pulmonary hypertension. Throughout this report, idiopathic PAH (IPAH) and familial (or heritable) PAH (FPAH) have been grouped as IPAH/FPAH. Drug- and toxin-induced PAH and associated PAH (APAH) have been grouped separately. The term primary pulmonary hypertension (PPH) that was used in studies before 2003 is synonymous with IPAH.

Pulmonary artery pressure (PAP): Measured directly during right heart catheterization. Mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg at rest is one of the diagnostic criteria for PAH.

Pulmonary capillary wedge pressure (PCWP): Provides an indirect estimate of left atrial pressure. The measurement is made with a balloon-tipped, multilumen catheter (Swan-Granz catheter), inserted into a peripheral vein and then advanced into the right atrium, right ventricle, pulmonary artery, and into a branch of the pulmonary artery. The normal value of the PCWP is 8 mm Hg to 10 mm Hg. A PCWP ≤ 15 mm Hg is one of the PAH diagnostic criteria. PCWP is used to calculate pulmonary vascular resistance.

Pulmonary vascular resistance (PVR): PVR = 80 x [mean PAP (mm Hg) – PCWP (mm Hg)] / cardiac output (L/min). Units are dyne (dyn).s/cm^5. A PVR > 240 dyn.s/cm^5 is one of the diagnostic criteria for PAH.

Supportive therapy: Refers to the following drug therapies: anticoagulants, diuretics, oxygen, and digoxin.

EXECUTIVE SUMMARY

Context and Policy Issues

Pulmonary arterial hypertension (PAH) is a chronic and progressive disease characterized by the elevation of mean pulmonary arterial pressure (mPAP), which leads to morbidity and premature mortality.[2] Although PAH affects males and females of all ethnicities and ages,[3] the disease is more common among women and people between 20 and 40 years of age.[4] In adults, the prevalence of PAH is approximately 12 to 50 cases per million people.[5-7] Epidemiological data for PAH in Canada are not available. Based on published registry data from France, Scotland, Spain, and the US,[8] the prevalence of PAH in Canada may be estimated to be between 10.6 and 26 cases per million people. Hence, the number of adult Canadians with PAH is estimated to be between 313 and 767. PAH can occur at any age from infancy to adulthood.[9] According to the National Institutes of Health Primary Pulmonary Hypertension Registry, although the overall median survival for adults and children was 2.8 years, the median survival in children was 10 months, if untreated.[10] The incidence of PAH for children was 0.48 cases per million per year, and the prevalence was 2.1 cases per million, according to the national registries from the United Kingdom.[11]

PAH is classified as Group 1 of the pulmonary hypertension (PH) classification, which was recently updated at the Fifth World Symposium on PH.[12] Four subgroups of Group 1 include idiopathic PAH (IPAH), heritable or familial PAH (FPAH), drug- and toxin-induced PAH, and PAH associated with concurrent medical conditions such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis. PAH is a complex and multifactorial disorder. The mechanisms contributing to disease progression involve vasoconstriction, endothelial dysfunction, dysregulated smooth muscle cell growth, inflammation, and thrombosis, which typically lead to overload of right ventricle and progressive right-sided heart failure.[13] The therapeutic aims of PAH drugs are to normalize these mechanisms.

Treatment of PAH is generally categorized as supportive therapy or advanced therapy. Supportive therapy includes use of diuretics, oxygen, anticoagulants, and digoxin. Many patients with PAH will receive supportive therapy despite limited or no evidence of effectiveness.[14] However, the majority of patients with PAH will require advanced therapy. Advanced therapy is directed at the disease itself. Eight drugs are approved in Canada for advanced therapy of PAH. They belong to four classes:

- Prostanoids (epoprostenol injectable, treprostinil injectable)
- Endothelin receptor antagonists (ERAs) (bosentan tablet, ambrisentan tablet, macitentan tablet)
- Phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil tablet and injectable, tadalafil tablet)
- Soluble guanylate cyclase (sGC) stimulator (riociguat tablet).

Macitentan and riociguat are two new drugs, which received Health Canada approval for treatment of PAH in November 2013 and March 2014, respectively. The approved doses of macitentan and riociguat were 10 mg once daily and max 2.5 mg three times daily, respectively. The approved dose of riociguat was made near the end of this review process and therefore the lower dose of max 1.5 mg three times daily was kept in the analyses and results of this report. Of note, epoprostenol, treprostinil, and bosentan are indicated for treatment of PAH patients with World Health Organization (WHO) functional class (FC) III or IV symptoms, while the other drugs are indicated for treatment of those with WHO FC II or III symptoms.

Choice of initial advanced therapy is based on PAH severity, comorbidities, adverse event profiles, physician's experience, patients' preference, long-term data available, and costs.

In patients who do not adequately respond to monotherapy (i.e., a single advanced therapy drug treatment), sequential addition of a second drug is usually recommended by PH specialists in Canada. Approximately 22% of PAH patients in Ontario used combination therapy between 2010 and 2012;[15] however, according to the clinical experts involved in the review, the current estimate may be closer to 50%, depending on the PAH clinic. Of note, there are two options for combination therapy: add a medication to an ongoing treatment (sequential [add-on] combination therapy), or start with a combination therapy from the beginning of treatment (upfront combination therapy). Given that the latter option is still being tested in clinical trials,[16,17] this report is limited to the first option; i.e., sequential (add-on) combination therapy.

The emergence of novel drug therapies necessitates consideration of their comparative effectiveness from both a clinical and an economic perspective, accounting for both monotherapy and combination therapy regimens. The aim of this therapeutic review is to compare the efficacy and safety of new and existing drug therapies for PAH, and to examine their cost-effectiveness.

Objectives

The objective of this therapeutic review is to conduct a systematic review to assess the comparative efficacy and safety and to determine the cost-effectiveness of drug therapies for the treatment of PAH in adults. The report seeks to answer to the following policy and research questions:

Policy Questions:

1. How do new drugs for advanced therapy of PAH compare with currently available drugs?
2. How does (add-on) combination therapy compare with monotherapy in patients with PAH?
3. Are there subgroups of patients (based on disease severity or other disease characteristics) who benefit more from specific agents when used either as monotherapy or (add-on) combination therapy?

Research Questions:

1. What is the comparative efficacy, safety, and cost-effectiveness of monotherapy with macitentan or riociguat compared with each other or with a PDE-5 inhibitor, another ERA, or a prostanoid?
2. What is the comparative efficacy, safety, and cost-effectiveness of dual (add-on) combination therapy versus monotherapy with PAH drugs?
3. What is the comparative efficacy, safety, and cost-effectiveness among different dual (add-on) combination therapies of PAH drugs?
4. What is the comparative efficacy, safety, and cost-effectiveness of triple (add-on) combination therapy versus dual (add-on) combination therapy with PAH drugs?

Findings will inform listing recommendations and decisions regarding the new PAH drugs in Canada.

Methods

A systematic review of drugs for the treatment of PAH was conducted. Randomized controlled trials (RCTs) and comparative observational studies of therapies for the treatment of PAH were identified through electronic databases, grey literature, and stakeholder consultation. Two

reviewers independently screened the titles and abstracts and independently evaluated the full-text publications for final article selection. Two reviewers also independently assessed the quality, including the risk of bias of the selected studies. Studies were included in the systematic review if they met the following inclusion criteria, as pre-specified in the review protocol: adults patients (aged 18 years or older) diagnosed with PAH and treated with one of the treatment therapies under review and reported outcomes related to clinical efficacy and safety. Treatment therapies specified in the protocol included macitentan and riociguat as the interventions and ambrisentan, bosentan, sildenafil, tadalafil, epoprostenol, treprostinil, and placebo as the comparators of interest. For drug therapies currently approved by Health Canada for treatment of PAH, only approved formulations and doses were included. Drug therapies not yet approved by Health Canada for treatment of PAH at the time this project was developed were not restricted to specific doses or formulations. Outcomes specified in the review protocol included death, hospitalization, clinical worsening, New York Heart Association (NYHA) or WHO FC (improved, worsened, unchanged), six-minute walk distance (6MWD), Borg dyspnea index (BDI), hemodynamic variables (pulmonary vascular resistance (PVR), pulmonary artery pressure [PAP], cardiac index), health-related quality of life, adverse events (AEs; both total and serious), and withdrawal due to AEs.

Direct pairwise meta-analyses were conducted for all outcomes where clinical, methodological, and statistical heterogeneity were deemed sufficiently low, using Review Manager 4.2 software. Indirect treatment comparisons were made using Bayesian network meta-analyses (NMAs), using WinBUGS software, for outcomes for which sufficient data were available to form stable networks; specifically, clinical worsening, NYHA or WHO FC (improved, worsened) and 6MWD. Sensitivity analyses were conducted to explore potential sources of heterogeneity.

Economic Model

The economic analysis is a cost-utility analysis, based on a Markov model designed to estimate the costs and efficacy of both monotherapy for PAH in treatment-naive patients and dual (add-on) therapies for PAH in treatment-experienced patients. Separate analyses were conducted for cohorts of patients beginning with FC II, FC III, and FC IV PAH. The primary outcome measure was the number of quality-adjusted life-years (QALYs) associated with treatment. Unfortunately, none of the clinical trials for PAH therapies directly measured quality of life in patients at baseline and follow-up using a method that would allow the calculation of utility values for patients receiving therapy. Consequently, the calculation of the utility gained with treatment must be inferred from a relationship between an improvement in a clinical measure and in quality of life. The only PAH clinical measure that has been shown to be related to quality of life is FC. Thus, the efficacy estimates of the treatments were derived from the NMA conducted by CADTH, based on the relative risk of improving and worsening in FC with treatment versus placebo. The nature of economic modelling is such that inclusion of more than one outcome measure can often lead to double counting. Other outcomes from the NMA were therefore not included within the analysis, as the inclusion of other outcomes aside from FC, which have similar indirect effects, will lead to overestimation of the benefits to be gained from treatment. An independent effect of treatment on mortality was also not incorporated within the model, as incorporating both the impact of treatment on FC and mortality separately would also lead to double counting and a consequent overestimation of the survival benefit with treatment. Treatment has an indirect effect on survival through its impact on both FC improvements and worsening. Other parameters were sourced from the published literature and clinical expert opinion. Drug costs were derived from the Saskatchewan Provincial Drug Formulary or from the manufacturer, if not listed within the formulary. Extensive deterministic sensitivity analyses were conducted to assess the impact of changes in parameter inputs (parameter uncertainty) and

model assumptions (structural uncertainty). A probabilistic sensitivity analysis was also conducted to estimate the extent of uncertainty surrounding the estimates.

This report was peer-reviewed by methodologists, PAH clinical experts, clinical drug experts, and health economists.

Patient Input

Pulmonary hypertension has a considerable impact on the lives of patients. Caring for a person living with PH is life-changing for caregivers. The condition-related symptoms and problems that impact the day-to-day life of a patient are difficulty breathing with or without exertion; palpitations or pounding of the chest; chest pain, ankle, leg, and abdomen swelling due to fluid retention; dizziness; syncope (fainting); and tingling of hands and feet due to low oxygen levels. Patients commonly experience depressed mood, anxiety, and feelings of helplessness and hopelessness as they are faced with a high risk of death within a few years.

Frequent medical appointments, tests, and hospitalizations are burdensome for patients and their caregivers. While not a cure, experience with currently available therapy is generally positive, with most responders reporting taking combination therapy. Patient input was received prior to Health Canada approval of macitentan and riociguat, so patient experience with these drugs is not included in this report. The medications (particularly intravenous [i.v.] therapies) help to keep PH stable and do play a role in increasing quality of life. However, the effectiveness of therapy varies considerably from patient to patient based on many factors, including a patient's age, gender, type of PH, severity of PH, and underlying medical conditions. In addition to the PH-specific treatments, most patients also take concomitant medication in order to control one of the many reported adverse effects of PH treatment.

Patients who have not had any experience with new drugs for PAH, such as macitentan and riociguat, are hopeful that they will reduce the symptoms of PAH and result in fewer AEs than currently available medications, resulting in an improved quality of life. Patients taking the new drugs felt that they were helping to decrease PAP, improve heart function, and delay progression of the disease. Often these patients had been treated with available drugs for PAH, with minimal or transient responses. The new drugs are generally thought of as being easier to use because they were either in oral form or provided other benefits (such as requiring no ice packs and not needing to be mixed twice a day).

Key Findings of Systematic Review

The systematic review included 20 unique studies, of which 15[18-31] studies had treatment-naive populations and five[32-36] had mixed populations (naive and pre-treated with a PAH drug). Of those five studies with mixed populations, three[33-35] provided data for certain clinical outcomes in naive and pre-treated subpopulations. One study[32] with a mixed population did not provide data on subpopulations based on treatment history. Thus, 18[18-31,33-35] provided comparisons of PAH treatments in treatment-naive populations (i.e., monotherapy) and four[33-36] provided comparisons between dual combination (add-on) therapy and background therapy. All included studies were RCTs (14 double-blinded and 18 placebo-controlled); no published comparative observational studies that met the inclusion criteria for the systematic review were identified in the literature search.

Evidence was available for the following drug therapies: macitentan (one RCT), riociguat (one RCT), ambrisentan (three RCTs), bosentan (four RCTs), sildenafil (one RCT), tadalafil (one RCT), epoprostenol (three RCTs), and treprostinil (four RCTs). NMAs were conducted for four

outcomes including clinical worsening, WHO FC improvement, WHO FC worsening, and 6MWD. For the remaining outcomes, only direct pairwise meta-analysis results are presented.

Monotherapy (Treatment-Naive Population)
For clinical worsening, data from eight treatment options (macitentan 10 mg, riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, and placebo) were subjected to meta-analyses. Despite the slight difference in definition among studies, clinical worsening (a mortality and morbidity composite outcome) was generally defined as time to first occurrence of all-cause death, worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, heart or lung transplantation, or atrial septostomy. Direct pairwise meta-analysis showed that all treatments were numerically favoured in reducing the risk of clinical worsening compared with placebo. Treatment effects (relative risk [RR]) ranged from 0.25 (tadalafil) to 0.59 (macitentan). A statistically significant difference versus placebo was reached for macitentan, ambrisentan 5 mg, and bosentan, but not for riociguat, ambrisentan 10 mg, sildenafil, and tadalafil in a treatment-naive population. The treatment effects estimated from NMA were similar in both magnitude and direction to the results of direct pairwise estimates, with relative risks ranging from 0.21 for tadalafil to 0.46 for macitentan. There were no statistically significant differences between drugs with respect to clinical worsening outcomes. Excluding the study examining the efficacy of macitentan (a long-term study with median follow-up of 115 weeks) from the analysis did not affect the effect sizes of other treatments. Likewise, sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect. Clinical worsening has been recommended for use as a clinically relevant primary outcome in studies evaluating drugs for the treatment of PAH, largely because of the low event rates for the individual mortality and morbidity components.[37] However, the definition of a clinically important difference between treatment groups with respect to clinical worsening in these studies has yet to be determined.

The severity of PAH is based on a number of clinical parameters, including the NYHA or WHO FC of symptoms, which ranges from class I to IV, with class IV being most severe.

For FC improvement, data from nine treatment options (riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil, and placebo) were available for analyses. Data for macitentan were not available for the treatment-naive population; only results for the total study population (i.e., treatment-naive plus treatment-experienced) regarding the proportion of patients with FC improvement were available from published sources for macitentan. Direct pairwise meta-analysis showed that, for naive populations, epoprostenol, sildenafil, and tadalafil showed statistically significant improvement in FC compared with placebo, while riociguat, ambrisentan, bosentan, and treprostinil did not. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. Epoprostenol, which had the highest treatment effect, was statistically significantly superior compared with all other treatments in the naive populations. Sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect. The minimal clinically important difference (MCID) of WHO FC improvement is unknown.

For FC worsening, data from eight treatment options (riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and placebo) were available for analyses. Data for macitentan were not available for the treatment-naive population; only results for the total study population (i.e., treatment-naive plus treatment-experienced) regarding the proportion of patients experiencing FC worsening were available from published sources. Direct pairwise meta-analysis showed that all treatments were

numerically favoured in the reduction of FC worsening compared with placebo. Statistically significant differences were reached only for ambrisentan (5 and 10 mg) and riociguat (max 2.5 mg) in naive populations. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. There were no statistically significant differences between riociguat and other drugs or between other drugs themselves. Sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect. The MCID of WHO FC worsening is unknown.

For 6MWD, data for all 11 treatment options (macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil, and placebo) were available for analysis. The 6MWD measures the distance a patient can walk in six minutes. Change from baseline in 6MWD is the most widely used outcome in trials of drugs for PAH. However, while some evidence suggests baseline 6MWD and absolute distance walked in six minutes are correlated with mortality and morbidity outcomes in PAH, change from baseline in 6MWD has been inconsistently correlated with these outcomes.[38] Change in 6MWD from baseline was used as the primary outcome in all of the included studies, except for the macitentan study, in which it was a secondary outcome. Direct pairwise meta-analysis showed that all drugs, except macitentan, statistically significantly increased 6MWD compared with placebo in the naive populations. The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. Increase in 6MWD with riociguat (both doses) was not statistically significantly different compared with all other drugs. Numerically, epoprostenol showed the highest increase in 6MWD compared with all remaining drugs. The mean differences in 6MWD relative to other drugs ranged from 18.3 m (compared with ambrisentan 5 mg) to 56.9 m (compared with macitentan 10 mg). The MCID for the change in 6MWD from baseline has been estimated to be 33.0 m (range: 25.1 m to 38.6 m). Sensitivity analysis was not performed for this outcome.

In summary, of the four outcomes analyzed using NMA, there were no statistically significant differences between drugs with respect to clinical worsening and FC worsening. For FC improvement and 6MWD, epoprostenol had highest activity in treatment-naive populations, while there were no apparent differences among the remaining treatments. Acknowledging the limitations in the available evidence, these findings suggest that there may not be statistically or clinically meaningful differences between drugs currently available in Canada for the treatment of PAH. There is, however, an exception with epoprostenol, which appears to be the most effective in improving clinical status, as measured by FC improvement and 6MWD.

Combination Therapy (Add-on)

Evidence of clinical worsening, FC improvement, FC worsening, and 6MWD was available for riociguat max 2.5 mg or tadalafil 40 mg added to ERA background therapy of ambrisentan or bosentan that had been stable for at least three months. Furthermore, evidence for clinical worsening and 6MWD was also available for addition of macitentan to PDE-5 inhibitor or prostanoid background therapy. However, the macitentan data could not be combined with those of riociguat or tadalafil in the NMA because of different background therapies and the much longer study duration of the macitentan RCT. The following findings address the comparison of dual therapy versus monotherapy:

- Addition of macitentan 10 mg to PDE-5 inhibitor or prostanoid background therapy statistically significantly reduced clinical worsening compared with background therapy alone.
- Addition of riociguat max 2.5 mg to ERA background therapy reduced clinical worsening versus ERA monotherapy, but this effect was not statistically significant. However, addition of

tadalafil 40 mg to ERA background therapy statistically significantly reduced clinical worsening versus ERA monotherapy.

- For FC improvement, there were no statistically significant differences between combination therapy of riociguat max 2.5 mg and ERA or of tadalafil 40 mg and ERA versus ERA alone.
- Addition of riociguat max 2.5 mg or tadalafil 40 mg to ERA background therapy reduced FC worsening versus ERA alone; however, neither combination resulted in a statistically significant difference versus monotherapy.
- Addition of macitentan 10 mg, riociguat max 2.5 mg, or tadalafil 40 mg to corresponding background therapy numerically improved 6MWD compared with background therapy alone. Statistically significant differences were reached for macitentan and tadalafil, but not for riociguat.
- There were no statistically significant differences between combination therapy of riociguat plus ERA and tadalafil plus ERA for clinical worsening, FC improvement, FC worsening, and 6MWD.

Other Efficacy Outcomes

Direct pairwise meta-analyses were performed for hospitalization, mortality, BDI, hemodynamics (PVR, mPAP, cardiac index), and health-related quality of life (HRQoL). These outcomes were mostly available for total populations; i.e., including both treatment-naive and treatment-experienced patients.

The number of deaths in all studies was relatively low, except in one study of epoprostenol and one study of treprostinil, where the percentage of patients who died in the placebo groups reached 25% (9% in the epoprostenol group) and 36% (10% in the treprostinil group), respectively, albeit among patients with more severe disease (predominantly NYHA or WHO FC III or IV). Epoprostenol showed a statistically significant lower risk of mortality compared with placebo, while there were no statistically significant differences between other drugs and placebo.

Of all drugs, except epoprostenol, macitentan 10 mg was the only drug that showed a statistically significant reduction in hospitalization compared with placebo.

Compared with placebo, all drugs improved breathlessness (measured by BDI), PVR, mPAP, and cardiac index. However, statistically significant improvements were less consistent across drugs for improved BDI scores as compared with hemodynamic parameters and cardiac index.

HRQoL was poorly reported in most studies, using different instruments such as the Short-Form (36-Item) health survey (SF-36), the EuroQol 5-Dimensions Questionnaire (EQ-5D), Living with Pulmonary Hypertension questionnaire, Minnesota Living with Heart Failure Questionnaire, Chronic Heart Failure Questionnaire, Nottingham Health Profile, and Dyspnea-Fatigue Rating. Overall, all drugs showed improvement in HRQoL compared with placebo. Statistically significant differences were not reached for bosentan.

Subgroup Analyses

The results for subgroup analyses with respect to age, baseline FC, baseline 6MWD, gender, PAH etiology, and PAH therapies at baseline were reported as point estimates in forest plots. Raw data were not available to perform meta-analysis. The study of macitentan reported subgroup analyses on clinical worsening and 6MWD, while the studies of riociguat, bosentan, sildenafil, and tadalafil reported subgroup analyses on 6MWD only. Overall, all five drugs showed improvement in clinical worsening and/or 6MWD in all patient subgroups.

Safety

Safety data from the published studies included in this review were available only for total populations; i.e., including both treatment-naive and treatment-experienced patients.

- Serious adverse events (SAEs) were less frequent with macitentan (45% versus 55%), riociguat (11% versus 18%), ambrisentan (9% versus 16%), and tadalafil (9% versus 15%) compared with placebo. In contrast, treprostinil (62% versus 20%) had frequent SAEs related to injection site reactions. Bosentan, sildenafil, and epoprostenol showed no numerically notable differences in SAEs compared with placebo.
- Discontinuation of treatment was more frequent with treprostinil than placebo (7.7% versus 0.4%). This was mainly due to abdominal subcutaneous injection site pain. There was no apparent difference between other drugs and placebo with respect to discontinuation of treatment due to AEs.
- Common AEs compared with placebo:
  - Risk of liver toxicity: bosentan (12% versus 2%)
  - Risk of peripheral edema: riociguat (18% versus 11%), ambrisentan (22% versus 11%), bosentan (13% versus 8%), and treprostinil (9% versus 3%)
    - Risk of anemia: macitentan (13% versus 3%), riociguat (8% versus 2%), and ambrisentan (68% versus 17%)
    - Risk of hypotension: riociguat (10% versus 2%), epoprostenol (13% versus 0%), and treprostinil (5% versus 2%)
    - Epoprostenol and treprostinil were frequently associated with nausea, diarrhea, jaw pain, headache, and injection site reactions.

Key Findings of Economic Analysis

For monotherapy versus supportive care, the results of the base case show that sildenafil would be considered the most cost-effective therapy for PAH in patients with FC II, III, or IV. Although sildenafil was found to be the most cost-effective PAH therapy in FC IV, its role as monotherapy in FC IV has been questioned.

In patients with FC II and III, sildenafil was both less costly and more effective than all comparator treatments including supportive care — sildenafil is therefore the dominant therapy. In FC IV, supportive care was less costly than treatment with sildenafil; however, provided a payer's willingness to pay per QALY was greater than $19,188, sildenafil would be the most cost-effective therapy. Of note, generic sildenafil is reimbursed by some of the drug plans. Using the generic cost of sildenafil would not change the conclusions of the analysis, as sildenafil would remain the most cost-effective option for adult patients with FC II and III PAH.

Although sildenafil dominated treatment with tadalafil in FC II and III, being both more effective and less costly, when compared with supportive care, tadalafil was dominant over supportive care in patients with FC II and III PAH. In FC IV, the incremental cost-utility ratio (ICUR) for tadalafil versus supportive care was $211,923 per QALY. In FC IV, all other treatments in comparison with supportive care produced ICURs of greater than $1,000,000 per QALY.

There were no studies comparing monotherapy with a PDE-5 inhibitor, the most cost-effective therapy based on the monotherapy analysis, with (add-on) therapy. There were, however, studies examining the use of add-on therapy with either an ERA plus tadalafil or an ERA plus riociguat versus an ERA alone. In interpreting the results of this analysis, one should bear in mind that an ERA alone was not cost-effective at willingness to pay of $50,000 per QALY, as compared with supportive care for any PAH functional class within the monotherapy analysis.

At a decision-maker's willingness to pay of less than approximately $88,000 per QALY, neither add-on therapy with an ERA plus tadalafil nor add-on therapy with an ERA plus riociguat would be considered cost-effective in PAH patients with FC II, III, or IV disease relative to an ERA alone. The ICUR for an ERA plus tadalafil versus an ERA alone in FC II patients was the lowest at $88,506 per QALY, followed by FC III at $156,513 per QALY and significantly higher in FC IV at $1,568,400 per QALY. The combination of an ERA plus riociguat was both more costly and more efficacious than an ERA plus tadalafil, resulting in comparative cost-effectiveness ratios of more than $500,000 per QALY in all three PAH FCs.

In deterministic sensitivity analyses, results were insensitive to changes in assumptions regarding discount rates, utility values, treatment costs, and health care costs in FC I; however, they were sensitive to the time horizon of the model, the percentage of patients initiating epoprostenol upon deteriorating to FC IV, and the incorporation of unadjusted estimates for the relative risk of improvement and worsening in FC with treatment only within FC IV.

The probabilistic sensitivity analysis suggests that there is a great deal of uncertainty regarding the estimates of costs and effectiveness associated with the PAH therapies under study. This uncertainty is primarily due to the significant uncertainty in the estimates produced from the NMA for the improvement and worsening in FC, which is reflected in the wide credible intervals reported for the relative risks. Even given the uncertainty within the clinical inputs, apart from sildenafil and tadalafil, the other PAH therapies had negligible probability of being the most cost-effective.

Strengths and Limitations

Strengths of the current review include its systematic approach to collecting evidence and performing data extraction, quality assessment, and summarizing the effects with pairwise meta-analyses and NMAs. Patient-relevant outcomes such as clinical worsening, FC improvement, FC worsening, and 6MWD were included. Relevant harm outcomes and outcomes on HRQoL were also collected in the review. The robustness of the NMA was supported by the relevant sensitivity analyses. A comprehensive economic evaluation was conducted using available cost data and the results of the NMA.

Key limitations of the review are related to the degree of availability of data in the public domain and the suitability of available data for statistical pooling. None of the four therapeutic review research questions could be fully answered. For instance, there were no studies meeting the inclusion criteria that compared the efficacy and safety of dual combination therapies (question 3) or triple combination therapy versus dual combination therapy (question 4). For the comparative efficacy of dual combination therapy versus monotherapy (question 2), data were available only for macitentan, riociguat, and tadalafil. However, NMAs could be conducted only between riociguat max 2.5 mg and tadalafil 40 mg (both with ERA background therapy) because the macitentan study used a different treatment background (PDE-5 inhibitor or prostanoid). For question 1, NMA was conducted to explore the comparative efficacy of monotherapy (naive populations) between treatments. However, data for macitentan for naive populations were available in the published article only for clinical worsening and 6MWD, but not for FC improvement or FC worsening.

No head-to-head RCTs comparing the efficacy and safety of any of the drugs were identified for inclusion in the review.

Several subgroups were identified as important for this review: age, gender, baseline 6MWD, baseline PAH etiology, baseline WHO FC, and background PAH therapy. Treatment outcomes according to these subgroups were not reported in the published articles. We were therefore unable to estimate the comparative treatment effects of PAH therapies based on these subgroups in the analysis to identify which treatment is better for specific subgroups and to account for related potential sources of bias.

In addition, evidence for add-on therapy was very limited; few comparative studies (i.e., RCTs or comparative observational studies) were identified for inclusion in the systematic review. Of those that were included, only two were appropriate for inclusion in an NMA. Patients who received add-on therapy in the studies were prevalent cases of PAH and had been stable on background therapy for at least three months. In studies that included both treatment-naive and treatment-experienced (i.e., add-on therapy) patients, combining naive and experienced patients makes interpreting the outcomes difficult. Although the numbers of naive and experienced patients appeared to be balanced between treatment groups in the studies, the presence of experienced patients in the total population might dilute the observed treatment effect. Also, there were no trials specifically designed to assess the comparative efficacy and safety of new treatments in patients who had failed or were intolerant to previous treatments; thus, it is uncertain to what extent the results of the current review are applicable to this patient population. According to the clinical experts involved in this review, in the clinical practice setting, the decision to intensify therapy by adding a new therapy to the existing one is proactive, made when patients fail to meet specific targets of response rather than waiting for a bad outcome to occur. Several studies on combination therapy did not meet the review inclusion criteria and were therefore excluded from data analysis. The results of those studies (one systematic review and eight single-group observational studies) were presented in Section 6.2.3. Most studies showed that combination therapy resulted only in a modest increase in 6MWD, with mixed evidence regarding the clinical improvement of the combination therapy compared with monotherapy. Therefore, a limited number of RCTs and lower-quality observational studies have demonstrated a modest improvement in certain PAH outcomes, but not all. High-quality studies are still needed to ascertain whether combination therapy shows improvement in outcomes including mortality, morbidity, FC improvement, and FC worsening compared with monotherapy.

In addition, two studies on combination therapy, one comparing sildenafil plus bosentan versus sildenafil alone (COMPASS-2), and the other comparing first-line ambrisentan plus tadalafil versus ambrisentan and tadalafil monotherapies (AMBITION), were ongoing at the initiation of this review. The results are not yet published and these were therefore excluded from the review.

Substantial heterogeneity in study designs, patient demographics, and disease characteristics (i.e., WHO FC at baseline and PAH etiology) may present as a threat to the validity of this review. However, these potential sources of bias were assessed early in the development of this review and methods to deal with these were determined a priori. To address the heterogeneity, we performed meta-regression and subgroup analyses using patient characteristics as covariates. However, the small number of studies in relation to the number of covariates may not have allowed for complete control of confounding. To assess the potential impact of heterogeneity derived from a mixed patient population, our analyses were performed on the treatment-naive population separated from the total study population. We also performed several sensitivity analyses by excluding SERAPHIN (a long-term study of macitentan) or by adjusting for baseline FC and baseline PAH etiology. There were no marked changes in the

magnitude and direction of the relative effects from the results of the unadjusted model for the base case, suggesting the robustness of the base-case results.

An additional limitation involved the inclusion of a long-term study of macitentan (SERAPHIN; median follow-up 115 weeks) together with shorter-term studies (range: 12 to 16 weeks' duration) in the NMA. To examine the effect of this potential source of heterogeneity, sensitivity analyses were performed by excluding the study of macitentan from the NMA, and the results did not show any changes in the magnitude and direction of the effect sizes of the remaining treatments. In more general terms, the fact that only one long-term RCT was identified for inclusion highlights the paucity of comparative long-term evidence for the efficacy and safety of drugs for the treatment of PAH. Extension studies were not included in the review because they lacked a comparator group. Although extension studies may be helpful in assessing the safety of medications, they are of uncertain value in assessing the efficacy of treatments. The lack of a comparator group and the potential for selection bias make the interpretation of the results unclear.

An example related to the aforementioned limitation is the limited long-term efficacy and safety data for sildenafil. The Health Canada–approved dose of sildenafil is 20 mg three times a day; however, in practice clinicians may increase the dose to 80 mg three times a day or more. The US FDA issued a warning in 2012 regarding the potential association between increasing sildenafil dose and increased risk of death with long-term use in pediatrics.[39] FDA is requiring the manufacturer of sildenafil to evaluate its effect on the risk of death in pediatrics and adults with PAH. Hence, there is a need for long-term RCT data to evaluate the potential long-term benefits and harm of these therapies.

Finally, safety data and data on hemodynamics were often reported without stratifying into treatment-naive or treatment-experienced populations in trials having mixed populations, such as the studies of macitentan, riociguat, tadalafil, and bosentan. This would largely compromise the interpretability of the comparative safety between different therapeutic regimens. Therefore, in this review, we were not able to conduct an NMA for those outcomes.

The economic analysis was limited by the lack of data regarding the impact of treatment on patients' HRQoL. As the only measure of clinical efficacy that has been demonstrated to be associated with quality of life is PAH FC, the impact of treatment on FC was incorporated as the measure of treatment efficacy within the economic model. This may not capture the full benefit of treatment, which would be better reflected through direct measurement of quality of life in patients receiving PAH therapies. A major limitation within the economic analysis is the quality of the clinical trials. The short-term nature of the clinical trials required assumptions regarding the long-term impacts of treatment, which may have introduced additional uncertainty within the results.

Conclusions and Implications for Decision- or Policy-Making

The objective of this therapeutic review was to assess the comparative efficacy and safety and to determine the cost-effectiveness of drug therapies for the treatment of PAH in adults.

Results from the systematic review and NMA suggest that there were no significant differences in clinical worsening and FC worsening between drugs used to treat PAH as monotherapy. For FC improvement and 6MWD, epoprostenol appeared to be the most effective treatment option in improving clinical status, while there were no apparent differences among other treatments.

Addition of macitentan on PDE-5 inhibitor or prostanoids background therapy and addition of riociguat or tadalafil on ERA background therapy produce improvement in clinical worsening, FC improvement, FC worsening, and/or 6MWD compared with monotherapy. There were no differences between combination therapy of riociguat plus ERA and tadalafil plus ERA for all four clinical outcomes.

All drugs showed improvement in pulmonary hemodynamics and HRQoL compared with placebo. AEs were treatment specific and may be an important consideration in treatment selection.

Key limitations of the review are related to the poor availability of data in the public domain and the suitability of available data for statistical pooling due to clinical and methodological heterogeneity. None of the four therapeutic review research questions could be fully answered.

Patient-group input suggests that patient experience with current available therapy is generally positive and the majority report taking combination therapy. Patients are hopeful that new drugs will reduce symptoms of PAH, will have fewer adverse effects, and will offer better quality of life than currently available medications.

Based on the economic analysis comparing the cost-effectiveness of single therapies for PAH, sildenafil would be considered the optimal therapy as it was dominant over other therapies in patients with FC II and III and dominated all therapies except supportive care in FC IV, in which case it resulted in an ICUR of less than $20,000 versus supportive care. Although sildenafil was found to be the most cost-effective PAH therapy in FC IV, its role as monotherapy in FC IV has been questioned. Tadalafil was also less costly and more effective than supportive care in patients with FC II and III PAH; however, sildenafil was dominant over tadalafil, being both less costly and more effective. All other therapies were more costly than sildenafil, tadalafil, and supportive care and resulted in ICUR compared with supportive care of greater than $140,000 per QALY. Extensive sensitivity analyses found the results to be relatively robust to changes in assumptions. The only scenarios that affected the results were reducing the time horizon to two years, reducing the percentage of patients initiating epoprostenol upon deteriorating to FC IV to 0, and incorporating unadjusted relative risks of improvement and worsening in FC from the NMA.

With respect to dual (add-on) therapy for PAH, unfortunately there were no comparisons examining the addition of treatments to either sildenafil or tadalafil; rather, studies have examined the addition of tadalafil and riociguat to existing ERA therapy. ERA monotherapy was not cost-effective compared with either sildenafil or supportive care; it is therefore challenging to draw conclusions from this analysis. ERA monotherapy was the most cost-effective strategy versus the combination of ERA plus tadalafil and versus ERA plus riociguat. The ICUR for ERA plus tadalafil ranged from $88,000 in FC II to $1.5 million in FC IV versus an ERA alone. The sequential ICUR for ERA plus riociguat versus ERA plus tadalafil was greater than $500,000 per QALY in all FCs. These results were robust to changes implemented within the sensitivity analysis, except in the case when the percentage of patients initiating epoprostenol upon deteriorating to FC IV was increased to 100%. In this case, for patients in FC II and III, the ICUR was below $40,000 per QALY for an ERA plus tadalafil versus an ERA alone.

In a separate analysis specific to macitentan in a cohort of patients with a proportion receiving additional therapy with a PDE-5 inhibitor, macitentan was not cost-effective unless a decision-maker's willingness to pay for a QALY exceeded $200,000.

Probabilistic sensitivity analysis revealed that there was a great deal of uncertainty surrounding the estimates of costs and QALYs for each of the therapies. Estimates of cost-effectiveness would be better informed by more head-to-head trials comparing therapies for PAH and longer-term follow-up of outcomes.

1 CONTEXT AND POLICY ISSUES

1.1 Pulmonary Arterial Hypertension

1.1.1 Description of the Medical Condition

Pulmonary arterial hypertension (PAH) is a chronic and progressive disease leading to morbidity and premature mortality. The diagnosis is usually confirmed by performing right-heart catheterization showing elevation of the mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg.[2] The pathological changes of PAH include lesions in distal pulmonary arteries, medial hypertrophy, intimal proliferative and fibrotic changes, and adventitial thickening with perivascular inflammatory infiltrates.[13] Vasoconstriction, endothelial dysfunction, dysregulated smooth muscle cell growth, inflammation, and thrombosis are contributory mechanisms to the disease progression.[13] This complex multifactorial disorder typically leads to overload of the right ventricle, progressive right-sided heart failure, and premature death.[13] The action of PAH drugs is aimed at normalizing these mechanisms.

1.1.2 Epidemiology

Although PAH affects males and females of all ethnicities and ages,[3] the disease is more common among women and people between 20 and 40 years of age.[4] In adults, the prevalence of PAH is approximately 12 to 50 cases per million people.[5-7] Data from four Western country registries recently reported the following PAH-specific prevalences:[8]

- France (French national registry): 15 PAH cases per million adults (age: 50 years ± 15)
- Scotland (Scottish Morbidity Record): 26 PAH cases per million adults (age: 52 years ± 12)
- Spain (Spanish national registry): 16 cases per million adults (age: 45 years ± 17)
- US (REVEAL registry): 10.6 cases per million adults (age: 50 years ± 14).

Epidemiological data for PAH in Canada are not available. Assuming the Canadian prevalence for PAH is within the range of those reported for these four Western countries, and considering that there were 29.5 million adults (defined as older than 15 years) in Canada in 2013,[40] it may be estimated that there are currently between 313 and 767 adult patients with PAH in Canada. The incidence of PAH for children was 0.48 cases per million per year, and the prevalence was 2.1 cases per million, according to the national registries from the United Kingdom.[11]

PAH is a life-threatening disease and, overall, patients with certain types of PAH will live a median of two to three years if left untreated.[10] The estimated median survival in children if left untreated has been estimated at 10 months.[10]

1.1.3 Disease Classification

The first classification of pulmonary hypertension (PH) was proposed in 1973. It was initially classified into two broad groups: primary PH and secondary PH. This classification has since undergone a number of revisions.[2] PH is now classified into five main groups; Group 1 is synonymous with PAH and its subgroups. Idiopathic PAH (IPAH) is the most common form of the disease (46%).[41] Additional subgroups of PAH include a heritable form, a form induced by drugs and toxins, a form in newborns, and forms associated with concurrent medical conditions such as connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, and chronic hemolytic anemia.[2,41] Of note, at the time the protocol for this review was prepared, the Dana Point 2008 PH Classification was in use.[2,41] This classification stemmed from the Fourth World Symposium on PH, held in Dana Point (California, US) in 2008,

during which an international group of experts updated and clarified previous PH classifications. These revisions led to the creation of a distinct group that was nonetheless still linked to the main Group 1; i.e., Group 1' pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH). This decision was based on the fact that both PVOD and PCH share characteristics with IPAH but also have a number of differences.[2,41] Because of the particular nature of PVOD and PCH, Group 1' was excluded from the scope of this therapeutic review. In 2013, the Fifth World Symposium on PH was held in Nice (France) and an updated PH Classification was recently published. Three new changes now affect Group 1: i) three genetic mutations were added to item 1.2.2, which is part of subgroup 1.2 (heritable PAH); i.e., caveolin-1 (CAV1), potassium channel super family K member-3 (KCNK3), and mothers against decapentaplegic 9 (Smad 9); ii) persistent pulmonary hypertension of the newborn (PPHN) was withdrawn from Group 1 because this entity carries more differences than similarities with other PAH subgroups; PPHN is now categorized as Group 1'' in the updated PAH Classification; iii) PH associated with chronic hemolytic anemia was moved from item 1.4.6, part of Group 1, to subgroup 5.1 (hematologic disorders), part of Group 5 (PH with unclear or multifactorial mechanism) (Table 1). Other minor revisions from the 2013 symposium mainly affect Groups 2 and 5.[12] Of note, the 2013 revisions to the PH Classification have no impact on the findings of this therapeutic review.

Table 1: Pulmonary Arterial Hypertension
1 Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1. BMPR2
1.2.2. ALK1, ENG, CAV1, KCNK3, Smad 9
1.2.3. Unknown
1.3 Drug- and toxin-induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; CAV1 = caveolin-1; ENG = endoglin; KCNK3 = potassium channel super family K member-3; Smad 9 = mothers against decapentaplegic 9.

PAH is associated with poor overall prognosis. A US national registry study conducted in the early 1980s (i.e., prior to the availability of PAH-specific pharmacological treatments), which included 187 patients with IPAH or familial PAH (FPAH) followed for up to five years, found that the median survival was 2.8 years.[10,42] At present, the average survival in adults after diagnosis is estimated at five to seven years.[43-45] From the REVEAL registry data (Registry to Evaluate Early and Long-Term PAH Disease Management), the one-year survival rate for PAH is approximately 91%.[46] Of note, the latter figure specifically applies to the 1,267 patients with IPAH/FPAH. Based on the analysis of 2,635 patients with PAH enrolled in the REVEAL registry (March 2006 to December 2009) and who met the traditional PAH definition, the one-, three-, five-, and seven-year survival rates are estimated to be 85%, 68%, 57%, and 49%, respectively. It is hypothesized that, among other factors, improvement in pharmacological treatments and care for patients with PAH played a role in this survival gain.[45]

1.2 Therapeutic Options

Treatment of PAH is generally categorized as supportive therapy or advanced therapy. Supportive therapy includes use of diuretics, oxygen, anticoagulants, and digoxin. Many patients with PAH will receive supportive therapy despite limited or no evidence of effectiveness.[14] Advanced therapy is directed at the disease itself. As supportive therapies are generally not effective in PAH, advanced therapy is almost always needed.[14]

There are eight drugs approved in Canada for advanced therapy of PAH. They belong to four classes of drugs; three of these classes have been available for some time in Canada: prostanoids (epoprostenol injectable, treprostinil injectable), endothelin receptor antagonists (ERAs; bosentan tablet, ambrisentan tablet, macitentan tablet), and phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil tablet and injectable, tadalafil tablet). Of note, the new ERA macitentan received Health Canada approval for the treatment of PAH in November 2013.[47] The first soluble guanylate cyclase (sGC) stimulator (riociguat) received approval for this indication in March 2014.[48]

The availability of the two new PAH drugs — macitentan and riociguat, with the latter also introducing a fourth drug class — increases the complexity of PAH therapy. Treatment options also increase for combination therapy, with riociguat being based on the concurrent use of drugs with different mechanisms of action. A recently published treatment algorithm for PAH reflects the increased number of therapeutic options now available to clinicians and patients.[49] Nevertheless, choice of initial advanced monotherapy is based on PAH severity, comorbidities, adverse event profiles, physician's experience, patients' preference, long-term data available, and costs.

With respect to combination therapy, there are two options: add a medication to an ongoing treatment [(sequential [add-on] combination therapy), or start with a combination therapy from the beginning of treatment (upfront combination therapy); the first option is the one currently being recommended.[49] Recent data from the REVEAL registry indicate that combination therapy is routinely used in the US, with approximately 65% of PAH patients on such therapy. A recent survey indicates that a majority of PH specialists in Canada support the use of combination therapy in patients who do not adequately respond to monotherapy.[50] Recent revision to the reimbursement policy for PAH drugs in Ontario included changes in funding for certain drug combinations and restricting prescribing of these to recognized PH treatment centres; this has led to 22% of PAH patients using combination therapy.[15] However, according to the clinical experts involved in the review, the current estimate may be closer to 50%, depending on the PAH clinic.

The emergence of novel drug therapies necessitates consideration of their comparative effectiveness from both a clinical and an economic perspective, accounting for both monotherapy and combination therapy regimens. The aim of this therapeutic review is to compare the efficacy and safety of new and existing drug therapies for PAH, and examine their cost-effectiveness. The clinical and cost-effectiveness evidence was reviewed by the Canadian Drug Expert Committee (CDEC) for the purpose of making recommendations. Recommendations and advice provided by CDEC are provided to CADTH–participating jurisdictional drug programs to inform their reimbursement policies and decisions. Further details regarding the approved therapeutic options for the treatment of PAH, according to the Health Canada product monographs, are included in Table 2.

Table 2: Summary of Health Canada–Approved Therapeutic Options of Interest Based on Product Monographs								
	Epoprostenol[51]	**Treprostinil**[52]	**Ambrisentan**[53]	**Bosentan**[54]	**Sildenafil**[55]	**Tadalafil**[56]	**Macitentan**[47]	**Riociguat**[57]
Mechanism of Action	Direct vasodilation of pulmonary and systemic arterial beds. Inhibition of platelet aggregation.	Direct vasodilation of pulmonary and systemic arterial beds. Inhibition of platelet aggregation.	Selective inhibition of the receptor that inhibits C-mediated vasoconstriction.	ERA; decreases pulmonary and systemic vascular resistance, resulting in increased cardiac output without increased heart rate.	Selective inhibition of PDE-5, thereby increasing cGMP, leading to selective vasodilation of the pulmonary vascular bed and systemic circulation. Inhibition of platelet aggregation.	Selective inhibition of PDE-5, thereby increasing cGMP, leading to selective vasodilation of the pulmonary vascular bed.	Endothelin receptor antagonist; decreases mean pulmonary arterial pressure without affecting systemic blood pressure, decreased pulmonary arterial hypertrophy, and right ventricular remodelling.	A stimulator of sGC, with a dual mode of action, acting in synergy with endogenous nitric oxide and also directly stimulating sGC independently of nitric oxide availability.
Approved Indications	Primary pulmonary hypertension and secondary pulmonary hypertension due to scleroderma spectrum of disease in NYHA FC III and IV patients who did not respond adequately to conventional therapy.	PAH in NYHA FC III and IV patients who did not respond adequately to conventional therapy.	Idiopathic ("primary") pulmonary arterial hypertension and PAH associated with connective tissue disease in patients with WHO FC II or III symptoms who have not responded to conventional therapy.	WHO FC III or IV primary pulmonary hypertension, or pulmonary hypertension secondary to scleroderma or congenital heart disease or HIV in patients who did not respond adequately to conventional therapy.	Oral: Primary pulmonary hypertension or pulmonary hypertension secondary to connective tissue disease in patients with WHO FC II or III who did not respond adequately to conventional therapy. Intravenous: Patients who are temporarily unable to take oral medication.	IPAH or PAH associated with connective tissue disease, congenital heart disease, or anorexigen use in patients with WHO FC II or III who have not responded to conventional therapy.	IPAH/FPAH of WHO FC II or III, or PAH associated with connective tissue disease or congenital heart disease.	PAH (WHO Group 1), as monotherapy or in combination with ERAs, in adult patients (≥ 18 years of age) with WHO FC II or III.
Route of Administration	Continuous chronic intravenous infusion via central venous catheter	Subcutaneous or intravenous (long-term)	Oral	Oral	Oral or intravenous	Oral	Oral	Oral
Recommended Dose	Initial: 2 ng/kg/min Incremental increase: 1 to 2 ng/kg/min, at 15-minute intervals minimally	Initial: 1.25 ng/kg/min If initial dose cannot be tolerated, rate should be reduced to 0.625 ng/kg/min Dose adjustment: based on PAH signs	Initial: 5 mg/day Increase: 10 mg/day may be necessary for patients with connective tissue disease	Initial: 62.5 mg twice daily for 4 weeks Increase: 125 mg twice daily	Oral: 20 mg three times daily Intravenous: 10mg three times daily; administered as an intravenous bolus injection	40 mg once daily Patients with mild renal insufficiency: 20 mg once daily, increased to 40 mg once daily based on	10 mg once daily	0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg three times daily

Table 2: Summary of Health Canada–Approved Therapeutic Options of Interest Based on Product Monographs								
	Epoprostenol[51]	**Treprostinil[52]**	**Ambrisentan[53]**	**Bosentan[54]**	**Sildenafil[55]**	**Tadalafil[56]**	**Macitentan[47]**	**Riociguat[57]**
		and symptoms and side effects				tolerability <u>Patients with mild or moderate hepatic impairment</u>: 20 mg once daily		
Contraindications (According to Product Monograph)	Patients with congestive heart failure due to severe left ventricular systolic dysfunction. Patients with known or suspected hypersensitivity to the drug, or any of its excipients. Patients who develop pulmonary edema during dose initiation.	Patients with known hypersensitivity to the drug, any of its excipients, or to structurally related compounds.	Patients with idiopathic pulmonary fibrosis. Patients with known hypersensitivity to the drug or any of the ingredients in the formulation. Patients who are pregnant or may become pregnant. Patients with clinically significant anemia.	Patients who are hypersensitive to drug or any excipient in the formulation. Patients who are pregnant. Patients with moderate or severe liver impairment. Concomitant use of cyclosporine A or glyburide.	Patients on nitrate drug therapy or utilizing short-acting nitrate-containing medications. Patients who are hypersensitive to drug or any ingredient in the formulation or component of the container.	Patients with severe renal insufficiency. Patients with severe hepatic impairment.	Patients who are hypersensitive to drug. Patients who are pregnant or may become pregnant.	PDE-5 inhibitors (sildenafil, tadalafil, vardenafil) Nitrates Nitric oxide donors, such as amyl nitrate Patients who are pregnant, or during nursing, or hypersensitive to drug or any ingredient in the formulation or component
Warnings and Precautions (According to Most Recent Product Monograph)	Abrupt withdrawal should be avoided. Not to be used in patients having pulmonary edema during dose initiation. Administration must be performed in hospital with adequate personnel and equipment for physiologic monitoring and emergency care.	Abrupt withdrawal should be avoided. Administration must be performed in hospital with adequate personnel and equipment for physiologic monitoring and emergency care. Dosage should be adjusted at the first sign of recurrence or worsening of symptoms	Potential development of decreases in hemoglobin and hematocrit. Potential for hepatic enzyme elevations; therefore, not to be used in patients with severe hepatic impairment, and used with caution in patients with moderate hepatic impairment.	Reversible increases in liver enzymes; potential for hepatic cirrhosis; liver failure. Potential for worsening of chronic heart failure, possibly due to fluid retention. Potential for decreases in hemoglobin.	Not recommended for patients with pulmonary veno-occlusive disease. Patients with abnormal discs or previously diagnosed with NAION, due to potential development of NAION. Concomitant administration of ritonavir.	Patients should not be administered nitrates (including nitroglycerin) within 48 hours of last dose of tadalafil. Potential to significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease. Patients with abnormal discs or	Potential for hepatic enzyme elevations; therefore, not to be used in patients with moderate-to-severe hepatic impairment. Potential for development of decrease in hemoglobin; not recommended for use in patients with severe anemia. Patients with	Risk of hypotension, particularly in patients with concomitant or underlying conditions such as low systemic blood pressure (e.g., systolic blood pressure < 95 mm Hg), coronary artery disease, hypovolemia, severe left

Table 2: Summary of Health Canada–Approved Therapeutic Options of Interest Based on Product Monographs								
	Epoprostenol[51]	**Treprostinil**[52]	**Ambrisentan**[53]	**Bosentan**[54]	**Sildenafil**[55]	**Tadalafil**[56]	**Macitentan**[47]	**Riociguat**[57]
	Increased risk for hemorrhagic complications in patients with other risk factors for bleeding.	attributable to PAH or the occurrence of intolerable adverse events.	Peripheral edema, with the possibility of pulmonary veno-occlusive disease.		Caution is advised when co-administered with alpha-blockers, as both are vasodilators with blood pressure lowering effects.	previously diagnosed with NAION, due to potential development of NAION.	moderate or severe renal impairment could experience hypotension and anemia.	ventricular outflow obstruction, or autonomic dysfunction, as well as in patients on antihypertensive therapy or with resting hypertension. Risk of additive or synergistic effects on systemic blood pressure when concomitantly used with PDE-5 inhibitors, nitrates, or nitric oxide donors. Risk of bleeding particularly in patients taking anticoagulants.

cGMP = cyclic guanosine monophosphate; ERA = endothelin receptor antagonist; FC = functioning class; FPAH = familial or heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NAION = non-arteritic anterior ischaemic optic neuropathy; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; sGC = soluble guanylate cyclase; WHO = World Health Organization.

2 POLICY QUESTIONS

There are three policy questions for this project. These reflect the information needs of CADTH jurisdictional clients. Policy questions also fed the deliberations of the CDEC members when they developed the therapeutic review recommendations.

1) How do new drugs for advanced therapy of PAH compare with currently available drugs?
2) How does (add-on) combination therapy compare with monotherapy in patients with PAH?
3) Are there subgroups of patients (based on disease severity or other disease characteristics) who benefit more from specific drugs when used either as monotherapy or (add-on) combination therapy?

3 RESEARCH QUESTIONS

1. What is the comparative efficacy, safety, and cost-effectiveness of monotherapy with macitentan or riociguat compared with monotherapy with each other or with a PDE-5 inhibitor, another ERA, or a prostanoid:
   a. in PAH patients, irrespective of disease severity or etiology?
   b. in PAH patients with functional class (FC) II?
   c. in PAH patients with FC III or IV?
   d. in PAH patients with different disease etiology, as defined in the Dana Point 2008 Classification?

2. What is the comparative efficacy, safety, and cost-effectiveness of dual (add-on) combination therapy involving either a PDE-5 inhibitor, an ERA, an sGC stimulator, or a prostanoid versus monotherapy:
   a. in PAH patients, irrespective of disease severity or etiology?
   b. in PAH patients with FC II?
   c. in PAH patients with FC III or IV?
   d. in PAH patients with different disease etiology, as defined in the Dana Point 2008 Classification?

3. What is the comparative efficacy, safety, and cost-effectiveness of dual (add-on) combination therapy involving either a PDE-5 inhibitor, an ERA, an sGC stimulator, or a prostanoid versus dual (add-on) combination therapy:
   a. in PAH patients, irrespective of disease severity or etiology?
   b. in PAH patients with FC II?
   c. in PAH patients with FC III or IV?
   d. in PAH patients with different disease etiology, as defined in the Dana Point 2008 Classification?

4. What is the comparative efficacy, safety, and cost-effectiveness of triple (add-on) combination therapy involving either a PDE-5 inhibitor, an ERA, an sGC stimulator, or a prostanoid versus dual (add-on) combination therapy:
   a. in PAH patients, irrespective of disease severity or etiology?
   b. in PAH patients with FC II?
   c. in PAH patients with FC III or IV?
   d. in PAH patients with different disease etiology, as defined in the Dana Point 2008 Classification?

4 METHODS

4.1 Systematic Review

4.1.1 Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy (APPENDIX 3).

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pulmonary arterial hypertension and riociguat, macitentan, epoprostenol, treprostinil, bosentan, ambrisentan, sildenafil, and tadalafil.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), clinical trials, and observational studies. Where possible, retrievals were limited to the human population. Retrieval was not limited by publication date but was limited to English language results. Conference abstracts were excluded from the search results. Regular alerts were established to update the search until recommendations by the CDEC, based on this review, were finalized. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Search Tool for Evidence-Based Medicine* checklist (http://www.cadth.ca/resources/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials and databases (free). Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacting appropriate experts.

4.1.2 Selection Criteria and Methods

Trials were included in the systematic review based on the pre-specified selection criteria (Table 3). For interventions currently approved by Health Canada for treatment of PAH, only approved formulations and doses were included in the systematic review. Interventions not yet approved by Health Canada for treatment of PAH at the time the protocol for this review was prepared, but expected to enter the Canadian market shortly, were not restricted to specific doses or formulations.

Two reviewers independently screened titles and abstracts relevant to the clinical research questions regarding available and emerging drugs for treatment of patients with PAH. Full texts of potentially relevant articles were retrieved and independently assessed for possible inclusion based on the predetermined selection criteria. The two reviewers then compared their chosen included and excluded studies; disagreements were discussed until consensus was reached. The study selection process was presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (
APPENDIX 4).

Table 3: Inclusion and Exclusion Criteria for Primary Studies	
Inclusion Criteria	
Study Design	Published RCTs and observational studies were considered to answer the four research questions. Only studies of ≥ 8 weeks in duration qualified for inclusion. Observational studies were limited to higher-quality design, defined for the purpose of this therapeutic review as comparative (prospective or retrospective) cohort and case-control studies (including nested case-control studies).
Population	Adult patients (≥ 18 years) diagnosed with PAH,[a] as defined in Table 1.
Interventions	• Macitentan — oral • Riociguat — oral

Comparators	• Drug therapies[b, c, d]
	  ○ Epoprostenol — injectable
	  ○ Treprostinil — injectable
	  ○ Bosentan — oral
	  ○ Ambrisentan — oral
	  ○ Sildenafil — oral and injectable
	  ○ Tadalafil — oral
	• Placebo or conventional medical treatment

Outcomes	**Ranking based on hierarchy of importance:** 1. Death (all-cause, PAH-related) 2. Hospitalization 3. Clinical worsening[e] 4. Improvement, unchanged or worsening in NYHA or WHO FC 5. 6MWD 6. Hemodynamic variables, including but not restricted to PVR, mPAP, and cardiac index 7. Quality of life 8. BDI 9. SAEs 10. AEs 11. Laboratory abnormalities 12. Withdrawals due to AEs
Exclusion Criteria	
Studies were excluded if they were in languages other than English, did not meet the selection criteria above, provided results of a qualitative or a non-comparative study, were follow-up or extension studies, or presented preliminary results in abstract form. Duplicate publications, narrative reviews, and editorials were also excluded.	

Table 3: Inclusion and Exclusion Criteria for Primary Studies

The following observational study designs will be excluded: before and after studies, single-group cohort studies with historical controls, case series, and case reports. Studies that enrolled patients with disease classified as Group 1' PH (i.e., PVOD or PCH) will be excluded. For the assessment of combination therapy, studies using upfront combination therapy will also be excluded. Abstracts will be excluded unless they present supplementary data for a RCT that has another full-text publication that may be used to assess the risk of bias.

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; NMA = network meta-analysis; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary hemangiomatosis ; PPH = primary pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; SAEs = serious adverse events; WHO = World Health Organization.

[a] Older studies may have enrolled patients with PPH. For the purpose of this therapeutic review, these studies will be included and categorized as studies that enrolled patients with IPAH.

[b] Formulations and doses approved and available in Canada only will be included.

[c] Drug regimens will include monotherapy, dual (add-on) therapy, and triple (add-on) therapy.

[d] Studies of PAH drugs not approved for use in Canada (e.g., iloprost) will be excluded from the main analyses. Such studies may, however, be included in sensitivity analyses of an NMA should such an analysis be performed. The effectiveness of PAH drugs not available in Canada will not be directly evaluated in this therapeutic review.

[e] The definition of clinical worsening may vary within the PAH literature; hence, the following definition will be used:

Clinical worsening is a composite end point of:

- death, or
- hospitalization (which is clearly predefined), or
- worsening of PAH requiring lung transplantation or atrial septostomy, or
- initiation of parenteral therapy (prostanoid, sildenafil), or
- discontinuation of the study treatment because of disease progression, or
- disease progression, where disease progression is defined as:
  - 6MWD decrease of 15% (from baseline) and worsening of NYHA or WHO FC, or
  - 6MWD decrease of 15% (from baseline) and need for additional therapy (including oral and parenteral drugs).

4.1.3 Data Extraction Strategy and Critical Appraisal of Included Studies

One reviewer performed data extraction for each article, using a pre-drafted data extraction form covering the following items:

- Baseline characteristics of trial participants
- Interventions evaluated, including dose, duration, and mode of administration
- Efficacy and safety results for specified outcomes
- Type of analysis (intention-to-treat [ITT] or per-protocol).

All extracted data were checked for accuracy by a second reviewer. Any disagreements were resolved through discussion until consensus was reached. Quality assessment of RCTs was performed independently by two reviewers using a standardized table based on major items from the SIGN 50 instrument for internal validity. Further critical appraisal was performed based on input from clinical experts.

Clinical outcomes included death (all-cause, PAH-related), hospitalization, clinical worsening, New York Heart Association (NYHA) or World Health Organization (WHO) heart failure FC (improved, unchanged, worsened), six-minute walk distance (6MWD), and Borg dyspnea index (BDI).

Hemodynamics variables included pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP), and cardiac index.

Health-related quality of life (HRQoL) data were captured wherever appropriate.

Safety outcomes included adverse events (AEs), SAEs and discontinuation of treatment due to adverse events.

4.1.4 Data Analysis Methods

Direct pairwise meta-analyses were performed for all outcomes, to obtain summary estimates for outcomes that were not analyzed by network meta-analysis (NMA) and to assess consistency of findings when NMA was undertaken.

Review Manager 4.2 was used for statistical analyses of direct pairwise comparisons in the clinical review. Where the quantitative pooling of results was deemed appropriate, a random effects model was used to estimate treatment efficacy between interventions. A fixed effects model was also performed for outcomes with rare events, and to examine if there were substantial impacts of heterogeneity on effect estimates.

Dichotomous outcomes were summarized using relative risk (RR), which compared the proportion of patients having the event between two treatment groups. In our study, the dichotomous outcomes include:

- Mortality
- Hospitalization
- Clinical worsening
- NYHA or WHO FC improvement
- NYHA or WHO FC unchanged
- NYHA or WHO FC worsening
- SAEs
- Discontinuation due to AEs

- Total withdrawal
- AEs (e.g., liver toxicity, edema, anemia, hypotension).

Continuous outcomes were summarized using weighted mean differences (WMDs). Where standard deviations (SDs) were not reported, they were calculated using standard errors, confidence intervals (CIs), t values, or *P* values.[58] Where no variance was reported, a value of SD was imputed using the coefficient of variation, which was calculated based on studies with similar population, study design, and intervention.[59] The continuous outcomes, analyzed as mean change from baseline, include:

- 6MWD
- BDI
- PVR
- PAP
- cardiac index.

For direct pairwise meta-analysis, statistical heterogeneity between studies was assessed using the chi-squared test and I^2, which quantifies the percentage of the total variation of effect estimates across studies that is due to heterogeneity rather than chance (sampling error), and lies between 0% (no observed heterogeneity) and 100% (significant heterogeneity).[60] Heterogeneity is considered to be low when I^2 is ≤ 25%, moderate when I^2 is between 25% and 75%, and high when I^2 is ≥ 75%. Attempts were made to explain substantial statistical heterogeneity ($P \leq 0.10$ for the chi-squared test or $I^2 \geq 50\%$) by subgroup analyses or elimination of outliers. Where substantial statistical heterogeneity continued to present in the subgroup analyses, the clinical outcomes were presented separately for each study and were reviewed qualitatively. The I^2 statistics, however, do not provide evidence about clinical heterogeneity in terms of study design, treatments, and baseline demographics and characteristics of patient population. Clinical heterogeneity was judged from patient demographics and baseline characteristics with the input from clinical experts.

The planned subgroup analyses included age (e.g., < 65 years, ≥ 65 years), baseline NYHA or WHO FC (II, III, or IV), baseline 6MWD (e.g., < 350 m, ≥ 350 m), gender (male, female), background pharmacotherapy (Yes, No), and disease etiology subtype of PAH (e.g., IPAH/FPAH or other). For studies that enrolled mixed populations, the analysis was stratified by specific subpopulations (i.e., treatment-naive patients and patients on background PAH therapy) as opposed to the total study population.

4.2 Network Meta-analysis Methods

Due to the lack of head-to-head comparisons, we conducted NMA to compare treatments that may not have been compared directly.

Bayesian NMAs were conducted respectively for four outcomes: clinical worsening, FC improvement, FC worsening, and 6MWD. Selection of the outcome measures for the NMA was based on input from clinical experts involved in this review. NMAs were not conducted for other efficacy outcomes (mortality and hospitalization) and AEs (including SAEs and withdrawal due to AEs) because data for patient subpopulations (treatment-naive and patients on background PAH therapy) were not available.

WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used for all NMAs.[61] A binomial likelihood model, which accounts for the use of multi-group trials, was used for

dichotomous outcomes and a normal likelihood model used for continuous outcomes. WinBUGS code for NMA of standard Bayesian random effects meta-analysis was adapted from code developed by the National Institute for Health and Care Excellence (NICE) Decision Support Unit.[62] Posterior densities for all unknown parameters were estimated using Markov Chain Monte Carlo methods. Model diagnostics including trace plots, autocorrelation plots, and the Brooks–Gelman–Rubin statistic were assessed to ensure model convergence. Model fit for NMA was assessed based on the deviance information criterion and comparison of residual deviance to number of unconstrained data points. Measures of effect were estimated according to the WinBUGS routine developed by the Evidence Synthesis Group, consisting of experts from the universities of Bristol and Leicester (code is available from their website). Median estimates were reported along with corresponding 95% credible intervals (CrI). For comparative purposes, both fixed effects and random effects NMAs were conducted. Random effects NMA differs from fixed effect NMA in that it allows for the variation of true treatment effect between studies due to heterogeneity. Prior distributions for overall effects of interest and study-specific effect estimates were assigned informative variance priors from external empirical evidence.[63] The informative priors were used in the random effects models for the between-studies SD of effect estimation.

Regarding interpretation of NMA estimates, if a 95% CrI for a risk ratio comparing two interventions did not include the value 1, this was interpreted as an indication that there is a less than 5% probability that there was no difference in effect between treatments.

4.2.1 Six-Minute Walk Distance

In this review, 6MWD was modelled as a continuous outcome based on the mean change from baseline observed within a treatment group as the input data.

4.2.2 Clinical Worsening, Functional Class Improvement, and Functional Class Worsening

Clinical worsening, FC improvement, and FC worsening were analyzed as binomial outcomes with the total number of patients with the event within a treatment group and the total number of patients randomized for that treatment group as the input data.

4.2.3 Exploring Heterogeneity and Inconsistency

NMA requires that studies be sufficiently similar in order for their results to be pooled. A wide range of patient and trial characteristics were recorded to allow for assessment of the heterogeneity of included trials. Heterogeneity was explored through selected meta-regressions and subgroup analyses based on patient treatment history (treatment-naive and patients on background PAH therapy), patient covariates (NYHA or WHO FC and PAH etiology at baseline) and treatment duration. Meta-regressions were performed when the variable was continuous in order to incorporate the maximum amount of information available from trials. Subgroup analyses were performed when the variable could be dichotomized (e.g., patient population was treatment-naive or on background PAH therapy).

An informal assessment of consistency was performed by comparing the treatment effects estimated via the NMA against the direct pairwise meta-analysis results. Furthermore, the network diagrams were examined to determine the number of independent loops in the network of evidence for which inconsistency in the evidence could occur.[64] In cases of star networks (that is, all interventions were compared with a common comparator but not against each other), independent loops would not be possible.

4.3 Pharmacoeconomic Analysis

A systematic review of the literature examining the cost-effectiveness of medical treatments for PAH was conducted. No studies specifically addressing the research questions were identified.

The literature review was, however, used to inform the current economic analysis including the provision of information regarding resource use, costs, transition probabilities, and utilities. The literature review also sought to compare the results of existing studies to enable contextualization of the current analysis.

Further details on the literature searches and results are presented in APPENDIX 15: Review of Previous Pharmacoeconomic Analyses.

4.3.1 Type of Economic Evaluation

The evaluation was a cost-utility analysis with the incremental cost per quality-adjusted life-year (QALY) as the primary outcome measure.

4.3.2 Target Population

The target population for the economic analysis included adult patients diagnosed with PAH. A cohort of patients 50 years of age diagnosed with NYHA FC II, III, or IV PAH was modelled within the analysis, as this was reflective of the average age of patients and severity of PAH within PAH registries. For the comparison of single therapies for PAH, the analysis was based on a treatment-naive population, meaning that patients had not previously received treatment for PAH with PDE-5 inhibitors, prostaglandins, guanylate cyclase stimulators, or ERAs. The comparison of add-on therapies included a mixed population of both treatment-naive patients and those who had previously received therapy for PAH.

4.3.3 Treatments

The medications modelled include prostaglandin inhibitor (epoprostenol), ERAs (bosentan, ambrisentan), PDE-5 inhibitors (sildenafil and tadalafil), and soluble guanylate cyclase (sGC) stimulator (riociguat). The prostaglandin inhibitor treprostinil was not included within the model due to a lack of clinical data on the relevant endpoints. The ERA macitentan was considered within a separate sensitivity analysis, as the results of the clinical trial were only reported in a mixed population of both treatment-naive and treatment-experienced patients, thereby precluding its inclusion within the NMA.

4.3.4 Perspective

The analysis was conducted from a third-party payer perspective, specifically a Canadian Ministry of Health.

4.3.5 Time Horizon

The base-case analysis models a lifetime horizon (30 years), with sensitivity analyses conducted at two years and 10 years.

4.3.6 Model Structure

A Markov model was created within Excel to estimate the long-term costs, life-years, and QALYs associated with PAH treatments. The model was structured to facilitate a comparison of single therapies versus supportive care alone and to compare add-on combination therapy versus single therapies. The lack of clinical data comparing add-on combination therapy or triple combination therapy versus other add-on combination therapy precluded the inclusion of these comparisons within the model. A cohort of patients with PAH enter the model at age 50, the average age of patients diagnosed with PAH.[65] The ratio of females to males within the cohort is 2.3:1, which reflects the distribution of PAH diagnosis reported in PAH registries, and the general overall mortality was adjusted based on this distribution.[6] Patients enter the model with FC II, III, or IV PAH, as these are the most common stages of the illness for diagnosis and initiation of treatment.

The cycle length within the model was three months. The basis for this cycle length was twofold: first, many of the clinical trials of therapies for PAH provided estimates of efficacy at 12 weeks; and second, this was deemed an appropriate time at which to assess efficacy of treatments, based on clinical expert opinion.

In the first cycle of the model after starting a new treatment, patients may improve from their initial FC state to the adjacent state. Although patients did not enter the model in FC I, they could improve from FC II to FC I during treatment.

In all cycles of the model, patients could remain in their current state or deteriorate to the adjacent more severe state. Given the short duration of the majority of RCTs evaluating the efficacy of the medications within the NMA, in most cases evidence of further improvement beyond 12 weeks is lacking. It was therefore assumed that patients would not experience improvements in FC due to treatment beyond the first cycle of the model, although the rate at which FC worsened in subsequent cycles was slower with treatment than with supportive care. This assumption was tested within sensitivity analyses.

Within the clinical trials, the transitions to improved FC and worsened FC were not stratified based on FC. Consequently, it was assumed that the overall relative risk of improvement or deterioration in FC with treatment would apply to all FC transitions (Table 4).

A mortality rate, adjusted based on the impact of PAH FC on the age-specific mortality rate for the general population, was applied within each of the states within the model.[66]

Regardless of previous therapy, upon deteriorating to FC IV, many patients initiate treatment with epoprostenol, generally in addition to existing therapy. Based on clinical expert opinion, epoprostenol was assumed to be initiated in 50% of patients upon deterioration to FC IV. Those in whom epoprostenol had been added were able to again improve to the adjacent FC (FC III) within the first cycle after initiation, but could only either remain within the same FC or deteriorate in subsequent cycles at a rate adjusted for the addition of epoprostenol. Patients entering the model in FC IV experienced the benefits of the PAH therapy within the first cycle; however, for those who remained in FC IV or deteriorated to FC IV in subsequent cycles, epoprostenol was assumed to be initiated in a percentage of patients as described above. The percentage of patients initiating epoprostenol was varied within sensitivity analyses.

It was assumed that all patients would receive supportive care in addition to specific PAH therapies. The cost of supportive therapies compared with PAH treatments is small and

therefore, provided the assumptions are consistent across all treatments, they should not bias cost-effectiveness estimates.

The costs, QALYs, and life-years associated with each of the treatments for PAH and with supportive care alone are estimated by the model. Both costs and effectiveness were discounted at a rate of 5% per annum within the base-case analysis. Discount rates of 0% are incorporated within sensitivity analyses.

Table 4: Model State Transitions and Descriptions

Model State at Start of Cycle	Model State at End of Cycle and Description
First Cycle of Model	
FC II	FC I — improve FC II — maintain FC IIIa — worsen Dead
FC III	FC II — improve FC IIIa — maintain FC IVa — worsen Dead
FC IV	FC IIIa — improve FC IVa — maintain Dead
Subsequent Model Cycles	
FC I	FC I — maintain FC II — worsen Dead
FC II	FC II — maintain FC IIIa — worsen Dead
FC IIIa[a]	FC IIIa — maintain FC IVa — worsen Dead
FC IVa[b]	FC IIIb — improve with initiation of epoprostenol FC IVb — maintain without initiation of epoprostenol FC IVc — maintain with initiation of epoprostenol Dead
FC IIIb[a]	FC IIIc — maintain on epoprostenol FC IVc — worsen on epoprostenol Dead
FC IVb[b]	FC IVb — maintain without epoprostenol Dead
FC IVc[b]	FC IVc — maintain on epoprostenol Dead

FC = functional class; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension.

[a] FC IIIa and IIIb refer to NYHA PAH functional class III patients; however, in the IIIa state, patients are receiving their initial PAH therapy alone, whereas in IIIb they are receiving their initial PAH therapy in combination with epoprostenol.

[b] FC IVa, IVb, and IVc refer to NYHA PAH functional class IV patients; however, in the IVa and IVc states, patients are receiving their initial PAH therapy alone, whereas in state IVb, they are receiving their initial PAH therapy in combination with epoprostenol. State IVc is a tunnel state into which patients transition if epoprostenol therapy is not initiated in state IVa.

4.3.7 Data Inputs

a) Natural History of the Disease

Transition probabilities for supportive care alone were derived from the placebo groups of the RCTs included within the NMA. The analysis produced estimates of the percentage of patients improving from a more severe FC to a less severe FC and the percentage of patients worsening from a less severe FC to a more severe FC. The data did not permit the estimates to be stratified based on initial FC and therefore it was assumed that the probability of improvement was the same for patients starting in FC II, III, or IV and probability of worsening was the same for patients starting in FC I, II, or III.

Mortality within the model consists of two components: age-specific mortality for the general population and PAH-related mortality. Age-specific mortality was derived from Canadian life tables.[67] These values were adjusted to incorporate PAH-related mortality that varied by FC. Treatments were assumed to have no independent effect on mortality, but rather affected mortality through delaying the progression of the disease.

Several registries were reviewed with respect to their suitability in informing the natural history with respect to survival by FC within the model. The Pulmonary Hypertension Connection (PHC) registry was deemed the most appropriate for the derivation of the relative risk of mortality based on PAH FC.[66] Although the National Institutes of Health (NIH) registry has been used to inform some previous models, it dates back to 1981 through 1985 and has been shown to significantly underestimate current survival of PAH patients.[10] The improved survival has been attributed in part to improved recognition of PAH and consequent improvement in diagnosis, the treatment of patients within PAH specialist centres, and possibly the availability of disease-specific therapies. More recent registries, including the REVEAL registry, the PHC registry, and an observational study by Ling, support improved survival as compared with the NIH predictions, which are reasonably consistent across the three sources.[46,66,68] As the REVEAL does not report the mortality risk stratified by FC, it was not helpful in informing the natural history within the model. Both the PHC registry and the Ling observational study do report survival by FC and therefore the PHC registry was selected as the source of mortality data for the model, which was validated against the data from the Ling study.

The PHC registry evaluated 578 patients between the years of 1982 and 2006. A survival analysis based on data from the registry found that those with FC II have an increased rate of death of 4.51 (95% CI, 1.37 to 14.84) as compared with FC I. The increased rate of mortality in FC III was 7.94 (95% CI, 2.53 to 24.97) and in FC IV, it was 11.6 (95% CI, 3.68 to 36.63) versus FC I. The increased mortality rate within FC I was calibrated to reflect the five-year survival of the overall cohort reported within the registry. The hazard rate for mortality relative to the general population for each PAH FC incorporated within the model is reported in Table 66. The predicted survival was externally validated against data from another PAH registry (see Model Validation section). The effect of incorporating shorter survival based on the NIH registry was also explored within sensitivity analyses.

Table 5: Hazard Rate for Mortality Relative to the General Population by Functional Class			
Parameters	**Base Estimate (95% CI)**	**Probability Distribution**	**Reference**
FC I	5.18		Thenappan 2010
FC II	22.35 (6.86 to 74.31)	Log-normal	Thenappan 2010
FC III	39.34 (12.67 to 125.04)	Log-normal	Thenappan 2010
FC IV	57.47 (18.43 to 183.43)	Log-normal	Thenappan 2010

CI = confidence interval; FC = functional class.

Given the relatively short duration of clinical trials for PAH treatments, there is only limited information regarding their effects on survival, most of which is based on open-label registry data. If both an impact of treatment on mortality and an impact of treatment on disease progression are incorporated within the model, this would lead to double counting and a consequent overestimation of the survival benefit with treatment. Incorporating the effect of treatment only on progression prevents this error and still incorporates an indirect effect of treatment on mortality.

b) Treatment Efficacy and Safety

Monotherapy Versus Supportive Care

Estimates of the effectiveness of PAH treatments relative to supportive care alone were derived from the NMA. The transition probabilities for PAH treatments were derived by applying the relative risks for FC improvement and FC worsening from the fixed effects NMA (adjusted for baseline FC) to the supportive care alone probabilities (see Table 6). Details of the estimation of the relative risks are provided within the clinical section of the report (Section 4.2).

Table 6: Transition Probabilities and Relative Risks for Single Therapies				
	Transition Probability for Supportive Care			
	FC Improvement		**FC Worsening**	
Supportive Care First cycles Subsequent cycles	 0.10 -		 0.123 0.123	
	Relative Risks Associated with Treatment Versus Supportive Care (From NMA fixed effect model, adjusted for baseline FC class)			
	FC Improvement Base Estimate (95% CrI)	**PSA Distribution**	**FC Worsening Base Estimate (95% CrI)**	**PSA Distribution**
Epoprostenol First cycles Subsequent cycles	 8.67 (2.20 to 17.22) -	 Log-normal	 0.60 (0.12 to 2.42) 0.60 (0.12 to 2.42)	 Log-normal Log-normal
Riociguat 2.5 mg t.i.d. First cycles Subsequent cycles	 1.40 (0.23 to 5.51) -	 Log-normal	 0.18 (0.05 to 0.62) 0.18 (0.05 to 0.62)	 Log-normal Log-normal
Bosentan First cycles Subsequent cycles	 1.09 (0.04 to 7.94) -	 Log-normal	 0.52 (0.18 to 1.30) 0.52 (0.18 to 1.30)	 Log-normal Log-normal
Ambrisentan 5 mg First cycles Subsequent cycles	 1.32 (0.41 to 3.62) -	 Log-normal	 0.10 (0.02 to 0.32) 0.10 (0.02 to 0.32)	 Log-normal Log-normal
Ambrisentan 10 mg First cycles Subsequent cycles	 1.44 (0.52 to 3.59) -	 Log-normal	 0.23 (0.05 to 0.78) 0.23 (0.05 to 0.78)	 Log-normal Log-normal
Sildenafil First cycles Subsequent cycles	 1.31 (1.46 to 9.11) -	 Log-normal	 0.23 (0.03 to 1.02) 0.23 (0.03 to 1.02)	 Log-normal Log-normal
Tadalafil First cycles Subsequent cycles	 2.85 (1.12 to 6.26) -	 Log-normal	 0.44 (0.11 to 1.39) 0.44 (0.11 to 1.39)	 Log-normal Log-normal

CrI = credible interval; FC = functional class, NMA = network meta-analysis; PSA = probabilistic sensitivity analysis; t.i.d = three times a day.

As stated above, improvements in the FC occurred only during the first 12 weeks of treatment; however, in subsequent cycles, the relative risk for deterioration in FC on treatment was applied to the supportive care probability of deterioration, thereby resulting in a reduction in the rate of deterioration with treatment. The estimates were based on the fixed effects NMA adjusted for differences in baseline FC between the included trials.

To ensure comparability of the comparator group, the relative risks for improvement and worsening of FC incorporated within the model were based on a patient population that was naive to PAH treatment. This resulted in the exclusion of two therapies from the analysis, specifically macitentan and treprostinil. Data regarding FC worsening was not available for treprostinil specific to the naive population within the trials. With respect to macitentan, the results of the primary clinical trial were reported for the entire population, which included both patients naive to treatment and those receiving other PAH therapies, which made up approximately 60% of the trial population. As macitentan has recently obtained a Notice of Compliance, it was one of the two main comparators of interest, and therefore a separate analysis specific to macitentan with a comparator group reflective of the clinical trial was conducted as a sensitivity analysis.

Add-on Combination Therapy Versus Monotherapy: Based on the NMA, there were only two add-on combination therapies that have been compared with monotherapy therapy suitable for inclusion within the analysis. The combinations of riociguat plus an ERA and of tadalafil plus an ERA were compared with placebo plus an ERA. Within the model for the cost of ERA therapy, the bosentan cost (brand name) was used, as it was the most common ERA within the tadalafil trial and the riociguat trial did not report which ERA patients received.

As was the case with single therapies, improvements in FC occurred during the first 12 weeks of therapy, with further effects of treatment limited to a reduction in the rate of worsening. The results of the fixed effects NMA were the source of the relative risks for treatment; however, the reporting within the clinical trials did not allow for the results to be adjusted based on baseline FC and therefore the unadjusted estimates were incorporated within this model (see Table 7).

Table 7: Transition Probabilities and Relative Risks for Add-on Combination Therapy (From NMA Fixed Effect model)

	Transition Probability for ERA Plus Placebo			
	FC Improvement		**FC Worsening**	
ERA plus placebo First cycles Subsequent cycles	 0.20 -		 0.13 0.13	
	Relative Risks Associated With Add-on Combination Therapy Versus ERA Plus Placebo			
	FC Improvement Base Estimate (95% CI)	**PSA Distribution**	**FC Worsening Base Estimate (95% CI)**	**PSA Distribution**
ERA plus riociguat First cycles Subsequent cycles	 1.84 (0.99 to 3.40) -	 Log-normal	 0.39 (0.11 to 1.24) 0.39 (0.11 to 1.24)	 Log-normal Log-normal
ERA plus tadalafil First cycles Subsequent cycles	 1.04 (0.63 to 1.67) -	 Log-normal	 0.55 (0.24 to 1.17) 0.55 (0.24 to 1.17)	 Log-normal Log-normal

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; NMA = network meta-analysis; PSA = probabilistic sensitivity analysis.

c) Costs

The costs incorporated within the model included those associated with medications, equipment, treatment of adverse events, and laboratory and therapeutic procedures and health care costs associated with initiation of therapy and with ongoing monitoring of PAH. The analysis was conducted from the perspective of the Canadian health care system with costs adjusted to 2013.[69]

Pulmonary Arterial Hypertension Medications:

PAH medications doses and costs used in the model are presented in Table 8 and Table 9.

Table 8: Cost Comparison Table for Medications Used for the Treatment of Pulmonary Arterial Hypertension						
Drug / Comparator	**Strength**	**Dosage Form**	**Price ($)**	**Average Use**	**Average Daily Drug Cost ($)**	**Average Annual Drug Cost ($)**
Stimulators of sGC						
Riociguat (Adempas)	0.5 mg 1.0 mg 1.5 mg 2.0 mg 2.5 mg	Tablet	42.7500[a]	1.0 to 2.5 mg three times daily	128.25	46,811
ERA						
Macitentan (Opsumit)	10 mg	Tablet	128.3333[a]	10 mg once daily	128.33	46,842
Ambrisentan (Volibris)	5 mg 10 mg	Tablet	122.5200	5 to 10 mg once daily	122.52	44,720
Bosentan (Tracleer and generics)	62.5 mg 125 mg	Tablet	64.1786 (Tracleer) 22.4625 (generics)	62.5 mg twice daily for four weeks then 125 mg twice daily	128.36 (Tracleer) 44.93 (generics)	46,851 (Tracleer) 16,398 (generics)
PDE-5i						
Sildenafil (Revatio)	20 mg	Tablet	11.1219	20 mg three times daily	33.37	12,178
Tadalafil (Adcirca)	20 mg	Tablet	13.3633	40 mg once daily	26.73	9,755
Parenteral Prostanoids						
Epoprostenol (Flolan)	0.5 mg/vial 1.5 mg/vial Plus: 2 x 50 mL diluant	Vial	18.6400 37.2800 10.6500	20 to 40 ng/kg/min Up to 60 ng/kg/min has been reported	71.40 to 121.51[b,c]	26,061 to 44,351[b,c]

ERA = endothelin receptor antagonist; PDE-5i = phosphodiesterase-5 inhibitors; sGC = soluble guanylate cyclase.
[a] List price confirmed by the manufacturer.
[b] Assumes a 70 kg patient.
[c] Unused medication discarded after 24 hours.
Source: Saskatchewan Drug Plan (April 2014) unless otherwise indicated.

Table 9: PAH Drug Costs per Cycle Within the Economic Model		
Drug/Comparator	**Strength**	**Drug Cost per 3-Month Cycle[a]**
Stimulators of sGC		
Riociguat (Adempas)	0.5 mg 1.0 mg 1.5 mg 2.0 mg 2.5 mg	$12,639
ERA		
Macitentan (Opsumit)	10 mg	$12,656
Ambrisentan (Volibris)	5 mg 10 mg	$12,074
Bosentan (Tracleer and generics)	62.5 mg 125 mg	$12,650 (Tracleer)
PDE-5i		
Sildenafil (Revatio)	20 mg	$3,288
Tadalafil (Adcirca)	20 mg	$2,634
Parenteral Prostanoids		
Epoprostenol (Flolan)	0.5 mg/vial 1.5 mg/vial Plus: 2 x 50 mL diluant Diluent	First cycle: $5,274[b,c] Subsequent cycles: $11,247[b,c]

ERA = endothelin receptor antagonist; PDE-5i = phosphodiesterase-5 inhibitors; PAH = pulmonary arterial hypertension; sGC = soluble guanylate cyclase.
[a] Includes 8% markup and $8.83 dispensing fee for a 3-month supply.
[b] Assumes a 70 kg patient.
[c] Unused medication discarded after 24 hours.
Source: Saskatchewan Drug Plan (April 2014) unless otherwise indicated.

Oral therapies were dosed according to the doses recommended by the Canadian product monographs, when available. Bosentan was assumed to be initiated at a dose of 62.5 mg twice daily and increased to 125 mg twice daily after four weeks.[54] Although a generic alternative for bosentan is available, the base-case analysis used the branded price of bosentan, as prescribing data indicated that it was the most commonly used product. This was confirmed by expert opinion and tested within sensitivity analyses. Ambrisentan may be dosed at 5 mg per day or 10 mg per day. When using the 10 mg dose, patients first begin therapy with 5 mg for two weeks and are then titrated up to 10 mg once daily.[53] Sildenafil, tadalafil, and macitentan do not require titration. Sildenafil is dosed at 20 mg three times per day and tadalafil at 40 mg once daily.[55,56] Macitentan is dosed at 10 mg once daily.[47] For riociguat, patients are started on a dose of 1.0 mg three times per day and titrated at two-week intervals up to a maximum of 2.5 mg three times per day.[48] In some cases, a dose reduction to 0.5 mg three times per day is required.

Epoprostenol is dosed based on body weight, requires titration at initiation, and exhibits dose creep over time due to the development of tachyphylaxis. The estimated dosing regimen was based on recommendations from the product monograph and validation from external clinical experts.[51] The dosing was based on a patient weight of 70 kg. The initial infusion rate of

epoprostenol was estimated at 2 ng/kg/min, increasing to 4 ng/kg/min by day 7 and then increasing at a rate of 2.5 ng/kg/min every 21 days throughout the first three months of treatment. The estimated mean rate of infusion for the remainder of the first year of treatment was 27 ng/kg/min, with increases of 5 ng/kg/min every two years until a ceiling of 50 ng/kg/min is reached. From these dose estimates, the mean cost for the first cycle and subsequent cycles of epoprostenol was calculated. Once reconstituted, epoprostenol solution is only stable for 24 hours; therefore, wastage was also included within the cost estimate.

The cost of diluent for epoprostenol was also incorporated. A previous Canadian cost-effectiveness analysis (CEA) estimated the requirement for diluent at two vials per day, at a cost of $10.65 each,[70] which is consistent with the current list price on the Saskatchewan Drug Formulary. [71]

Prices for medications were sourced from the Saskatchewan drug plan[71] in all cases except for riociguat and macitentan, which are not yet marketed within Canada, and therefore the prices were confirmed directly with the manufacturer. In all cases, a markup of 8% was applied to the drug costs and a dispensing fee of $8.83 every three months.

Supportive Care Therapies: In the supportive care cohort and for patients on active treatment, it was assumed that a proportion of patients received supportive care therapies. These included a diuretic (furosemide), an anticoagulant (warfarin), digoxin, and oxygen. The percentage of patients receiving furosemide, warfarin, and digoxin were sourced from the REVEAL PAH registry, which reported that 53.4% of PAH patients were receiving warfarin, 69.3% furosemide, and 26.4% digoxin. [72] Alternative estimates based on expert opinion were tested within sensitivity analysis, in which 90% of patients received diuretics, 25% digoxin, and 40% oral anticoagulants. Patients receiving warfarin were assumed to undergo monthly international normalized ratio (INR) testing, the cost of which was also incorporated into the overall cost of supportive care therapies. [73]

Oxygen therapy varies by FC, with increased usage with greater severity of disease. A health technology assessment conducted in the UK in 2009 estimated that 5% of patients in FC II would be receiving oxygen, 27% in FC III, 71% in FC IV of those in the active treatment group, and 100% of those in FC IV in the supportive care group.[1] These values were confirmed by Canadian clinical experts and were incorporated into the model. The cost for provision of home oxygen therapy was $389 per month based on the Home Oxygen Therapy Policy and Administration Manual April 2014, published by the Ontario Ministry of Health and Long-Term Care.[74]

Further details are provided in Table 233, APPENDIX 18: Resource Use Estimates.

Initiation Cost: For each active therapy, there is a cost associated with initiation of treatment. The standard diagnostic procedures for PAH were not included within the model, as they would be expected to occur regardless of treatment. Oral therapies were assumed to be initiated at home and therefore did not incur any initiation costs.

Based on expert opinion, approximately 50% of patients would initiate epoprostenol within the hospital with the remaining 50% initiating therapy as a hospital day case. In cases where hospitalization was required, the duration of hospitalization was estimated at six days, on a general ward, and the appropriate physician costs were also included.[75,76] In those having the treatment initiated as a day case, the corresponding cost of a Canadian hospital day case was

incorporated, which includes pharmacy costs. Additional costs included 10 hours of nurse training time and the cost for the procedure for inserting the central venous catheter.

Monitoring and Administration Costs: The costs of monitoring both the disease and treatments and the cost of equipment required for administration of the medication were included in the model.

The cost of the equipment required for administration of epoprostenol was estimated at $52.26 per day, based on a previous Canadian CEA.[70] Additionally, it was assumed that the central line would be replaced every two years, based on expert opinion. The cost of this procedure was therefore incorporated into the ongoing costs for epoprostenol.

For patients receiving ERAs (ambrisentan, bosentan, or macitentan), both liver function testing and pregnancy tests are recommended.[47,53,54] For ambrisentan and bosentan, liver function tests are recommended on a monthly basis, whereas with macitentan, they are conducted on an annual basis. The recommended interval for pregnancy tests is monthly with macitentan and bosentan and annually with ambrisentan.

All PAH patients are recommended to have an annual echocardiogram and renal function tests and biannual blood work, the costs of which were also incorporated into the model.
The costs for the laboratory tests were sourced from the Ontario Laboratory Fee Schedule.[73]

Adverse events: With respect to oral therapies, it was assumed that AEs were either minor, in which case the patient would remain on therapy or AEs would lead to treatment discontinuation. No costs or utility deficits were incorporated for minor AEs, as the impact on the cost-effectiveness estimates would be insignificant relative to the other resources included in the model. In the case of more severe AEs on oral therapy, it was assumed that patients would discontinue therapy and move to the next most cost-effective therapy based on this analysis. These assumptions were supported by expert clinical opinion.

As epoprostenol is administered via a central venous catheter, there is an increased risk of both catheter site infections and sepsis with treatment. Based on published literature, the annual rate of sepsis in patients receiving epoprostenol was 0.14 episodes per person per year and the annual rate of catheter site infections was 0.24 episodes per person per year.[77] The estimated disutility associated with an episode of sepsis was 0.11 for a three-month cycle.[78] The cost per episode of sepsis was sourced from published literature and estimated as $16,288.[79] The cost per catheter site infection was $138.96. Of note, there is a wide range of severity of catheter site infections, with some requiring no intervention and others requiring catheter replacement and antibiotic therapy. The cost of the replacement of the catheter was therefore assumed to be the cost of the catheter site infection. Given the cost of these relative to the cost of epoprostenol therapy, this should not affect the results of the analysis.

The mortality associated with sepsis was also incorporated into the model for those patients receiving epoprostenol. In the study by McLaughlin, four of the 162 patients within the study died of sepsis potentially due to the central venous catheter. The patients were followed for a mean of 36.4 months. This produced an estimated incremental three-month probability of mortality from sepsis on epoprostenol of 0.002.[77]

Related to functional class: During clinical trials for iloprost, Schering Inc. collected resource-use data relating to physician and nurse visits, hospital admissions, and emergency room visits, which were reported in detail by FC within the health technology assessment conducted by

NICE in 2009.[1]These values were validated by Canadian expert opinion to reflect Canadian treatment patterns. Canadian costs were applied to the resource use estimates and an average cost per cycle for PAH management was derived for each FC. The costs of the nurse visits were based on an assumed duration of 15 minutes (Table 10).

Table 10: Health Care Utilization Costs by Functional Class

Health State	Physician and Nurse Visits	Hospitalizations and Emergency Room Visits
FC I	$0	$0
FC II	$118.43	$502.23
FC III	$228.37	$1,872.56
FC IV	$265.32	$6,408.56

FC = functional class.

Table 11 presents a summary of sources of unit costs.

Table 11: Unit Costs

Resource	Unit Cost	Treatments to Which Costs Are Applicable	Source
Initiation Costs			
Hospitalization	$2,340.16 per day	Epoprostenol	Ontario Case Costing Initiative 2009/2010
Physician	$31.00 to $79.85 per day	Epoprostenol	Ontario Schedule of Benefits for Physician Services 2014
Day case	$2,241.00 per case	Epoprostenol	Ontario Case Costing Initiative 2009/2010
Nurse training	$45.28 per hour	Epoprostenol	Living in Canada, Salaries for Registered Nurses 2010
CVC insertion	$258.06 per procedure	Epoprostenol	Ontario Schedule of Benefits for Physician Services 2014
Monitoring Costs			
Liver function test	$15.51 per test	Ambrisentan, bosentan, macitentan	Ontario Schedule of Benefits for Laboratory Services 2014
Pregnancy test	$10.86 per test	Ambrisentan, bosentan, macitentan	Ontario Schedule of Benefits for Laboratory Services 2014
INR test	$6.20 per test	All patients receiving warfarin as supportive care	Ontario Schedule of Benefits for Laboratory Services 2014
Echocardiogram	$204.05 per test	All therapies	Ontario Schedule of Benefits for Physician Services 2014
Complete blood cell count	$16.03 per test	All therapies	Ontario Schedule of Benefits for Laboratory Services 2014

Table 11: Unit Costs			
Resource	**Unit Cost**	**Treatments to Which Costs Are Applicable**	**Source**
Renal function test	$16.03 per test	All therapies	Ontario Schedule of Benefits for Laboratory Services 2014
Adverse Events			
Replacement of CVC	$138.96 per replacement	Epoprostenol	Ontario Schedule of Benefits for Physician Services 2014
Sepsis	$16,288.00 per episode	Epoprostenol	Letarte 2002
Catheter site infection	$138.96 per episode	Epoprostenol	Ontario Schedule of Benefits for Physician Services 2014
Equipment			
Infusion pump supplies and tubing	$52.56 per day	Epoprostenol	Einarson 2003

CVC = central venous catheter; INR = international normalized ratio;

d) Utilities

The direct measure of the change in quality of life with initiation PAH therapies has not been reported within the literature. Consequently, to evaluate the impact of treatment on patients' utility requires that changes in utility be estimated from improvements in clinical end points.

Although the primary outcome measure in the majority of the clinical trials was 6MWD, a search of the literature did not produce any references that would allow for the conversion of an improvement in 6MWD to an improvement in patients' quality of life and the associated change in utility. The decision was therefore made to base the progression of the disease within the model on FC, as information is available relating functional class with utility. A bosentan clinical trial reported the mean utility value and estimates of uncertainty derived from the SF-36 for patients in each PAH FC.[80]

Although these patients were receiving bosentan therapy, it was assumed that the quality of life assessed was reflective of the respective FC of the patient's disease regardless of treatment. These values have been used in a number of previous health economic analyses, including the health technology assessment completed by NICE in 2009.[1]

Table 12: Utility Values by Functional Class for Base Case			
Variable Description	**Base Estimate (SE)**	**Probability Distribution**	**Reference**
FC I	0.73 (0.046)	Beta (24.24, 67.57)	Keogh et al. 2007[80]
FC II	0.67 (0.051)	Beta (27.03, 56.24)	Keogh et al. 2007[80]
FC III	0.60 (0.051)	Beta (35.88, 54.72)	Keogh et al. 2007[80]
FC IV	0.52 (0.051)	Beta (55.82, 61.04)	Keogh et al. 2007[80]

FC = functional class; SE = standard error.

There were two additional studies reporting utility values for PAH patients by FC, both of which were estimated by clinical experts using the EQ-5D. In the first study by Highland, the EuroQol health state utility values for each FC as estimated by clinical experts were adjusted by the authors for each treatment in order to incorporate the effects of adverse events.[81] This method produced an estimated utility of 0 for FC IV and significantly lower utility values for patients receiving epoprostenol as compared with bosentan, for patients in the same FC. Additionally, the method by which the values were adjusted is unclear.

In the second study by Roman, the primary set of utility values used within the analysis were those provided within the study by Keogh; however, a second set of values provided by Spanish clinical experts was tested within sensitivity analyses.[82]

Adjustments were also made to the utility values for those patients receiving epoprostenol treatment to account for the disutility associated with the development of sepsis in a proportion of patients as a result of the need for a central venous catheter. The disutility was sourced from a study that assessed the quality of life in 93 sepsis survivors for the six months after diagnosis. The estimated per-cycle utility decrement associated with a sepsis diagnosis is 0.108.[78]

4.3.8 Assumptions Within the Economic Model

The following is a summary of the assumptions that have been incorporated within the model:

- In a single three-month cycle of the model, patients can either maintain their FC or they can improve or deteriorate to only the adjacent FCs. Patients therefore do not improve or deteriorate by two FCs within a single cycle of the model. This assumption was based on that fact that data on the number of classes by which patients improved or deteriorated were generally unavailable and it was assumed unlikely that many patients would move over two FCs in one three-month cycle This was supported by expert clinical opinion.
- Improvements with treatment occur within the first three months of initiation of therapy. In subsequent cycles of the model, treatment is not associated with further improvements in FC, but treatment does reduce the probability of deterioration.
- The impact of treatment on the rate at which patients deteriorate continues beyond the first cycle.
- Mortality in PAH is assumed to be associated with FC.
- PAH treatments do not have a direct effect on mortality; rather, they may have an indirect effect on survival through improvements and reductions in deterioration in FC.
- Utility values in PAH are associated with FC.
- 50% of patients deteriorating to FC IV will initiate epoprostenol therapy in addition to their existing treatment. For those starting in FC IV, 50% of those who do not improve within the first cycle initiate epoprostenol in the subsequent cycle.
- The overall improvements and worsening of FC as estimated within the NMA apply to transitions between all FCs regardless of the initial FC of the patient.
- Supportive care therapies are received by a percentage of patients regardless of PAH treatment.
- AEs with oral therapies are assumed to be either minor and therefore do not affect estimates of cost or QALYs, or result in discontinuation of therapy with a move to the next most cost-effective therapy.

4.3.9 Exploratory Analysis With Macitentan

As discussed above, in the study examining macitentan compared with supportive care, for the treatment of PAH, 61% of the patients within both groups of the trial were also receiving other

PAH therapies, specifically PDE-5 inhibitors. A separate analysis was conducted to compare macitentan with supportive care, assuming 61% of patients were receiving PDE-5 inhibitors. To do so, the average cost of continued therapy and monitoring of the two marketed PDE-5 inhibitors were incorporated within both the supportive care and the macitentan groups for 61% patients. The remaining values for the model were derived as per the base case described above.

4.3.10 Sensitivity Analyses

a) Deterministic Sensitivity Analyses

Extensive univariate sensitivity analyses were conducted to estimate the impact of assumptions regarding model parameters and their uncertainty on the results of the CEA. Analyses included:

Parameter Uncertainty

- The use of alternative utility valuations for each FC[82]
- Cost of bosentan (generic rather than branded price)
- Removing markup and dispensing fees
- Dosing of epoprostenol (assuming both high and low extremes)
- Cost of epoprostenol vial and diluent
    - Using lower per diem costs for equipment
    - The base-case analysis incorporated the cost of Flolan, the most commonly prescribed version of epoprostenol. The sensitivity analysis incorporated an alternative lower priced epoprostenol, Caripul.
- Waning of treatment effect with respect to the reduction in the rate of deterioration in FC with treatment
    - Incorporation of unadjusted values for relative risk of improvement and worsening in FC with PAH therapies
    - Incorporation of survival estimates from NIH registry.[10]

Structural Uncertainty

- Discount rate of 0% per annum for costs and efficacy
- Time horizon of two years and 10 years
- Percentage of patients initiating epoprostenol upon deteriorating to FC IV (varied from 0% to 100%).

A threshold analysis specific to macitentan was also conducted to determine the minimal price change necessary for the therapy to be cost-effective relative to supportive care.

b) Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis was conducted to assess the impact of parameter uncertainty on the results of the analysis. The parameters within the analysis included the relative risk of improvement and worsening in FC, the hazard rates for mortality with deteriorating FC, and the utility values. Relative risks and hazard rates were modelled using a log-normal distribution and utilities were modelled using a beta distribution. A Monte Carlo simulation was conducted with 5,000 replications.

The results of the probabilistic sensitivity analysis (PSA) are presented through plots of the 95% confidence ellipses around the outcomes and in a cost-effectiveness acceptability curve (CEAC) depicting the probability that each treatment option is the most cost-effective at a range of threshold values for a QALY.

4.3.11 Model Validation

One of the challenges in developing a model for PAH is with respect to the estimation of mortality with supportive care. There are a number of registries for PAH; however, the majority of patients within the registries are receiving therapy for PAH and therefore the mortality rate is not reflective of supportive care alone. Data from the National Health Lung and Blood Institute PAH registry published by D'Alonzo in 1991 have often been used to estimate outcomes for patients on supportive care.[10] However, survival within the registry is significantly worse than that which is reported within more current registries. Although it may be surmised that this is due to improved medications for PAH, the evidence supporting an impact of PAH therapies on mortality is conflicting. One meta-analysis published in 2007 did not find a survival benefit with PAH therapies, whereas a second published in 2009 did.[83,84] Although newer treatments may have had an impact on survival, it is likely that additional changes in treatment outside of medications may also have changed in the past 20 years. The model was therefore calibrated to ensure the average overall survival with all treatments reflected the survival estimates of the PHC registry.[66]

The predicted survival within the model was validated through comparison of the predicted one-, three-, and five-year estimates with that of registry data from Ling. This registry enrolled incident cases of treatment-naive PAH and followed patients for up to nine years within the UK and Ireland (n = 482).[68] The survival estimates produced by the model were 93% at one year, 77% at three years, and 61% at five years. These were comparable with those reported within the registry: 93% at one year, 73% at three years, and 61% at five years.

5 RESULTS

5.1 Selection of Primary Studies

The original literature search identified 1,685 citations. Upon screening the titles and abstracts, 92 potential relevant publications were retrieved for further scrutiny, as well as nine potential references identified through other sources. Of the 101 potential relevant reports, a total of 43 reports describing 20 unique studies were selected for inclusion (all were RCTs; no comparative observational studies were identified for inclusion). Of the 20 included studies, 15[18-31] studies had treatment-naive populations and five[32-36] had mixed populations (naive and pre-treated with a PAH drug). Of those five studies with mixed populations, three[33-35] provided data of certain clinical outcomes for naive and pre-treated subpopulations. One study[32] with mixed population did not provide data of subpopulations based on treatment history. Thus, 18 studies[18-31,33-35] provided comparisons of PAH treatments in treatment-naive populations, and four[33-36] provided comparisons between dual combination (add-on) therapy and background therapy.

To be considered for inclusion, a trial needed to have at least two relevant treatment groups of employing interventions of interest. Seven studies[18,21,24,29,30,34,35] had at least one treatment group excluded, as the intervention dosage was not consistent with current recommendations in Canada or the treatment groups did not meet our inclusion criteria. All studies, except one,[24] had a placebo group.

The trial selection process appears in a PRISMA flowchart in APPENDIX 4. Included and excluded studies are listed in APPENDIX 5 and APPENDIX 6, respectively.

5.2 Study and Patient Characteristics

5.2.1 Monotherapy

Nineteen out of 20 studies included in this review randomized a total of 3,831 patients; of these, 3,155 patients were assigned to the PAH drugs of interest or to a dose approved in Canada. Of the included studies, 15 included only patients who were treatment naive to the studied PAH drugs, and four had mixed populations, in which the naive population ranged from 36% to 85%, and the population experienced to one of the PAH drugs ranged from 15% to 64%. The patients who were pre-treated with a PAH drug before randomization continued to have that drug plus the new studied drug during the study. This was referred to as add-on therapy and is further described in Section 5.2.2. One small trial (N = 22)[26] studied the transition from epoprostenol to treprostinil, where it randomized patients pre-treated with epoprostenol to placebo or treprostinil and stopped epoprostenol during the eight-week treatment. These patients were considered to be naive to treprostinil. Summary of trial characteristics are presented in Table 13.

Four studies[33-36] provided comparisons between dual combination (add-on) therapy and monotherapy, and none provided comparisons between dual therapy versus dual therapy or triple therapy versus dual therapy.

Four small studies[23,25-27] randomized 22 to 32 patients, while the largest study randomized 742 patients.[35] The epoprostenol studies[19,20,27] were published between 1990 and 2000, treprostinil studies[25,26,28,31] were published between 2002 and 2010, and bosentan studies[21-23,29,32] were published between 2001 and 2008. The studies on macitentan[35] and riociguat[33] were published

as recently as 2013, and the studies of ambrisentan,[18] sildenafil,[30] and tadalafil[34] were published in 2008, 2005, and 2009, respectively.

All studies were multi-centre. Six were from a single country (five in the US[19,20,25-27] and one from India[31]), and the remainder were multinational trials.

Table 13: Summary of Trial Characteristics

Trial Characteristics	Categories	Studies (n)
Publication status	Unique RCTs	19
	Placebo-controlled	18
Country	Multinational	13
	Single country	6
Study design	Double-blind	14
	Open-label	5
Treatment history	Naive (monotherapy)	18
	Add-on (combination therapy)	4
Sponsors	Manufacturer	18
	Not reported	1
Publication year	1990 to 2013	
Randomized sample size	23 to 742	
Study duration (weeks)	8 to 144	

n = number; RCT = randomized controlled trial.

a) Treatments Evaluated

Table 14: Summary of Treatments Evaluated

Treatment Evaluated	Dose Specification	Study (N)
Ambrisentan	Oral 5 mg q.d.	2
	Oral 10 mg q.d.	1
Bosentan	Oral 125 mg b.i.d.	5
Macitentan	Oral 10 mg q.d.	1
Riociguat	Oral max 1.5 mg t.i.d.	1
	Oral max 2.5 mg t.i.d.	1
Sildenafil	Oral 20 mg t.i.d.	1
Tadalafil	Oral 40 mg q.d.	1
Epoprostenol	I.v. infusion; initiate with 2 ng/kg/min, then incremental increase from 1 to 2 ng/kg/min at 15-minute intervals minimally	3
Treprostinil	S.c. injection or i.v. infusion; initiate with 1.25 ng/kg/min; dose adjustment based on PAH signs and symptoms, and side effects	4

b.i.d. = twice a day; i.v. = intravenous; kg = kilogram; max = maximum; mg = milligram; min = minute; n = number; ng = nanogram; PAH = pulmonary arterial hypertension; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.

Treatments evaluated included ambrisentan (three RCTs),[18,24] bosentan (five RCTs),[21-23,29,32] macitentan (one RCT),[35] riociguat (one RCT),[33] sildenafil (one RCT),[30] tadalafil (one RCT),[34] epoprostenol (three RCTs),[19,20,27] and treprostinil (four RCTs).[25,26,28,31] Two ambrisentan studies (ARIES-1 and ARIES-2) were published together in one article.[18] Dose specification and route of administration of treatment evaluated are shown in Table 14.

Eighteen studies used a placebo as a comparator.[18-23,25-35] Patients in the placebo group were treated with conventional therapy, which were anticoagulants, oral vasodilators, diuretics, cardiac glycosides, or supplemental oxygen. There was one dose-comparative study of ambrisentan,[24] and there were no trials that had active comparisons. STRIDE-2 was a placebo-controlled trial of sitaxsentan, with an open-label bosentan group used for observational purposes only. Since sitaxsentan was not an intervention of interest in this review, only the placebo and bosentan groups of STRIDE-2 were included in data analysis.

For drugs approved by Health Canada, treatment doses were selected for analysis based on recommended doses. Because riociguat had not yet been approved by Health Canada for treatment of PAH at the time this review was initiated, both doses (max 1.5 mg and max 2.5 mg) were included.

b) Study Design and Outcomes

All of the included studies were RCTs. Fourteen studies were double-blinded[18,21-25,28,30-35] and five studies were open-label.[19,20,26,27,29]

All studies reported 6MWD as an outcome. Of the 17 studies that specified a primary end point, 14 had a primary end point of 6MWD,[18-21,23,24,28-34] one had change in systemic pulse oximetry as the primary end point,[22] one had clinical deterioration as the primary end point,[26] and one had time to clinical worsening, a composite outcome, as the primary end point.[35] Time to clinical worsening was reported in 10 studies: ambrisentan (n = 2),[18] bosentan (n = 4),[21,23,29,32] macitentan (n = 1),[35] riociguat (n = 1),[33] sildenafil (n = 1),[30] and tadalafil (n = 1).[34]

The NYHA or WHO FC was reported as secondary outcome in 13 studies for FC improved,[18-23,27,30,31,33-35] in 12 studies for FC unchanged,[18-23,30,31,33-35] and in 14 studies for FC worsened.[18-23,29-35] Other secondary outcomes included BDI, reported in 13 studies;[18,19,21,23,25,26,28,30,31,33-35] PVR in 12 studies;[19,20,22-25,27,28,30,33-35] PAP in 13 studies;[19,20,22-25,27,28,30,32-35] and cardiac index in 12 studies.[19-25,28,30,32-35]

HRQoL was reported in studies of ambrisentan,[18] bosentan,[32] macitentan,[35] riociguat,[33] sildenafil,[30] tadalafil,[34] epoprostenol,[20] and treprostinil,[28] using different instruments.

c) Study Duration

Three studies had a study duration of eight weeks,[25-27] 11 had 12 weeks,[18-20,23,24,28,30-33] three had 16 weeks,[21,22,34] one had 18 weeks,[29] and one had three years.[35] The SERAPHIN study (macitentan), which had the longest study duration (three years), was also the largest study included in this review (N = 742).[35] The studies with the shortest study duration (eight weeks) were small studies (N = 26,[25] 22,[26] 23[27]).

d) Funding

One study did not report the source of funding,[26] while all other studies were funded by manufacturers.

e) Populations

All studies included patients with PAH, including both IPAH/FPAH and associated PAH (APAH); however, three studies had primarily IPAH/FPAH in their patient population,[20,25,27] and two studies had solely APAH as their patient population.[19,22] For studies that had populations of mixed PAH etiology, IPAH/FPAH ranged from 57% to 95%, while APAH ranged from 5% to 43%.

All studies included patients who mostly had baseline NYHA or WHO FC of II and III. One study had patients of FC II only,[32] and two studies had patients of FC III only.[22,23] In other studies, patients of FC II ranged from 5% to 52% and patients of FC III ranged from 43% to 95%. Few patients were in FC I (0% to 6%), and patients in FC IV ranged from 0% to 26%. Studies of epoprostenol had the highest proportion of patients in FC IV (17% to 26%).[19,20,27]

In all studies, the majority of patients were female (range from 61% to 88%), and the ratio of female to male ranged from 1.6:1 to 7.3:1. The mean age across studies ranged from 32 to 55 years. Ten studies reported mean time from diagnosis of PAH that ranged from 15 to 46 months. The mean baseline of 6MWD values ranged from 226 m to 435 m, and three epoprostenol studies had lowest mean values of 6MWD at baseline (from 226 m to 294 m).[19,20,27] Across studies, the mean baseline PAP ranged from 48 to 76 mm Hg, the mean baseline PVR ranged from 811 to 3,250 dyn.s/cm^5, and the mean baseline cardiac index ranged from 2.0 to 2.7 L/min/m^2. The BREATHE-5 study (N = 54)[22] had 100% patients of WHO FC III and mean PVR of 3,250 dyn.s/cm^5, while the study by Channick et al. (N = 32)[23] also had 100% patients of WHO FC III but had a mean PVR of 912 dyn.s/cm^5.

5.2.2 Add-on Therapy

A total of five studies using add-on therapy were identified. Four double-blind, placebo-controlled trials with mixed populations (naive and previously treated with a PAH drug) were identified.[32-35] Experienced patients continued to receive background therapy in addition to the experimental drug. One double-blind, placebo-controlled trial had patients who were previously treated with ambrisentan for at least four months.[36]

The EARLY study (N = 185), which compared bosentan (125 mg) with placebo, had 15% of patients who had been treated with sildenafil.[32] All patients were of WHO FC II. In the total population, the percentages of IPAH/FPAH and APAH were 61% and 39%, respectively. The mean age was 45 years, and the ratio of female to male was 2.2:1. Subgroup data for naive and experienced populations were not available.

The PATENT-1 study (N = 443), which compared riociguat (max 1.5 mg or max 2.5 mg) with placebo, had 50% of patients who had been treated with ERA (44%) and prostanoid (6%).[33] Patients were mostly of WHO FC II (42%) and III (53%). In the total population, the percentages of IPAH/FPAH and APAH were 63% and 37%, respectively. The mean age was 51 years, and the ratio of female to male was 3.8:1. Subgroup data for naive and experienced populations were available for outcomes including 6MWD, clinical worsening, WHO FC (improved, unchanged, and worsened), BDI, and PVR.

The PHIRST study (N = 405), which compared tadalafil (2.5 mg, 10 mg, 20 mg, or 40 mg) with placebo, had 54% of patients who had been treated with bosentan.[34] Patients were mostly of WHO FC II (32%) and III (65%). In the total population, the percentages of IPAH/FPAH and APAH were 63% and 37%, respectively. The mean age was 54 years, and the ratio of female to male was 3.5:1. Subgroup data for naive and experienced populations were available for outcomes including 6MWD, clinical worsening, and WHO FC (improved, unchanged, and worsened).

The SERAPHIN study (N = 742), which compared macitentan (3 mg or 10 mg) with placebo, had 64% of patients who had been treated with PDE-5 inhibitor (61.4%) and prostanoid (5.4%).[35] Patients were mostly of WHO FC II (52%) and III (46%). In the total population, the percentages of IPAH/FPAH and APAH were 57% and 43%, respectively. The mean age was 46

years, and the ratio of female to male was 3.3:1. Subgroup data for naive and experienced populations were available for outcomes including 6MWD, clinical worsening, and WHO FC (improved).

The study by Zhuang et al. (N = 124), which compared tadalafil 40 mg with placebo, had all patients who had been previously treated with ambrisentan.[36] Patients were mostly of WHO FC II (57%) and III (39%). The percentage of IPAH/FPAH and APAH were 63% and 37%, respectively. The mean age was 52 years, and the ratio of female to male was 3.8:1. The outcomes were 6MWD, WHO FC (worsened, unchanged, improved), clinical worsening, hospitalization, mean PAP, PVR, cardiac output, and safety outcomes (death, adverse events).

Table 15 and Table 16 provide overviews of study characteristics and patient characteristics, respectively. More details of study and patient characteristics are presented in APPENDIX 7.

Table 15: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Study duration**	**Outcome(s)**
ARIES-1 (2008)[18] DB RCT, multi-centre, multi-country, including US, Mexico, South America, Australia, and Europe	Randomized: N = 202 Completed: N = 183 (91%)	Patients (mean age: 48 to 53 years); PAH (idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use); WHO FC I to IV Treatment history: naive	**Ambrisentan oral 5 mg q.d.** (n = 67) **Ambrisentan oral 10 mg q.d.** (n = 67) **Placebo** (n = 67)	12 weeks	6MWD Clinical worsening WHO FC (improved, unchanged, worsened) QoL Borg dyspnea Death AEs
ARIES-2 (2008)[18] DB RCT, multi-centre, multi-country, including Europe, Israel, and South America	Randomized: N = 192 Completed: N = 170 (89%)	Patients (mean age: 50 to 52 years); PAH (idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use); WHO FC I to IV Treatment history: naive	**Ambrisentan oral 5 mg q.d.** (n = 63) **Placebo** (n = 65)	12 weeks	6MWD Clinical worsening WHO FC (improved, unchanged, worsened) QoL Borg dyspnea Death AEs
Badesch et al. (2000)[19] Open-label RCT, multi-centre in the US	Randomized: N = 111 Completed: N = 102 (92%)	Patients (mean age: 53 to 57 years); PAH (associated with connective tissue disease); NYHA FC II to IV Treatment history: naive	**Epoprostenol plus conventional therapy** (n = 56) **Conventional therapy** (n = 55)	12 weeks	6MWD Cardiopulmonary hemodynamics Borg dyspnea NYHA FC (improved, unchanged, worsened) Death AEs

Table 15: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Study duration**	**Outcome(s)**
Barst et al. (1996)[20] Open-label RCT, multi-centre in the US	Randomized: N = 81 Completed: N = 71 (88%)	Patients (mean age: 40 years); PAH (idiopathic); NYHA FC III or IV Treatment history: unclear	**Epoprostenol plus conventional therapy** (n = 41) **Conventional therapy** (n = 40)	12 weeks	6MWD QoL NYHA FC (improved, worsened, unchanged) Cardiopulmonary hemodynamics Death AEs
BREATHE-1 (2002)[21] DB RCT, multi-centre, multi-country, including Europe, North America, Israel, and Australia	Randomized: N = 213 Completed: N = 193 (91%)	Patients (mean age: 47 to 50 years); PAH (idiopathic or associated with connective tissue disease); WHO FC III or IV Treatment history: naive	**Bosentan oral 125 mg b.i.d.** (n = 74) **Placebo** (n = 69)	16 weeks	6MWD Borg dyspnea WHO FC (improved, unchanged, worsened) Clinical worsening Death AEs
BREATHE-5 (2006)[22] DB RCT, multi-centre, multi-country, including Europe, North America, Israel, and Australia	Randomized: N = 54 Completed: N = 50 (93%)	Patients (mean age: 37 to 44 years); Eisenmenger syndrome — PAH associated with congenital heart disease; WHO FC III Treatment history: naive	**Bosentan oral 125 mg b.i.d.** (n = 37) **Placebo** (n = 17)	16 weeks	6MWD WHO FC (improved, unchanged, worsened) Cardiopulmonary hemodynamics AEs

Table 15: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Study duration**	**Outcome(s)**
Channick et al. (2001)[23] DB RCT, multi-centre in US and France	Randomized: N = 32 Completed: N = 30 (94%)	Patients (mean age: 47 to 52 years); PAH (idiopathic or associated with connective tissue disease); WHO FC III and IV Treatment history: naive	**Bosentan oral 125 mg b.i.d.** (n = 21) **Placebo** (n = 11)	12 weeks	6MWD Cardiopulmonary hemodynamics Borg dyspnea WHO FC (improved, unchanged, worsened) Clinical worsening AEs
EARLY (2008)[32] DB RCT, multi-centre, multi-country (21 countries)	Randomized: N = 185 Completed: N = 163 (88%)	Patients (mean age: 44 to 45 years); PAH (idiopathic, familial, or associated with HIV, anorexigen use, atrial septal defect of less than 1 cm in diameter, ventricular septal defect of less than 1 cm in diameter, patent ductus arteriosus, or connective tissue or autoimmune diseases); WHO FC II Treatment history: mixed	**Bosentan oral 125 mg b.i.d.** (n = 92) **Placebo** (n = 93)	12 weeks	6MWD Cardiopulmonary hemodynamics Borg dyspnea WHO FC (worsened) Clinical worsening QoL Death AEs
Galiè et al. (2005)[24] DB RCT, multi-centre, multi-country, including US, Europe, and Australia	Randomized: N = 64 Completed: N = 58 (91%)	Patients (mean age: 48 to 53 years); PAH (idiopathic or associated with collagen vascular disease, anorexigen use, or HIV infection); WHO FC II and III Treatment history: naive	**Ambrisentan oral 5 mg** (n = 16) **Ambrisentan oral 10 mg** (n = 13)	12 weeks	6MWD Borg dyspnea WHO FC (improved) QoL Clinical worsening Cardiopulmonary hemodynamics Death AEs

Table 15: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Study duration**	**Outcome(s)**
McLaughlin et al. (2002)[25] DB RCT, multi-centre in the US	Randomized: N = 26 Completed: N = 24 (92%)	Patients (mean age: 37 years); PAH (idiopathic); WHO FC III and IV Treatment history: unclear	**Treprostinil s.c.** (n = 17) **Placebo** (n = 9)	8 weeks	AEs cardiopulmonary hemodynamics 6MWD Borg dyspnea
PATENT-1 (2013)[33] DB RCT, multi-centre, multi-country (30 countries)	Randomized: N = 443 Completed: N = 405 (91%)	Patients (mean age: 49 to 51 years); PAH (idiopathic, familial, or associated with connective tissue disease, congenital heart disease, portal hypertension with liver cirrhosis, or anorexigen use); WHO FC I to IV Treatment history: mixed	**Riociguat oral max 1.5 mg t.i.d** (n = 63) **Riociguat oral max 2.5 mg t.i.d** (n = 254) **Placebo** (n = 126)	12 weeks	6MWD Cardiopulmonary hemodynamics WHO FC (improved, unchanged, worsened) Clinical worsening Borg dyspnea QoL Death AEs
PHIRST (2009)[34] DB RCT, multi-centre, multi-country, including Canada, US, Europe, and Japan	Randomized: N = 405 Completed: N = 341 (84%)	Patients (mean age: 53 to 55 years); PAH (idiopathic, familial, or associated with anorexigen use, connective tissue disease, HIV infection, or congenital systemic-to-pulmonary shunts); WHO FC I to IV Treatment history: mixed	**Tadalafil oral 40 mg q.d** (n = 79) **Placebo** (n = 82)	16 weeks	6MWD WHO FC (improved, unchanged, worsened) Clinical worsening Borg dyspnea QoL Cardiopulmonary hemodynamics Death AEs

Table 15: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Study duration**	**Outcome(s)**
Rubenfire et al. (2007)[26] Open-label, RCT, multi-centre in the US	Randomized: N = 22 Completed: N = 13 (59%)	Patients (mean age: 42 to 47 years); PAH (idiopathic, familial, or associated with scleroderma, congenital systemic-to-pulmonary shunts, HIV or portal hypertension); WHO FC II or III Treatment history: transition from epoprostenol to treprostinil or placebo	**Treprostinil s.c.** (n = 14) **Placebo** (n = 8)	8 weeks	Clinical deterioration 6MWD Borg dyspnea AEs
Rubin et al. (1990)[27] Open-label, RCT, multi-centre in the US	Randomized: N = 23 Completed: N = 19 (83%)	Patients (age: 15 to 66 years); PAH (idiopathic); NYHA FC II to IV Treatment history: naive	**Epoprostenol i.v.** (n = 11) **Conventional therapy** (n = 12)	8 weeks	Cardiopulmonary hemodynamics 6MWD NYHA FC (improved) Death AEs
SERAPHIN (2013)[35] DB RCT, multi-centre, multi-country (39 countries)	Randomized: N = 742 Completed: N = 587 (79%)	Patients (mean age: 46 years); PAH (idiopathic, familial, or associated with connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, or drug use or toxin exposure); WHO FC II to IV Treatment history: mixed	**Macitentan oral 10 mg q.d** (n = 242) **Placebo** (n = 250)	36 months Mean: 85 to 104 weeks	Clinical worsening 6MWD WHO FC (improved) Borg dyspnea QoL Cardiopulmonary hemodynamics Death AEs

Table 15: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Study duration**	**Outcome(s)**
Simonneau et al. (2002)[28] DB RCT, multi-centre, multi-country, including Canada, Mexico, US, Australia, Austria, Belgium, France, Germany, Israel, Italy, Poland, Spain, UK	Randomized: N = 470 Completed: N = 423 (90%)	Patients (mean age: 45 years); PAH (idiopathic or associated with connective tissue diseases or with congenital systemic-to-pulmonary shunts); NYHA FC II to IV Treatment history: naive	**Treprostinil plus conventional therapy** (n = 233) **Placebo plus conventional therapy** (n = 236)	12 weeks	6MWD Borg dyspnea Cardiopulmonary hemodynamics QoL Death AEs
STRIDE-2 (2006)[29] Open-label, RCT, multi-centre, multi-country	Randomized: N = 245 Completed: N = 214 (87%)	Patients (mean age: 54 years); PAH (idiopathic or associated with connective tissue diseases, repaired atrial septal defect, ventricular septal defect, or patent ductus arteriosus at least one year before enrolment); WHO FC II to IV Treatment history: naive	**Bosentan oral 125 mg b.i.d.** (n = 60) **Placebo** (n = 62)	18 weeks	6MWD WHO FC (worsened) Clinical worsening Borg dyspnea AEs

Table 15: Summary of Included Trials					
Study and Design	**Disposition**	**Population**	**Interventions**	**Study duration**	**Outcome(s)**
SUPER (2005)[30] DB RCT, multi-centre, multi-country, including US, Mexico, South America, and Israel	Randomized: N = 277 Completed: N = 265 (96%)	Patients (mean age: 47 to 51 years); PAH (idiopathic or associated with connective tissue diseases, or occurring after surgical repair of congenital systemic-to-pulmonary shunts that had been performed at least 5 years previously); WHO FC II to IV Treatment history: naive	**Sildenafil oral 20 mg t.i.d.** (n = 69) **Placebo** (n = 70)	12 weeks	6MWD Cardiopulmonary hemodynamics Borg dyspnea WHO FC (improved, unchanged, worsened) Clinical worsening QoL Death AEs
TRUST (2010)[31] DB RCT, multi-centre in India	Randomized: N = 44 Completed: N = 31 (70%)	Patients (mean age: 32 years); PAH (idiopathic — sporadic or familial, or associated with HIV infection, or collagen vascular disease); stable NYHA FC III or IV Treatment history: naive	**Treprostinil i.v.** (n = 30) **Placebo** (n = 14)	12 weeks	6MWD Borg dyspnea NYHA FC (improved, unchanged, worsened) Clinical worsening (only *P* value). Death AEs
Zhuang et al. (2014)[36] DB RCT, China	Randomized: N = 124 Completed: N = 113 (91%)	Patients (mean age: 52 years); PAH (idiopathic or familial, anorexigen use, connective tissue disease, associated with an atrial septal defect); stable WHO FC Treatment history: experienced (ambrisentan)	**Tadalafil oral 40 mg q.d** (n = 60) **Placebo** (n = 64)	16 weeks	6MWD Cardiopulmonary hemodynamics WHO FC (improved, unchanged, worsened) Clinical worsening Hospitalization Death AEs

6MWD = six-minute walk distance; AEs = adverse events; b.i.d. = twice a day; DB = double-blind; FC = functional class; i.v. = intravenous; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; q.d. = once a day; QoL = quality of life; RCT = randomized controlled trial; s.c. = subcutaneous; t.i.d. = three times a day; WHO = World Health Organization.

Table 16: Summary of Patient Baseline Characteristics															
Study	**Age (years), mean ± SD**	**Sex (%)**		**Time from diagnosis (months), mean ± SD**	**PAH etiology (%)**		**WHO or NYHA FC (%)**				**6MWD (m) mean ± SD**	**PAP (mm Hg) mean ± SD**	**PVR (dyn.s/cm$^{5)}$ mean ± SD**	**Cardiac index, (L/min/m^2) mean ± SD**	**Treatment history**
		M	**F**		**IPAH/FPAH**	**APAH**	**I**	**II**	**III**	**IV**					
ARIES-1 (2008)[18]	50 ± 16	16	84	NR	63	37	3	32	58	7	341 ± 76	50 ± 15	871 ± 472	2.5 ± 0.8	Naive
ARIES-2 (2008)[18]	51 ± 15	25	75	NR	65	35	2	45	51	2	348 ± 84	49 ± 14	901 ± 565	2.4 ± 0.7	Naive
Badesch et al. (2000)[19]	55 ± 12	14	86	14.8 ± 19	0	100	0	4.5	78.5	17	Median: 256	50 ± 10	1,017 ± 516	2.0 ± 0.6	Naive
Barst et al. (1996)[20]	40 ± 16	27	73	29 ± 45	100	0	0	0	74	26	294 ± 132	60 ± 12	1,280 ± 480	2.0 ± 0.9	Naive
BREATHE-1 (2002)[21]	48 ± 16	22	78	29 ± 40	71	29	0	0	92	8	335 ± 75	54 ± 16	971 ± 640	2.4 ± 0.8	Naive
BREATHE-5 (2006)[22]	39 ± 12	39	61	23 ± 14	0	100	0	0	100	0	333 ± 78	76 ± 17	3,250 ± 1,377	2.5 ± 0.4	Naive
Channick et al. (2001)[23]	51 ± 13	12	88	26 ± 26	86	14	0	0	100	0	358 ± 85	55 ± 12	912 ± 427	2.4 ± 0.8	Naive
EARLY (2008)[32]	45 ± 17	31	69	40 ± 72	61	39	0	100	0	0	435 ± 79	52 ± 18	822 ± 458	2.7 ± 0.7	Mixed (85% naive, 15% experienced)
Naive	nr	nr	nr	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Experienced	nr	nr	nr	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Galiè et al. (2005)[24]	51 ± 16	16	84	NR	61	39	0	36	64	0	343 ± 79	49 ± 13	840 ± 407	2.4 ± 0.6	Naive
McLaughlin et al. (2003)[25]	37 ± 17	19	81	NR	100	0	0	0	96	4	378 ± 96	61 ± 17	1,981 ± 815	2.3 ± 0.2	Naive
PATENT-1 (2013)[33]	51 ± 17	21	79	NR	63	37	3	42	53	1	363 ± 69	49 ± 15	811 ± 475	2.5 ± 0.7	Mixed (50% naive, 50% experienced)
Naive	48 ± 18	23	77	NR	68	32	5	51	44	1	364 ± 71	50 ± 16	882 ± 528	2.5 ± 0.7	
Experienced	53 ± 15	19	81	NR	60	40	2	34	63	1	363 ± 68	47 ± 14	739 ± 400	2.6 ± 0.6	
PHIRST (2009)[34]	54 ± 16	22	78	NR	63	37	1	32	65	2	344 ± 76	54 ± 14	879 ± 438	2.5 ± 0.6	Mixed (46% naive, 54% experienced)
Naive	57 ± 16	25	75	NR	65	35	1	30	66	3	335 ± 78	NR	NR	NR	
Experienced	51 ± 15	19	81	NR	57	43	1	34	64	1	351 ± 75	NR	NR	NR	

Table 16: Summary of Patient Baseline Characteristics															
Study	**Age (years), mean ± SD**	**Sex (%)**		**Time from diagnosis (months), mean ± SD**	**PAH etiology (%)**		**WHO or NYHA FC (%)**				**6MWD (m) mean ± SD**	**PAP (mm Hg) mean ± SD**	**PVR (dyn.s/cm$^{5)}$ mean ± SD**	**Cardiac index, (L/min/m^2) mean ± SD**	**Treatment history**
		M	**F**		**IPAH/FPAH**	**APAH**	**I**	**II**	**III**	**IV**					
Rubenfire et al. (2007)[26]	45 ± 12	14	86	49 ± 37	73	27	6	51	43	0	432 ± 95	NR	NR	NR	Naive to treprostinil
Rubin et al. (1990)[27]	36 ± 14	30	70	NR	100	0	0	9	65	26	226 ± nr	61 ± nr	1,744 ± nr	nr	Naive
SERAPHIN (2013)[35]	46 ± 16	23	77	32 ± 48	57	43	0	52	46	2	360 ± 100	54 ± 18	1,026 ± 697	2.4 ± 0.8	Mixed (36% naive, 64% experienced)
Naive	nr	NR	NR	NR	NR	NR	NR	NR	NR	NR	340 ± 110	NR	NR	NR	
Experienced	nr	NR	NR	NR	NR	NR	NR	NR	NR	NR	360 ± 111	NR	NR	NR	
Simonneau et al. (2002)[28]	44 ± 15	19	81	46 ± 92	58	42	0	11	82	7	327 ± 84	61 ± 15	2,040 ± 1,201	2.3 ±1.5	Naive
STRIDE-2 (2006)[29]	54 ± 15	22	78	NR	59	41	0	37	59	4	337 ± 80	48 ± 14	880 ± 560	2.4 ± 0.6	Naive
SUPER (2005)[30]	49 ± 16	25	75	NR	63	37	0	39	58	3	343 ± 81	53 ± 15	957 ± 513	2.3 ± 0.7	Naive
TRUST (2010)[31]	32 ± nr	39	61	20 ± NR	95	5	0	0	95	5	250 ± 69	63 ± 20	2,071 ± 1,272	2.7 ± 1.7	Naive
Zhuang et al. (2014)[36]	52 ± 13	21	79	NR	63	37	0	57	39	4	150 to 400 m	52 ± 10	840 ± 407	2.6 ± 0.9	Experienced

6MWD = six-minute walk distance; APAH = associated pulmonary hypertension; F = female; FC = functional class; FPAH = familial pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; M = male; NR = not reported; NYHA = New York Heart Association; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; SD = standard deviation; WHO = World Health Organization.

5.3 Critical Appraisal of Included Studies

5.3.1 Monotherapy

The methodological approaches to randomization and allocation concealment were generally adequate in most studies (**APPENDIX 8**). Demographic and baseline characteristics were generally balanced between intervention and comparator groups. Overall, the characteristics of patients in the included studies were reflective of those in the general PAH population, according to the clinical experts. In studies with mixed populations, randomization was stratified by PAH treatment background so that the distributions between groups were even for treatment-naive and treatment-experienced patients. However, there was a lack of information regarding the WHO FC of patients receiving add-on therapy. In three studies with epoprostenol, the intervention groups had higher baseline 6MWD than those of the placebo groups (average: 278 m versus 239 m),[19,20,27] suggesting that patients in the placebo groups were sicker than those in the epoprostenol groups. Two studies with bosentan had longer mean time since diagnosis in the placebo groups compared with the intervention groups (average: 40.4 months versus 28.0 months).[23,32]

For injectable agents, all three studies with epoprostenol were open label,[19,20,27] while three out four studies with treprostinil were double-blinded.[25,28,31] Therefore, biases related to open-label trial design were more likely to occur in the epoprostenol studies. One small open-label study (Rubenfire et al.[26] [N = 22]) evaluated the transition from intravenous epoprostenol to subcutaneous treprostinil. Patients in this study had been stable on epoprostenol and the epoprostenol dose was withdrawn during the study period. The placebo group performed much worse in the clinical outcomes than the treprostinil group, and this study was therefore likely an outlier among the treprostinil studies. In STRIDE-2, a sitaxsentan study,[29] an open-label bosentan group was used for observational purpose. Biases for bosentan group in this study appeared to be directed toward the null hypothesis, where there were no differences between bosentan and placebo for WHO FC change and time to clinical worsening.

Of the 20 included studies, the clinical outcome of 17 was analyzed based on the ITT approach,[18-21,23,24,26,28-36] while two studies used a per-protocol approach.[22,27] One study did not specify whether an ITT or per-protocol approach was used in the analyses.[25] Thirteen studies had sufficient power for their primary analysis,[18,19,21-24,26,30,32-35] which was mostly change from baseline in 6MWD in all except SERAPHIN, in which the primary analysis was clinical worsening.[35] However, those studies were not powered to detect 6MWD for individual subgroups based on background therapy (i.e., naive and add-on) in some studies with mixed populations. In addition, many studies also lacked statistical power to detect differences between treatment groups for secondary outcomes, including clinical worsening and change in WHO FC. Many studies had small sample sizes, in which the number of patients in each group was at most 60 to 70.

Change in 6MWD was used as a primary end point in 14 studies.[18-21,23,24,28-34] However, it was found that improvement in 6MWD did not reflect the benefit in clinical outcomes, such as all-cause death, hospitalization, and initiation of PAH rescue therapy.[38] A large and long-term study, SERAPHIN, used clinical worsening, a composite end point of morbidity and mortality, as the primary end point.[35] A study using the REVEAL registry data showed that clinical worsening correlated well with mortality, and suggested it be used as a primary end point in clinical trial design.[85] In addition to SERAPHIN, 11 studies also reported clinical worsening, with slightly different definitions, as a secondary outcome.[18,21,23,24,29-34]

Treatment duration varied from eight weeks to three years, with the majority being 12 to 16 weeks. The SERAPHIN study reported its primary end point, time to clinical worsening, over a median treatment period of 115 weeks, and other secondary outcomes, including 6MWD, at month 6. Clinical worsening was not an outcome in studies of epoprostenol.[19,20,27]

There was some degree of heterogeneity in patient baseline characteristics across studies with respect to mean age, gender ratio, time from diagnosis of PAH, PAH etiology, proportion of NYHA or WHO FC, 6MWD, and hemodynamic parameters. For instance, all three studies of epoprostenol had the largest proportion of patients with NYHA/WHO FC IV (average 23%), and relatively lower baseline 6MWD (mean 259 m) compared with the other studies, suggesting that patients in the epoprostenol studies were sicker than those in the other studies. All patients in BREATHE-5 had Eisenmenger syndrome, a PAH associated with congenital heart disease. This study was not considered in the NMA subgroup analyses because it was a small trial (N = 54) and those patients might have been included in other studies.

Total withdrawals varied across studies (from 4% in SUPER[30] to 41% in Rubenfire et al.[26]). In the study of Rubenfire et al.,[26] most of the withdrawals were from the placebo group. The long-term study SERAPHIN had a total withdrawal of 21%,[35] while the remaining studies with short-term treatment duration had total withdrawal rates that varied from 6% to 17%. Studies with marked differences between treatment groups in the total withdrawals were ARIES-1 & -2 (placebo 16% versus ambrisentan 7%) and Barst et al. (placebo 25% versus epoprostenol 7%). The approach used to handle missing data was last observation carried forward. However, the higher withdrawal rate in one group compared with the other may affect the outcome assessment, although an ITT approach was used for the analyses in those studies.

5.3.2 Add-on Therapy

Of the four studies[32-35] with mixed populations, two reported baseline patient characteristics of the naive and experienced populations.[33,34] The values were similar to those of the total populations. Baseline characteristics were balanced between treatment groups in patients on bosentan background in the PHIRST study.[34] Detailed baseline characteristics between treatment groups in treatment-experienced patients in the PATENT-1 study were not available.[33] Subgroup analyses based on background therapy were exploratory.

One study had patients who had been previously treated with ambrisentan for at least four months.[36] Tadalafil or placebo were added to ambrisentan for 16 weeks. Baseline characteristics were balanced between treatment groups. Total withdrawal rates were similar between treatment groups. The ITT approach was used for analysis of treatment efficacy.

5.4 Data Synthesis

There were a total of 11 treatment strategies, including placebo, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and treprostinil. Dosing regimens for these agents are described in Table 17. For each outcome evaluated, the number of treatment strategies and pairwise comparisons are described in Table 18.

Raw data are presented in APPENDIX 9 (Table 127 to Table 162). Results of pairwise meta-analyses by treatment are shown in APPENDIX 10 (Table 163 to Table 172). Data on treatment-related adverse events are shown in Table 173. Summaries of results from direct pairwise meta-analysis are presented in Table 174 and Table 175.

Table 17: Summary of Interventions Evaluated		
Interventions	**Individual Trials (n)**	**Patients (n)**
Treatment strategies included in the NMA		
Ambrisentan oral 5 mg q.d.	3	146
Ambrisentan oral 10 mg q.d.	2	80
Bosentan oral 125 mg b.i.d.	5	284[a]
Macitentan oral 10 mg q.d.	1	242[a]
Riociguat oral max 1.5 mg t.i.d.	1	63[a]
Riociguat oral max 2.5 mg t.i.d.	1	254[a]
Sildenafil oral 20 mg t.i.d.	1	69
Tadalafil oral 40 mg q.d.	1	79[a]
Epoprostenol i.v.	3	108
Treprostinil s.c. or i.v.	4	294
Placebo	18	1,286[a]

b.i.d. = twice a day; i.v. = intravenous; n = number; NMA = network meta-analysis; q.d. = once daily; s.c. = subcutaneous; t.i.d. = three times a day.

[a] Number of patients were from total population (naive & experienced).

Table 18: Overview of Evidence and Analyses Performed					
Outcomes	**Population**	**No. of Treatment Strategies**	**No. of Pairwise Comparisons**	**No. of Studies and Patients**	**Type of Analysis Conducted**
Mortality (all-cause)	Total	11	11	19 RCTs (N = 2,890)	Pairwise
Clinical worsening	Total	9	10	10 RCTs (N = 2,046)	Pairwise and NMA
	Naive	8	8	9 RCTs (N = 1,212)	Pairwise and NMA
	Add-on	4	3	4 RCTs (N = 904)	Pairwise and NMA
FC, improved	Total	11	12	13 RCTs (N = 2,046)	Pairwise and NMA
	Naive	9	9	12 RCTs (N = 1,214)	Pairwise and NMA
	Add-on	3	2	3 RCTs (N = 401)	Pairwise and NMA
FC, unchanged	Total	11	12	12 RCTs (N = 2,026)	Pairwise
	Naive	9	9	11 RCTs (N = 1,195)	Pairwise
	Add-on	3	2	3 RCTs (N = 401)	Pairwise
FC, worsened	Total	11	12	14 RCTs (N = 2,333)	Pairwise and NMA
	Naive	9	9	12 RCTs (N = 1,327)	Pairwise and NMA
	Add-on	3	2	3 RCTs (N = 401)	Pairwise and NMA
6MWD	Total	11	12	19 RCTs (N = 2,899)	Pairwise and NMA
	Naive	11	12	18 RCTs (N = 2,100)	Pairwise and NMA
	Add-on	5	5	4 RCTs (N = 797)	Pairwise and NMA
Hospitalization	Total	10	11	9 RCTs (N = 2,244)	Pairwise
Borg dyspnea index	Total	11	12	13 RCTs (N = 1,990)	Pairwise
	Naive	8	8	11 RCTs (N = 1,478)	Pairwise
	Add-on	2	1	1 RCT (N = 191)	Pairwise
PVR	Total	9	10	11 RCTs (N = 1,520)	Pairwise
	Naive	6	5	9 RCTs (N = 1,089)	Pairwise
	Add-on	3	2	2 RCTs (N = 293)	Pairwise

Table 18: Overview of Evidence and Analyses Performed					
Outcomes	**Population**	**No. of Treatment Strategies**	**No. of Pairwise Comparisons**	**No. of Studies and Patients**	**Type of Analysis Conducted**
mPAP	Total	9	10	12 RCTs (N = 1,706)	Pairwise
	Naive	6	6	10 RCTs (N = 1,121)	Pairwise
	Add-on	3	2	2 RCTs (N = 299)	Pairwise
Cardiac index	Total	9	10	12 RCTs (N = 1,803)	Pairwise
	Naive	6	6	10 RCTs (N = 1,154)	Pairwise
	Add-on	3	2	2 RCTs (N = 298)	Pairwise
Serious AEs	Total	10	10	14 RCTs (N = 2,687)	Pairwise
Treatment discontinuation due to AEs	Total	10	10	16 RCTs (N = 2,772)	Pairwise
Total withdrawal	Total	10	10	17 RCTs (N = 3,103)	Pairwise

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; NMA = network meta-analysis; mPAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; RCT = randomized controlled trial.

5.4.1 Efficacy of Pulmonary Arterial Hypertension Drugs in Total and Naive Populations

a) Mortality (All-Cause)

Only direct pairwise meta-analyses were performed for this outcome.

Nineteen studies reported mortality. All-cause mortality was analyzed for total populations irrespective of the pre-treatment background in EARLY,[32] PATENT-1,[33] PHIRST,[34] and SERAPHIN[35] studies.

Table 19 shows that the proportion of patients who died from all-causes was not statistically significantly different between any of the PAH treatments and the placebo groups.

The number of deaths in all studies was relatively low. Of the five bosentan studies (BREATHE-1,[21] BREATHE-5,[22] Channick,[23] EARLY,[32] STRIDE-2[29]), there were no deaths in BREATHE-5[22] or the study by Channick et al.[23] Of the four treprostinil studies (McLaughlin,[25] Rubenfire,[26] Simonneau,[28] TRUST[31]), there were no deaths in the studies by McLaughlin et al.[25] or Rubenfire et al.[26] Of the three epoprostenol studies (Badesch,[19] Barst,[20] Rubin[27]), the study by Barst et al.[20] reported eight patients who died in the placebo group and none in the epoprostenol group (RR = 0.06; 95% CI, 0.00 to 0.96). The pooled estimate showed that epoprostenol significantly lowered the risk of mortality compared with placebo. In SERAPHIN,[35] the rates of mortality from any cause by the end of the study (median follow-up 129 weeks) were 14.0% and 17.6% in the macitentan 10 mg and placebo groups, respectively. In PATENT-1,[33] there were two deaths in the placebo group and none in the riociguat max 2.5 mg group during 12 weeks of treatment.

Likewise, there were a total of two deaths in the placebo group and none in the tadalafil 40 mg group during 16 weeks of treatment in PHIRST[34] and Zhuang et al.[36]

Table 19: Meta-analysis Results for Mortality of PAH Treatments Compared With Placebo

Treatment	Background	No. of Patients	Het (I^2)	Placebo Effects[a]	RR (95% CI),[b] Fixed
Ambrisentan oral 5 mg q.d.	Naive	262[18]	0%	0.04 (0.03, 0.05)	0.28 (0.05 to 1.67)
Ambrisentan oral 10 mg q.d.	Naive	134[18]	NA	0.04 (0.03, 0.05)	0.50 (0.05 to 5.38)
Bosentan oral 125 mg b.i.d.	Total	536[21-23,29,32]	0%	0.01 (0, 0.03)	0.45 (0.10 to 1.98)
Macitentan oral 10 mg q.d.	Total	492[35]	NA	0.18	0.80 (0.53 to 1.20)
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	0.016	1.00 (0.09 to 10.82)
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	0.016	0.10 (0.00 to 2.06)
Sildenafil oral 20 mg t.i.d.	Naive	139[30]	NA	0.014	1.01 (0.06 to 15.90)
Tadalafil oral 40 mg q.d.	Total	279[34,36]	0%	0.015 (0.013, 0.016)	0.35 (0.04 to 3.33)
Epoprostenol i.v.	Naive	215[19,20,27]	39.0%	0.20 (0.09, 0.25)	**0.33 (0.13** to **0.85)**
Treprostinil s.c. or i.v.	Naive	516[25,26,28,31]	55.0%	0.02 (0, 0.36)	0.56 (0.18 to 1.75)

b.i.d. = twice a day; CI = confidence interval; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RCTs = randomized controlled trials; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day; vs = versus.

[a] Median (min, max); (min, max) was not reported for single study.

[b] Bold indicates statistically significant difference.

b) Clinical Worsening

Ten RCTs reported clinical worsening as an outcome, for which there were 10 pairwise comparisons including eight active treatments (ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg) compared with placebo, and two dose comparisons of ambrisentan (10 mg versus 5 mg) and riociguat (max 2.5 mg versus max 1.5 mg). The patient populations in the EARLY (bosentan),[32] PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] and SERAPHIN (macitentan)[35] studies consisted of naive and experienced subpopulations, while only naive patients were included in other studies. The EARLY study had data for the total population only.

Direct Pairwise Meta-analyses:

Among eight active treatments, ambrisentan 5 mg, bosentan 125 mg, macitentan 10 mg (total population), riociguat max 2.5 mg (total population), and tadalafil 40 mg (total population) all showed statistically significant reductions in clinical worsening compared with placebo (Table 20). Other treatments, including ambrisentan 10 mg, riociguat max 1.5 mg (total population), and sildenafil 20 mg, showed no statistically significant differences compared with placebo because of wide confidence intervals. The relative risks of all eight active treatments compared with placebo ranged from 0.19 (for riociguat max 2.5 mg) to 0.68 (for macitentan 10 mg). For bosentan, the pooled result of four studies (BREATHE-1,[21] Channick,[23] EARLY,[32] STRIDE-2[29])

favoured bosentan with moderate statistical heterogeneity (RR = 0.39; 95% CI, 0.16 to 0.92; I^2 = 50.7%). When the STRIDE-2 study, which had an open-label bosentan group, was excluded, statistical heterogeneity was abolished (RR = 0.26; 95% CI, 0.13 to 0.55; I^2 = 0%).

In naive patient populations, macitentan 10 mg showed statistically significant differences compared with placebo (RR = 0.59, 95% CI 0.40 to 0.86), while riociguat max 2.5 mg (RR = 0.27; 95% CI, 0.05 to 1.43) and tadalafil 40 mg (RR = 0.25; 95% CI, 0.06 to 1.10) did not. The pooled result of bosentan studies (excluding EARLY) for the naive population did not significantly favour bosentan with moderate statistical heterogeneity (RR = 0.46; 95% CI, 0.16 to 1.32; I^2 = 55.1%). When the STRIDE-2 study was excluded, statistical heterogeneity was abolished and a statistically significant difference between bosentan and placebo was observed (RR = 0.29; 95% CI, 0.11 to 0.72; I^2 = 0%).

There were significant differences in clinical worsening between doses of ambrisentan (10 mg versus 5 mg: RR = 1.00; 95% CI, 0.21 to 4.78) or riociguat (max 2.5 mg versus max 1.5 mg: RR = 0.37; 95% CI, 0.06 to 2.18).

Table 20: Meta-analysis Results for Clinical Worsening of PAH Treatments Compared With Placebo

Treatment	Background	No. of patients	Het (I^2)	Placebo Effects[a]	RR (95% CI),[b] Random
Ambrisentan oral 5 mg q.d.	Naive	262[18]	0%	0.16 (0.09, 0.22)	**0.32 (0.13 to 0.78)**
Ambrisentan oral 10 mg q.d.	Naive	134[18]	NA	0.16 (0.09, 0.22)	0.50 (0.13 to 1.92)
Bosentan oral 125 mg b.i.d.	Total	482[21,23,29,32]	50.7%	0.18 (0.14, 0.27)	**0.39 (0.16 to 0.92)**
	Naive	297[21,23,29]	55.1%	0.20 (0.16, 0.27)	0.46 (0.16 to 1.32)
Macitentan oral 10 mg q.d.	Total	492[35]	NA	0.46	**0.68 (0.54 to 0.85)**
	Naive	184[35]	NA	0.50	**0.59 (0.40 to 0.86)**
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	0.06	0.50 (0.11 to 2.29)
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	0.06	**0.19 (0.05 to 0.69)**
	Naive	189[33]	NA	0.06	0.27 (0.05 to 1.43)
Sildenafil oral 20 mg t.i.d.	Naive	139[30]	NA	0.10	0.43 (0.12 to 1.61)
Tadalafil oral 40 mg q.d.	Total	161[34]	NA	0.16	**0.32 (0.11 to 0.94)**
	Naive	74[34]	NA	0.22	0.25 (0.06 to 1.10)

b.i.d. = twice a day; CI = confidence interval; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RCTs = randomized controlled trials; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day; vs = versus.
[a] Median (min, max); (min, max) was not reported for single study.
[b] Bold indicates statistically significant difference.

Network Meta-analyses:
The evidence networks for clinical worsening of total populations and naive populations with the indicated number of RCTs available for each pairwise comparison are shown in Figure 1 and Figure 2, respectively. Of the 19 studies, 10 had data of clinical worsening of total populations and nine had data for naive populations.

Figure 1: Evidence Network for Clinical Worsening of Total Populations

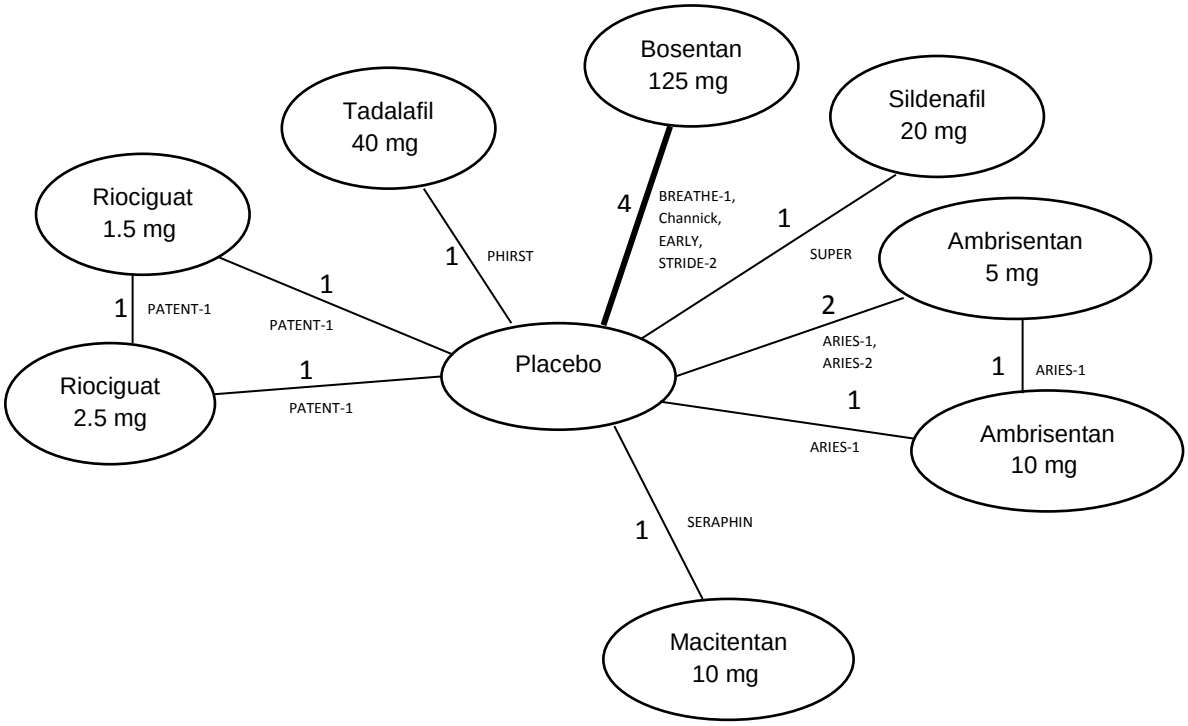
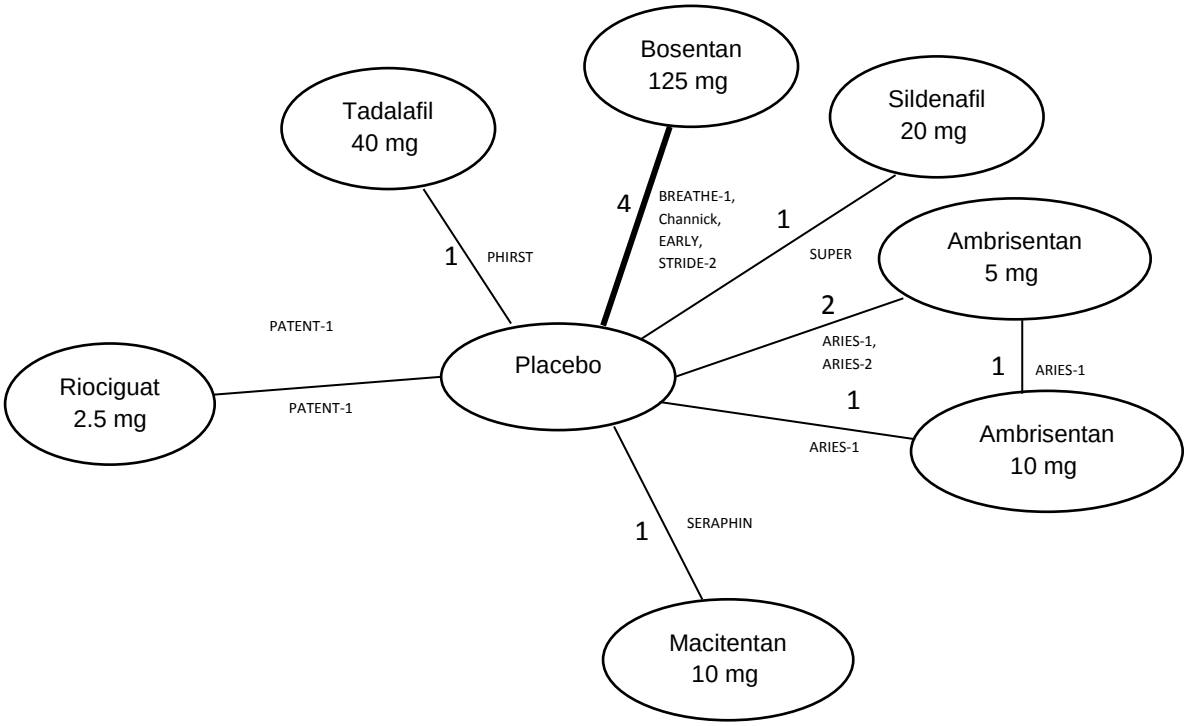
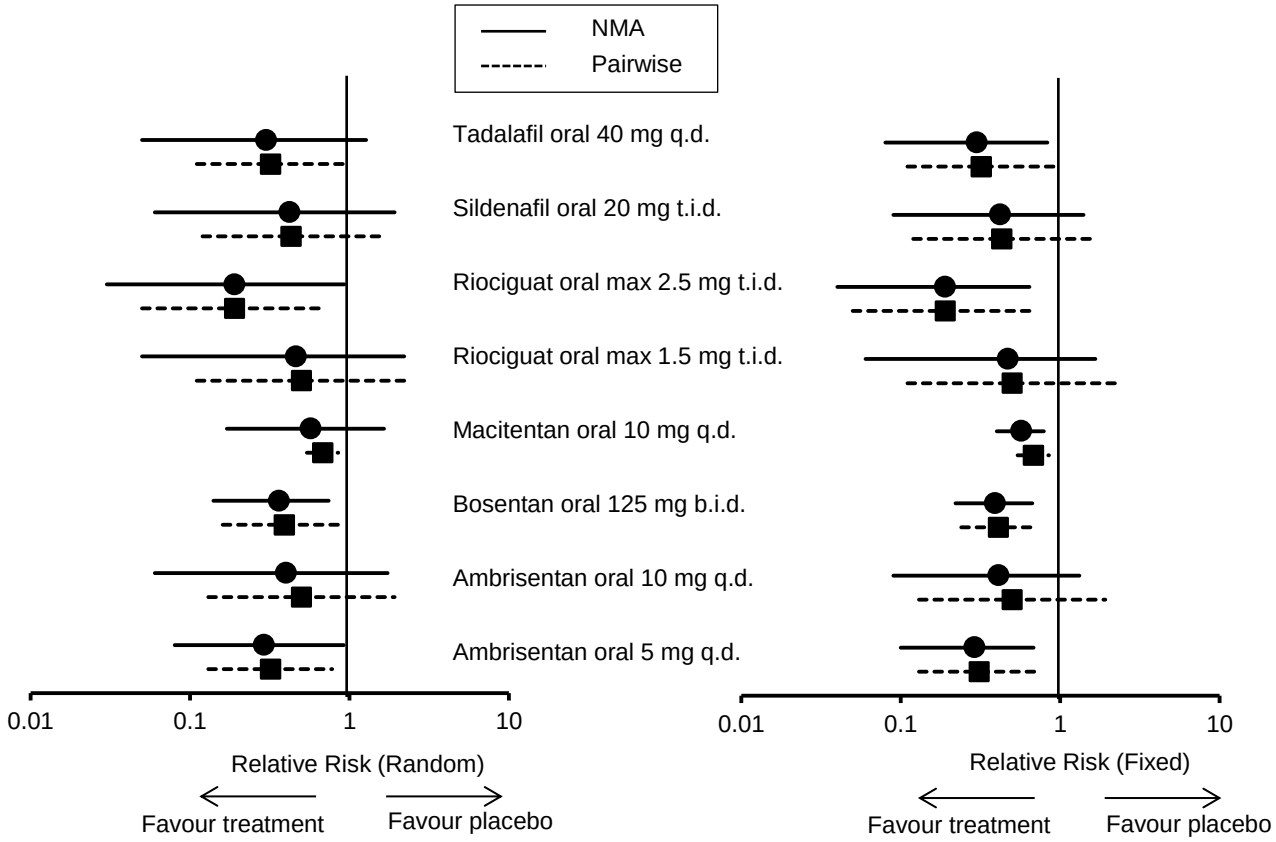


Figure 2: Evidence Network for Clinical Worsening of Naive Populations



Base case: Summaries of results comparing pairwise meta-analysis and NMA (both random and fixed effect models) for clinical worsening are presented in Table 176 for total populations and in Table 177 for naive populations in APPENDIX 11. Based on qualitative assessment, the results of direct pairwise estimates and NMA estimates are similar in both magnitude and direction.

Figure 3: Clinical Worsening for Different Treatment Strategies Compared With Placebo for Total Populations

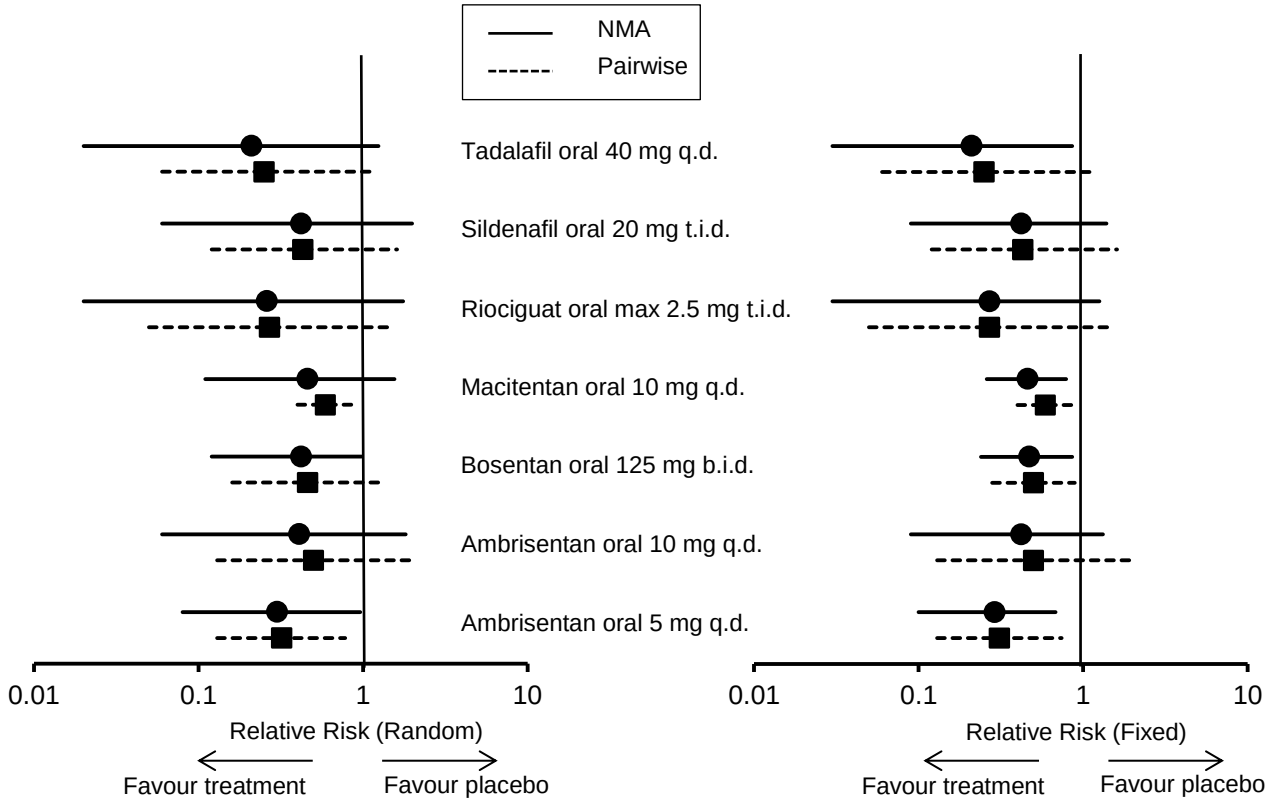


b.i.d. = twice a day; NMA = network meta-analysis; q.d. = once a day; t.i.d. = three times a day.

Figure 3 and Figure 4 illustrate the NMA results for the effect of all treatments relative to a common comparator (placebo) for total populations and naive populations, respectively. Table 198 to Table **201** in APPENDIX 12 present full NMA results, comparing among all available treatment strategies for total populations and naive populations using both random and fixed effects models.

In the total populations, the NMA results showed that macitentan and riociguat had no statistically significant differences compared with other treatments due to overlapping of credible intervals. However, all treatments were numerically favoured in the reduction of clinical worsening compared with placebo (Figure 3). The credible intervals were wider with the random effects model than with the fixed effects model. As a result, statistically significant difference was reached only for riociguat max 2.5 mg three times daily, bosentan 125 mg twice daily, and ambrisentan 5 mg once daily, from both random and fixed effects models. The relative risk for riociguat max 2.5 mg three times daily was 0.19, while those of other treatments ranged from 0.29 (ambrisentan 5 mg once daily) to 0.57 (macitentan 10 mg once daily).

Figure 4: Clinical Worsening for Different Treatment Strategies Compared With Placebo for Naive Populations



b.i.d. = twice a day; NMA = network meta-analysis; q.d. = once a day; t.i.d. = three times a day.

In the naive populations, macitentan and riociguat also showed no significant differences compared with other treatments. Likewise, all treatments were numerically favoured in the reduction of clinical worsening compared with placebo (Figure 4). However, statistical significance was reached only for bosentan 125 mg twice daily and ambrisentan 5 mg once daily in both the random and fixed effects models. Treatment effects ranged from 0.21 (tadalafil 40 mg) to 0.46 (macitentan 10 mg once daily). Due to overlapping of credible intervals, there were no statistically significant differences between treatments.

Sensitivity analyses: Sensitivity analysis was performed by excluding SERAPHIN, a macitentan study in which clinical worsening was evaluated up to the end of treatment (median follow-up, 115 weeks). Excluding macitentan from the analysis did not affect the effect sizes of other treatments in both random and fixed effects models for total populations or for naive populations (Table 178 and Table 179 in APPENDIX 11; Table 202 to Table **205** in APPENDIX 12). Sensitivity analysis of clinical worsening excluding the study with a different outcome definition — i.e., Channick et al. (2001)[23] — did not show any changes in the magnitude and direction of the effect sizes of all treatments (data not shown).

Sensitivity analyses of clinical worsening for treatments compared with placebo, using binomial models adjusted for baseline FC and baseline PAH etiology, revealed no marked change in the magnitude and direction of the relative treatment effect from the results of the unadjusted model for the reference case, therefore indicating the robustness of the reference case results. A comparison of base-case results of treatments against placebo to results using adjusted models is presented in Table 180 and Table 181 in APPENDIX 11.

c) Functional Class Improvement

Thirteen RCTs reported FC improvement as an outcome, for which there were 12 pairwise comparisons including 10 active treatments (ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil) compared with placebo, and two dose comparisons of ambrisentan (10 mg versus 5 mg) and riociguat (max 2.5 mg versus max 1.5 mg). The patient populations in the PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] and SERAPHIN (macitentan)[35] studies consisted of naive and experienced subpopulations, while only naive patients were in populations of other studies. Data of naive populations were available for riociguat max 2.5 mg and tadalafil 40 mg, but not for macitentan 10 mg.

Direct Pairwise Meta-analyses:

Macitentan showed statistically significant improvement in FC compared with placebo for the total population (RR = 1.66; 95% CI, 1.12 to 2.47), but data for the naive population were not available. Riociguat (at both doses: max 1.5 mg and max 2.5 mg) and tadalafil 40 mg did not show statistically significant improvement in FC compared with placebo for total populations (Table 21).

For other naive populations, ambrisentan (at both 5 mg and 10 mg doses), bosentan 125 mg, riociguat max 2.5 mg, and treprostinil did not show statistically significant improvement in FC compared with placebo, while the results significantly favoured sildenafil (RR = 3.91; 95% CI, 1.55 to 9.88) and epoprostenol (RR = 10.18; 95% CI, 1.91 to 54.24; I^2 = 59.0%). Among epoprostenol studies, the study by Badesch et al.[19] included patients who had PH secondary to the scleroderma spectrum of disease, while the other two studies (Barst et al.[20] and Rubin et al.[27]) included patients with IPAH. The meta-analysis results of Badesch et al.[19] and of Barst et al.[20] and Rubin et al.[27] remained as significantly favouring epoprostenol (Table 21).

There were no differences in FC improvement between doses of ambrisentan (10 mg versus 5 mg: RR = 1.05; 95% CI, 0.62 to 1.79) or riociguat (max 2.5 mg versus max 1.5 mg: RR = 0.88; 95% CI, 0.53 to 1.45).

Table 21: Meta-analysis Results for FC Improvement of PAH Treatments Compared With Placebo					
Treatment	**Bkg**	**No. of Patients**	**Het (I^2)**	**Placebo Effects[a]**	**RR (95% CI)[b], Random**
Ambrisentan oral 5 mg q.d.	Naive	262[18]	0%	0.21 (0.17, 0.24)	1.06 (0.66 to 1.69)
Ambrisentan oral 10 mg q.d.	Naive	134[18]	NA	0.21 (0.17, 0.24)	1.25 (0.71 to 2.20)
Bosentan oral 125 mg b.i.d.	Naive	229[21-23]	18.6%	0.12 (0.09, 0.3)	1.81 (0.98 to 3.34)
Macitentan oral 10 mg q.d.	Total	492[35]	NA	0.13	**1.66 (1.12 to 2.47)**
Riociguat oral max 1.5 mg t.i.d.	Total	188[33]	NA	0.14	1.65 (0.89 to 3.06)
Riociguat oral max 2.5 mg t.i.d.	Total	379[33]	NA	0.14	1.45 (0.89 to 2.37)
	Naive	189[33]	NA	0.15	0.97 (0.47 to 1.97)
Sildenafil oral 20 mg t.i.d.	Naive	138[30]	NA	0.07	**3.91 (1.55 to 9.88)**
Tadalafil oral 40 mg q.d.	Total	161[34]	NA	0.21	1.10 (0.61 to 1.98)
	Naive	74[34]	NA	0.21	**2.33 (1.01 to 5.41)**
Epoprostenol i.v.	Naive	211[19,20,27]	59.0%	0.03 (0, 0.22)	**10.18 (1.91 to 54.24)**
Badesch	Naive	111[19]	NA		**42.25 (2.62 to 680.61)**
Barst & Rubin	Naive	100[20,27]	46.8%		**6.31 (1.44 to 27.65)**
Treprostinil s.c. or i.v.	Naive	44[31]	NA	0.21	2.33 (0.80 to 6.77)

b.i.d. = twice a day; Bkg = background; CI = confidence interval; FC = functional class; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; q.d. = once a day; PAH = pulmonary arterial hypertension; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day.

[a] Median (min, max); (min, max) was not reported for single study.

[b] Bold indicates statistically significant difference.

Network Meta-analyses:

The evidence networks for FC improvement of total populations and naive populations with the indicated number of RCTs available for each pairwise comparison are shown in Figure 5 and Figure 6, respectively. Of the 19 studies, 13 included data of FC improvement of total populations and 12 included data for naive populations.

Figure 5: Evidence Network for Functional Class Improvement of Total Populations

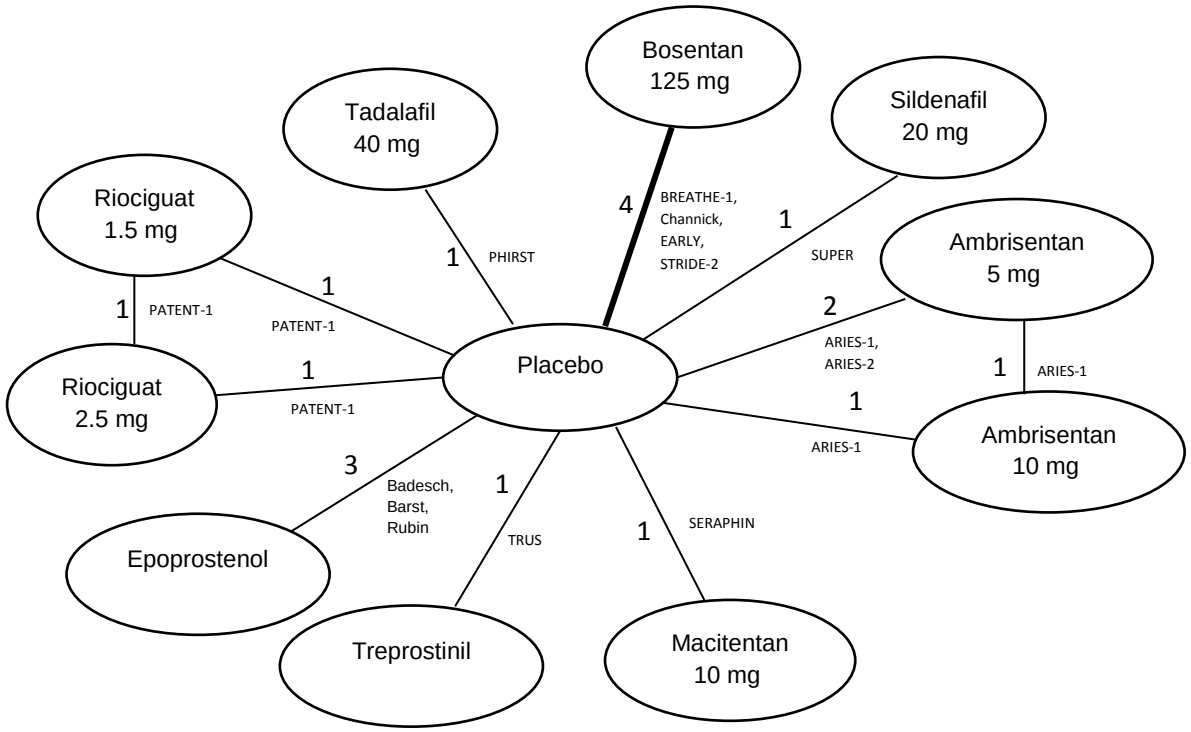
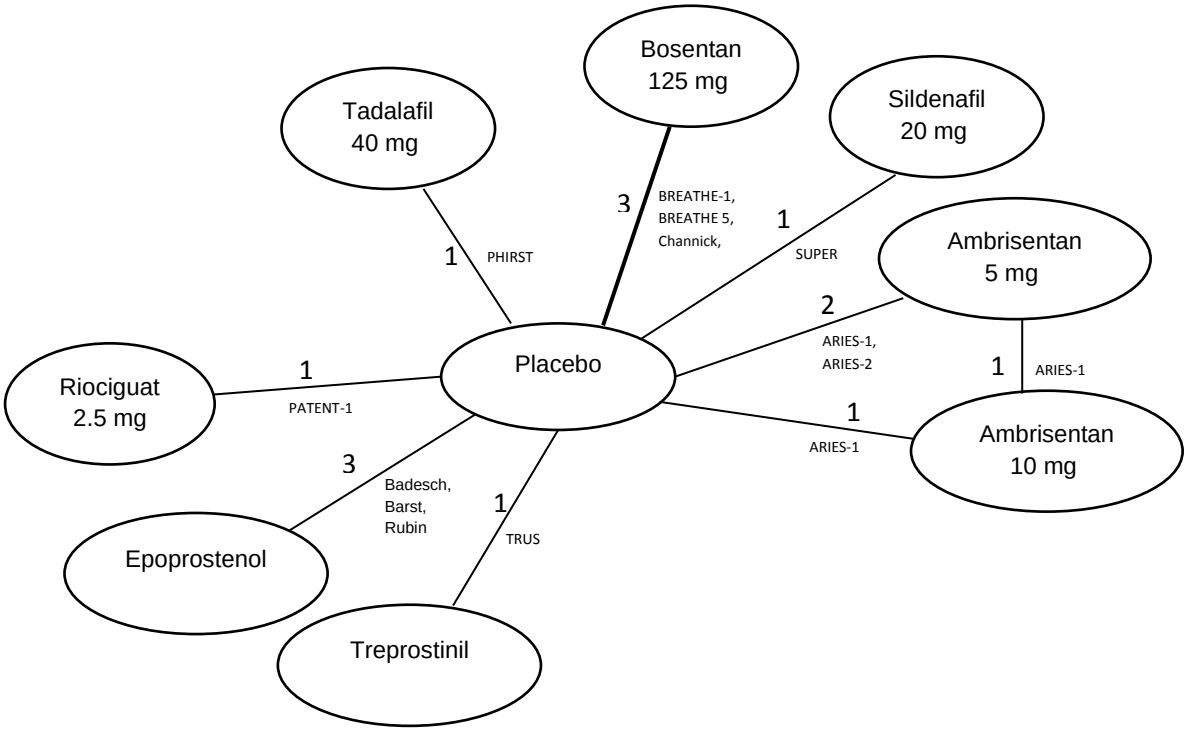


Figure 6: Evidence Network for Functional Class Improvement of Naive Populations



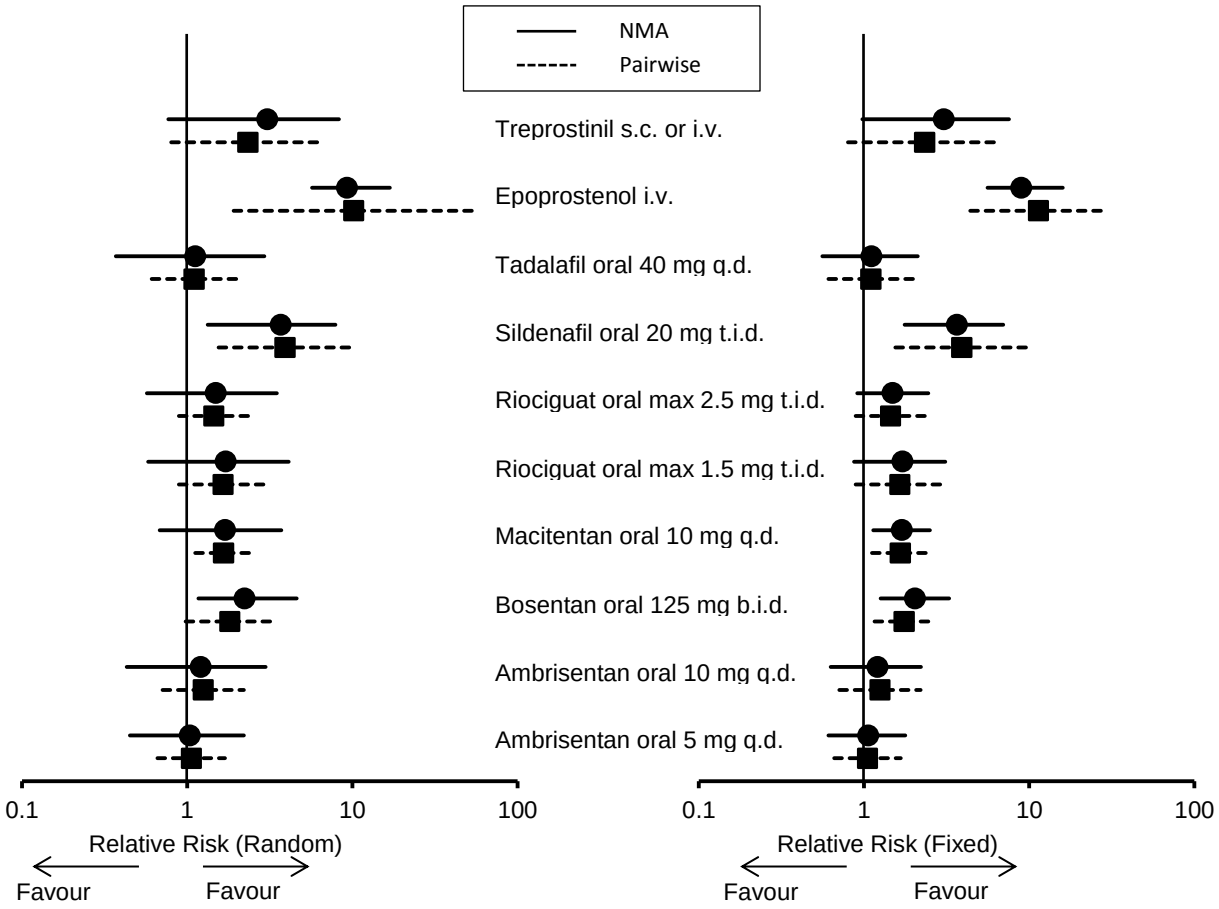
Base Case: Summaries of results comparing pairwise meta-analysis and NMA (both random and fixed effect models) for FC improvement are presented in Table 182 for total populations and in Table 183 for naive populations in APPENDIX 11. Based on qualitative assessment, the results of direct pairwise estimates and NMA estimates are similar in both magnitude and direction.

Figure 7 and Figure 8 illustrate the NMA results for the effect of all treatments relative to a common comparator (placebo) for total populations and naive populations, respectively.

Table 206 to Table **209** in APPENDIX 12 present full NMA results comparing among all available treatment strategies for total populations and naive populations, using both random and fixed effects models.

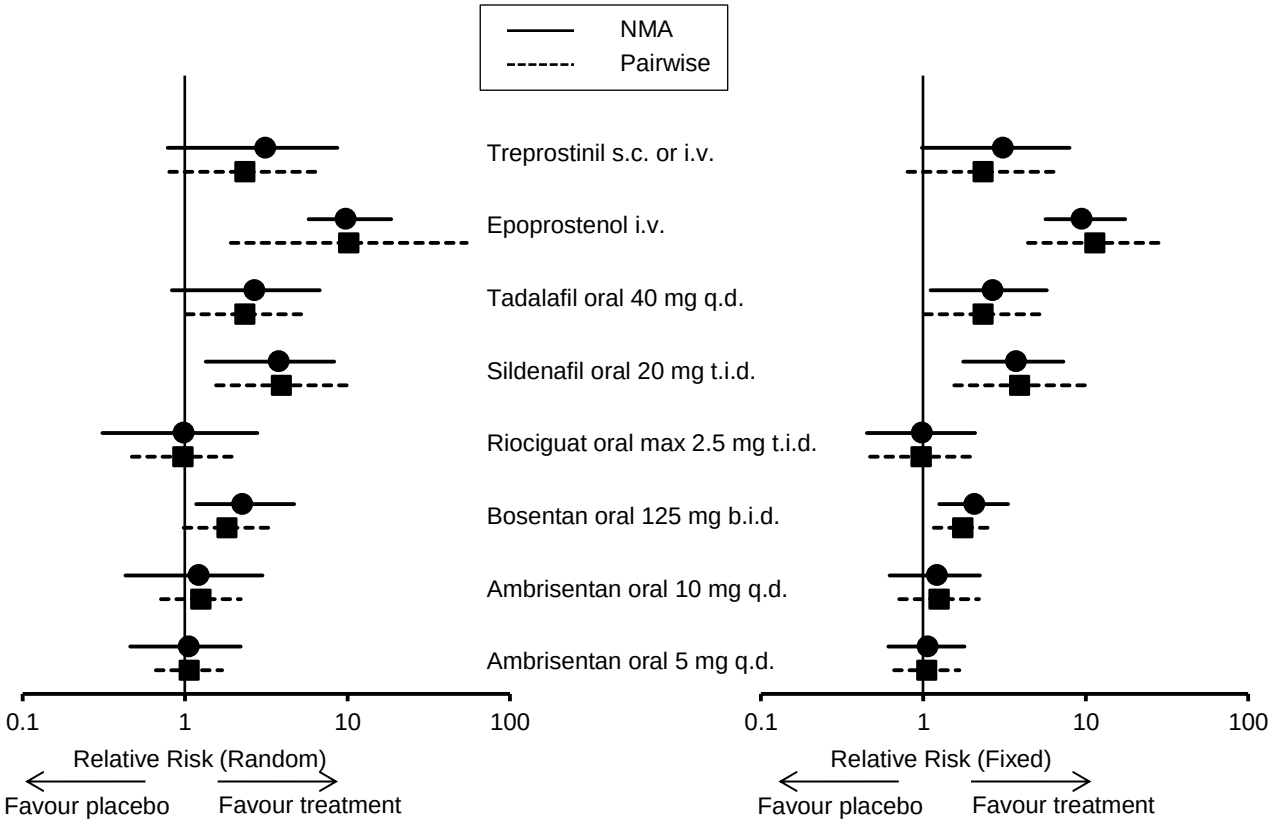
In the total populations, the NMA results showed that epoprostenol was associated with statistically better FC improvement compared with all other treatments including macitentan and riociguat. There were no significant differences between macitentan or riociguat and the remaining treatments in the random effects model. Compared with placebo, bosentan 125 mg twice daily, macitentan 10 mg once daily, riociguat max 1.5 mg three times daily, riociguat max 2.5 mg three times daily, sildenafil 20 mg three times daily, epoprostenol i.v., and treprostinil s.c. or i.v. were numerically favoured in the FC improvement (Figure 7). The credible intervals were wider with a random effects model than with the fixed effects model. Of all treatments, epoprostenol had highest activity (RR = 9.31), followed by sildenafil (RR = 3.69) and treprostinil (RR = 3.06). The relative risks of bosentan, macitentan, and riociguat were relatively similar and ranged from 1.49 to 2.23. Ambrisentan (both doses) and tadalafil had the lowest activity (RR from 1.04 to 1.21). The observation was supported by the full NMA results, shown in Table 206 and Table 207 in APPENDIX 12**,** wherein epoprostenol was ranked first, followed by sildenafil, which was significantly better than riociguat max 2.5 mg, ambrisentan 5 mg and 10 mg, and tadalafil in the fixed effects model.

Figure 7: Functional Class Improvement for Different Treatment Strategies Compared With Placebo for Total Populations



b.i.d. = twice a day; i.v. = intravenous; NMA = network meta-analysis; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.

Figure 8: Functional Class Improvement for Different Treatment Strategies Compared With Placebo for Naive Population



b.i.d. = twice a day; i.v. = intravenous; NMA = network meta-analysis; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.

Similar observations were obtained for naive populations, where epoprostenol had highest activity (RR = 9.72) compared with other treatments, including riociguat max 2.5 mg (Figure 8; Table 208 and Table 209 in APPENDIX 12). Treatment with the next level of activity included sildenafil (RR = 3.76) and treprostinil (RR = 3.11), followed by bosentan (RR = 2.24) and tadalafil (RR = 2.67). Data for macitentan and riociguat max 1.5 mg were not available for naive populations. Riociguat max 2.5 mg (RR = 0.98) and ambrisentan (RR = 1.05 for 5 mg; RR = 1.21 for 10 mg) showed no difference in FC improvement compared with placebo.

Sensitivity Analyses: Sensitivity analysis was performed by excluding SERAPHIN, a macitentan study in which FC improvement was evaluated up to the end of six months. Excluding macitentan from the analysis did not affect the effect sizes of other treatments in both random and fixed effects models for total populations (Table 184 in APPENDIX 11; Table 210 and Table 211 in APPENDIX 12). Sensitivity analyses of FC improvement for treatments compared with placebo, using binomial models adjusted for baseline FC and baseline PAH etiology, revealed no marked change in the magnitude and direction of the relative treatment effect from the results of the unadjusted model for the reference case, therefore indicating the robustness of the reference case results. A comparison of base-case results of treatments against placebo to results using adjusted models is presented in Table 186 in APPENDIX 11.

d) Functional Class Worsening

Fourteen RCTs reported FC worsening as an outcome, for which there were 12 pairwise comparisons, including 10 active treatments (ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil) compared with placebo, and two dose comparisons of ambrisentan (10 mg versus 5 mg) and riociguat (max 2.5 mg versus max 1.5 mg). The patient populations in the PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] SERAPHIN (macitentan)[35] and EARLY (bosentan)[32] studies consisted of naive and experienced subpopulations, while only naive patients were included in other studies. The EARLY[32] study reported data for total population only. Data for naive populations were available for riociguat max 2.5 mg and tadalafil 40 mg, but not for macitentan 10 mg.

Direct Pairwise Meta-analyses:

All treatments showed numerical reduction in FC worsening compared with placebo (Table 22). Statistically significant differences were observed in ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg (total), macitentan 10 mg (total), riociguat max 2.5 mg (total and naive), and one study of epoprostenol by Badesch et al.[19] The relative risks of other treatments including bosentan 125 mg (naive), riociguat max 1.5 mg (total), sildenafil 20 mg, tadalafil 40 mg (total and naive), and treprostinil had wider confidence intervals. The significant difference between bosentan and placebo observed in the total population was mainly contributed by the EARLY study (RR = 0.25; 95% CI, 0.07 to 0.85),[32] which was excluded in the analysis of naive populations. No difference in FC worsening between epoprostenol and placebo was observed in the study by Barst et al.[20]

There were no significant differences in FC worsening between doses of ambrisentan (10 mg versus 5 mg: RR = 3.00; 95% CI, 0.32 to 28.12) or riociguat (max 2.5 mg versus max 1.5 mg: RR = 0.45; 95% CI, 0.16 to 1.29).

Table 22: Meta-analysis Results for FC Worsening of PAH Treatments Compared With Placebo					
Treatment	**Background**	**No. of Patients**	**Het (I^2)**	**Placebo Effects[a]**	**RR (95% CI)[b], Random**
Ambrisentan oral 5 mg q.d.	Naive	262[18]	0%	0.17 (0.16, 0.19)	**0.14 (0.04 to 0.45)**
Ambrisentan oral 10 mg q.d.	Naive	134[18]	NA	0.17 (0.16, 0.19)	**0.27 (0.08 to 0.93)**
Bosentan oral 125 mg b.i.d.	Total	536[21-23,29,32]	0%	0.13 (0.06, 0.18)	**0.41 (0.21 to 0.80)**
	Naive	351[21-23,29]	0%	0.09 (0.06, 0.18)	0.51 (0.22 to 1.14)
Macitentan oral 10 mg q.d.	Total	491[35]	NA	0.21	**0.33 (0.20 to 0.55)**
Riociguat oral max 1.5 mg t.i.d.	Total	188[33]	NA	0.14	0.55 (0.21 to 1.42)
Riociguat oral max 2.5 mg t.i.d.	Total	379[33]	NA	0.14	**0.25 (0.11 to 0.53)**
	Naive	189[33]	NA	0.17	**0.24 (0.09 to 0.67)**
Sildenafil oral 20 mg t.i.d.	Naive	138[30]	NA	0.10	0.29 (0.06 to 1.37)
Tadalafil oral 40 mg q.d.	Total	161[34]	NA	0.16	0.64 (0.28 to 1.46)
	Naive	74[34]	NA	0.22	0.50 (0.16 to 1.52)
Epoprostenol i.v.	Naive	192[19,20]	82.4%	0.16 (0.08, 0.24)	No pooling
Badesch	Naive	111[19]	NA		**0.15 (0.04 to 0.64)**
Barst	Naive	81[20]	NA		1.63 (0.42 to 6.36)
Treprostinil s.c. or i.v.	Naive	44[31]	NA	0.14	0.10 (0.00 to 1.89)

b.i.d. = twice a day; CI = confidence interval; FC = functional class; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day.

[a] Median (min, max); (min, max) was not reported for single study.

[b] Bold indicates statistically significant difference.

Network Meta-analyses:

The evidence networks for FC worsening of total populations and naive populations with the indicated number of RCTs available for each pairwise comparison are shown in Figure 9 and Figure 10, respectively. Of the 19 studies, 14 included data of FC worsening of total populations and 12 included data for naive populations.

Figure 9: Evidence Network for Functional Class Worsening of Total Populations

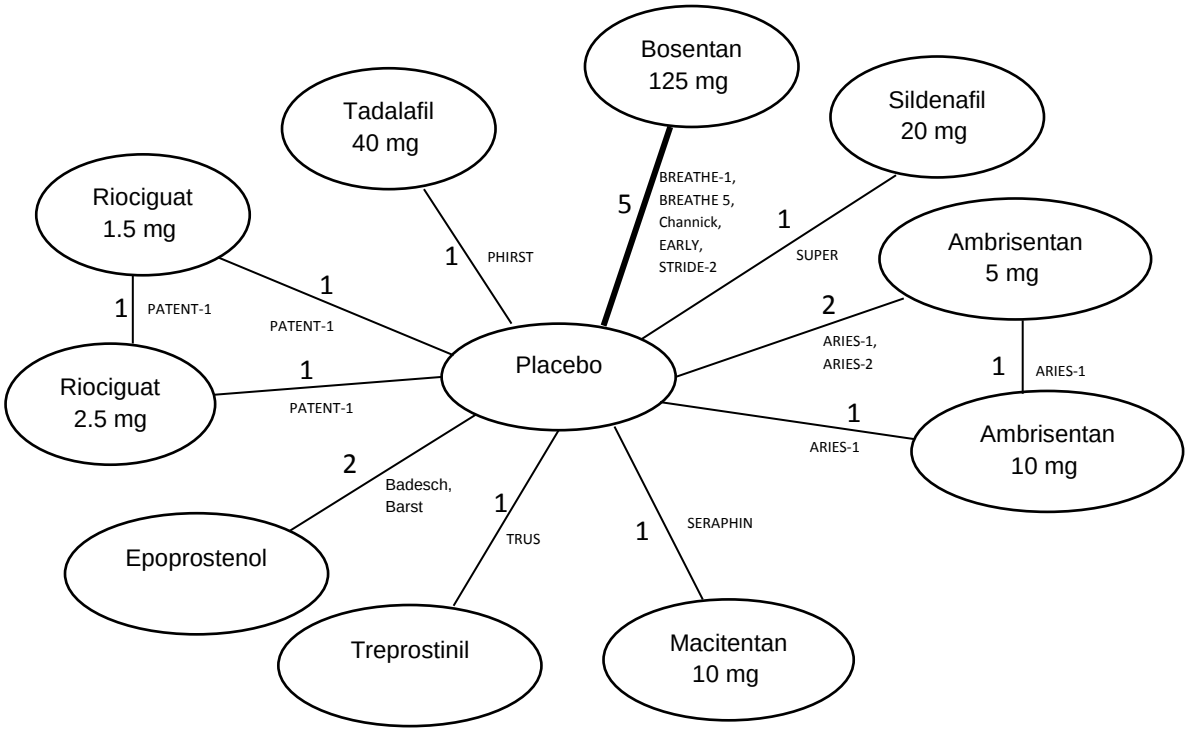
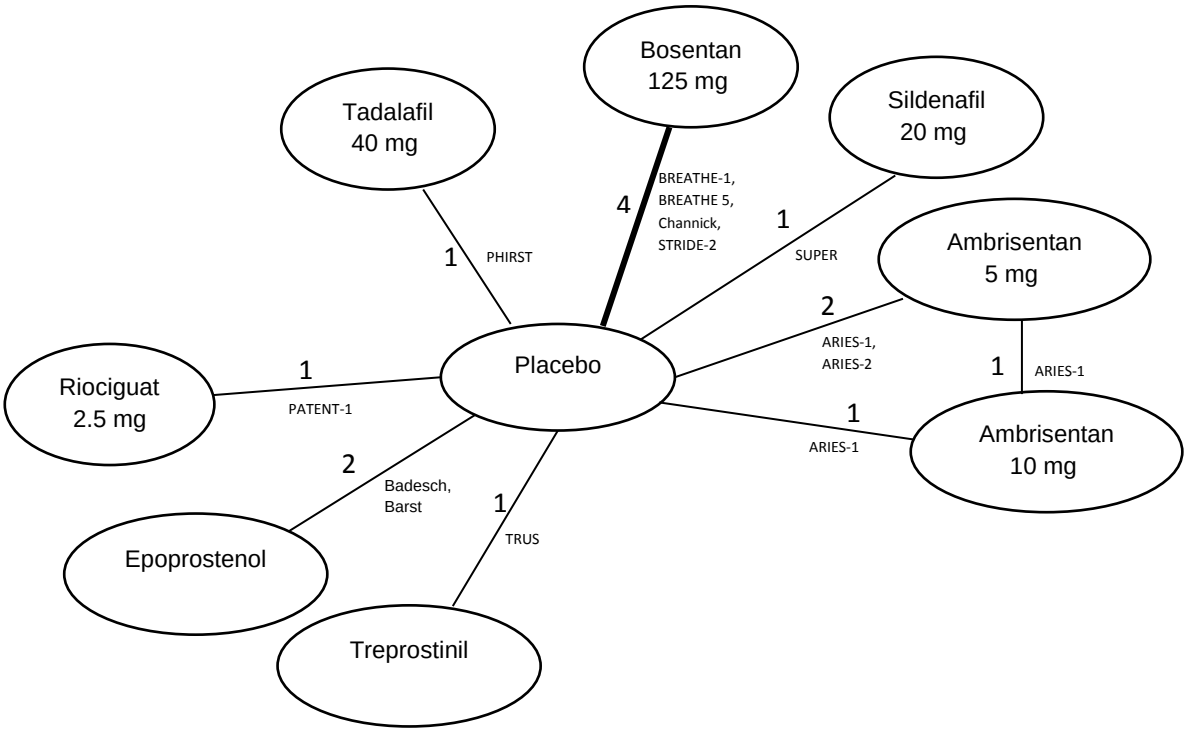


Figure 10: Evidence Network for Functional Class Worsening of Naive Populations

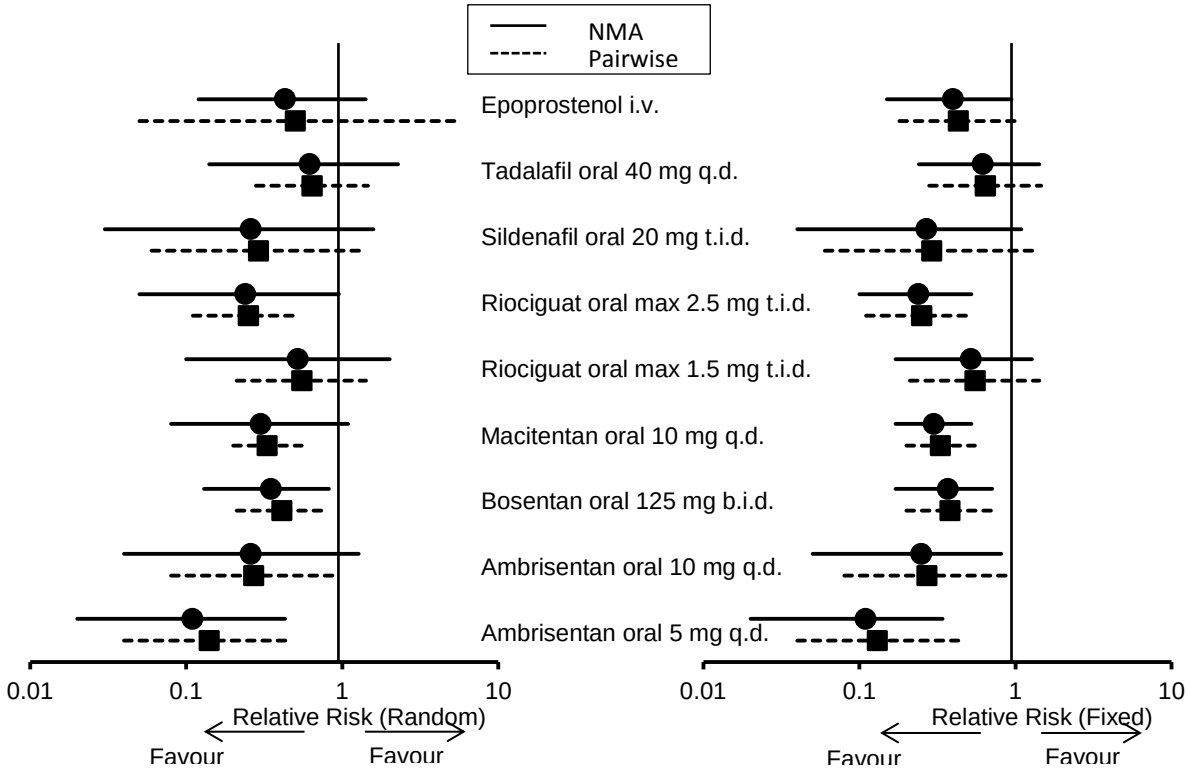


Base case: Summaries of results comparing pairwise meta-analysis and NMA (both random and fixed effect models) for FC worsening are presented in Table 187 for total populations and in Table 188 for naive populations in APPENDIX 11. Based on qualitative assessment, the results of direct pairwise estimates and NMA estimates are consistent; that is, they are similar in both magnitude and direction.

Figure 11 and Figure 12 illustrate the NMA results for the effect of all treatments relative to a common comparator (placebo) for total populations and naive populations, respectively. Table 212 to Table 215 in APPENDIX 12 present full NMA results comparing among all available treatment strategies for total populations and naive populations, using both random and fixed effects models.

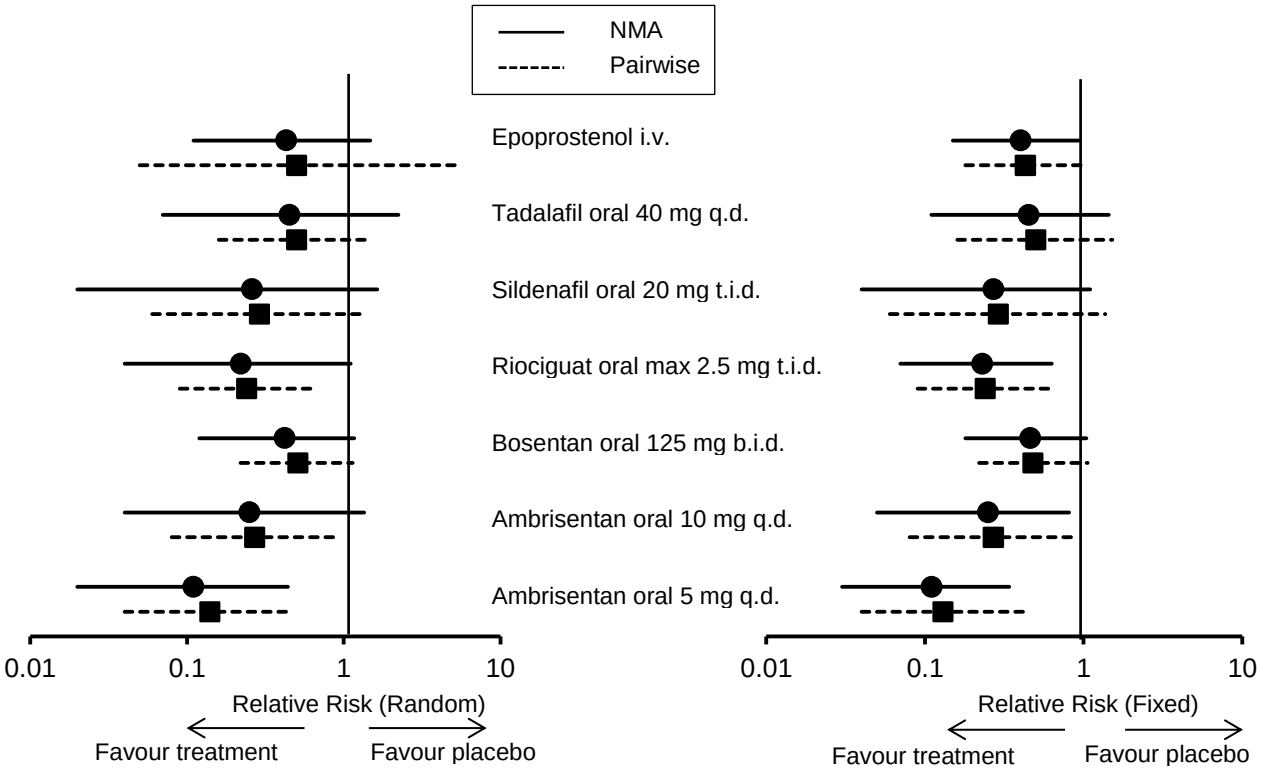
In the total populations, the NMA results showed that macitentan and riociguat had no statistically significant differences compared with other treatments due to overlapping of credible intervals (Table 212 and Table 213 in APPENDIX 12). However, all treatments were numerically favoured in the reduction of FC worsening compared with placebo (Figure 11). The credible intervals were wider with a random effects model than with the fixed effects model. As a result, statistically significant difference was reached only for riociguat max 2.5 mg three times daily, bosentan 125 mg twice daily, and ambrisentan 5 mg once daily from both random and fixed effects models. The relative risks ranged from 0.11 (ambrisentan 5 mg once daily) to 0.62 (tadalafil 40 mg once daily).

Figure 11: Functional Class Worsening for Different Treatment Strategies Compared With Placebo for Total Populations



b.i.d. = twice a day; i.v. = intravenous; NMA = network meta-analysis; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.

Figure 12: Functional Class Worsening for Different Treatment Strategies Compared With Placebo for Naive Populations



b.i.d. = twice a day; i.v. = intravenous; NMA = network meta-analysis; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.

In the naive populations, a similar observation was obtained. Due to the overlap of credible intervals, there were no statistically significant differences between riociguat max 2.5 mg and other treatments (Table 214 and Table 215 in APPENDIX 12). Compared with placebo, the relative risks ranged from 0.11 (ambrisentan 5 mg q.d.) to 0.45 (tadalafil 40 mg q.d.). Data for macitentan and riociguat max 1.5 mg were not available for naive populations.

Sensitivity Analyses:
Sensitivity analysis was performed by excluding SERAPHIN, a macitentan study in which FC worsening was evaluated up to the end of six months. Excluding macitentan from the analysis did not affect the effect sizes of other treatments in both random and fixed effects models for total populations (Table 189 in APPENDIX 11; Table 216 and Table 217 in APPENDIX 12). Sensitivity analyses of FC worsening for treatments compared with placebo, using binomial models adjusted for baseline FC and baseline PAH etiology, revealed no marked change in the magnitude and direction of the relative treatment effect from the results of the unadjusted model for the reference case, therefore indicating the robustness of the reference case results. A comparison of base-case results of treatments against placebo to results using adjusted models is presented in Table 190 in APPENDIX 11.

e) Functional Class Unchanged

Only direct pairwise meta-analyses were performed for this outcome.

Twelve RCTs reported FC unchanged as an outcome, for which there were 12 pairwise comparisons including 10 active treatments (ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and treprostinil) compared with placebo, and two dose comparisons of ambrisentan (10 mg versus 5 mg) and riociguat (max 2.5 mg versus max 1.5 mg). The patient populations in the PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] and SERAPHIN (macitentan)[35] studies consisted of naive and experienced subpopulations, while only naive patients were included in other studies. Data for naive populations were available for riociguat max 2.5 mg and tadalafil 40 mg, but not for macitentan 10 mg.

Table 23 shows that the proportion of patients who maintained FC was statistically different between the placebo and ambrisentan 5 mg groups, placebo and bosentan groups, or placebo and epoprostenol groups. There were fewer patients in the bosentan and epoprostenol groupswhose FC was unchanged compared with the placebo groups, while the reverse was observed for ambrisentan 5 mg. Other treatments showed no statistically significant differences in FC unchanged compared with placebo.

There were no differences in FC unchanged between doses of ambrisentan (10 mg versus 5 mg: RR = 0.94; 95% CI, 0.74 to 1.18) or riociguat (max 2.5 mg versus max 1.5 mg: RR = 1.11; 95% CI, 0.92 to 1.33).

f) Six-Minute Walk Distance

Nineteen RCTs reported 6MWD as an outcome, for which there were 12 pairwise comparisons including 10 active treatments (ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and treprostinil) compared with placebo, and two dose comparisons of ambrisentan (10 mg versus 5 mg) and riociguat (max 2.5 mg versus max 1.5 mg). The patient populations in the PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] SERAPHIN (macitentan),[35] and EARLY (bosentan)[32] studies consisted of naive and experienced subpopulations, while only naive patients were included in other studies. The EARLY[32] study reported data for the total population only. Data for naive populations were available for riociguat max 1.5 mg, riociguat max 2.5 mg, tadalafil 40 mg, and macitentan 10 mg.

Direct Pairwise Meta-analyses:

All treatments showed numerical improvement in 6MWD compared with placebo (Table 24). The increase in 6MWD for active treatments compared with placebo ranged from 15.30 m to 71.30 m. Statistically significant differences between placebo and active treatments were reached in both total and naive populations, except the naive population of macitentan 10 mg. There was substantial statistical heterogeneity (I^2 = 85.8%) among four trials (McLaughlin,[25] Rubenfire,[26] Simonneau,[28] TRUST[31]) of treprostinil. When the study by Rubenfire et al.,[26] which studied the transition of epoprostenol to treprostinil, was excluded from the analysis, the statistical heterogeneity was markedly reduced, and the pooled results of the three trials remaining significantly favoured treprostinil (WMD = 34.52; 95% CI, 0.24 to 68.80; I^2 = 35.7%).

There were no differences in the change of 6MWD between doses of ambrisentan (10 mg versus 5 mg: WMD = 13.92; 95% CI, –6.36 to 34.20) or riociguat (max 2.5 mg versus max 1.5 mg: WMD = –1.00; 95% CI, –22.13 to 20.13).

Table 23: Meta-analysis Results for FC Unchanged of PAH Treatments Compared With Placebo					
Treatment	**Background**	**No. of Patients**	**Het (I^2)**	**Placebo Effects[a]**	**RR (95% CI)[b], Random**
Ambrisentan oral 5 mg q.d.	Naive	262[18]	0%	0.62 (0.60, 0.65)	**1.23 (1.05 to 1.45)**
Ambrisentan oral 10 mg q.d.	Naive	134[18]	NA	0.62 (0.60, 0.65)	1.10 (0.85 to 1.43)
Bosentan oral 125 mg b.i.d.	Naive	229[21-23]	0%	0.73 (0.64, 0.82)	**0.82 (0.67 to 0.99)**
Macitentan oral 10 mg q.d.	Total	491[35]	NA	0.66	1.07 (0.95 to 1.21)
Riociguat oral max 1.5 mg t.i.d.	Total	188[33]	NA	0.71	0.96 (0.78 to 1.17)
Riociguat oral max 2.5 mg t.i.d.	Total	379[33]	NA	0.71	1.06 (0.93 to 1.21)
	Naive	189[33]	NA	0.68	1.17 (0.97 to 1.41)
Sildenafil oral 20 mg t.i.d.	Naive	138[30]	NA	0.83	0.83 (0.69 to 1.01)
Tadalafil oral 40 mg q.d.	Total	161[34]	NA	0.63	1.06 (0.84 to 1.33)
	Naive	74[34]	NA	0.62	0.83 (0.55 to 1.23)
Epoprostenol i.v.	Naive	192[19,20]	0%	0.72 (0.68, 0.76)	**0.74 (0.60 to 0.93)**
Treprostinil s.c. or i.v.	Naive	44[31]	NA	0.64	0.78 (0.46 to 1.32)

b.i.d. = twice a day; CI = confidence interval; FC = functional class; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RCTs = randomized controlled trials; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day.

[a] Median (min, max); (min, max) was not reported for single study.

[b] Bold indicates statistically significant difference.

Table 24: Meta-analysis Results for 6MWD of PAH Treatments Compared With Placebo					
Treatment	**Bkg**	**No. of Patients**	**Het (I^2)**	**Placebo Effects[a]**	**WMD (95% CI)[b], Random**
Ambrisentan oral 5 mg q.d.	Naive	264[18]	49.6%	–8.95 (–10.1, –7.8)	**44.53 (16.23 to 72.84)**
Ambrisentan oral 10 mg q.d.	Naive	134[18]	NA	–8.95 (–10.1, –7.8)	**54.10 (29.48 to 78.72)**
Bosentan oral 125 mg b.i.d.	Total	536[21-23,29,32]	0%	–7.9 (–9.7, –6.0)	**30.70 (16.64 to 44.77)**
	Naive	351[21-23,29]	0%	–7.3 (–9.7, –6.0)	**38.17 (20.14 to 56.21)**
Macitentan oral 10 mg q.d.	Total	492[35]	NA	–9.4	**21.90 (5.58 to 38.22)**
	Naive	183[35]	NA	–12.2	15.30 (–15.10 to 45.70)
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	–6.0	**37.00 (12.38 to 61.62)**
	Naive	98[33]	NA	–6.0	**55.40 (20.76 to 90.04)**
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	–6.0	**36.00 (18.93 to 53.07)**
	Naive	189[33]	NA	–6.0	**38.00 (13.07 to 62.94)**
Sildenafil oral 20 mg t.i.d.	Naive	139[30]	NA	–3.7	**43.70 (25.81 to 61.59)**
Tadalafil oral 40 mg q.d.	Total	155[34]	NA	9.2	**31.90 (14.63 to 49.17)**
	Naive	72[34]	NA	–6.0	**44.40 (18.93 to 69.87)**
Epoprostenol i.v.	Naive	215[19,20,27]	23.3%	–15 (–36, 87)	**71.30 (33.35 to 109.25)**
Treprostinil s.c. or i.v.	Naive	561[25,26,28,31]	85.8%	–23.8 (–357, –6)	No pooling
Excluding Rubenfire et al.[26]	Naive	539[25,28,31]	35.7%	–22.0 (–25.5, –6)	**34.52 (0.24 to 68.80)**

6MWD = six-minute walk distance; b.i.d. = twice a day; bkg = background; CI = confidence interval; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RCTs = randomized controlled trials; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day; WMD = weighted mean difference.

[a] Median (min, max); (min, max) was not reported for single study.

[b] Bold indicates statistically significant difference.

Network Meta-analyses:

The evidence networks for 6MWD of total populations and naive populations with the indicated number of RCTs available for each pairwise comparison are shown in Figure 13 and Figure 14, respectively. All 19 studies had data for 6MWD of total populations and 18 had data for naive populations.

Figure 13: Evidence Network for Six-Minute Walk Distance of Total Populations

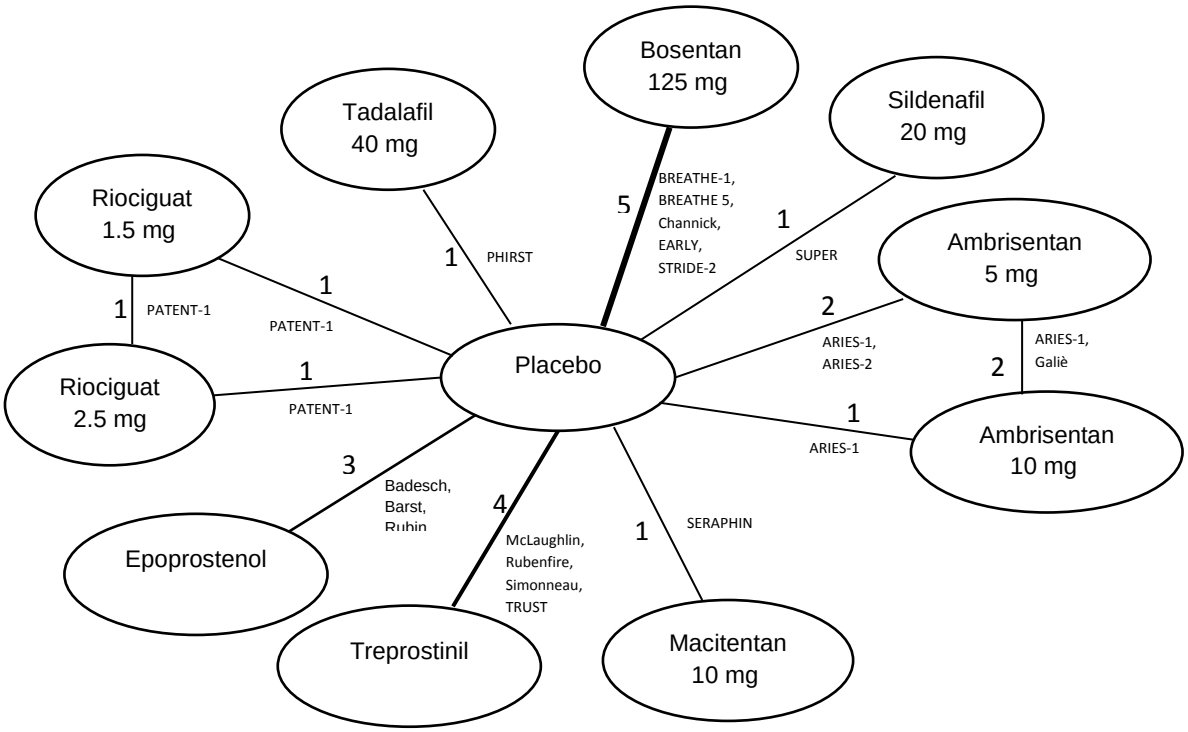
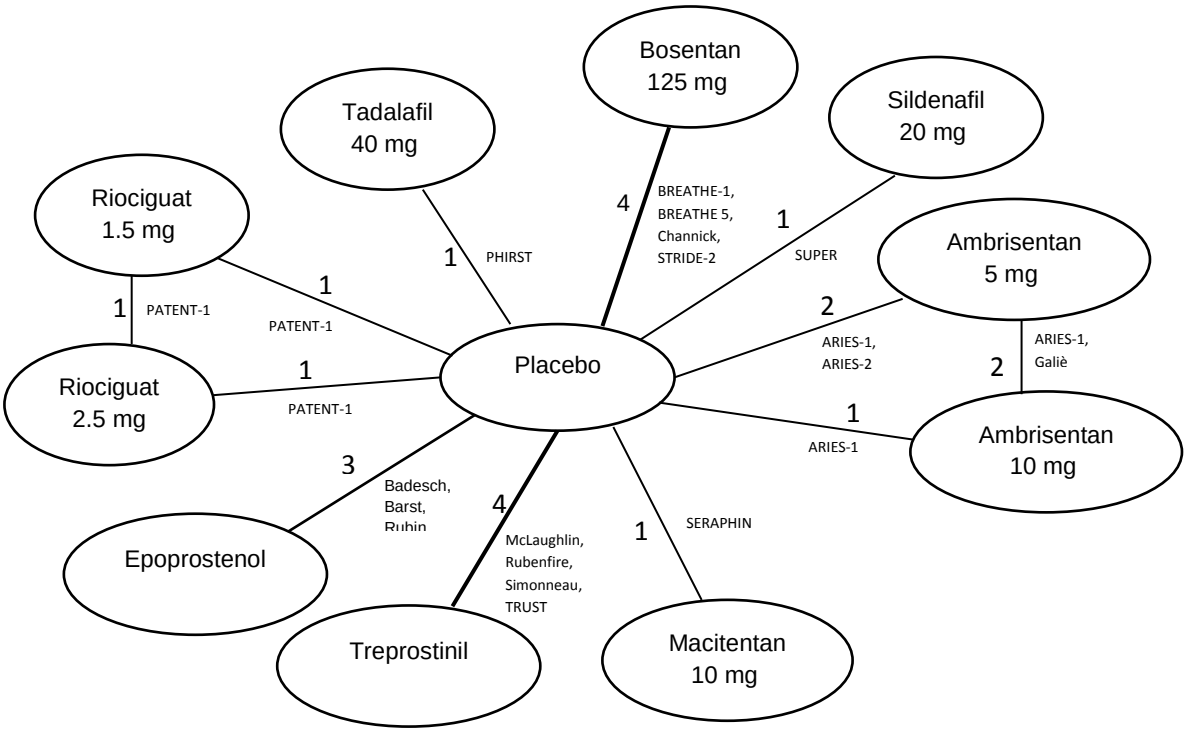


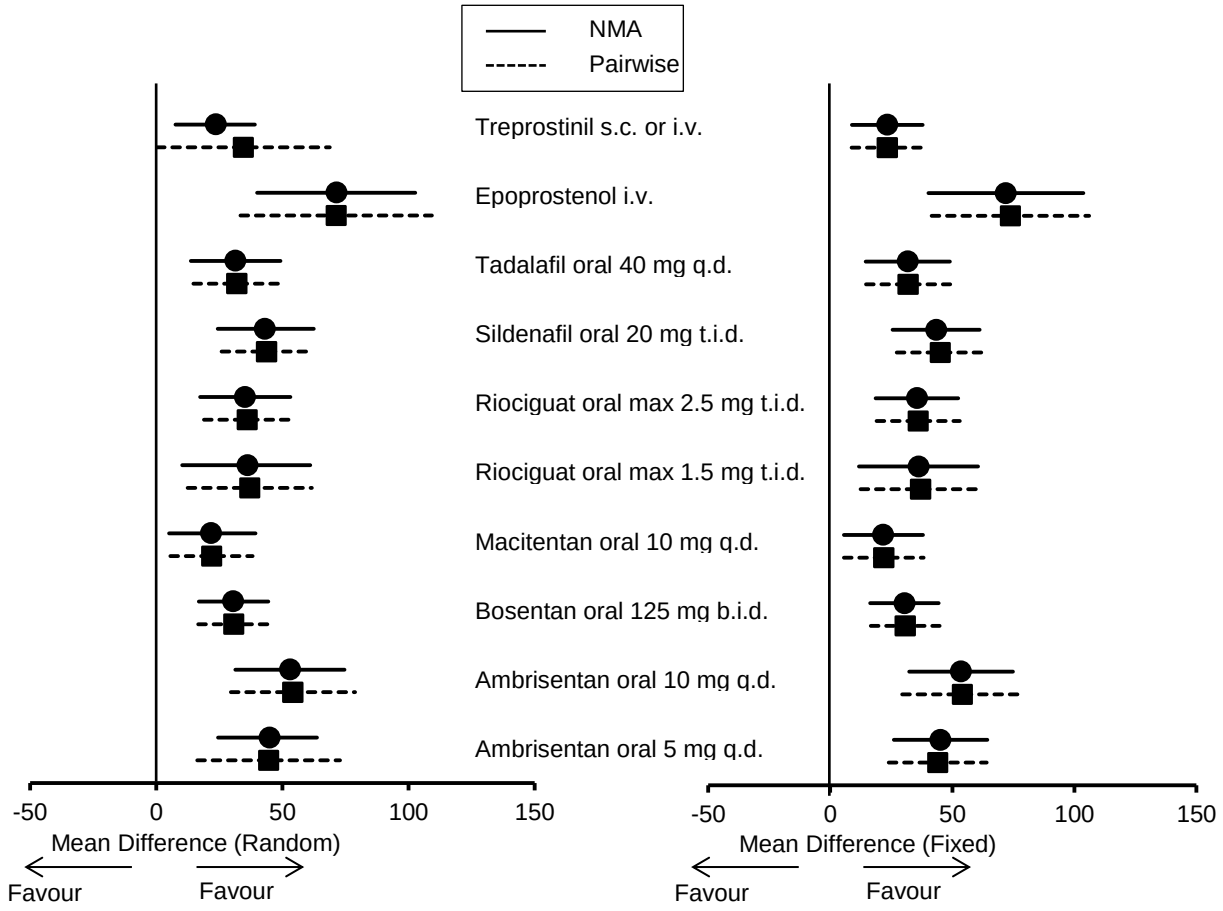
Figure 14: Evidence Network for Six-Minute Walk Distance of Naive Populations



Base Case: Summaries of results comparing pairwise meta-analysis and NMA (both random and fixed effect models) for 6MWD are presented in Table 192 for total populations and in Table 193 for naive populations in APPENDIX 11. Based on qualitative assessment, the results of direct pairwise estimates and NMA estimates are consistent; that is, they are similar in both magnitude and direction.

Figure 15 and Figure 16 illustrate the NMA results for the effect of all treatments relative to a common comparator (placebo) for total populations and naive populations, respectively. Table 218 to Table **221** in APPENDIX 12 present full NMA results comparing among all available treatment strategies for total populations and naive populations. The study by Rubenfire et al. (2007)[26] was excluded from the analyses as it studied the transition from epoprostenol to treprostinil, in which the 6MWD got worse in both groups at the end of the eight-week treatment compared with baseline.

Figure 15: Six-Minute Walk Distance for Different Treatment Strategies Compared With Placebo for Total Populations

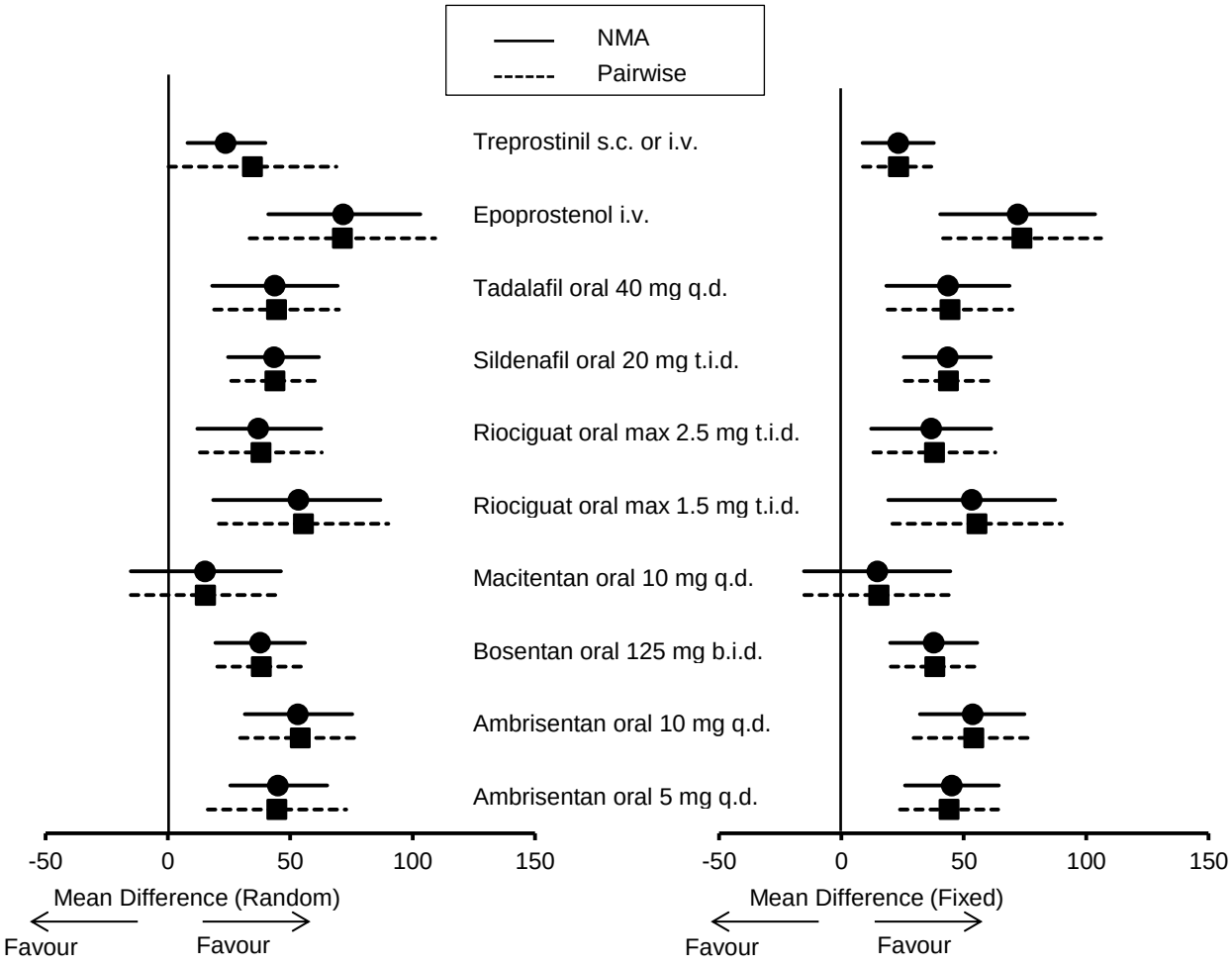


b.i.d. = twice a day; i.v. = intravenous; NMA = network meta-analysis; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.

In the total populations, the NMA results showed that all treatments had statistically significant improvement in 6MWD compared with placebo with both random and fixed effects models (Figure 15; Table 192 in APPENDIX 11). In the random effects model, epoprostenol had the largest mean difference (MD = 71.5 m), followed by ambrisentan 10 mg (MD = 53.1 m). For the remaining treatments, mean difference in 6MWD ranged from 21.8 m (macitentan 10 mg) to 45.0 m (ambrisentan 5 mg). Use of epoprostenol resulted in statistically increased 6MWD compared with macitentan 10 mg (MD = 49.8; 95% CrI, 13.0 to 86.1), treprostinil (MD = 47.9; 95% CrI, 13.0 to 82.7), bosentan 125 mg (MD = 41.2; 95% CrI, 6.7 to 75.2), and tadalafil 40 mg (MD = 40.3; 95% CrI, 3.2 to 75.7). Use of ambrisentan 10 mg resulted in statistically increased 6MWD compared with macitentan 10 mg (MD = 31.3; 95% CrI, 3.5 to 58.5), and treprostinil (MD = 29.3; 95% CrI, 3.4 to 56.0). Taken together, improvement in 6MWD of macitentan was significantly less than with epoprostenol and ambrisentan 10 mg in both random and fixed effects models. Likewise, improvement in 6MWD of riociguat max 2.5 mg was significantly less than with epoprostenol in the fixed effects model. Both macitentan and riociguat showed no statistically significant difference compared with each other and with the remaining treatments.

For most of other pairwise comparisons, there were no statistically significant differences between treatments because of the overlapping of the credible intervals (Table 218 and Table 219 in APPENDIX 12).

Figure 16: Six-Minute Walk Distance for Different Treatment Strategies Compared With Placebo for Naive Populations



b.i.d. = twice a day; i.v. = intravenous; NMA = network meta-analysis; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day

In the naive populations, all treatments, except macitentan 10 mg, had statistically significant improvement in 6MWD compared with placebo with both random and fixed effects models (Figure 16; Table 193 in APPENDIX 11). Epoprostenol had the largest mean difference (MD = 71.7 m), followed by ambrisentan 10 mg (MD = 53.2 m). For other treatments, mean difference in 6MWD ranged from 15.2 m (macitentan 10 mg) to 45.0 m (ambrisentan 5 mg). Use of epoprostenol showed statistically increased 6MWD compared with macitentan 10 mg (MD = 56.9; 95% CrI, 12.9 to 98.2), treprostinil (MD = 47.9; 95% CrI, 14.0 to 83.9). Use of ambrisentan 10 mg resulted in statistically increased 6MWD compared with macitentan 10 mg (MD = 38.3; 95% CrI, 0.7 to 74.4), and treprostinil (MD = 29.6; 95% CrI, 2.9 to 56.6). Overall, macitentan 10 mg did not show any significant difference in 6MWD compared with placebo and with other treatments (except epoprostenol and ambrisentan 10 mg). Improvement in 6MWD of riociguat

(both doses) was significantly better than placebo, but not significantly different compared with all other treatments. For most of the other pairwise comparisons, there were no statistically significant differences between treatments because of the overlapping of the credible intervals (Table 220 and Table 221 in APPENDIX 12).

Sensitivity Analyses: No sensitivity analysis was performed for 6MWD.

g) Hospitalization

Only direct pairwise meta-analyses were performed for this outcome.

Nine RCTs reported hospitalization as an outcome, for which there were 11 pairwise comparisons including nine active treatments (ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, treprostinil) compared with placebo, and two dose comparisons of ambrisentan (10 mg versus 5 mg) and riociguat (max 2.5 mg versus max 1.5 mg). Studies of epoprostenol did not report the proportion of patients who were hospitalized. The patient populations in the PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] and SERAPHIN (macitentan)[35] studies consisted of naive and experienced subpopulations, but only hospitalization data for total population were available from the published articles of those studies. Other studies had naive populations.

Statistically significant reduction in hospitalization was observed for macitentan 10 mg compared with placebo (RR = 0.59; 95% CI, 0.43 to 0.81). Other treatments, including ambrisentan 5 mg, bosentan 125 mg, riociguat (both doses), sildenafil, and tadalafil, showed numerical favour in the reduction of hospitalization compared with placebo, but the results did not reach statistical significance (Table 25).

There were no differences in hospitalization between doses of ambrisentan (10 mg versus 5 mg: RR = 1.00; 95% CI, 0.15 to 6.89) or riociguat (max 2.5 mg versus max 1.5 mg: RR = 0.75; 95% CI, 0.03 to 18.27).

Table 25: Meta-analysis Results for Hospitalization of PAH Treatments Compared With Placebo					
Treatment	**Background**	**No. of Patients**	**Het (I^2)**	**Placebo Effects[a]**	**RR (95% CI)[b], Fixed**
Ambrisentan oral 5 mg q.d.	Naive	262[18]	29.2%	0.08 (0.03, 0.14)	0.37 (0.12 to 1.14)
Ambrisentan oral 10 mg q.d.	Naive	134[18]	NA	0.08 (0.03, 0.14)	1.00 (0.15 to 6.89)
Bosentan oral 125 mg b.i.d.	Naive	265[21,29]	0%	0.10 (0.07, 0.13)	0.45 (0.18 to 1.14)
Macitentan oral 10 mg q.d.	Total	492[35]	NA	0.32	**0.59 (0.43 to 0.81)**
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	0.03	0.22 (0.01 to 4.03)
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	0.03	0.12 (0.01 to 1.10)
Sildenafil oral 20 mg t.i.d.	Naive	139[30]	NA	0.10	0.29 (0.06 to 1.35)
Tadalafil oral 40 mg q.d.	Total	285[34,36]	0%	0.03 (0.02, 0.03)	0.35 (0.06 to 2.20)
Treprostinil s.c. or i.v.	Naive	469[28]	NA	0.17	0.96 (0.64 to 1.44)

b.i.d. = twice a day; CI = confidence interval; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RCTs = randomized controlled trials; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day.

[a] Median (min, max); (min, max) was not reported for single study.

[b] Bold indicates statistically significant difference.

h) Borg Dyspnea Index

Only direct pairwise meta-analyses were performed for this outcome.

Thirteen RCTs reported BDI as an outcome, for which there were 12 pairwise comparisons including 10 active treatments (ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and treprostinil) compared with placebo, and two dose comparisons of ambrisentan (10 mg versus 5 mg) and riociguat (max 2.5 mg versus max 1.5 mg). The patient populations in the PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] and SERAPHIN (macitentan)[35] studies consisted of naive and experienced subpopulations, while only naive patients were included in other studies. Data for naive populations were available for riociguat max 2.5 mg only.

All treatments showed numerical decrease (improvement) in BDI compared with placebo (Table 26). Statistically significant differences were reached for ambrisentan (10 mg), macitentan 10 mg (total), riociguat max 2.5 mg (total), sildenafil, epoprostenol, and treprostinil. There was substantial statistical heterogeneity (I^2 = 86.3%) among four trials (McLaughlin,[25] Rubenfire,[26] Simonneau,[28] TRUST[31]) of treprostinil. Patients in the study by McLaughlin et al.[25] and TRUST[31] were mostly IPAH with FC III, while those in the study by Simonneau et al.[28] were a mix of IPAH and APAH with FC II and III. All the separate results of Rubenfire and Simonneau, and the pooled results of MacLaughlin and TRUST showed they significantly favoured treprostinil (Table 26).

There were no statistically significant differences in BDI between doses of ambrisentan (10 mg versus 5 mg: WMD = –0.60, 95% CI, –1.25 to 0.05) or riociguat (max 2.5 mg versus max 1.5 mg: WMD = –0.10, 95% CI, –0.42 to 0.22).

Table 26: Meta-analysis Results for BDI of PAH Treatments Compared With Placebo

Treatment	Bkg	No. of Patients	Het (I^2)	Placebo Effects[a]	WMD (95% CI), Random
Ambrisentan oral 5 mg q.d.	Naive	262[18]	63.2%	0.4 (0, 0.8)	–0.73 (–1.61 to 0.15)
Ambrisentan oral 10 mg q.d.	Naive	134[18]	NA	0.4 (0, 0.8)	**–0.90 (–1.60 to –0.20)**
Bosentan oral 125 mg b.i.d.	Naive	175[21,23]	35.1%	0.8 (0.3, 1.3)	–0.71 (–1.74 to 0.32)
Macitentan oral 10 mg q.d.	Total	492[35]	NA	0.4	**–0.50 (–0.86 to –0.14)**
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	0.1	–0.40 (–0.84 to 0.04)
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	0.1	**–0.50 (–0.92 to –0.08)**
	Naive	189[33]	NA	0.02	–0.42 (–1.02 to 0.18)
Sildenafil oral 20 mg t.i.d.	Naive	133[30]	NA	0	**–0.80 (–1.48 to –0.12)**
Tadalafil oral 40 mg q.d.	Total	155[34]	NA	0.4	–1.10 (–2.30 to 0.10)
Epoprostenol	Naive	91[19]	NA	0.62	**–2.41 (–3.85 to –0.97)**
Treprostinil s.c. or i.v.	Naive	561[25,26,28,31]	86.3%	0.7 (–0.2, 5.6)	No pooling
Rubenfire	Naive	22[26]	NA	5.6	**–5.02 (–7.21 to –2.83)**
Simonneau	Naive	469[28]	NA	–0.2	**–0.90 (–1.46 to –0.34)**
McLaughlin &TRUST	Naive	70[25,31]	33.6%	1.0, 0.4	**–1.89 (–2.74 to –1.03)**

b.i.d. = twice a day; BDI = Borg dyspnea index; Bkg = background; CI = confidence interval; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RCTs = randomized controlled trials; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day; WMD = weighted mean difference.
[a] Median (min, max).

i) Pulmonary Vascular Resistance

Only direct pairwise meta-analyses were performed for this outcome.

Eleven RCTs reported PVR as an outcome, for which there were 10 pairwise comparisons including eight active treatments (bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and treprostinil) compared with placebo, and two dose comparisons of ambrisentan (10 mg versus 5 mg) and riociguat (max 2.5 mg versus max 1.5 mg). The patient populations in the PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] and SERAPHIN (macitentan)[35] studies consisted of naive and experienced subpopulations, while only naive patients were included in other studies. Data for naive populations were available for riociguat max 2.5 mg only. In the PHIRST[34] and SERAPHIN[35] studies, PVR was measured from subsets of the total populations.

All treatments showed numerical decrease (improvement) in PVR compared with placebo (Table 27). Statistically significant differences were reached for all treatments, except tadalafil.

There were no statistically significant differences in PVR between doses of ambrisentan (10 mg versus 5 mg: WMD = –68.00; 95% CI, –245.34 to 109.34) or riociguat (max 2.5 mg versus max 1.5 mg: WMD = –55.00; 95% CI, –140.24 to 30.24).

Table 27: Meta-analysis Results for PVR of PAH Treatments Compared With Placebo

Treatment	Bkg	No. of Patients	Het (I^2)	Placebo Effects[a]	WMD (95% CI), Random
Bosentan oral 125 mg b.i.d.	Naive	83[22,23]	0%	173 (155, 191)	**–424.94 (–588.75 to –261.13)**
Macitentan oral 10 mg q.d.	Total	124[35]	NA	504	**–529.00 (–812.41 to –245.59)**
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	–9	**–159.00 (–255.48 to –62.52)**
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	–9	**–214.00 (–277.92 to –150.08)**
	Naive	170[33]	NA	17	**–276.00 (–385.68 to –166.32)**
Sildenafil oral 20 mg t.i.d.	Naive	130[30]	NA	49	**–171.00 (–308.82 to –33.18)**
Tadalafil oral 40 mg q.d.	Total	158[34,36]	0%	–49 (–108, 11)	–180.89 (–376.15 to 14.37)
Epoprostenol	Naive	211[19,20,27]	0%	74 (–16, 120)	**–432.87 (–552.45 to –313.30)**
Treprostinil s.c. or i.v.	Naive	495[25,28]	0%	56 (16, 96)	**–378.85 (–503.74 to –253.96)**

b.i.d. = twice a day; Bkg = background; CI = confidence interval; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day; WMD = weighted mean difference.
[a] Median (min, max).

j) Mean Pulmonary Artery Pressure

Only direct pairwise meta-analyses were performed for this outcome.

Twelve RCTs reported mPAP as an outcome, for which there were nine pairwise comparisons including eight active treatments (bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and treprostinil) compared with placebo, and one dose comparison of riociguat (max 2.5 mg versus max 1.5 mg). In addition, the study by Galiè et al.[24] had results of dose comparisons between ambrisentan 10 mg and 5 mg). The patient populations in the PHIRST (tadalafil),[34] PATENT-1 (riociguat),[33] SERAPHIN (macitentan),[35] and EARLY (bosentan)[32] studies consisted of naive and experienced subpopulations, while only naive patients were included in other studies. The EARLY[32] study reported data for total population only. Data for naive populations were available for riociguat max 2.5 mg only. In the PHIRST[34] and SERAPHIN[35] studies, mPAP was measured from subsets of total populations.

All treatments showed numerical decrease (improvement) in mPAP compared with placebo (Table 28). Statistically significant differences were reached for all treatments, except macitentan and tadalafil. The pooled result of the two treprostinil studies (MD = –1.13; 95% CI,

–5.95 to 3.29) was not significant, and had high statistical heterogeneity (I^2 = 61.9%). When the results were presented separately, the small study by McLaughlin et al. (N = 26)[25] showed no difference, while the result of the larger study by Simonneau et al. (N = 469)[28] significantly favoured treprostinil (MD = –3.00; 95% CI, –4.53 to –1.47).

Ambrisentan 10 mg had significant decrease in mPAP compared with ambrisentan 5 mg (MD = –9.00; 95% CI, –12.64 to –5.36; from the study by Galiè et al.[24]), while there was no difference in mPAP between doses of riociguat (max 2.5 mg versus max 1.5 mg: MD = 0.00; 95% CI, –1.99 to 1.99).

Table 28: Meta-analysis Results for mPAP of PAH Treatments Compared With Placebo

Treatment	Background	No. of patients	Het (I^2)	Placebo Effects[a]	WMD (95% CI)[b], Random
Bosentan oral 125 mg b.i.d.	Total	269[22,23,32]	0%	3.0 (0.5, 5.1)	**–5.83 (–8.61 to –3.05)**
	Naive	84[22,23]	0%	2.8 (0.5, 5.1)	**–5.89 (–9.31 to –2.47)**
Macitentan oral 10 mg q.d.	Total	124[35]	NA	6.6	–2.70 (–10.83 to 5.43)
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	–0.5	**–3.50 (–5.88 to –1.12)**
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	–0.5	**–3.50 (–5.41 to –1.59)**
Total	Naive	172[33]	NA	–0.3	**–4.10 (–7.52 to –0.68)**
Sildenafil oral 20 mg t.i.d.	Naive	130[30]	NA	0.6	**–2.70 (–5.23 to –0.17)**
Tadalafil oral 40 mg q.d.	Total	158[34,36]	0%	–2.6 (–3.0, –2.2)	–2.53 (–7.34 to 2.28)
Epoprostenol	Naive	211[19,20,27]	0%	0.9 (0, 1.9)	**–6.13 (–8.50 to –3.76)**
Treprostinil s.c. or i.v.	Naive	495[25,28]	61.9%	–0.65 (–2.0, 0.7)	–1.33 (–5.95 to 3.29)
McLaughlin	Naive	26[25]	NA	–2.0	2.00 (–3.85 to 7.85)
Simonneau	Naive	469[28]	NA	0.7	**–3.00 (–4.53 to –1.47)**

b.i.d. = twice a day; Bkg = background; CI = confidence interval; Het = heterogeneity; i.v. = intravenous; mPAP = mean pulmonary artery pressure; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RCTs = randomized controlled trials; s.c. = subcutaneous; t.i.d. = three times a day; WMD = weighted mean difference.
[a] Median (min, max); (min, max) was not reported for single study.
[b] Bold indicates statistically significant difference.

k) Cardiac Index

Only direct pairwise meta-analyses were performed for this outcome.

Twelve RCTs reported cardiac index as an outcome, for which there were nine pairwise comparisons including eight active treatments (bosentan 125 mg, macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and treprostinil) compared with placebo, and one dose comparison of riociguat (max 2.5 mg versus max 1.5 mg). In addition, the study by Galiè et al.[24] included results of dose comparisons between ambrisentan 10 mg and 5 mg). The patient populations in the PHIRST (tadalafil),[34]

PATENT-1 (riociguat),[33] SERAPHIN (macitentan),[35] and EARLY (bosentan)[32] studies consisted of naive and experienced subpopulations, while only naive patients were included in other studies. The EARLY[32] study reported data for total population only. Data for naive populations were available for riociguat max 2.5 mg only. In the PHIRST[34] and SERAPHIN[35] studies, cardiac index was measured from subsets of total populations.

All treatments showed numerical increase (improvement) in cardiac index compared with placebo (Table 29). Statistically significant differences were reached for all treatments, except sildenafil 20 mg and tadalafil 40 mg. There was substantial statistical heterogeneity (I^2 = 86.3%) among four trials (BREATHE-1,[21] BREATHE-5,[22] Channick,[23] and EARLY[32]) of bosentan. The separate results of BREATHE-1 (WMD = 0.36, 95% CI 0.08 to 0.64),[21] Channick et al. (WMD = 1.00; 95% CI, 0.74 to 1.26)[23] and EARLY (WMD = 0.24; 95% CI, 0.03 to 0.45)[32] significantly favoured bosentan, while that of BREATHE-5 (WMD = 1.10; 95% CI, 0.49 to 2.69)[22] did not.

When the EARLY study was excluded from the analysis of naive populations, the pooled WMD of the cardiac index for the BREATHE-1,[21] BREATHE-5,[22] and Channick[23] studies significantly favoured bosentan (WMD = 0.71; 95% CI, 0.53 to 0.90), but with substantial heterogeneity (I^2 = 82.2%). The separate results of BREATHE-1[21] and Channick et al.[23] significantly favoured bosentan, while that of BREATHE-5[22] did not.

Riociguat max 2.5 mg had a significant decrease in cardiac index compared with riociguat max 1.5 mg (WMD = 0.29, 95% CI 0.15 to 0.43), while there was no difference in PAP between doses of ambrisentan (10 mg versus 5 mg: WMD = -0.10, 95% CI -0.42 to 0.22).

Table 29: Meta-analysis Results for Cardiac Index of PAH Treatments Compared With Placebo

Treatment	Background	No. of Patients	Het (I^2)	Placebo Effects[a]	WMD (95% CI)[b], Random
Bosentan oral 125 mg b.i.d.	Total	323[21-23,32]	86.3%	–0.19 (–0.5, –0.15)	No pooling
	Naive	138[21-23]	82.2%	–0.2 (–0.5, –0.18)	No pooling
Macitentan oral 10 mg q.d.	Total	124[35]	NA	–0.48	**0.61 (0.32 to 0.90)**
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	–0.02	**0.27 (0.18 to 0.36)**
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	–0.02	**0.56 (0.43 to 0.69)**
	Naive	170[33]	NA	–0.1	**0.70 (0.48 to 0.92)**
Sildenafil oral 20 mg t.i.d.	Naive	130[30]	NA	–0.02	0.23 (–0.17 to 0.63)
Tadalafil oral 40 mg q.d.	Total	158[34,36]	0%	0.08 (–0.01, 0.17)	0.29 (–0.07 to 0.65)
Epoprostenol	Naive	192[19,20]	0%	–0.15 (–0.2, –0.10)	**0.58 (0.38 to 0.78)**
Treprostinil s.c. or i.v.	Naive	495[25,28]	5.9%	–0.03 (–0.06, 0)	**0.20 (0.07 to 0.33)**

b.i.d. = twice a day; CI = confidence interval; Het = heterogeneity; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day; WMD = weighted mean difference.

[a] Median (min, max); (min, max) was not reported for single study.

[b] Bold indicates statistically significant difference.

5.4.2 Efficacy of Pulmonary Arterial Hypertension Drugs in Treatment-Experienced Populations (Add-on Therapy)

Of the four studies that had mixed populations (i.e., naive and PAH pre-treated),[32-35] PATENT-1 (riociguat),[33] PHIRST (tadalafil),[34] and SERAPHIN (macitentan)[35] reported data for naive and pre-treated populations separately. The EARLY (bosentan) study, whose population had 15% of patients experienced with sildenafil, reported data for total population only.[32]

In the PATENT-1 study, 50% of its population were pre-treated with either ERAs (mostly bosentan, 88%) or non-infusible prostanoids (12%).[33] In the PHIRST study, 54% of the patient population had been pre-treated with bosentan.[34] In the SERAPHIN study, 64% of the patient population had been pre-treated with PDE-5 inhibitors (92%) or non-infusible prostanoids (8%).[35] The study by Zhuang et al. (2014) had only patients who had been pre-treated with ambrisentan.[36] In those studies, patients continued having background therapy in addition to the studied drug or placebo during the treatment period.

a) Clinical Worsening

Direct Pairwise Meta-analyses:

The addition of macitentan 10 mg, riociguat max 2.5 mg, or tadalafil 40 mg to the PAH pre-treated background improved clinical worsening compared with placebo (Table 30). Statistically significant differences were reached for macitentan 10 mg and riociguat max 2.5 mg in the overall pre-treated populations. However, when data for riociguat were reported separately with respect to ERA or prostanoids background, the treatment effects were still numerically in favour of riociguat, but the differences were not statistically significant because of wider confidence intervals. The addition of tadalafil to bosentan or ambrisentan background significantly reduced the proportion of patients having clinical worsening compared with placebo.

Table 30: Meta-analysis Results for Clinical Worsening of PAH Treatments Compared With Placebo

Treatment	Background	No. of Patients	RR (95% CI)[a], Random
Macitentan oral 10 mg q.d.	PDE-5i or prostanoids	308[35]	**0.74 (0.55 to 0.98)**
Riociguat oral max 2.5 mg t.i.d.	Overall	191[33]	**0.11 (0.01 to 1.00)**
Riociguat oral max 2.5 mg t.i.d.	ERA	167[33]	0.16 (0.02 to 1.50)
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	27[33]	0.13 (0.01 to 2.81)
Tadalafil oral 40 mg q.d.	Bosentan or ambrisentan	211[34,36]	**0.39 (0.17 to 0.89)**

CI = confidence interval; ERA = Endothelin receptor antagonist; No. = number; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; q.d. = once a day; RR = relative risk; t.i.d. = three times a day.
[a] Bold indicates statistically significant difference.

Network Meta-analyses:

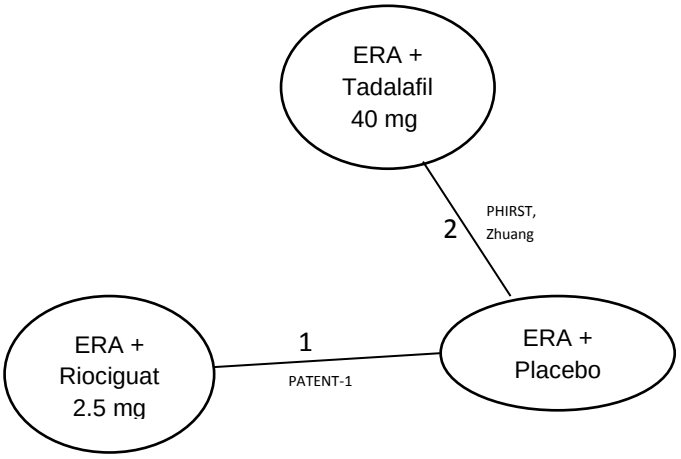
NMA was conducted to compare between treatments of riociguat max 2.5 mg three times a day (PATENT-1) and tadalafil 40 mg once a day (PHIRST, Zhuang) in patients with ERA background. The evidence network is shown in Figure 17.

Summaries of results comparing pairwise meta-analysis and NMA (both random and fixed effect models) for clinical worsening are presented in Table 194 in APPENDIX 11. Based on

qualitative assessment, the results of direct pairwise estimates and NMA estimates are consistent; that is, they are similar in both magnitude and direction.

Figure 18 illustrates the NMA results for the effect of ERA plus riociguat and ERA plus tadalafil relative to ERA plus placebo. Table 222 and Table 223 in APPENDIX 12 present full NMA results obtained using random and fixed effects models, respectively.

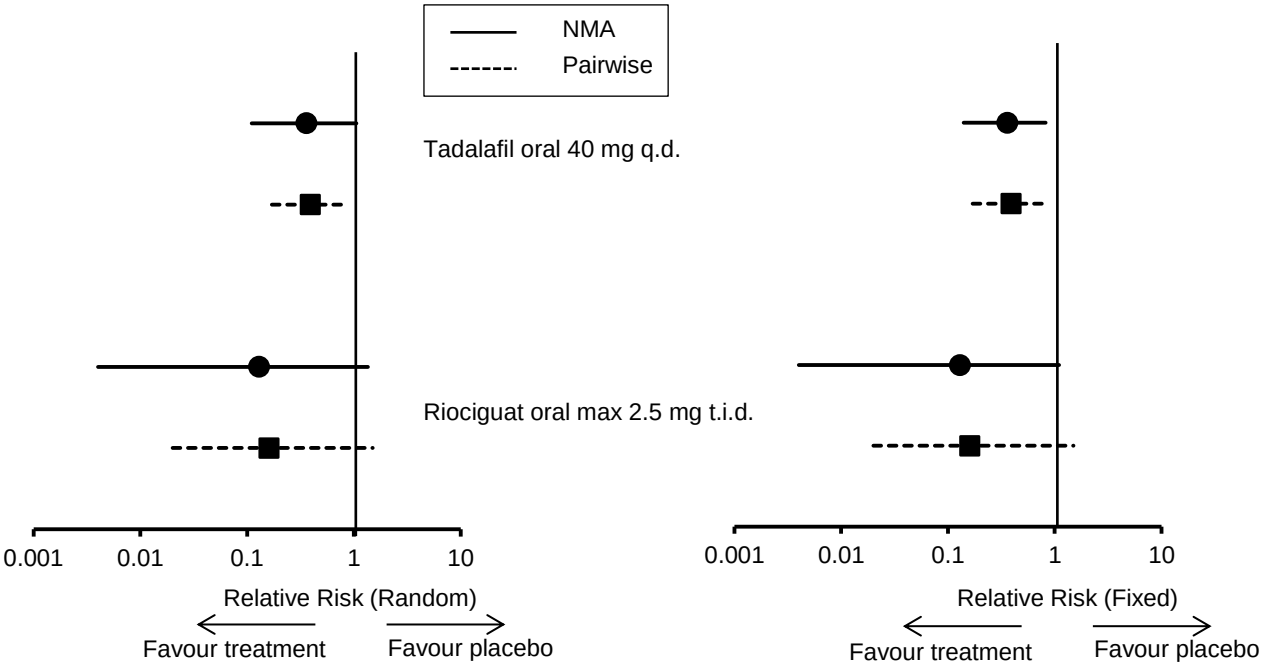
Figure 17: Evidence Network for Clinical Worsening, FC Improvement, FC Worsening, and 6MWD of Populations With ERA Background



6MWD = six-minute walk distance; ERA = endothelin receptor antagonist; FC = functional class.

In the ERA background populations, addition of riociguat max 2.5 mg or tadalafil 40 mg reduced clinical worsening compared with placebo. However, statistical significance could not be reached due to wide credible intervals in the random effects model. Due to overlapping credible intervals, a significant difference between riociguat and tadalafil also could not be reached, as shown in the full NMA results (Table 222 and Table 223 in APPENDIX 12).

Figure 18: Clinical Worsening for Riociguat and Tadalafil Compared With Placebo for Populations With ERA Background



ERA = endothelin receptor antagonist; NMA = network meta-analysis; q.d. = once a day; t.i.d. = three times a day.

b) Functional Class Improvement

Direct pairwise meta-analyses:

Table 31 shows that the proportion of patients who improved FC was not significantly different between the riociguat and placebo groups in PATENT-1,[33] or between the tadalafil and placebo groups in PHIRST[34] (RR = 0.39; 95% CI 0.13 to 1.13) and in Zhuang et al.[36] (RR = 1.39; 95% CI 0.87 to 2.21). The treatment effects numerically favoured riociguat in both ERA or prostanoids pre-treated populations.

Table 31: Meta-analysis Results for FC Improvement of PAH Treatments Compared With Placebo

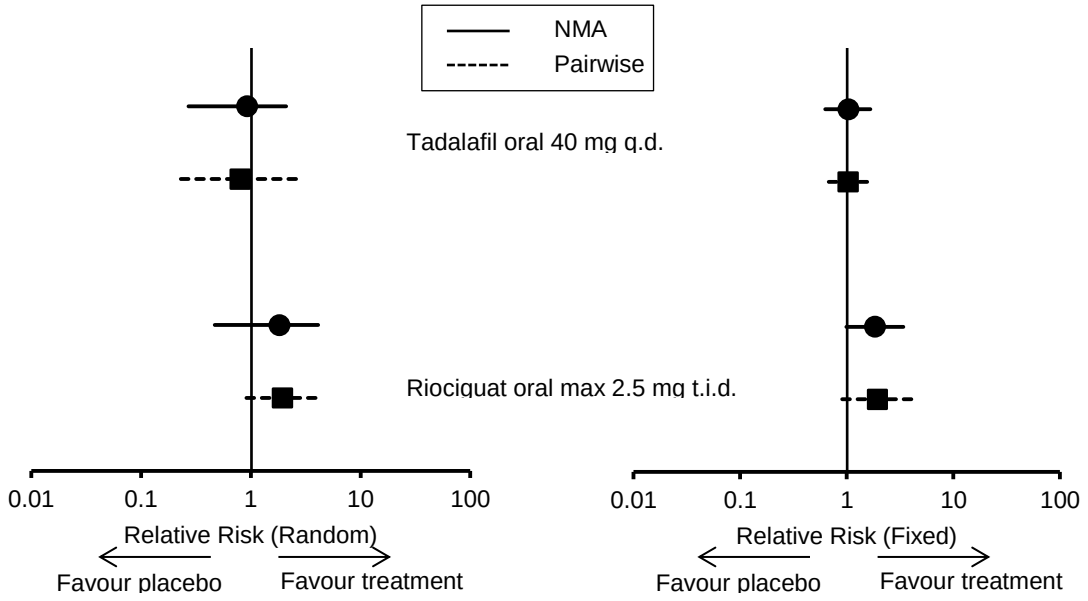
Treatment	Background	No. of Patients	RR (95% CI), Random
Riociguat oral max 2.5 mg t.i.d.	Overall	190[33]	1.91 (0.94 to 3.88)
Riociguat oral max 2.5 mg t.i.d.	ERA	166[33]	1.94 (0.91 to 4.15)
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	27[33]	2.10 (0.30 to 14.53)
Tadalafil oral 40 mg q.d.	Bosentan or ambrisentan	211[34,36]	No pooling (I^2 = 79.0%)

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RR = relative risk; t.i.d. = three times a day.

Network Meta-analyses:
NMA was conducted to compare between treatments of riociguat max 2.5 mg three times a day (PATENT-1) and tadalafil 40 mg once a day (PHIRST, Zhuang) in patients with ERA background. The evidence network is shown in Figure 17.

Summaries of results comparing pairwise meta-analysis and NMA (both random and fixed effect models) for FC improvement are presented in Table 195 in APPENDIX 11. Based on qualitative assessment, the results of direct pairwise estimates and NMA estimates are consistent; that is, they are similar in both magnitude and direction.

Figure 19: Functional Class Improvement for Riociguat and Tadalafil Compared with Placebo for Populations with ERA background



ERA = endothelin receptor antagonist; FC = functional class; NMA = network meta-analysis; q.d. = once a day; t.i.d. = three times a day.

Figure 19 illustrates the NMA results for the effect of ERA plus riociguat and ERA plus tadalafil relative to ERA plus placebo. Table 224 and Table 225 in APPENDIX 12 present full NMA results obtained using random and fixed effects models, respectively.

In the ERA background populations, the addition of riociguat max 2.5 mg or tadalafil 40 mg did not show any statistically significant improvement in FC compared with placebo (Table 195 in APPENDIX 11). There was also no significant difference in FC improvement between riociguat max 2.5 mg and tadalafil 40 mg, as shown in the full NMA results (Table 224 and Table 225 in APPENDIX 12). However, riociguat max 2.5 mg appeared to show numerical improvement in FC compared with tadalafil 40 mg (RR = 0.70; 95% CI, 0.10 to 4.32).

c) Functional Class Worsening

Direct Pairwise Meta-analyses:

The addition of riociguat to a PAH pre-treated population (overall) significantly reduced the proportion of patients who worsened FC (RR = 0.26; 95% CI, 0.08 to 0.85). However, when data for riociguat were reported separately with respect to ERA or prostanoids background, the treatment effects were still numerically in favour of riociguat, but the differences were no longer statistically significant. The addition of tadalafil to patients with bosentan or ambrisentan background had no significant difference in FC worsening compared with placebo (Table 32).

Table 32: Meta-analysis Results for FC Worsening of PAH Treatments Compared With Placebo

Treatment	Background	No. of Patients	RR (95% CI)[a], Random
Riociguat oral max 2.5 mg t.i.d.	Overall	190[33]	**0.26 (0.08 to 0.85)**
Riociguat oral max 2.5 mg t.i.d.	ERA	166[33]	0.39 (0.12 to 1.22)
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	27[33]	0.13 (0.01 to 2.81)
Tadalafil oral 40 mg q.d.	Bosentan or ambrisentan	211[34,36]	0.57 (0.26 to 1.24)

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RR = relative risk; t.i.d. = three times a day.
[a] Bold indicates statistically significant difference.

Network Meta-analyses:

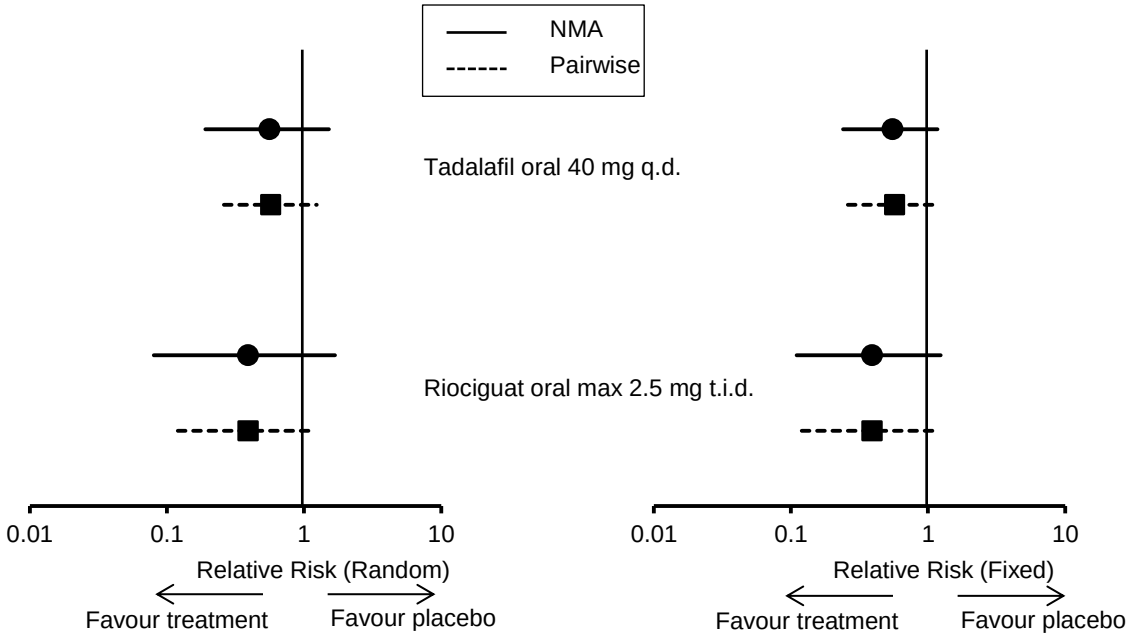
NMA was conducted to compare between treatments of riociguat max 2.5 mg three times a day (PATENT-1) and tadalafil 40 mg once a day (PHIRST, Zhuang) in patients with ERA background. The evidence network is shown in Figure 17.

Summaries of results comparing pairwise meta-analysis and NMA (both random and fixed effect models) for FC worsening are presented in Table 196 in APPENDIX 11. Based on qualitative assessment, the results of direct pairwise estimates and NMA estimates are consistent; that is, they are similar in both magnitude and direction.

Figure 20 illustrates the NMA results for the effect of ERA plus riociguat and ERA plus tadalafil relative to ERA plus placebo. Table 226 and Table 227 in APPENDIX 12 present the full NMA results obtained using random and fixed effects models, respectively.

In the ERA background populations, the addition of riociguat max 2.5 mg or tadalafil 40 mg did not show any statistically significant reduction in FC worsening compared with placebo. There was also no significant difference in FC worsening between riociguat max 2.5 mg and tadalafil 40 mg, as shown in full NMA results (Table 226 and Table 227 in APPENDIX 12).

Figure 20: FC Worsening for Riociguat and Tadalafil Compared With Placebo for Populations With ERA Background



ERA = endothelin receptor antagonist; FC = functional class; NMA = network meta-analysis; q.d. = once a day; t.i.d. = three times a day.

d) Functional Class Unchanged

Only direct pairwise meta-analyses were performed for this outcome.

Table 33 shows that the proportion of patients who maintained FC was not significantly different between the riociguat and placebo groups or between the tadalafil and placebo groups.

Table 33: Meta-analysis Results for FC Unchanged of PAH Treatments Compared With Placebo

Treatment	Background	No. of Patients	RR (95% CI), Random
Riociguat oral max 2.5 mg t.i.d.	Overall	190[33]	0.95 (0.79 to 1.15)
Riociguat oral max 2.5 mg t.i.d.	ERA	166[33]	0.94 (0.77 to 1.14)
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	27[33]	0.98 (0.57 to 1.70)
Tadalafil oral 40 mg q.d.	Bosentan or ambrisentan	211[34]	1.13 (0.87 to 1.47)

CI = confidence interval; ERA = endothelin receptor antagonist; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RR = relative risk; t.i.d. = three times a day.

e) Six-Minute Walk Distance

Direct Pairwise Meta-analyses:

The addition of macitentan 10 mg, riociguat max 2.5 mg, or tadalafil 40 mg to PAH pre-treated background significantly increased 6MWD compared with placebo (Table 34). The treatment effects failed to reach statistical significance with riociguat max 1.5 mg in the overall background population or riociguat max 2.5 mg in the ERA background population. Treatment effect significantly favoured riociguat max 2.5 mg in the prostanoid pre-treated population (WMD = 105.00; 95% CI, 27.81 to 182.19), despite the small sample size (N = 24).

Table 34: Meta-analysis Results for 6MWD of PAH Treatments Compared With Placebo

Treatment	Background	No. of Patients	WMD (95% CI), Random
Macitentan oral 10 mg q.d.	PDE-5i or prostanoids	308[35]	**25.70 (7.04 to 44.36)**
Riociguat oral max 1.5 mg t.i.d.	Overall	91[33]	17.60 (–17.25 to 52.45)
Riociguat oral max 2.5 mg t.i.d.	Overall	191[33]	**32.30 (9.07 to 55.53)**
Riociguat oral max 2.5 mg t.i.d.	ERA	167[33]	23.40 (–0.65 to 47.45)
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	24[33]	**105.00 (27.81 to 182.19)**
Tadalafil oral 40 mg q.d.	Bosentan or ambrisentan	207[34,36]	**34.66 (26.52 to 42.80)**

6MWD = six-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; PDE-5i = phosphodiesterase type 5 inhibitor; t.i.d. = three times a day; WMD = weighted mean difference.

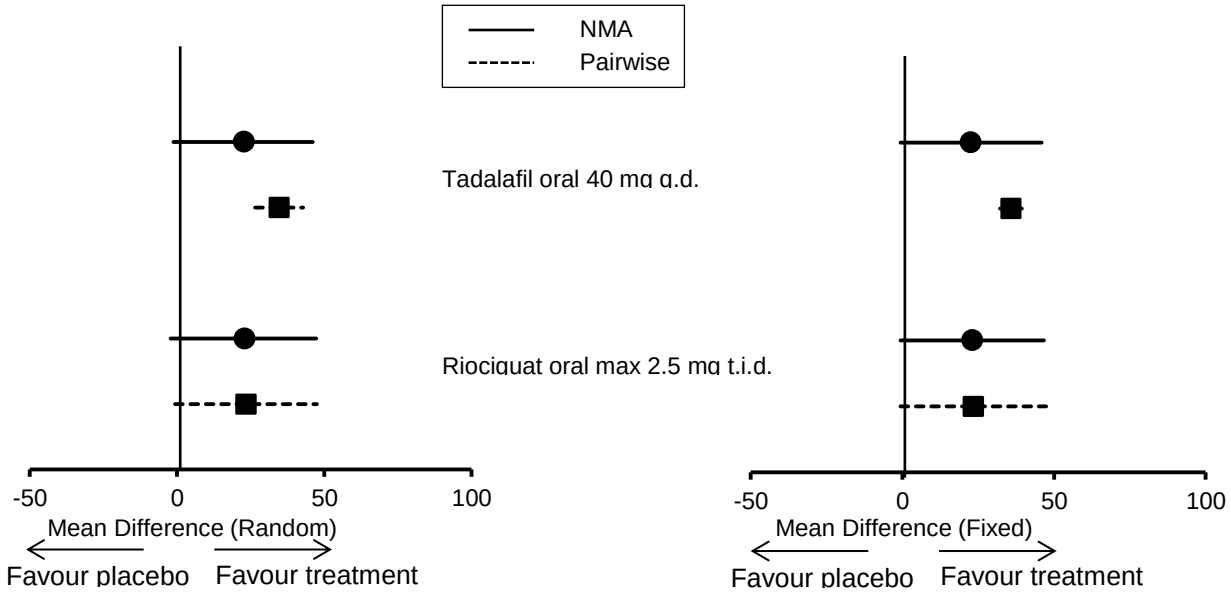
[a] Bold indicates statistically significant difference.

Network Meta-analyses:

NMA was conducted to compare between treatments of riociguat max 2.5 mg three times a day (PATENT-1) and tadalafil 40 mg once a day (PHIRST, Zhuang) in patients with ERA background. The evidence network is shown in Figure 17.

Summaries of results comparing pairwise meta-analysis and NMA (both random and fixed effect models) for 6MWD are presented in Table 197 in APPENDIX 11. Based on qualitative assessment, the results of direct pairwise estimates and NMA estimates are consistent; that is, they are similar in both magnitude and direction.

Figure 21: 6MWD for Riociguat and Tadalafil Compared With Placebo for Populations With ERA Background



6MWD = six-minute walk distance; ERA = endothelin receptor antagonist; NMA = network meta-analysis; q.d. = once a day; t.i.d. = three times a day.

Figure 21 illustrates the NMA results for the effect of ERA plus riociguat and ERA plus tadalafil relative to ERA plus placebo. Table 228 and Table 229 in APPENDIX 12 present the full NMA results obtained using random and fixed effects models, respectively.

In the ERA background populations, the addition of riociguat max 2.5 mg or tadalafil 40 mg did not show any statistically significant improvement in 6MWD compared with placebo, although both active treatments showed numerical favour in improving 6MWD (both had a mean difference of 23 m). There was also no significant difference in 6MWD between riociguat max 2.5 mg and tadalafil 40 mg, as shown in the full NMA results (Table 228 and Table 229 in APPENDIX 12).

f) Borg Dyspnea Index

Only direct pairwise meta-analyses were performed for this outcome.

In the overall pre-treated populations, the addition of riociguat max 2.5 mg showed a statistically significant decrease (improvement) in BDI compared with placebo (WMD = –0.70; 95% CI, –1.30 to –0.10). However, when data were reported separately with respect to ERA or prostanoids background, the treatment effects were still numerically in favour of riociguat, but the differences failed to reach statistical significance (Table 35).

Table 35: Meta-analysis Results for BDI of PAH Treatments Compared With Placebo			
Treatment	**Background**	**No. of Patients**	**WMD (95% CI)[a], Random**
Riociguat oral max 2.5 mg t.i.d.	Overall	191[33]	**–0.70 (–1.30 to –0.10)**
Riociguat oral max 2.5 mg t.i.d.	ERA	167[33]	–0.60 (–1.24 to 0.04)
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	27[33]	–0.40 (–1.68 to 0.88)

BDI = Borg dyspnea index; CI = confidence interval; ERA = endothelin receptor antagonists; No. = number; PAH = pulmonary arterial hypertension; t.i.d. = three times a day; WMD = weighted mean difference.
[a] Bold indicates statistically significant difference.

g) Pulmonary Vascular Resistance

Only direct pairwise meta-analyses were performed for this outcome.

The addition of riociguat max 2.5 mg showed a statistically significant decrease (improvement) in PVR compared with placebo in the overall background, as well as in the ERA or prostanoids pre-treated populations (Table 36). Despite a smaller sample size (N = 27), the treatment effect of riociguat was larger in the prostanoid pre-treated population (WMD = –320.00; 95% CI, –529.25 to –110.75) compared with that in the ERA background (WMD = –128.00; 95% CI, –213.00 to –42.97). The addition of tadalafil 40 mg to ambrisentan background had no significant difference in PVR compared with placebo.

Table 36: Meta-analysis Results for PVR of PAH Treatments Compared With Placebo			
Treatment	**Background**	**No. of Patients**	**WMD (95% CI)[a], Random**
Riociguat oral max 2.5 mg t.i.d.	Overall	169[33]	**–152.00 (–233.41 to –70.59)**
Riociguat oral max 2.5 mg t.i.d.	ERA	148[33]	**–128.00 (–213.00 to –42.97)**
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	24[33]	**–320.00 (–529.25 to –110.75)**
Tadalafil oral 40 mg q.d.	Ambrisentan	124[36]	–106.00 (–439.36 to 227.36)

CI = confidence interval; ERA = endothelin receptor antagonists; No. = number; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; q.d. = once a day; t.i.d. = three times a day; WMD = weighted mean difference.
[a] Bold indicates statistically significant difference.

h) Pulmonary Artery Pressure

Only direct pairwise meta-analyses were performed for this outcome.

The addition of riociguat max 2.5 mg showed a statistically significant decrease (improvement) in PAP compared with placebo in the ERA and prostanoids pre-treated populations (Table 37). Despite a smaller sample size (N = 27), the treatment effect of riociguat was larger in the prostanoid pre-treated population (WMD = –6.00; 95% CI, –11.16 to –0.84) compared with that in the ERA background (WMD = –2.40; 95% CI, –4.63 to –0.17). The addition of tadalafil 40 mg to ambrisentan background had no significant difference in PAP compared with placebo.

Table 37: Meta-analysis Results for PAP of PAH Treatments Compared With Placebo			
Treatment	**Background**	**No. of Patients**	**WMD (95% CI)[a], Random**
Riociguat oral max 2.5 mg t.i.d.	ERA	149[33]	**–2.40 (–4.63 to –0.17)**
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	26[33]	**–6.00 (–11.16 to –0.84)**
Tadalafil oral 40 mg q.d.	Ambrisentan	124[36]	–4.00 (–13.78 to 5.78)

CI = confidence interval; ERA = endothelin receptor antagonists; No. = number; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; q.d. = once a day; t.i.d. = three times a day; WMD = weighted mean difference.
[a] Bold indicates statistically significant difference.

i) Cardiac Index

Only direct pairwise meta-analyses were performed for this outcome.

The addition of riociguat max 2.5 mg showed a statistically significant increase (improvement) in cardiac index compared with placebo in the ERA and prostanoids pre-treated populations (Table 38). The addition of tadalafil 40 mg to ambrisentan background had no significant difference in cardiac index compared with placebo.

Table 38: Meta-analysis Results for Cardiac Index of PAH Treatments Compared With Placebo			
Treatment	**Background**	**No. of Patients**	**WMD (95% CI)[a], Random**
Riociguat oral max 2.5 mg t.i.d.	ERA	148[33]	**0.40 (0.22 to 0.58)**
Riociguat oral max 2.5 mg t.i.d.	Prostanoids	26[33]	**0.50 (0.04 to 0.96)**
Tadalafil oral 40 mg q.d.	Ambrisentan	124[36]	0.17 (–0.39 to 0.73)

CI = confidence interval; ERA = endothelin receptor antagonists; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; t.i.d. = three times a day; WMD = weighted mean difference.
[a] Bold indicates statistically significant difference.

5.4.3 Safety

a) Serious Adverse Events (Other Than Death)

Fourteen studies reported SAEs. SAEs were analyzed for total populations irrespective of the pre-treatment background in the EARLY,[32] PATENT-1,[33] PHIRST,[34] and SERAPHIN[35] studies. The events in the two doses of ambrisentan (5 mg and 10 mg) were combined for the analysis.

Table 39 shows that there were no statistically significant differences between PAH treatments including bosentan 125 mg, riociguat max 1.5 mg, sildenafil 20 mg, tadalafil 40 mg, and epoprostenol compared with placebo. The rates of SAEs were 11.4% and 18.3% in the riociguat max 2.5 mg and placebo groups, respectively; however, the treatment effect failed to reach statistical significance (RR = 0.63; 95% CI, 0.38 to 1.04). Similarly, rates of SAEs were 8.9% and 14.6% in the tadalafil 40 mg and placebo groups, respectively; however, the treatment effect failed to reach statistical significance (RR = 0.61; 95% CI, 0.25 to 1.46).

SAEs were significantly lowered in the ambrisentan (5 mg and 10 mg) (RR = 0.55; 95% CI, 0.32 to 0.96) and macitentan 10 mg (RR = 0.82; 95% CI, 0.68 to 0.98) groups compared with the placebo groups. In the ARIES-1 and 2 studies, SAEs that were less frequent in the ambrisentan than in the placebo groups were right ventricular failure (1.9% versus 6.1%) and PH worsening

(1.1% versus 3.8%).[86] Similar results were found for macitentan 10 mg compared with placebo: PAH worsening (13.2% versus 22.5%) and right ventricular failure (9.5% versus 16.1%).[87] In contrast, the study by Simonneau et al.[28] showed significantly more SAEs associated with treprostinil (61.9%) compared with placebo (20.2%) (RR = 3.15; 95% CI, 2.39 to 4.14). The SAEs frequently associated with treprostinil compared with placebo included injection site pain (39.4% versus 1.7%), injection site reaction (38.1% versus 0.9%), injection site bleed or bruise (4.2% versus 0.9%), rash (4.2% versus 0%), headache (3.4% versus 1.7%), pain (2.5% versus 0.9%), edema (1.7% versus 0%), and hypoxia (1.7% versus 0.4%).[88] Severe symptoms of heart failure were less frequent in treprostinil than in placebo (2.5% versus 4.7%).[88]

Table 39: Meta-analysis Results for SAEs of PAH Treatments Compared With Placebo

Treatment	Background	No. of Patients	Heterogeneity (I^2)	RR (95% CI), Random
Ambrisentan oral 5 mg & 10 mg q.d.	Naive	393[18]	NA	**0.55 (0.32 to 0.96)**
Bosentan oral 125 mg b.i.d.	Total	414[21-23,32]	0%	1.00 (0.61 to 1.64)
Macitentan oral 10 mg q.d.	Total	491[35]	NA	**0.82 (0.68 to 0.98)**
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	0.96 (0.50 to 1.84)
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	0.63 (0.38 to 1.04)
Sildenafil oral 20 mg t.i.d.	Naive	139[30]	NA	1.10 (0.54 to 2.24)
Tadalafil oral 40 mg q.d.	Total	161[34]	NA	0.61 (0.25 to 1.46)
Epoprostenol i.v.	Naive	111[19]	NA	0.95 (0.72 to 1.26)
Treprostinil s.c. or i.v.	Naive	535[26,28,31]	93.5%	No pooling
Simonneau[a]		469[28]	NA	**3.15 (2.39 to 4.14)**
Rubenfire		22[26]	NA	0.19 (0.02 to 1.54)
TRUST		44[31]	NA	0.57 (0.31 to 1.05)

AE = adverse event; b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RR = relative risk; SAE = serious adverse event; s.c. = subcutaneous; t.i.d. = three times a day.

[a] Reported as "severe" AEs in the published article.

b) Drug Discontinuation Due to Adverse Events

Sixteen studies reported drug discontinuation due to AEs. This outcome was analyzed for total populations irrespective of the pre-treatment background in the EARLY,[32] PATENT-1,[33] PHIRST,[34] and SERAPHIN[35] studies. The events in the two doses of ambrisentan (5 mg and 10 mg) were combined for the analysis.

Table 40 shows that there were no statistically significant differences between PAH treatments and placebo, except for treprostinil in the study by Simonneau et al.[28] In this study, the rates of drug discontinuation due to AEs for treprostinil and placebo were 7.7% and 0.4%, respectively

(RR = 18.23; 95% CI, 2.45 to 135.46). Discontinuation of treprostinil treatment was mainly due to abdominal subcutaneous injection site pain. [28]

Table 40: Meta-analysis Results for Drug Discontinuation Due to AEs of PAH Treatments Compared With Placebo

Treatment	Background	No. of Patients	Heterogeneity (I^2)	RR (95% CI), Random
Ambrisentan oral 5 mg & 10 mg q.d.	Naive	329[18]	NA	0.84 (0.23 to 3.06)
Bosentan oral 125 mg b.i.d.	Total	536[21-23,29,32]	0%	0.76 (0.42 to 1.36)
Macitentan oral 10 mg q.d.	Total	491[35]	NA	0.87 (0.53 to 1.41)
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	0.29 (0.04 to 2.27)
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	0.57 (0.21 to 1.53)
Sildenafil oral 20 mg t.i.d.	Naive	139[30]	NA	3.04 (0.13 to 73.43)
Tadalafil oral 40 mg q.d.	Total	161[34]	NA	0.61 (0.25 to 1.46)
Epoprostenol i.v.	Naive	111[19]	NA	Not estimable
Treprostinil s.c. or i.v.	Naive	535[26,28,31]	85.3%	No pooling
Simonneau	Naive	469[28]	NA	**18.23 (2.45 to 135.46)**
McLaughlin	Naive	26[25]	NA	2.78 (0.15 to 52.35)
Rubenfire	Naive	22[26]	NA	0.16 (0.04 to 0.60)
TRUST	Naive	44[31]	NA	0.23 (0.02 to 2.36)

AE = adverse event; b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day.

c) Total Withdrawal (Including Death)

Eighteen studies reported total withdrawal. This outcome was analyzed for total populations irrespective of the pre-treatment background in the EARLY,[32] PATENT-1,[33] PHIRST,[34] and SERAPHIN[35] studies. The events in the two doses of ambrisentan (5 mg and 10 mg) were combined for the analysis.

Table 41 shows that total withdrawal including death was significantly lowered in ambrisentan (ARIES-1 and 2: 7.6% versus 15.9%; RR = 0.45; 95% CI, 0.24 to 0.85), in epoprostenol (Barst and Badesch: 4.1% versus 12.6%; RR = 0.33; 95% CI, 0.11 to 0.95), and in treprostinil (Rubenfire: 14.3% versus 87.5%; RR = 0.16; 95% CI, 0.04 to 0.60) compared with placebo. Of note, the study by Rubenfire et al.[26] studied the transition of epoprostenol to treprostinil, and seven out of eight patients in the placebo group withdrew from the study due to clinical deterioration. In contrast, in the study by Simonneau et al.,[28] significantly more patients withdrew in the treprostinil group compared with the placebo group (14.2% versus 6.4%; RR = 2.23; 95% CI, 1.24 to 3.99).

There were no significant differences in total withdrawal between placebo and other treatments including bosentan, macitentan, riociguat, sildenafil, and tadalafil.

Table 41: Meta-analysis Results for Total Withdrawal of PAH Treatments Compared With Placebo				
Treatment	**Background**	**No. of Patients**	**Heterogeneity (I^2)**	**RR (95% CI)**
Ambrisentan oral 5 mg & 10 mg q.d.	Naive	329[18]	NA	**0.45 (0.24 to 0.85)**
Bosentan oral 125 mg b.i.d.	Total	536[21-23,29,32]	10.7%	0.72 (0.44 to 1.16)
Macitentan oral 10 mg q.d.	Total	491[35]	NA	0.77 (0.54 to 1.11)
Riociguat oral max 1.5 mg t.i.d.	Total	189[33]	NA	0.80 (0.33 to 1.96)
Riociguat oral max 2.5 mg t.i.d.	Total	380[33]	NA	0.56 (0.29 to 1.09)
Sildenafil oral 20 mg t.i.d.	Naive	139[30]	NA	1.01 (0.15 to 7.00)
Tadalafil oral 40 mg q.d.		285[34,36]	0%	0.82 (0.42 to 1.57)
Epoprostenol i.v.	Naive	192[19,20]	0%	**0.33 (0.11 to 0.95)**
Treprostinil s.c. or i.v.	Naive	535[26,28,31]	82.1%	No pooling
Simonneau	Naive	469[28]	NA	**2.23 (1.24 to 3.99)**
McLaughlin	Naive	26[25]	NA	2.78 (0.15 to 52.35)
Rubenfire	Naive	22[26]	NA	**0.16 (0.04 to 0.60)**
TRUST	Naive	44[31]	NA	0.54 (0.22 to 1.32)

b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; No. = number; PAH = pulmonary arterial hypertension; q.d. = once a day; RR = relative risk; s.c. = subcutaneous; t.i.d. = three times a day.

d) Treatment-Related Adverse Events

Liver Toxicity:

Liver toxicity, as measured by the increase in aminotransferases (ALT or AST) more than three times the upper limit of normality, was more frequent in the bosentan (11.6%) compared with placebo (2.4%) groups. The meta-analysis result of five bosentan studies[21-23,29,32] yielded a relative risk of 3.29 (95% CI, 1.47 to 7.37; I^2 = 0%).

There were no significant differences in liver toxicity between placebo and other treatments including macitentan, riociguat, sildenafil, tadalafil, epoprostenol, and treprostinil.

Peripheral Edema:

Compared with placebo, peripheral edema was more frequently associated with ambrisentan (both doses combined from ARIES-1 and 2: 21.8% versus 10.6%; RR = 2.06; 95% CI, 1.17 to 3.61), bosentan (pooled results of BREATHE-1, BREATHE-5, EARLY, STRIDE-2: 13.3% versus 7.9%; RR = 1.61; 95% CI, 0.93 to 2.79; I^2 = 0%), riociguat (both doses combined from PATENT-1: 18.3% versus 11.1%; RR = 1.65; 95% CI, 0.95 to 2.84), and treprostinil (Simonneau: 9.0% versus 2.5%; RR = 3.55; 95% CI, 1.46 to 8.62).

There were no differences in peripheral edema between placebo and other treatments including macitentan, sildenafil, tadalafil, and epoprostenol.

Anemia:

Compared with placebo, anemia (as defined by the decrease in hemoglobin ≥ 1 g/dL) was more frequently associated with ambrisentan 5 mg (63.8% versus 17.4%; RR = 3.66; 95% CI, 2.47 to 5.43), ambrisentan 10 mg (73.1% versus 17.4%; RR = 4.20; 95% CI, 2.82 to 6.25), macitentan 10 mg (13.2% versus 3.2%; RR = 4.12; 95% CI, 1.94 to 8.75), and riociguat max 2.5 mg (8.3% versus 2.4%; RR = 3.47; 95% CI, 1.06 to 11.42).

There was no significant difference in anemia between the bosentan and placebo groups in BREATHE-1[21] (6.8% versus 0%; RR = 10.27; 95% CI, 0.58 to 182.29). Other studies did not report anemia as an adverse event.

Hypotension:
Compared with placebo, hypotension was more frequently associated with riociguat max 2.5 mg (9.8% versus 2.4%; RR = 4.13; 95% CI, 1.27 to 13.43). Hypotension was also numerically higher in the epoprostenol (Badesch: 12.5% versus 0%) and treprostinil (Simonneau and McLaughlin: 5.2% versus 2.0%) compared with the placebo groups, but the differences did not reach statistical significance.

There were no differences in hypotension between placebo and ambrisentan, between placebo and bosentan, or between placebo and macitentan. Hypotension was not reported in studies on sildenafil and tadalafil.

Others:
Epoprostenol in the study by Badesch et al.[19] had a higher incidence of nausea (41% versus 16%), diarrhea (50% versus 5%), jaw pain (75% versus 0%), headache (46% versus 5%), and injection site reaction (14% versus 0%) compared with placebo. A similar observation was found for treprostinil compared with placebo: diarrhea (27.1% versus 15.5%),[26,28,31] jaw pain (15.5% versus 4.7%),[26,28,31] headache (30.7% versus 24.4%),[26,28,31] and injection site reaction (84.0% versus 25.3%).[25,26,28]

5.4.4 Health-Related Quality of Life

The summary of HRQoL for ambrisentan, macitentan, riociguat, sildenafil, tadalafil, epoprostenol, and treprostinil compared with placebo is presented in APPENDIX 13.

a) Ambrisentan
In ARIES-1,[18] ambrisentan 5 mg and 10 mg showed no statistically significant differences in physical functioning and other items of the SF-36 scales compared with placebo. In contrast, ambrisentan 5 mg in ARIES-2[18] showed significant improvement for physical functioning (P = 0.005) and several other SF-36 scales, including role–physical, vitality, role–emotional, and general health. The change value in both trials met that of the MCID, which was between 3 and 5 points for any given domain.

Using Subject Global Assessment in the study by Galiè et al.,[24] the mean score for all ambrisentan dose groups (1 mg, 2.5 mg, 5 mg, and 10 mg) combined improved by 11.3 ± 2.4 mm at week 12 compared with baseline. There were no differences among dose groups.

b) Bosentan
Of the five bosentan studies included in this review, only EARLY[32] reported quality of life using the SF-36 health survey. There were no statistically significant differences between bosentan and placebo for any of the eight components of SF-36.

c) Macitentan
At month 6, macitentan of both doses (3 mg and 10 mg) showed significant improvements in seven out of eight domains (P < 0.05, except general health perception) of SF-36 compared with placebo.[89] Both doses reduced the risk of deterioration of the physical and mental components of HRQoL over the entire treatment duration. It was unclear, however, whether the change met the MCID value, which was between 3 and 5 points for any given domain.

d) Riociguat

The EQ-5D and Living with Pulmonary Hypertension (LPH) questionnaire were used to assess quality of life in PATENT-1.[33] On EQ-5D, riociguat at both the 1.5 mg and 2.5 mg doses showed improvement in quality of life, but the differences between riociguat and placebo were not statistically significant. Although statistical significance could not be reached, the change in EQ-5D by riociguat compared with placebo exceeded the MCID, which ranged from 0.033 to 0.074. Change in LPH by riociguat was statistically significant and met the MCID value, which was 7 points (range: 4.41 to 11.02) for total score.

e) Sildenafil

The SF-36 and EQ-5D were used to assess quality of life in SUPER.[30] Compared with placebo, sildenafil 20 mg showed statistically significant improvements in physical functioning ($P < 0.001$), general health ($P < 0.001$) and vitality scores ($P < 0.05$) of SF-36. Improvements were also observed in the current health status ($P < 0.01$) and utility index ($P < 0.01$) scores of the EQ-5D. The change values met those of the MCID.

f) Tadalafil

The SF-36 and EQ-5D were used to assess quality of life in PHIRST.[34] On SF-36, tadalafil 40 mg had statistically significant improvements in six of the eight domains of the SF-36 ($P < 0.01$), except role–emotional and mental health. On the EQ-5D, tadalafil 40 mg displayed improvements in all sections ($P < 0.02$). It was unclear, however, whether the change values met those of the MCID.

g) Epoprostenol

Only the study by Barst et al.[20] reported quality of life in patients with PPH (now, IPAH/FPAH) using the Chronic Heart Failure Questionnaire, Nottingham Health Profile, and Dyspnea-Fatigue Rating. Compared with placebo, there were significant improvements with epoprostenol in all four parts (dyspnea, fatigue, emotional, and mastery) of the Chronic Heart Failure Questionnaire, in two of six parts of the Nottingham Health Profile, and in the Dyspnea-Fatigue Rating ($P < 0.01$). The MCID values for those instruments were unclear.

h) Treprostinil

Only the study by Simonneau et al.[28] used the Minnesota Living with Heart Failure Questionnaire (global, physical, and emotional) to assess quality of life in PAH patients. Compared with placebo, treprostinil showed significant improvement only in physical dimension score. The MCID values for this instrument were unclear.

5.4.5 Subgroup Analyses

Five studies of bosentan,[21] macitentan,[35] riociguat,[33] sildenafil,[30] and tadalafil[34] provided subgroup analyses with respect to age, baseline FC, baseline 6MWD, gender, PAH etiology, and PAH therapies at baseline. The latter was described in detail in Sections 4.4.1 and 4.4.2 for macitentan, riociguat, and tadalafil. The macitentan study (SERAPHIN) reported subgroup analyses on clinical worsening and 6MWD, while other studies reported subgroup analyses on 6MWD.

a) Bosentan

The combined doses of bosentan (125 mg and 250 mg) numerically improved 6MWD in all patient subgroups (Table 42). However, statistically significant differences were not reached for male patients, patients with baseline 6MWD less than 350 m, and patients with congenital heart disease.

Table 42: Subgroup Analyses of Bosentan (Combined 125 mg & 250 mg) Versus Placebo		
Baseline Variable	**No. of Patients**	**Effect Size (95% CI)**
6MWD (16 weeks)		***(LS Mean Difference)***
All patients	213	44.2 (21.4 to 67.0)
Gender		
Males	45	46.8 (–8.6 to 106.1)
Females	168	43.1 (18.2 to 68.0)
Age		
< 50 years	99	50.5 (15.0 to 85.9)
≥ 50 years	114	40.3 (10.3 to 70.3)
WHO FC		
III	195	40.2 (17.8 to 62.5)
IV	18	138.5 (23.7 to 253.4)
6MWD		
< 350 m	110	35.4 (–0.1 to 70.8)
≥ 350 m	103	52.4 (22.3 to 82.5)
PAH etiology		
Idiopathic/familial	199	44.0 (20.2 to 67.8)
Congenital heart disease	14	39.0 (–53.9 to 131.9)

6MWD = six-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; LS = least squares; PAH = pulmonary arterial hypertension; WHO = World Health Organization.
Source: BREATHE-1;[21] FDA clinical report.[90]

b) Macitentan

For clinical worsening, macitentan at a 10 mg dose significantly improved in patients irrespective of gender, PAH etiology (except congenital shunts), or background PAH therapies (Table 43).

Macitentan at a 10 mg dose significantly improved 6MWD in patients with baseline FC III or IV (but not FC I or II), and in patients with PAH background therapies (but not naive) (Table 43).

Table 43: Subgroup Analyses of Macitentan 10 mg Versus Placebo		
Baseline Variable	**No. of Patients**	**Effect Size (95% CI)**
Clinical Worsening (Median 115 Weeks)		***(Hazard Ratio)***
All patients	492	0.6 (0.4 to 0.7)
Gender		
Males	113	0.5 (0.3 to 0. 9)
Females	379	0.6 (0.4 to 0.8)
PAH etiology		
Connective tissue disease	155	0.6 (0.3 to 1.0)
Congenital shunts	47	0.4 (0.1 to 1.3)
Idiopathic/other	287	0.5 (0.4 to 0.8)
Background PAH therapies		
Yes	308	0.6 (0.4 to 0.9)
No	183	0.5 (0.3 to 0.7)
6MWD (6 months)		*(LS mean difference)*
All patients	491	22.8 (4.0 to 41.5)
WHO FC		
I or II	250	12.3 (–8.1 to 32.7)
III or IV	241	37.0 (5.4 to 68.6)
Background PAH therapies		
Yes (with PDE-5i or prostanoids)	308	25.9 (4.5 to 47.3)
No (naive)	183	17.8 (–17.8 to 53.3)

6MWD = six-minute walk distance; CI = confidence interval; FC = functional class; LS = least squares; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; WHO = World Health Organization.
Source: SERAPHIN;[35] FDA clinical report.[87]

c) Riociguat

Riociguat max 2.5 mg numerically improved 6MWD in all patient subgroups (Table 44). However, statistically significant differences were not reached for males, patients with baseline FC I or II, and patients with APAH (connective tissue disease or other forms of PAH).

Table 44: Subgroup Analyses of Riociguat Max 2.5 mg Versus Placebo		
Baseline Variable	**No. of Patients**	**Effect Size (95% CI)**
6MWD (12 Weeks)		***(LS Mean Difference)***
All patients	380	35.8 (20.1 to 51.5)
Gender		
Males	79	31.4 (–9.3 to 72.1)
Females	301	36.9 (20.2 to 53.6)
Age		
< 65 years	282	27.3 (8.1 to 46.4)
≥ 65 years	98	54.8 (30.2 to 79.4)
WHO FC		
I or II	177	12.1 (–8.1 to 32.4)
III or IV	202	59.7 (36.4 to 83.0)
6MWD		
< 320 m	94	57.3 (20.5 to 94.2)
≥ 320 m	286	29.2 (11.7 to 46.6)
< 380 m	192	49.5 (25.2 to 73.8)
≥ 380 m	188	25.0 (4.4 to 45.6)
PAH etiology		
Idiopathic/Familial	241	42.8 (23.4 to 62.2)
Connective tissue disease	96	28.1 (–4.4 to 60.6)
Other forms of PAH	43	18.2 (–32.5 to 69.0)
Background PAH therapies		
No (naive)	189	38.4 (14.5 to 62.3)
Yes	191	35.7 (15.0 to 56.3)
With ERA	167	25.9 (5.3 to 46.5)
With prostanoids	24	101.3 (26.5 to 176.0)

6MWD = six-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; LS = least squares; PAH = pulmonary arterial hypertension; WHO = World Health Organization
Source : PATENT-1;[33] FDA clinical report[91]

d) Sildenafil

Sildenafil 20mg significantly improved 6MWD in all patient subgroups (data summarized as a forest plot in the SUPER published article; data not shown).[30]

e) Tadalafil

Tadalafil 40 mg improved 6MWD in all patient subgroups. However, statistically significant differences were not reached for male patients and patients with PAH etiology other than idiopathic or connective tissue disease (Table 45).

Table 45: Subgroup Analyses of Tadalafil 40 mg Versus Placebo		
Baseline Variable	**No. of Patients**	**Effect Size (95% CI)**
6MWD (16 weeks)		***(LS Mean Difference)***
All patients	155	33 (15 to 50)
Gender		
Males	36	25 (–18 to 67)
Females	119	34 (14 to 53)
Age		
< median (54 years)	81	34 (8 to 60)
≥ median (54 years)	74	28 (4 to 52)
WHO FC		
I or II	51	24 (0 to 48)
III or IV	104	36 (11 to 60)
6MWD		
< 325 m	53	49 (17 to 82)
≥ 325 m	102	26 (5 to 45)
PAH etiology		
Idiopathic	97	24 (1 to 47)
Connective tissue disease	33	49 (15 to 83)
Repaired S-P shunts	8	51 (–88 to 191)
Others	17	44 (–25 to 113)

6MWD = six-minute walk distance; CI = confidence interval; FC = functional class; LS = least squares; PAH = pulmonary arterial hypertension; S-P = systemic-to-pulmonary; WHO = World Health Organization
Source: PHIRST;[34] FDA clinical report[92]

5.5 Pharmacoeconomic Evaluation

As presented in APPENDIX 15, the majority of studies identified in the literature review were of poor to moderate quality, with estimates of treatment efficacy derived using erroneous methodology. Based on the available published literature, the following may be surmised:

- In general, the evidence supports the cost-effectiveness of the oral agents as compared with supportive or palliative care in PAH FC III.
- Treatment with prostaglandin drugs was generally not found to be cost-effective.
- When comparing drugs, sildenafil was generally found to be the least costly drug, whereas epoprostenol was generally the most costly. The comparative efficacy of the treatments has not been well established due to the lack of head-to-head clinical trials and due to inadequate information on the comparability of the populations studied with each of the drugs. It is therefore not possible to provide conclusions regarding the relative cost-effectiveness of the oral drugs or of the prostaglandins based on currently available literature.

5.5.1 Base-Case Analysis

a) Monotherapy Versus Supportive Care

Pulmonary Arterial Hypertension Functional Class II:

The results of the base case comparing single PAH therapies and supportive care in FC II are presented in Table 46.

In a cohort of patients with PAH FC II, the most effective treatment with respect to gains in QALYs was sildenafil, which generated 4.882 QALYs; followed by ambrisentan 5 mg (4.772 QALYs); riociguat (4.455 QALYs); ambrisentan 10 mg (4.293 QALYs); tadalafil (4.030 QALYs); bosentan (3.643 QALYs); and supportive care (3.174 QALYs).

The least costly therapy was also sildenafil, with an average total cost of $142,985. Tadalafil resulted in greater costs than sildenafil at $151,529, followed by supportive care ($156,998), ambrisentan 10 mg ($378,680), ambrisentan 5 mg ($381,930), riociguat ($392,420), and bosentan ($404,989).

For all treatments other than supportive care, drug therapy constituted the greatest proportion of total costs (range of 60% to 91.2% of total costs) (APPENDIX 19) For supportive care, the costs of drug therapy (epoprostenol after move into FC IV) in combination with supportive care therapy costs constituted the greatest proportion of total costs (40.9%). Hospitalization costs constituted the second greatest proportion of total costs (range from 4.9% to 38.5%) for all treatments except epoprostenol. For epoprostenol, equipment constituted 25.5% of total costs.

As sildenafil is both the least costly and most effective therapy, it dominates all other treatments.

As compared with supportive care, both sildenafil and tadalafil are less costly, whereas ambrisentan 5 mg and 10 mg, riociguat, and bosentan are all more costly (Table 47). All treatments resulted in greater QALYs than supportive care. When considering cost-effectiveness in comparison with supportive care, both sildenafil and tadalafil dominate supportive care as they resulted in greater QALYs at lower costs. All other treatments resulted in ICURs greater than $140,000 per QALY versus supportive care. With respect to the incremental net benefit of treatment over supportive care, at a willingness to pay of $50,000 per QALY, only sildenafil and tadalafil would be considered cost-effective. Only at a willingness to pay of $200,000 per QALY would other therapies — specifically ambrisentan 5 mg, ambrisentan 10 mg, and riociguat — be potentially cost-effective.

Table 46: Results of Base-Case Deterministic Analysis for Monotherapy in Functional Class II

Treatment	Total Costs	Total QALYs	Versus Sildenafil		
			Incremental Costs	Incremental QALYs	ICUR
Sildenafil	$142,985	4.882	Ref	Ref	Dominates all treatments
Dominated Treatments					
Tadalafil	$151,529	4.030	$8,545	–0.852	Dominated by sildenafil
Supportive care	$156,998	3.174	$14,013	–1.708	Dominated by sildenafil
Ambrisentan 10 mg	$378,680	4.293	$235,695	–0.589	Dominated by sildenafil
Ambrisentan 5 mg	$381,930	4.772	$238,945	–0.110	Dominated by sildenafil
Riociguat	$392,420	4.455	$249,436	–0.426	Dominated by sildenafil
Bosentan	$404,989	3.643	$262,004	–1.239	Dominated by sildenafil

Dominated = more costly and fewer QALYs; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Table 47: Results of Incremental Net Benefit Analysis for Monotherapy Versus Supportive Care in Functional Class II					
		Incremental Net Benefit Versus Supportive Care			
Treatment	**ICUR vs. Supportive Care**	**ʎ = $30,000**	**ʎ = $50,000**	**ʎ = $100,000**	**ʎ = $200,000**
Sildenafil	Dominates supportive care	$65,250	$99,408	$184,804	$355,594
Tadalafil	Dominates supportive care	$31,145	$48,263	$91,058	$176,647
Ambrisentan 10 mg	$198,043	–$188,101	–$165,714	–$109,746	$2,190
Ambrisentan 5 mg	$140,746	–$176,988	–$145,025	–$65,118	$94,696
Riociguat	$183,676	–$196,971	–$171,336	–$107,250	$20,923
Bosentan	$528,428	–$233,912	–$224,526	–$201,061	–$154,131

ICUR = incremental cost-utility ratio; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

PAH Functional Class III:
Similar results were found for patients with PAH FC III as in FC II. (Table 48) Although the costs associated with treatment were greater in FC III, sildenafil remained the least costly treatment at $172,911, followed by tadalafil ($198,287), supportive care ($205,888), ambrisentan 5 mg ($347,915), ambrisentan 10 mg ($373,606), riociguat ($375,719), bosentan ($419,630), and epoprostenol ($430017). Sildenafil was also the most effective treatment, generating 3.366 QALYs. The next most effective treatment was ambrisentan 5 mg (3.226 QALYs), followed by epoprostenol (3.123 QALYs), ambrisentan 10 mg (3.060 QALYs), tadalafil (3.006 QALYs), bosentan (2.812 QALYs), and finally supportive care (2.640 QALYs).

As in FC II, for all treatments other than supportive care, drug therapy constituted the greatest proportion of total costs (range of 50.5% to 80.3% of total costs) (APPENDIX 19). For supportive care, the costs of drug therapy (epoprostenol after move into FC IV) in combination with supportive care therapy costs constituted the greatest proportion of total costs (42.1%). Hospitalization costs were higher than in FC II and constituted the second greatest proportion of total costs (range from 12.9% to 37.4%) for all treatments except epoprostenol. For epoprostenol, equipment constituted 23.6% of total costs.

Given that sildenafil is both less costly and more effective than all other treatments, it is the dominant therapy.

In comparing PAH treatments with supportive care, both sildenafil and tadalafil are dominant over supportive care as they are both less costly and more effective (Table 49). In contrast to the results for patients with PAH FC II, even at a willingness to pay of $200,000 per QALY, the other treatments would not be considered cost-effective versus supportive care.

Table 48: Results of Base-Case Deterministic Analysis for Monotherapy in Functional Class III					
Treatment	**Total Costs**	**Total QALYs**	**Versus sildenafil**		
			Incremental Costs	**Incremental QALYs**	**ICUR**
Sildenafil	$172,911	3.366	Ref	Ref	Dominates all treatments
Dominated Treatments					
Tadalafil	$198,287	3.006	$25,376	–0.360	Dominated by sildenafil
Supportive care	$205,888	2.640	$32,977	–0.726	Dominated by sildenafil
Ambrisentan 5 mg	$347,915	3.226	$175,003	–0.139	Dominated by sildenafil
Ambrisentan 10 mg	$373,606	3.060	$200,695	–0.306	Dominated by sildenafil
Riociguat	$375,719	3.117	$202,808	–0.249	Dominated by sildenafil
Bosentan	$419,630	2.812	$246,719	–0.553	Dominated by sildenafil
Epoprostenol	$430,017	3.123	$257,106	–0.243	Dominated by sildenafil

Dominated = more costly and fewer QALYs; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Table 49: Results of Incremental Net Benefit Analysis for Monotherapy Versus Supportive Care in Functional Class III					
		Incremental Net Benefit Versus Supportive Care			
Treatment	**ICUR vs. supportive care**	**ʎ = $30,000**	**ʎ = $50,000**	**ʎ = $100,000**	**ʎ = $200,000**
Sildenafil	Dominates supportive care	$54,759	$69,281	$105,584	$178,190
Tadalafil	Dominates supportive care	$18,588	$25,913	$44,224	$80,847
Ambrisentan 5 mg	$242,106	–$124,427	–$112,695	–$83,363	–$24,700
Ambrisentan 10 mg	$398,804	–$155,101	–$146,690	–$125,662	–$83,607
Riociguat	$355,814	–$155,512	–$145,966	–$122,100	–$74,370
Bosentan	$1,237,643	–$208,561	–$205,107	–$196,472	–$179,202
Epoprostenol	$463,926	–$2069,635	–$199,973	–$175,817	–$127,506

ICUR = incremental cost-utility ratio; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

PAH Functional Class IV:

In PAH FC IV, supportive care was the least costly therapy at $261,757 followed by sildenafil ($265,798), tadalafil ($281,680), epoprostenol ($410,629), ambrisentan 5 mg ($462,341), ambrisentan 10 mg ($464,624), riociguat ($473,287), and bosentan ($483,042) (Table 50). Sildenafil was the most effective treatment, generating 2.573 QALYs, followed by epoprostenol

(2.463 QALYs), tadalafil (2.456 QALYs), ambrisentan 5 mg (2.428 QALYs), riociguat (2.420 QALYs), ambrisentan 10 mg (2.416 QALYs), bosentan (2.379 QALYs), and supportive care (2.632 QALYs).

For all treatments, drug therapy constituted the greatest proportion of total costs (range of 36.8% to 66.9% of total costs) (APPENDIX 19). Hospitalization costs were higher than in FC II and III and constituted the second greatest proportion of total costs (range from 18.9% to 35.6%) for all treatments except epoprostenol. For epoprostenol, equipment constituted 21.4% of total costs.

Compared with supportive care alone, sildenafil generated greater QALYs, but at a greater cost, resulting in an ICUR of $19,188 per QALY (Table 51). At a willingness to pay of $50,000 per QALY, sildenafil would be considered cost-effective versus supportive care alone. All other therapies were both more costly than sildenafil and less effective and were therefore dominated by sildenafil. Even at a willingness to pay of $200,000 per QALY, none of the therapies apart from sildenafil were cost-effective relative to supportive care.

Table 50: Results of Base-Case Deterministic Analysis for Monotherapy in Functional Class IV

Treatment	Total Costs	Total QALYs	Versus Supportive Care			Incremental ICUR
			Incremental Costs	Incremental QALYs	ICUR	
Supportive care	$261,757	2.362	Ref	Ref	Ref	Ref
Sildenafil	$265,798	2.573	$4,041	0.211	$19,188	$19,188
Dominated Treatments						
Tadalafil	$281,680	2.456	$19,923	0.094	$211,923	Dominated by sildenafil
Epoprostenol	$410,629	2.463	$148,872	0.102	$1,452,414	Dominated by sildenafil
Ambrisentan 5 mg	$462,341	2.428	$200,584	0.066	$3,046,866	Dominated by sildenafil
Ambrisentan 10 mg	$464,624	2.416	$202,867	0.054	$3,754,093	Dominated by sildenafil
Riociguat	$473,287	2.420	$211,530	0.058	$3,646,553	Dominated by sildenafil
Bosentan	$483,042	2.379	$221,285	0.017	$13,284,345	Dominated by sildenafil

Dominated = more costly and fewer QALYs; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Table 51: Results of Incremental Net Benefit Analysis Monotherapy Versus Supportive Care in Functional Class IV					
		Incremental Net Benefit Versus Supportive Care			
Treatment	**ICUR vs. Supportive Care**	**ʎ = $30,000**	**ʎ = $50,000**	**ʎ = $100,000**	**ʎ = $200,000**
Sildenafil	$19,188	$2,277	$6,489	$17,019	$38,080
Tadalafil	$211,923	–$17,103	–$15,222	–$10,522	–$1,121
Epoprostenol	$1,452,414	–$145,797	–$143,747	–$138,622	–$128,372
Ambrisentan 5 mg	$3,046,866	–$198,609	–$197,293	–$194,001	–$187,418
Ambrisentan 10 mg	$3,754,093	–$201,246	–$200,165	–$197,463	–$192,060
Riociguat	$3,646,553	–$209,790	–$208,630	–$205,729	–$199,928
Bosentan	$13,284,345	–$220,786	–$220,452	–$219,620	–$217,954

ICUR = incremental cost-utility ratio; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

b) Add-on Therapy Versus Monotherapy

Functional Class II:

In patients with PAH FC II, the addition of tadalafil or riociguat to ERA therapy resulted in greater costs ($475,367 for ERA plus tadalafil and $742,909 for ERA plus riociguat) as compared with an ERA alone ($434,326); however, add-on therapy also generated greater QALYs. ERA plus tadalafil generated 3.652 QALYs and ERA plus riociguat generated 4.175 QALYs as compared with 3.189 QALYs with an ERA alone.

For all treatments, drug therapy constituted the greatest proportion of total costs (range of 75.7% to 91.9% of total costs) (APPENDIX 19). Hospitalization costs constituted the second greatest proportion of total costs (range from 4.8% to 14.2%).

As compared with an ERA alone, add-on therapy with an ERA plus tadalafil resulted in an ICUR of $88,506 per QALY and an ERA plus riociguat produced an ICUR of $312,876 per QALY. When the combination of ERA plus riociguat is compared with ERA plus tadalafil, the ICUR was $511,973 per QALY.

Table 52: Results of Base-Case Deterministic Analysis for Add-on Therapies in Functional Class II						
Treatment	**Total Costs**	**Total QALYs**	**Versus ERA alone**			**Incremental ICUR**
			Incremental Costs	**Incremental QALYs**	**ICUR**	
ERA plus placebo	$434,326	3.189	Ref	Ref	Ref	Ref
ERA plus tadalafil	$475,367	3.652	$41,041	0.464	$88,506	$88,506
ERA plus riociguat	$742,909	4.175	$308,583	0.986	$312,876	$511,973

ERA = endothelin receptor antagonist; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; ref = reference.

Functional Class III:

Consistent with the results in patients with PAH FC II, treatment with an ERA alone was less costly at $448,729 than either treatment with the combination of an ERA plus tadalafil at $476,719 or with an ERA plus riociguat at $674,033 in patients with PAH FC III. Treatment with the combination of an ERA plus riociguat was the most effective, generating 3.084 QALYs, followed by an ERA plus tadalafil (2.840 QALYs) and an ERA alone (2.661 QALYs).

For all treatments, drug therapy constituted the greatest proportion of total costs (range of 70.6% to 85.8% of total costs) (APPENDIX 19). Hospitalization costs constituted the second greatest proportion of total costs (range from 8.6% to 17.2%).

The ICUR for an ERA plus tadalafil versus an ERA alone was higher than in FC II at $156,513 per QALY. In comparing an ERA plus riociguat versus an ERA plus tadalafil, the ICUR was $809,183 per QALY.

Table 53: Results of Base-Case Deterministic Analysis for Add-on Therapies in Functional Class III

Treatment	Total Costs	Total QALYs	Versus ERA alone			Incremental ICUR
			Incremental Costs	Incremental QALYs	ICUR	
ERA plus placebo	$448,729	2.661	Ref	Ref	Ref	Ref
ERA plus tadalafil	$476,719	2.840	$27,991	0.179	$156,513	$156,513
ERA plus riociguat	$674,033	3.084	$225,304	0.423	$533,035	$809,183

ERA = endothelin receptor antagonist; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; ref = reference.

Functional Class IV:
In PAH FC IV, the results for add-on therapies were consistent with those in FC II and III, with an ERA alone being the least costly therapy and ERA plus riociguat being the most effective therapy.

For all treatments, drug therapy constituted the greatest proportion of total costs (range of 66.9% to 79.2% of total costs) (APPENDIX 19). Hospitalization costs constituted the second greatest proportion of total costs (range from 12.2% to 19.2%).

As a result of smaller incremental benefits compared with an ERA alone, the ICURs were greater in FC IV than in class II and class III. For an ERA plus tadalafil, the ICUR versus an ERA alone is $1,568,400 per QALY and for an ERA plus riociguat versus an ERA plus tadalafil, it is $1,995,139 per QALY.

Table 54: Results of Base-Case Deterministic Analysis for Add-on Therapies in Functional Class IV						
Treatment	**Total Costs**	**Total QALYs**	**Versus ERA alone**			**Incremental ICUR**
			Incremental Costs	**Incremental QALYs**	**ICUR**	
ERA plus placebo	$481,451	2.376	Ref	Ref	Ref	Ref
ERA plus tadalafil	$524,151	2.403	$42,700	0.027	$1,568,400	$1,568,400
ERA plus riociguat	$693,932	2.488	$212,481	0.112	$1,891,704	$1,995,139

ERA = endothelin receptor antagonist; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; ref = reference.

5.5.2 Deterministic Sensitivity Analysis

a) Summary

As with all models, a number of assumptions were made with respect to both the structure of the model and regarding the input parameters. Extensive univariate sensitivity analyses were conducted to assess the robustness of the results.

The results of the sensitivity analyses are presented for single therapies first by FC, and then for add-on therapy versus monotherapy. Following these are the results of an exploratory analysis examining the cost-effectiveness of macitentan in PAH.

Univariate Sensitivity Analysis for Comparison of Single Therapies

Univariate Sensitivity Analyses for Single Therapies in Pulmonary Arterial Hypertension Functional Class II:

Sensitivity Analyses Regarding the Percentage of Patients Adding Epoprostenol Therapy Upon Deteriorating to Functional Class IV:

In the base-case analysis, it was assumed that 50% of patients would add epoprostenol therapy to their existing PAH therapies upon deteriorating to FC IV. This was based on expert clinical advice reflecting the current Canadian treatment approach. To assess the uncertainty regarding the percentage of patients who would initiate epoprostenol therapy upon deteriorating to FC IV, this value was varied between 0% and 100%. The results presented in Table 55 show that increasing the percentage initiating epoprostenol to 100% did not alter the base-case results, as sildenafil remained the dominant treatment. When the percentage was reduced to 0%, supportive care was less costly than sildenafil and therefore sildenafil was no longer the dominant therapy; however, sildenafil produced greater QALYs than supportive care, resulting in an ICUR of $36,485 per QALY.

Table 55: Results of Univariate Sensitivity Analysis for PAH FC II Regarding the Percentage of Patients Adding Epoprostenol Therapy Upon Deteriorating to FC IV	
Scenario	**Result**
Base-case analysis 50% of patients initiating epoprostenol in FC IV	Sildenafil dominated all other therapies
Decrease percentage to 0% of patients initiating epoprostenol in FC IV	If ʎ < $36,485 per QALY, supportive care is most cost-effective If ʎ > $36,485 per QALY, sildenafil is most cost-effective therapy
Increase percentage to 100% of patients initiating epoprostenol in FC IV	Sildenafil dominated all other therapies

FC = functional class; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating a Generic Price for Bosentan:

Incorporating the generic price for bosentan within the model reduced the costs associated with bosentan; however, it remained more costly than sildenafil and less effective, and therefore sildenafil remained the optimal therapy.

Table 56: Results of Univariate Sensitivity Analysis for PAH Functional Class II Incorporating a Generic Price for Bosentan	
Scenario	**Result**
Base-case analysis	Sildenafil dominated all other therapies
Generic price for bosentan	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Removing the Markup and Dispensing Fee Costs for all Medications:

A sensitivity analysis in which the markup and dispensing fee costs for all medications were removed from the costs of therapy did not affect the results of the study, with sildenafil remaining the dominant treatment strategy.

Table 57: Results of Univariate Sensitivity Analysis for PAH Functional Class II Removing the Markup and Dispensing Fee Costs for all Medications	
Scenario	**Result**
Base-case analysis	Sildenafil dominated all other therapies
No markup or dispensing fees for medications	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Examining High and Low Costs of Epoprostenol in Subsequent Cycles (Post-Titration):

Epoprostenol is dosed based on patients' body weight and patients' response, with most patients receiving increasing doses with continued long-term treatment. The effect of differing doses of epoprostenol on the results of the analysis were tested by incorporating both a low cost of epoprostenol based on minimal dosing recommendations and a high cost of epoprostenol based on maximum dosing recommendations. The results of these analyses were consistent with the base-case analysis in which sildenafil dominated all other therapies.

Table 58: Results of Univariate Sensitivity Analysis for PAH Functional Class II Incorporating High and Low cost for Epoprostenol	
Scenario	**Result**
Base-case analysis	Sildenafil dominated all other therapies
Increase epoprostenol cost to $44,351 per annum for subsequent cycles	Sildenafil dominated all other therapies
Decrease epoprostenol cost to $26,061 per annum for subsequent cycles	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol Supplies:

In the base-case analysis, the cost of epoprostenol infusion pump supplies and tubing were estimated at $52.56 per day; however, the cost that the Saskatchewan Provincial Formulary reimburses is $46.00 per day. A sensitivity analysis was conducted with this alternative price of supplies. The reduced cost for epoprostenol supplies did not affect the results of the analysis, with sildenafil remaining the dominant therapy.

Table 59: Results of Univariate Sensitivity Analysis for PAH Functional Class II Incorporating Lower Cost for Epoprostenol Supplies	
Scenario	**Result**
Base-case analysis	Sildenafil dominated all other therapies
Reduced cost of epoprostenol supplies	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol (Based on Caripul):

In the base-case analysis, the cost of epoprostenol was based on the brand product Flolan, as it is the most commonly prescribed version of epoprostenol. There is, however, an alternative epoprostenol product available, under the brand name Caripul, which is less costly with respect to both the drug vial and the diluent required for dissolution ($17.18 and $34.45 per 0.5 mg and 1.5 mg vials, respectively, and $3.15 per 50 mL vials of sterile water for injection). Incorporating the lower cost of Caripul within this analysis did not change the results relative to the base case, with sildenafil remaining dominant over other therapies.

Table 60: Results of Univariate Sensitivity Analysis for PAH Functional Class II Incorporating Lower Cost for Epoprostenol (Based on Caripul)	
Scenario	**Result**
Base-case analysis (epoprostenol cost first cycle: $5,274 and subsequent cycles: $11,247	Sildenafil dominated all other therapies
Decreased cost of epoprostenol (epoprostenol cost first cycle: $3,069 and subsequent cycles: $8,587)	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Examining Health Care Costs Within Functional Class I:

Health care usage costs for patients with PAH FC I were assumed to be 0 within the base case, primarily due to a lack of data availability. Although this is unlikely to have a significant impact on the results, given that only those patients beginning in FC II are able to enter FC I, and they

would do so only during the first cycle, when improvements due to treatment are applied. To test the impact of this assumption, a sensitivity analysis was conducted, equating the health care costs in FC I with those of FC II. This change had little impact on the results, with sildenafil remaining the dominant treatment versus other therapies and supportive care.

Table 61: Results of Univariate Sensitivity Analysis for PAH FC II Examining Health Care Costs for FC I

Scenario	Result
Base-case analysis (health care costs equal $0)	Sildenafil dominated all other therapies
Health care costs equal to FC II ($620.70 per 3-month cycle)	Sildenafil dominated all other therapies

FC = functional class; PAH = pulmonary arterial hypertension.

Sensitivity Analysis Around Utility Values:

Within the base-case analysis, the utility values for each of the PAH FC states were derived from Keogh, which were measured in patients with PAH.[80]

Alternative values were published by Roman in 2012, which were derived by Spanish PAH clinical experts using the EQ-5D and were incorporated into the analysis to test the impact of utility values on the results.[82] The results of the base-case analysis and the analysis incorporating alternate utility values were consistent, with sildenafil dominating all other treatments.

Table 62: Results of Univariate Sensitivity Analysis for PAH FC II Around Utility Values

Scenario	Result
Base case — FC I: 0.73; FC II: 0.67; FC III: 0.60; FC IV: 0.52 (based on Keogh et al. 2007)	Sildenafil dominated all other treatments
Alternate utility values — FC I: 0.73; FC II: 0.63; FC III: 0.51; FC IV: 0.43 (based on Roman et al. 2012)	Sildenafil dominated all other treatments

FC = functional class; PAH = pulmonary arterial hypertension.

Sensitivity Analysis Around Discount Rate:

In the base-case analysis, both costs and QALYs were discounted at a rate of 5% per annum as per the CADTH economic guideline recommendation. To test the impact of discounting on the results, a 0% discount rate for both costs and QALYs was implemented within the sensitivity analysis. The results were consistent across both analyses, with sildenafil dominating all other treatments.

Table 63: Results of Univariate Sensitivity for PAH Functional Class II Around Discount Rate	
Scenario	**Result**
Base case — 5% per annum for costs and QALYs	Sildenafil dominated all other treatments
Alternate value — 0% per annum for costs and QALYs	Sildenafil dominated all other treatments

PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Time Horizon:

The base-case analysis employed a time horizon of 30 years. In order to test the impact of time horizon on the results, alternate time horizons of two years and 10 years were examined within the sensitivity analysis. Reducing the time horizon to 10 years did not affect the results, with sildenafil remaining the dominant therapy relative to all other treatments. On the other hand, reducing the time horizon to two years resulted in supportive care being the least costly therapy. Sildenafil was both more costly and more effective than supportive care, resulting in an ICUR of $132,643 per QALY. All other therapies were dominated by sildenafil, except epoprostenol, which produced an ICUR versus sildenafil of $4,909,504 per QALY.

Table 64: Results of Univariate Sensitivity Analysis for PAH Functional Class II Around Time Horizon	
Scenario	**Result**
Base case — 30 years	Sildenafil dominated all other treatments
Alternate duration — 2 years	If ʎ < $132,643 per QALY, supportive care is most cost-effective If $132,643 < ʎ > $4,909,504 per QALY, sildenafil is most cost-effective therapy If ʎ > $4,909,504 per QALY, epoprostenol is most cost-effective therapy
Alternate duration — 10 years	Sildenafil dominated all other treatments

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around the Waning of Treatment Effect:

Three alternative scenarios with respect to the persistence of the effect of treatment on reducing the rate of worsening in FC over the long term were tested within sensitivity analyses. Within the base-case analysis, the treatment effect was assumed to persist for the duration of the model (30 years). Within the sensitivity analyses, the effect on FC worsening was assumed to persist for the first 18 months and then wane over the next two, five, or 10 years. The short-term duration of the clinical trials for PAH therapies makes the estimation of long-term effects of treatment challenging. The assumption of the persistence of effect for 18 months was based on an Australian observational study which found that patients were maintained on monotherapy for an average of 18 months before being switched to combination therapy.

As expected, the shorter the duration of effect of treatment, the less cost-effective the treatment appears. If the effect on worsening in FC is assumed to be maintained for 18 months and then wane over the next two years, the incremental cost-effectiveness ratio (ICER) for sildenafil versus supportive care is $53,141 per QALY, whereas it is $26,627 per QALY if the effects wane over five years and $9,594 per QALY if they wane over 10 years.

Table 65: Results of Univariate Sensitivity Analysis for PAH Functional Class II Around Waning of Treatment Effect	
Scenario	**Result**
Base case — treatment effect to reduce worsening in functional class maintained for full duration of model (30 years)	Sildenafil dominated all other treatments
Treatment effect maintained for 18 months, then decreases by 12.5% per cycle, resulting in treatment having same effect as supportive care alone at 3.5 years	If ʎ < $53,141 per QALY, supportive care is most cost-effective If ʎ > $53,141 per QALY, sildenafil is most cost-effective therapy
Treatment effect maintained for 18 months, then decreases by 5% per cycle, resulting in treatment having same effect as supportive care alone at 6.5 years	If ʎ < $26,627 per QALY, supportive care is most cost-effective If ʎ > $26,627 per QALY, sildenafil is most cost-effective therapy
Treatment effect maintained for 18 months, then decreases by 2.5% per cycle, resulting in treatment having same effect as supportive care alone at 11.5 years	If ʎ < $9,594 per QALY, supportive care is most cost-effective If ʎ > $9,594 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Unadjusted Estimates for Improvement and Worsening in Functional Class:

In the base-case analysis, the estimates for the relative risk of improvement and worsening in FC sourced from the NMA were adjusted for differences in baseline FC within the clinical trials. Within this sensitivity analysis, the unadjusted estimate for improvement and worsening of FC were incorporated within the model. Sildenafil remained the least costly and most effective therapy, dominating all other treatments apart from epoprostenol; however, epoprostenol would only be considered the most cost-effective treatment at willingness to pay values greater than $1.8 million per QALY.

Table 66: Results of Univariate Sensitivity Analysis for PAH Functional Class II Incorporating Unadjusted Estimates for Improvement and Worsening in Functional Class	
Scenario	**Result**
Base case — estimates for improvement and worsening functional class adjusted for baseline functional class	Sildenafil dominated all other treatments
Unadjusted estimates for improvement and worsening in functional class	If ʎ < $1,776,080 per QALY, sildenafil is most cost-effective If ʎ > $1,776,080 per QALY, epoprostenol is most cost-effective therapy Sildenafil dominated all other treatments as it was less costly and more effective

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Survival Based on National Institutes of Health Registry:

In the base-case analysis, the relative risk of mortality by FC with supportive care was informed by the PHC registry. Within this sensitivity analysis, the estimates were derived from the older NIH registry, in which survival was predicted to be lower than with the PHC registry. The results differed from the baseline in that supportive care was now the least costly therapy; however, provided a decision-maker's willingness to pay was greater than $27,743 (and less than $741,073) per QALY, sildenafil is the most cost-effective therapy. At willingness to pay values greater than $741,073, ambrisentan 5 mg is the most cost-effective therapy.

Table 67: Results of Univariate Sensitivity Analysis for PAH Functional Class II Incorporating Survival Based on NIH Registry

Scenario	Result
Base case	Sildenafil dominated all other treatments
Unadjusted estimates for improvement and worsening in functional class	If ʎ < $27,743 per QALY, supportive care is most cost-effective If $27,743 < ʎ > $741,073 per QALY, sildenafil is most cost-effective therapy If ʎ > $741,073 per QALY, ambrisentan 5 mg is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Univariate Sensitivity Analyses for Single Therapies in Pulmonary Arterial Hypertension Functional Class III:

Sensitivity Analyses Regarding the Percentage of Patients Adding Epoprostenol Therapy upon Deteriorating to Functional Class IV:

When the percentage of patients initiating epoprostenol upon deteriorating to FC IV was increased from the base case of 50% to 100%, sildenafil continued to dominate all other therapies. When the percentage was reduced to 0%, supportive care was less costly than sildenafil therapy; however, sildenafil produced greater QALYs. Given a willingness to pay of greater than $34,891 per QALY, sildenafil would be considered the optimal treatment.

Table 68: Results of Univariate Sensitivity Analysis for PAH FC III Regarding the Percentage of Patients Adding Epoprostenol Therapy Upon Deteriorating to FC IV

Scenario	Result
Base-case analysis — 50% of patients initiating epoprostenol in FC IV	Sildenafil dominated all other therapies
Decrease percentage to 0% of patients initiating epoprostenol in FC IV	If ʎ < $34,891 per QALY, supportive care is most cost-effective If ʎ > $34,891 per QALY, sildenafil is most cost-effective therapy
Increase percentage to 100% of patients initiating epoprostenol in FC IV	Sildenafil dominated all other therapies

FC = functional class; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Generic Price for Bosentan:

The incorporation of a generic price for bosentan within the model reduced the costs associated with bosentan therapy; however, sildenafil remained less costly and produced greater QALYs and therefore is still the dominant therapy.

Table 69: Results of Univariate Sensitivity Analysis for PAH Functional Class III Incorporating Generic Price for Bosentan

Scenario	Result
Base-case analysis	Sildenafil dominated all other therapies
Generic price for bosentan	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Removing the Markup and Dispensing Fee Costs for all Medications:

Removing the markup costs and dispensing fees for all medications within the model did not affect the results of the analysis, with sildenafil remaining the dominant treatment.

Table 70: Results of Univariate Sensitivity Analysis for PAH Functional Class III Removing the Markup and Dispensing Fee Costs for all Medications

Scenario	Result
Base-case analysis	Sildenafil dominated all other therapies
No markup or dispensing fees for medications	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Examining High and Low Costs of Epoprostenol in Subsequent Cycles (Post-Titration):

When alternative higher and lower costs for epoprostenol were incorporated within the model, the results were consistent with the base-case analysis, in which sildenafil dominated all other therapies.

Table 71: Results of Univariate Sensitivity Analysis for PAH Functional Class III Incorporating High and Low Cost for Epoprostenol

Scenario	Result
Base-case analysis	Sildenafil dominated all other therapies
Increase epoprostenol cost to $44,351 per annum for subsequent cycles	Sildenafil dominated all other therapies
Decrease epoprostenol cost to $26,061 per annum for subsequent cycles	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol Supplies:

Incorporating a lower cost for epoprostenol infusion supplies of $46.00 per day rather than $52.56 per day, as in the base case, did not change the results of the analysis, as sildenafil remained the dominant therapy.

Table 72: Results of Univariate Sensitivity Analysis for PAH Functional Class III Incorporating Lower Cost for Epoprostenol Supplies	
Scenario	**Result**
Base-case analysis	Sildenafil dominated all other therapies
Reduced cost of epoprostenol supplies	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol (Based on Caripul):

Incorporating a lower cost for epoprostenol based on the pricing of Caripul did not change the results of the analysis, as sildenafil remained the dominant therapy.

Table 73: Results of Univariate Sensitivity Analysis for PAH Functional Class III Incorporating Lower Cost for Epoprostenol (based on Caripul)	
Scenario	**Result**
Base-case analysis (epoprostenol cost first cycle: $5,274; subsequent cycles: $11,247)	Sildenafil dominated all other therapies
Decreased cost of epoprostenol (epoprostenol cost first cycle: $3,069; subsequent cycles: $8,587)	Sildenafil dominated all other therapies

PAH = pulmonary arterial hypertension.

Sensitivity Analysis Around Utility Values:

The incorporation of alternate utility values derived by Spanish PAH clinical experts did not alter the results of the analysis, with sildenafil dominating all other treatments.

Table 74: Results of Univariate Sensitivity Analysis for PAH FC III Around Utility Values	
Scenario	**Result**
Base case — FC I: 0.73; FC II: 0.67; FC III: 0.60; FC IV: 0.52 (based on Keogh et al. 2007)	Sildenafil dominated all other treatments
Alternate utility values — FC I: 0.73; FC II: 0.63; FC III: 0.51; FC IV: 0.43 (based on Roman et al. 2012)	Sildenafil dominated all other treatments

FC = functional class; PAH = pulmonary arterial hypertension.

Sensitivity Analysis Around Discount Rate:

Reducing the discount rate from 5% to 0% per annum for costs and QALYs did not change the results of the model, as sildenafil continued to dominate all other therapies.

Table 75: Results of Univariate Sensitivity Analysis for PAH Functional Class III Around Discount Rate	
Scenario	**Result**
Base case — 5% per annum for costs and QALYs	Sildenafil dominated all other treatments
Alternate value — 0% per annum for costs and QALYs	Sildenafil dominated all other treatments

PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Time Horizon:

Reducing the time horizon from 30 years to 10 years or two years did not significantly affect the interpretation of the results, as at 10 years, sildenafil remained the dominant therapy, and at two years, sildenafil was the most cost-effective therapy at willingness to pay values of less than $4,167,636 per QALY.

Table 76: Results of Univariate Sensitivity Analysis for PAH Functional Class III around Time Horizon

Scenario	Result
Base case — 30 years	Sildenafil dominated all other treatments
Alternate duration — 2 years	If ʎ < $4,167,636 per QALY, sildenafil is most cost-effective If ʎ > $4,167,636 per QALY, epoprostenol is most cost-effective therapy All other therapies were dominated by sildenafil
Alternate duration — 10 years	Sildenafil dominated all other treatments

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around the Waning of Treatment Effect:

As was the case in patients with PAH FC II, when the treatment effects on worsening FC are assumed to persist for shorter durations, sildenafil appears less cost-effective relative to supportive care; however, even when the effects persisted for 18 months and waned over a two-year period, the ICUR remained below $50,000 per QALY.

Table 77: Results of Univariate Sensitivity Analysis for PAH Functional Class III Around Waning of Treatment Effect

Scenario	Result
Base case — treatment effect to reduce worsening in functional class maintained for full duration of model (30 years)	Sildenafil dominated all other treatments
Treatment effect maintained for 18 months, then decreases by 12.5% per cycle, resulting in treatment having same effect as supportive care alone at 3.5 years	If ʎ < $33,243 per QALY, supportive care is most cost-effective If ʎ > $33,243 per QALY, sildenafil is most cost-effective therapy
Treatment effect maintained for 18 months, then decreases by 5% per cycle, resulting in treatment having same effect as supportive care alone at 6.5 years	If ʎ < $42 per QALY, supportive care is most cost-effective If ʎ > $42 per QALY, sildenafil is most cost-effective therapy
Treatment effect maintained for 18 months, then decreases by 2.5% per cycle, resulting in treatment having same effect as supportive care alone at 11.5 years	Sildenafil dominated all other treatments

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Unadjusted Estimates for Improvement and Worsening in Functional Class:

Consistent with the results within FC II, when unadjusted estimates for improvements and worsening of FC were incorporated within the model, sildenafil remained the least costly and most effective treatment. Sildenafil dominated all other treatments except epoprostenol, which

would be considered the most cost-effective treatment only at willingness to pay values of greater than $1.7 million per QALY.

Table 78: Results of Univariate Sensitivity Analysis for PAH Functional Class III Incorporating Unadjusted Estimates for Improvement and Worsening in Functional Class

Scenario	Result
Base case — estimates for improvement and worsening functional class adjusted for baseline functional class	Sildenafil dominated all other treatments
Unadjusted estimates for improvement and worsening in functional class	If ʎ < $1,727,151 per QALY, sildenafil is most cost-effective If ʎ > $1,727,151 per QALY, epoprostenol is most cost-effective therapy Sildenafil dominated all other treatments as it was less costly and more effective

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Survival Based on National Institutes of Health Registry:

With reduced survival estimates, supportive care becomes the least costly therapeutic option; however, provided a decision-maker's willingness to pay per QALY is greater than $23,887, sildenafil would be considered the most cost-effective therapy.

Table 79: Results of Univariate Sensitivity Analysis for PAH Functional Class III Incorporating Survival Based on NIH Registry

Scenario	Result
Base case	Sildenafil dominated all other treatments
Unadjusted estimates for improvement and worsening in functional class	If ʎ < $23,887 per QALY, supportive care is most cost-effective If ʎ > $23,887 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Univariate Sensitivity Analyses for Single Therapies in Pulmonary Arterial Hypertension Functional Class IV:

Sensitivity Analyses Regarding the Percentage of Patients Adding Epoprostenol Therapy upon Deteriorating to Functional Class IV:

Within the base-case analysis, which assumes that 50% of patients initiate epoprostenol upon deteriorating to FC IV, at a willingness to pay of less than $19,188 per QALY, supportive care would be considered optimal; however, at a willingness to pay of greater than $19,188, sildenafil would be considered optimal. Decreasing the percentage of patients initiating epoprostenol upon deteriorating to FC IV to 0% resulted in supportive care being the optimal therapy at willingness to pay values of less than $150,686 per QALY. Sildenafil would be considered optimal only at values greater than $150,686 per QALY. Conversely, if all patients deteriorating to FC IV initiated epoprostenol, sildenafil dominated all other therapies.

Table 80: Results of Univariate Sensitivity Analysis for PAH FC IV Regarding the Percentage of Patients Adding Epoprostenol Therapy Upon Deteriorating to FC IV	
Scenario	**Result**
Base-case analysis — 50% of patients initiating epoprostenol in FC IV	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Decrease percentage to 0% of patients initiating epoprostenol in FC IV	If ʎ < $150,686 per QALY, supportive care is most cost-effective If ʎ > $150,686 per QALY, sildenafil is most cost-effective therapy
Increase percentage to 100% of patients initiating epoprostenol in FC IV	Sildenafil dominated all other therapies

FC = functional class; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Generic Price for Bosentan:

Although the incorporation of a generic price for bosentan reduced the costs for bosentan, they are still higher than those of sildenafil. As bosentan produced fewer QALYs than sildenafil, sildenafil continued to dominate bosentan.

Table 81: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Incorporating Generic Price for Bosentan	
Scenario	**Result**
Base-case analysis	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Generic price for bosentan	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Removing the Markup and Dispensing Fee Costs for all Medications:

Removing the markup costs and dispensing fees for all medications within the model resulted in supportive care being the optimal therapy below a willingness to pay threshold of $3,621 and sildenafil being the optimal therapy at values greater than $3,621.

Table 82: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Removing the Markup and Dispensing Fee Costs for all Medications	
Scenario	**Result**
Base-case analysis	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
No markup or dispensing fees for medications	If ʎ < $3,621 per QALY, supportive care is most cost-effective If ʎ > $3,621 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Examining High and Low Costs of Epoprostenol in Subsequent Cycles (Post-Titration):

When a higher cost of epoprostenol was incorporated within the model, the costs of supportive care increased, resulting in them being higher than the costs for sildenafil; therefore, sildenafil

dominated all other therapies. On the other hand, when the cost of epoprostenol was lowered, the costs of both supportive care and sildenafil also reduced; however, the reduction was greater with supportive care. This resulted in supportive care being the optimal therapy at willingness to pay values lower than $41,946 per QALY and sildenafil being optimal at values greater than $41,946.

Table 83: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Incorporating High and Low Cost for Epoprostenol

Scenario	Result
Base-case analysis	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Increase epoprostenol cost to $44,351 per annum for subsequent cycles	Sildenafil dominated all other therapies
Decrease epoprostenol cost to $26,061 per annum for subsequent cycles	If ʎ < $41,946 per QALY, supportive care is most cost-effective If ʎ > $41,946 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY ; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol Supplies:

Incorporating a lower cost for epoprostenol infusion supplies of $46.00 per day rather than $52.56 per day, as in the base case, did not change the conclusions of the analysis; however, sildenafil was now the most cost-effective therapy at willingness to pay values of greater than $25,550 per QALY, rather than at greater than $19,188 per QALY, as in the base case.

Table 84: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Incorporating Lower Cost for Epoprostenol Supplies

Scenario	Result
Base-case analysis	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Reduced cost of epoprostenol supplies	If ʎ < $25,550 per QALY, supportive care is most cost-effective If ʎ > $25,550 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY ; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol (Based on Caripul):

Lowering the price of epoprostenol to that of Caripul resulted in reduced costs with both supportive care and sildenafil, with the reduction being greater with supportive care. This resulted in supportive care being the optimal therapy at willingness to pay values lower than $47,355 and sildenafil being optimal at values greater than $47,366.

Table 85: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Incorporating Lower Cost for Epoprostenol (Based on Caripul)

Scenario	Result
Base-case analysis (epoprostenol cost first cycle: $5,274; subsequent cycles: $11,247	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Decreased cost of epoprostenol (epoprostenol cost first cycle: $3,069; subsequent cycles: $8,587)	If ʎ < $47,366 per QALY, supportive care is most cost-effective If ʎ > $47,366 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY ; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Utility Values:

The incorporation of alternate utility values derived by Spanish PAH clinical experts had little impact on the results, with supportive care being the optimal therapy at a willingness to pay per QALY of $21,286 and sildenafil being optimal above this value.

Table 86: Results of Univariate Sensitivity Analysis for PAH FC IV Around Utility Values

Scenario	Result
Base case — FC I: 0.73; FC II: 0.67; FC III: 0.60; FC IV: 0.52 (based on Keogh et al. 2007)	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Alternate utility values — FC I: 0.73; FC II: 0.63; FC III: 0.51, FC IV: 0.43 (based on Roman et al. 2012)	If ʎ < $21,286 per QALY, supportive care is most cost-effective If ʎ > $21,286 per QALY, sildenafil is most cost-effective therapy

FC = functional class; ʎ = lambda, willingness to for a QALY pay ; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Discount Rate:

Reducing the discount rate from 5% to 0% per annum did not change the results of the model, as sildenafil continued to dominate all other therapies.

Table 87: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Around Discount Rate

Scenario	Result
Base case — 5% per annum for costs and QALYs	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Alternate value — 0% per annum for costs and QALYs	If ʎ < $30,606 per QALY, supportive care is most cost-effective If ʎ > $30,606 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY ; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Time Horizon:

Reducing the time horizon from 30 years to 10 years and two years improved the cost-effectiveness of sildenafil with the ICUR versus supportive care reducing to $5,406 per QALY at 10 years and sildenafil dominating all other therapies at two years.

Table 88: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Around Time Horizon

Scenario	Result
Base case — 30 years	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Alternate duration — 2 years	Sildenafil dominated all other treatments
Alternate duration — 10 years	If ʎ < $5,406 per QALY, supportive care is most cost-effective If ʎ > $5,406 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around the Waning of Treatment Effect:

Assuming the treatment effects on worsening FC were maintained for an initial 18 months and then waned over a two-, five-, or 10-year period resulted in the ICUR for sildenafil versus supportive care increasing to values greater than $50,000 per QALY. The cost-effectiveness of sildenafil versus supportive care is therefore contingent upon the persistence of the treatment effects over the long term in patients with PAH FC IV.

Table 89: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Around Waning of Treatment Effect

Scenario	Result
Base case — treatment effect to reduce worsening in functional class maintained for full duration of model (30 years)	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Treatment effect maintained for 18 months, then decreases by 12.5% per cycle, resulting in treatment having same effect as supportive care alone at 3.5 years	If ʎ < $156,132 per QALY, supportive care is most cost-effective If ʎ > $156,132 per QALY, sildenafil is most cost-effective therapy
Treatment effect maintained for 18 months, then decreases by 5% per cycle, resulting in treatment having same effect as supportive care alone at 6.5 years	If ʎ < $102,563 per QALY, supportive care is most cost-effective If ʎ > $102,563 per QALY, sildenafil is most cost-effective therapy
Treatment effect maintained for 18 months, then decreases by 2.5% per cycle, resulting in treatment having same effect as supportive care alone at 11.5 years	If ʎ < $69,092 per QALY, supportive care is most cost-effective If ʎ > $69,092 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Unadjusted Estimates for Improvement and Worsening in Functional Class:

With the incorporation of the unadjusted estimates for improvement and worsening in FC within the model, supportive care remains the least costly therapy in FC IV. As in the base case, sildenafil is the most cost-effective therapy versus supportive care; however, the ICER for sildenafil versus supportive care increased to $93,756 within this sensitivity analysis. Epoprostenol is the only other therapy that may be cost-effective, but only at willingness to pay values of greater than $13 million per QALY.

Table 90: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Incorporating Unadjusted Estimates for Improvement and Worsening in Functional Class	
Scenario	**Result**
Base case — estimates for improvement and worsening functional class adjusted for baseline functional class	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Unadjusted estimates for improvement and worsening in functional class	If ʎ < $93,756 per QALY, supportive care is most cost-effective If $93,756 < ʎ > $13,441,746 per QALY, sildenafil is most cost-effective therapy If ʎ > $13,441,746 per QALY epoprostenol is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Survival Based on National Institutes of Health Registry:

With reduced survival estimates based on the NIH registry, supportive care remains the least costly therapy in FC IV. The ICUR for sildenafil versus supportive care increased to $42,234, indicating that at a willingness to pay value greater than $42,234, sildenafil would be the most cost-effective strategy.

Table 91: Results of Univariate Sensitivity Analysis for PAH Functional Class IV Incorporating Survival Based on NIH Registry	
Scenario	**Result**
Base case	If ʎ < $19,188 per QALY, supportive care is most cost-effective If ʎ > $19,188 per QALY, sildenafil is most cost-effective therapy
Unadjusted estimates for improvement and worsening in functional class	If ʎ < $42,234 per QALY, supportive care is most cost-effective If ʎ > $42,234 per QALY, sildenafil is most cost-effective therapy

ʎ = lambda, willingness to pay for a QALY; NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

c) Univariate Sensitivity Analysis for Comparison of Add-on Therapies Versus Single Therapies

Univariate Sensitivity Analyses for Add-on Therapies in Pulmonary Arterial Hypertension Functional Class II:

Sensitivity Analyses Regarding the Percentage of Patients Adding Epoprostenol Therapy upon Deteriorating to Functional Class IV:

Decreasing the percentage of patients initiating epoprostenol therapy upon deterioration to FC IV from 50% to 0% resulted in an increase in the ICUR for an ERA plus tadalafil versus ERA plus placebo to $141,612 per QALY. Conversely, increasing the percentage of patients initiating epoprostenol to 100% resulted in a decrease in the ICUR for ERA plus tadalafil versus ERA plus placebo to $29,456 per QALY. The ICUR for ERA plus riociguat versus ERA plus tadalafil remained at approximately $500,000 per QALY, regardless of the percentage of patients initiating epoprostenol upon deteriorating.

Table 92: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH FC II Regarding the Percentage of Patients Adding Epoprostenol Therapy Upon Deteriorating to FC IV	
Scenario	**Result**
Base-case analysis — 50% of patients initiating epoprostenol in FC IV	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
Decrease percentage to 0% of patients initiating epoprostenol in FC IV	If ʎ < $141,612 per QALY, an ERA plus placebo is most cost-effective, If $141,612 < ʎ > $525,811 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $525,811 per QALY, an ERA plus riociguat is most cost-effective
Increase percentage to 100% of patients initiating epoprostenol in FC IV	If ʎ < $29,456 per QALY, an ERA plus placebo is most cost-effective If $29,456 < ʎ > $497,255 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $497,255 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; FC = functional class; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating a Generic Price for Bosentan:

As the cost used for the ERA within these combinations was that of bosentan, reducing the cost to a generic price lowered the costs in all treatment groups and resulted in a reduction in the ICUR for an ERA plus tadalafil versus an ERA plus placebo to $51,771 per QALY. The ICUR for an ERA plus riociguat versus an ERA plus tadalafil remained at approximately $500,000 per QALY.

Table 93: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class II Incorporating a Generic Price for Bosentan	
Scenario	**Result**
Base-case analysis	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
Generic price for bosentan	If ʎ < $51,771 per QALY, an ERA plus placebo is most cost-effective If $51,771 < ʎ > $474,394 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $474,394 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Removing the Markup and Dispensing Fee Costs for all Medications:

Removing the markup costs and dispensing fees for all medications within the model did not change the conclusions of the analysis; however, the ICUR for an ERA plus tadalafil versus and ERA plus placebo decreased somewhat, from $88,506 per QALY in the base case to $76,406.

Table 94: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class II Removing the Markup and Dispensing Fee Costs for All Medications	
Scenario	**Result**
Base-case analysis	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
No markup or dispensing fees for medications	If ʎ < $76,406 per QALY, an ERA plus placebo is most cost-effective If $76,406 < ʎ > $471,036 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $471,036 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Examining High and Low Costs of Epoprostenol in Subsequent Cycles (Post-Titration):

Increasing and decreasing the costs of epoprostenol therapy did not significantly change the results relative to the base-case analysis.

Table 95: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class II Incorporating High and Low Cost for Epoprostenol	
Scenario	**Result**
Base-case analysis	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
Increase epoprostenol cost to $44,351 per annum for subsequent cycles	If ʎ < $78,754 per QALY, an ERA plus placebo is most cost-effective If $78,754 < ʎ > $506,924 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $506,924 per QALY, an ERA plus riociguat is most cost-effective
Decrease epoprostenol cost to $26,061 per annum for subsequent cycles	If ʎ < $96,720 per QALY, an ERA plus placebo is most cost-effective If $96,720 < ʎ > $516,226 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $516,226 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol Supplies:

Incorporating a lower cost for epoprostenol infusion supplies did not significantly change the results of the analysis.

Table 96: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class II Incorporating a Lower Cost for Epoprostenol Supplies

Scenario	Result
Base-case analysis (health care costs equal $0)	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
Reduced cost of epoprostenol supplies	If ʎ < $90,816 per QALY, an ERA plus placebo is most cost-effective If $90,816 < ʎ > $513,177 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $513,177 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Examining Health Care Costs Within Functional Class I:

Assuming health care costs for patients in FC I to be equivalent to those in FC II did not significantly change the results relative to the base-case analysis.

Table 97: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH FC II Examining Health Care Costs Within FC I

Scenario	Result
Base-case analysis (health care costs equal $0)	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
Health care costs equal to FC II ($620.70 per 3-month cycle)	If ʎ < $90,065 per QALY, an ERA plus placebo is most cost-effective If $90,065 < ʎ > $516,207 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $516,207 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; FC = functional class; ʎ = lambda, willingness to pay for a QALY ; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Utility Values:

Implementing alternative utility values based on clinical expert opinion did not significantly alter the results of the analysis.

Table 98: Results of Univariate Sensitivity for Add-on Therapies in PAH FC II Around Utility Values

Scenario	Result
Base case — FC I: 0.73; FC II: 0.67; FC III: 0.60; FC IV: 0.52 (based on Keogh et al. 2007)	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
Alternate utility values — FC I: 0.73; FC II: 0.63; FC III: 0.51; FC IV: 0.43 (based on Roman et al. 2012)	If ʎ < $84,994 per QALY, an ERA plus placebo is most cost-effective If $84,994 < ʎ > $479,145 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $479,145 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; FC = functional class; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Discount Rate:

Results were consistent with the base-case analysis when a 0% discount rate was incorporated within the analysis.

Table 99: Results of Univariate Sensitivity Analysis in PAH Functional Class II Around Discount Rate

Scenario	Result
Base case — 5% per annum for costs and QALYs	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
Alternate value — 0% per annum for costs and QALYs	If ʎ < $90,828 per QALY, an ERA plus placebo is most cost-effective If $90,828 < ʎ > $449,132 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $449,132 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Time Horizon:

Reducing the time horizon to 10 years did not significantly change the results relative to the base case; however, decreasing the time horizon to two years increased the ICUR for ERA plus tadalafil versus ERA alone to $401,758 per QALY, and for ERA plus riociguat versus ERA plus tadalafil, the ICUR was more than $2 million per QALY.

Table 100: Results of Univariate Sensitivity Analysis in PAH Functional Class II Around Time Horizon

Scenario	Result
Base case — 30 years	If ʎ < $88,506 per QALY, an ERA plus placebo is most cost-effective If $88,506 < ʎ > $511,973 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $511,973 per QALY, an ERA plus riociguat is most cost-effective
Alternate duration — 2 years	If ʎ < $401,758 per QALY, an ERA plus placebo is most cost-effective If $401,758 < ʎ > $2,005,365 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $2,005,365 per QALY, an ERA plus riociguat is most cost-effective
Alternate duration — 10 years	If ʎ < $73,770 per QALY, an ERA plus placebo is most cost-effective If $73,770 < ʎ > $622,741 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $622,741 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Univariate Sensitivity Analyses for Add-on Therapies in Pulmonary Arterial Hypertension Functional Class III:

Sensitivity Analyses Regarding the Percentage of Patients Adding Epoprostenol Therapy upon Deteriorating to Functional Class IV:

Decreasing the percentage of patients initiating epoprostenol upon deterioration to FC IV did not change the conclusions of the analysis relative to the base case; however, increasing the percentage to 100% resulted in the ICUR for an ERA plus tadalafil versus an ERA plus placebo dropping to $38,200 per QALY.

Table 101: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH FC III Regarding the Percentage of Patients Adding Epoprostenol Therapy Upon Deteriorating to FC IV

Scenario	Result
Base-case analysis — 50% of patients initiating epoprostenol in FC IV	If ʎ < $156,513 per QALY, an ERA plus placebo is most cost-effective If $156,513 < ʎ > $809,183 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $809,183 per QALY, an ERA plus riociguat is most cost-effective
Decrease percentage to 0% of patients initiating epoprostenol in FC IV	If ʎ < $253,905 per QALY, an ERA plus placebo is most cost-effective, If $253,905 < ʎ > $824,805 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $824,805 per QALY, an ERA plus riociguat is most cost-effective
Increase percentage to 100% of patients initiating epoprostenol in FC IV	If ʎ < $38,200 per QALY, an ERA plus placebo is most cost-effective If $38,200 < ʎ > $791,424 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $791,424 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; FC = functional class; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating Generic Price for Bosentan:

Incorporating a generic price for bosentan reduced the estimated ICURs; however, they remained above $100,000 per QALY for an ERA plus tadalafil versus an ERA plus placebo, and greater than $700,000 per QALY for an ERA plus riociguat versus an ERA plus tadalafil.

Table 102: Results of Univariate Sensitivity Analysis for Add-on Therapies in Functional Class III Incorporating Generic Price for Bosentan

Scenario	Result
Base-case analysis	If ʎ < $156,513 per QALY, an ERA plus placebo is most cost-effective If $156,513 < ʎ > $809,183 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $809,183 per QALY, an ERA plus riociguat is most cost-effective
Generic price for bosentan	If ʎ < $120,522 per QALY, an ERA plus placebo is most cost-effective If $120,522 < ʎ > $773,003 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $773,003 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Removing the Markup and Dispensing Fee Costs for all Medications:

Removing the markup costs and dispensing fees for all medications within the model did not change the conclusions of the analysis.

Table 103: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class III Removing the Markup and Dispensing Fee Costs for all Medications

Scenario	Result
Base-case analysis	If ʎ < $156,513 per QALY, an ERA plus placebo is most cost-effective If $156,513 < ʎ > $809,183 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $809,183 per QALY, an ERA plus riociguat is most cost-effective
No markup or dispensing fees for medications	If ʎ < $134,736 per QALY, an ERA plus placebo is most cost-effective If $134,736 < ʎ > $742,929 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $742,929 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Examining High and Low Costs of Epoprostenol in Subsequent Cycles (Post-Titration):

Extremes of costs for epoprostenol altered the ICUR somewhat, but did not change the interpretation of the findings relative to the base-case analysis.

Table 104: Results of Univariate Sensitivity Analysis for Add-on Therapies in Functional Class III Incorporating High and Low Cost for Epoprostenol

Scenario	Result
Base-case analysis	If ʎ < $156,513 per QALY, an ERA plus placebo is most cost-effective If $156,513 < ʎ > $809,183 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $809,183 per QALY, an ERA plus riociguat is most cost-effective
Increase epoprostenol cost to $44,351 per annum for subsequent cycles	If ʎ < $136,355 per QALY, an ERA plus placebo is most cost-effective If $136,355 < ʎ > $796,998 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $796,998 per QALY, an ERA plus riociguat is most cost-effective
Decrease epoprostenol cost to $26,061 per annum for subsequent cycles	If ʎ < $173,490 per QALY, an ERA plus placebo is most cost-effective If $173,490 < ʎ > $819,444 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $819,444 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol Supplies:

As was the case in patients with FC II PAH, incorporating a lower cost for epoprostenol infusion supplies did not significantly change the results of the analysis.

Table 105: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class III Incorporating a Lower Cost for Epoprostenol Supplies

Scenario	Result
Base-case analysis (health care costs equal $0)	If ʎ < $156,513 per QALY, an ERA plus placebo is most cost-effective If $156,513 < ʎ > $809,183 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $809,183 per QALY, an ERA plus riociguat is most cost-effective
Reduced cost of epoprostenol supplies	If ʎ < $161,264 per QALY, an ERA plus placebo is most cost-effective If $161,264 < ʎ > $812,065 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $812,065 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Utility Values:

Implementing alternative utility values based on clinical expert opinion did not significantly alter the results of the analysis.

Table 106: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class III Around Utility Values

Scenario	Result
Base case — FC I: 0.73; FC II: 0.67; FC III: 0.60; FC IV: 0.52 (based on Keogh et al. 2007)	If ʎ < $156,513 per QALY, an ERA plus placebo is most cost-effective If $156,513 < ʎ > $809,183 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $809,183 per QALY, an ERA plus riociguat is most cost-effective
Alternate utility values — FC I: 0.73; FC II: 0.63; FC III: 0.51; FC IV: 0.43 (based on Roman et al. 2012)	If ʎ < $163,370 per QALY, an ERA plus placebo is most cost-effective If $163,370 < ʎ > $786,237 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $786,237 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; FC = functional class; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Discount Rate:

Results were consistent with the base-case analysis when a 0% discount rate was incorporated within the analysis.

Table 107: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class III Around Discount Rate

Scenario	Result
Base case — 5% per annum for costs and QALYs	If ʎ < $156,513 per QALY, an ERA plus placebo is most cost-effective If $156,513 < ʎ > $809,183 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $809,183 per QALY, an ERA plus riociguat is most cost-effective
Alternate value — 0% per annum for costs and QALYs	If ʎ < $160,103 per QALY, an ERA plus placebo is most cost-effective If $160,103 < ʎ > $736,248 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $736,248 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Time Horizon:

Reducing the time horizon to 10 years did not significantly alter the results; however, decreasing the time horizon to two years resulted in the add-on therapies being less cost-effective relative to single ERA therapy.

Table 108: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class III Around Time Horizon

Scenario	Result
Base case — 30 years	If ʎ < $156,513 per QALY, an ERA plus placebo is most cost-effective If $156,513 < ʎ > $809,183 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $809,183 per QALY, an ERA plus riociguat is most cost-effective
Alternate duration — 2 years	If ʎ < $368,156 per QALY, an ERA plus placebo is most cost-effective If $368,156 < ʎ > $2,018,486 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $2,018,486 per QALY, an ERA plus riociguat is most cost-effective
Alternate duration — 10 years	If ʎ < $143,685 per QALY, an ERA plus placebo is most cost-effective If $143,685 < ʎ > $891,412 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $891,412 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Univariate Sensitivity Analyses for Add-on Therapies in Pulmonary Arterial Hypertension Functional Class IV:

The ICUR for an ERA plus tadalafil compared with an ERA plus placebo remained more than $1 million per QALY in all univariate sensitivity analyses, as did the ICUR for an ERA plus riociguat compared with an ERA plus tadalafil.

Sensitivity Analyses Regarding the Percentage of Patients Adding Epoprostenol Therapy Upon Deteriorating to Functional Class IV:

Table 109: Results of Univariate Sensitivity Analysis for Add-on Therapies in FC IV Regarding the Percentage of Patients Adding Epoprostenol Therapy Upon Deteriorating to FC IV

Scenario	Result
Base-case analysis — 50% of patients initiating epoprostenol in FC IV	If ʎ < $1,568,400 per QALY, an ERA plus placebo is most cost-effective If $1,568,400 < ʎ > $1,995,139 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,995,139 per QALY, an ERA plus riociguat is most cost-effective
Decrease percentage to 0% of patients initiating epoprostenol in FC IV	If ʎ < $1,509,505 per QALY, an ERA plus placebo is most cost-effective, If $1,509,505 < ʎ > $1,895,584 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,895,584 per QALY, an ERA plus riociguat is most cost-effective
Increase percentage to 100% of patients initiating epoprostenol in FC IV	If ʎ < $1,644,086 per QALY, an ERA plus placebo is most cost-effective If $1,644,086 < ʎ > $2,121,614 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $2,121,614 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; FC = functional class; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating a Generic Price for Bosentan

Table 110: Results of Univariate Sensitivity Analysis for Add-on Therapies in Functional Class IV Incorporating a Generic Price for Bosentan	
Scenario	**Result**
Base-case analysis	If ʎ < $1,568,400 per QALY, an ERA plus placebo is most cost-effective If $1,568,400 < ʎ > $1,995,139 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,995,139 per QALY, an ERA plus riociguat is most cost-effective
Generic price for bosentan	If ʎ < $1,532,608 per QALY, an ERA plus placebo is most cost-effective If $1,532,608 < ʎ > $1,959,483 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,959,483 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

Sensitivity Analysis Removing the Markup and Dispensing Fee Costs for all Medications:

Table 111: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class IV Removing the Markup and Dispensing Fee Costs for all Medications	
Scenario	**Result**
Base-case analysis	If ʎ < $1,568,400 per QALY, an ERA plus placebo is most cost-effective If $1,568,400 < ʎ > $1,995,139 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,995,139 per QALY, an ERA plus riociguat is most cost-effective
No markup or dispensing fees for medications	If ʎ < $1,435,071 per QALY, an ERA plus placebo is most cost-effective If $1,435,071 < ʎ > $1,835,597 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,835,597 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

Sensitivity Analysis Examining High and Low Costs of Epoprostenol in Subsequent Cycles (Post-Titration):

Table 112: Results of Univariate Sensitivity Analysis for Add-on Therapies in Functional Class IV Incorporating High and Low Cost for Epoprostenol	
Scenario	**Result**
Base-case analysis	If ʎ < $1,568,400 per QALY, an ERA plus placebo is most cost-effective If $1,568,400 < ʎ > $1,995,139 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,995,139 per QALY, an ERA plus riociguat is most cost-effective
Increase epoprostenol cost to $44,351 per annum for subsequent cycles	If ʎ < $1,541,810 per QALY, an ERA plus placebo is most cost-effective If $1,541,810 < ʎ > $1,968,430 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,968,430 per QALY, an ERA plus riociguat is most cost-effective
Decrease epoprostenol cost to $26,061 per annum for subsequent cycles	If ʎ < $1,590,793 per QALY, an ERA plus placebo is most cost-effective If $1,590,793 < ʎ > $2,017,633 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $2,017,633 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

Sensitivity Analysis Incorporating a Lower Cost for Epoprostenol Supplies:

Table 113: Results of Univariate Sensitivity Analysis for Add-on Therapies in PAH Functional Class IV Incorporating a Lower Cost for Epoprostenol Supplies	
Scenario	**Result**
Base-case analysis (health care costs equal $0)	If ʎ < $1,568,400 per QALY, an ERA plus placebo is most cost-effective If $1,568,400 < ʎ > $1,995,139 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,995,139 per QALY, an ERA plus riociguat is most cost-effective
Reduced cost of epoprostenol supplies	If ʎ < $1,574,662 per QALY, an ERA plus placebo is most cost-effective If $1,574,662 < ʎ > $2,001,416 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $2,001,416 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Utility Values:

Table 114: Results of Univariate Sensitivity Analysis for Add-on Therapies in Functional Class IV Around Utility Values	
Scenario	**Result**
Base case — FC I: 0.73; FC II: 0.67; FC III: 0.60; FC IV: 0.52 (based on Keogh et al. 2007)	If ʎ < $1,568,400 per QALY, an ERA plus placebo is most cost-effective If $1,568,400 < ʎ > $1,995,139 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,995,139 per QALY, an ERA plus riociguat is most cost-effective
Alternate utility values — FC I: 0.73; FC II: 0.63; FC III: 0.51; FC IV: 0.43 (based on Roman et al. 2012)	If ʎ < $1,739,856 per QALY, an ERA plus placebo is most cost-effective If $1,739,856 < ʎ > $2,212,323 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $2,212,323 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; FC = functional class; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Discount Rate

Table 115: Results of Univariate Sensitivity Analysis for Add-on Therapies in Functional Class IV Around Discount Rate	
Scenario	**Result**
Base case — 5% per annum for costs and QALYs	If ʎ < $1,568,400 per QALY, an ERA plus placebo is most cost-effective If $1,568,400 < ʎ > $1,995,139 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,995,139 per QALY, an ERA plus riociguat is most cost-effective
Alternate value — 0% per annum for costs and QALYs	If ʎ < $1,441,948 per QALY, an ERA plus placebo is most cost-effective If $1,441,948 < ʎ > $1,874,797 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,874,797 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

Sensitivity Analysis Around Time Horizon:

Table 116: Results of Univariate Sensitivity Analysis for Add-on Therapies in Functional Class IV Around Time Horizon	
Scenario	**Result**
Base case — 30 years	If ʎ < $1,568,400 per QALY, an ERA plus placebo is most cost-effective If $1,568,400 < ʎ > $1,995,139 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $1,995,139 per QALY, an ERA plus riociguat is most cost-effective
Alternate duration — 2 years	If ʎ < $4,303,955 per QALY, an ERA plus placebo is most cost-effective If $4,303,955 < ʎ > $3,324,151 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $3,324,151 per QALY, an ERA plus riociguat is most cost-effective
Alternate duration – 10 years	If ʎ < $1,659,375 per QALY, an ERA plus placebo is most cost-effective If $1,659,375 < ʎ > $2,100,909 per QALY, an ERA plus tadalafil is most cost-effective If ʎ > $2,100,909 per QALY, an ERA plus riociguat is most cost-effective

ERA = endothelin receptor antagonist; ʎ = lambda, willingness to pay for a QALY; QALY = quality-adjusted life-year.

5.5.3 Exploratory Analysis With Macitentan

Within the macitentan analysis, a portion of patients within both the supportive care group and the macitentan group were assumed to be receiving concurrent therapy with PDE-5 inhibitors, as was the case within the clinical trial which was used to estimate the efficacy of the treatment. The costs of this concurrent therapy were therefore included for both supportive care and macitentan.

Regardless of PAH FC, macitentan generated greater QALYs than supportive care, but at a greater cost. For all FCs, drug therapy constituted the greatest proportion of total costs for both supportive care and macitentan, with hospitalization costs constituting the second greatest proportion (APPENDIX 19: Breakdown of Costs by Cost Category). The ICUR for macitentan versus supportive care increased with increasing severity of disease, resulting in a value of $244,615 per QALY in FC II, $449,652 per QALY in FC III, and $4,267,664 per QALY in FC IV.

Table 117: Results of Macitentan Versus Supportive Care in Naive and Experienced Patients					
Treatment	**Total Costs**	**Total QALYs**	**Versus Supportive Care**		
			Incremental Costs	**Incremental QALYs**	**ICUR**
Functional Class II					
Supportive Care	$163,361	3.464	Ref	Ref	Ref
Macitentan	$444,935	4.615	$281,574	1.151	$244,615
Functional Class III					
Supportive Care	$217,796	2.757	Ref	Ref	Ref
Macitentan	$405,505	3.175	$187,709	0.417	$449,652
Functional Class IV					
Supportive Care	$294,836	2.403	Ref	Ref	Ref
Macitentan	$510,813	2.453	$215,977	0.051	$4,267,664

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Threshold Analysis for Macitentan:
Reducing the price of macitentan by 75% to $32.08 per tablet resulted in macitentan being cost-effective in both PAH FC II and PAH FC III, with the ICUR for macitentan versus supportive care being $12,678 per QALY in FC II and macitentan dominating supportive care in FC III, as it is both less costly and more efficacious. A price reduction of approximately 62% would result in the ICUR for macitentan versus supportive care being approximately $50,000 per QALY in both FC II and III. Even with a price reduction of 90%, macitentan would not be considered cost-effective in FC IV.

Table 118: Macitentan Threshold Analysis

PAH Functional Class	Price Reduction	New Unit Price	ICUR Versus Supportive Care
Functional Class II	50%	$64.17	$89,987
	60%	$51.33	$59,063
	75%	$32.08	$12,678
	80%	$25.67	Dominant
	90%	$12.83	Dominant
Functional Class III	50%	$64.17	$122,443
	60%	$51.33	$57,005
	75%	$32.08	Dominant
	80%	$25.67	Dominant
	90%	$12.83	Dominant
Functional Class IV	50%	$64.17	$1,968,121
	60%	$51.33	$1,508,236
	75%	$32.08	$818,409
	80%	$25.67	$588,466
	90%	$12.83	$128,581

ICUR = incremental cost-utility ratio; PAH = pulmonary arterial hypertension.

5.5.4 Probabilistic Sensitivity Analysis

a) Summary

The results for the PSA organized by functional class are presented below, beginning with the comparative cost-effectiveness of monotherapy and followed by the comparative cost-effectiveness of add-on versus monotherapy.

Probabilistic Sensitivity Analysis for Monotherapy Versus Supportive Care

Probabilistic Sensitivity Analysis for Monotherapy Versus Supportive Care in PAH Functional Class II:
The estimated costs and QALYs derived from the PSA were on balance slightly higher than those estimated within the deterministic analysis; however, the calculation of the ICURs produced similar results, with sildenafil dominating all other therapies. Results are presented in Table 119 below. The cost-effectiveness frontier consisted solely of sildenafil at values of willingness to pay for a QALY ranging from $0 to $200,000. At willingness to pay values of greater than $30,000 per QALY, the probability that sildenafil was the most cost-effective was approximately 80%. There was near to 0% probability that other treatments were cost-effective, apart from tadalafil, which was the most cost-effective treatment in approximately 20% of replications at willingness to pay values from $30,000 to $200,000 per QALY (Figure 22).

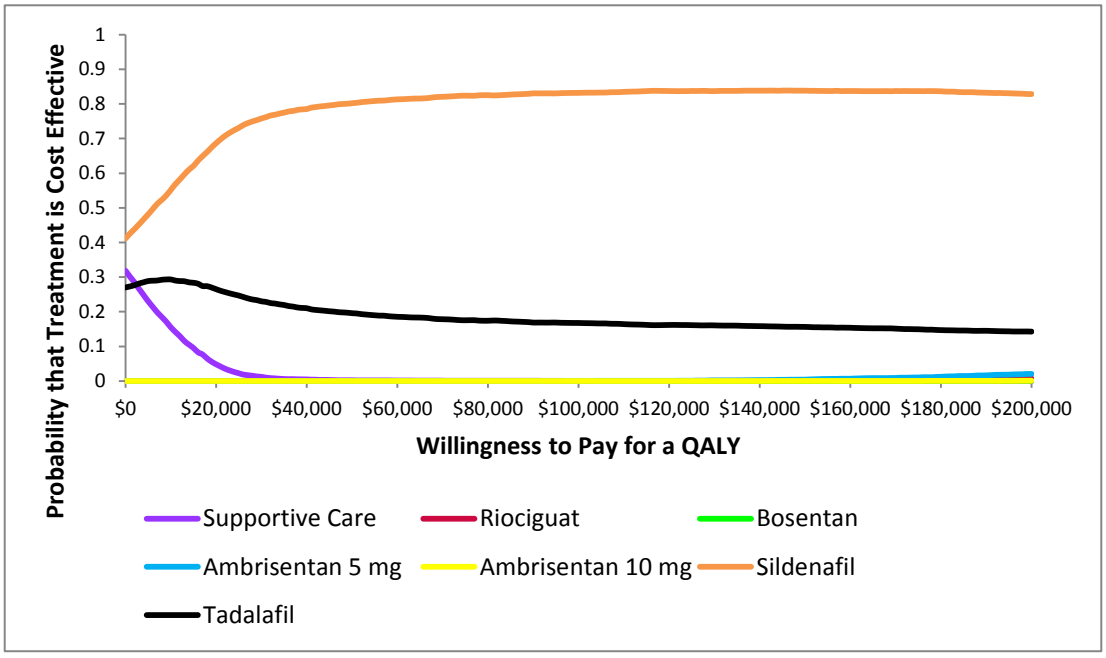
The confidence ellipses found in Figure 23 provide a visual representation of the uncertainty surrounding the estimates of incremental costs and QALYs for each treatment versus supportive care. As is evident from the graph, there is a great deal of uncertainty surrounding the estimates; however, the majority of the ellipse for both sildenafil and tadalafil falls below a willingness to pay threshold of $50,000 per QALY. The ellipses for all other treatments are above this threshold.

Table 119: Results of Probabilistic Sensitivity Analysis for Single Therapies in PAH Functional Class II

Treatment	Total Costs	Total QALYs	Versus Sildenafil		
			Incremental Costs	Incremental QALYs	ICUR
Sildenafil	$153,104 ($79,239 to $280,136)	4.926 (2.926 to 7.049)	Ref	Ref	Dominates all treatments
Dominated Treatments					
Tadalafil	$161,733 ($67,264 to $334,473)	4.112 (2.341 to 6.096)	$8,629 (–$53,756 to $112,934)	–0.815 (–2.517 to –0.694)	Dominated by sildenafil
Supportive care	$170,175 ($46,496 to $368,094)	3.169 (1.797 to 5.047)	$17,072 (–$47,153 to $130,905)	–1.757 (–3.335 to –0.571)	Dominated by sildenafil
Ambrisentan 5 mg	$388,550 ($219,300 to $581,225)	4.830 (2.777 to 7.069)	$235,446 ($131,579 to $350,228)	–0.096 (–1.801 to 1.392)	Dominated by sildenafil
Ambrisentan 10 mg	$389,992 ($209,328 to $625,549)	4.341 (2.501 to 6.498)	$236,888 ($120,812 to $393,966)	–0.585 (–2.244 to –0.851)	Dominated by sildenafil
Riociguat	$404,928 ($224,294 to $631,000)	4.552 (2.586 to 6.697)	$251,825 ($132,866 to $393,587)	–0.374 (–2.11 to 1.155)	Dominated by sildenafil
Bosentan	$420,974 ($205,058 to $732,150)	3.793 (2.102 to 5.832)	$267,871 ($118,811 to $484,017)	–1.133 (–2.837 to 0.317)	Dominated by sildenafil

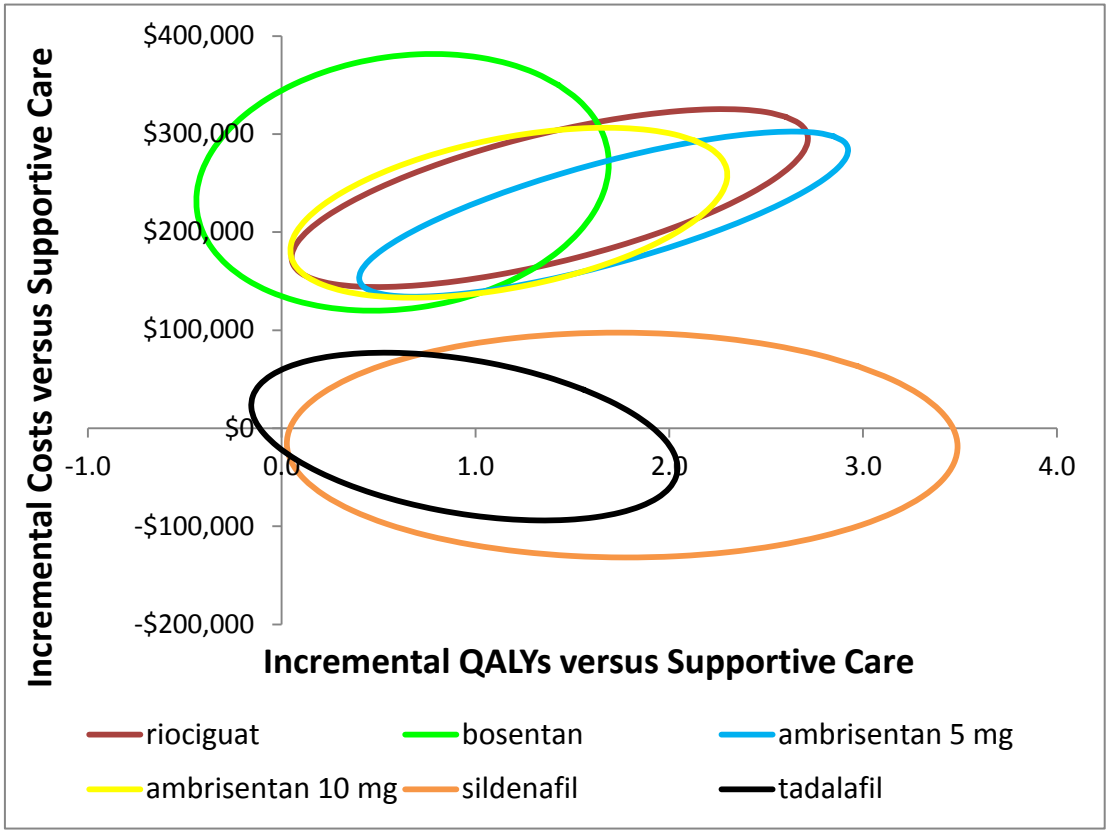
Dominated = more costly and fewer QALYs; ICUR = incremental cost-utility ratio; mg = milligram; PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

Figure 22: Cost-Effectiveness Acceptability Curve for Monotherapy in Pulmonary Arterial Hypertension Functional Class II



QALY = quality-adjusted life-year.

Figure 23: Confidence Ellipses for PSA Results in PAH Functional Class II — Incremental Costs Versus Incremental QALYs Versus Supportive Care



PAH = pulmonary arterial hypertension; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Probabilistic Sensitivity Analysis for Monotherapy Versus Supportive Care in PAH Functional Class III:

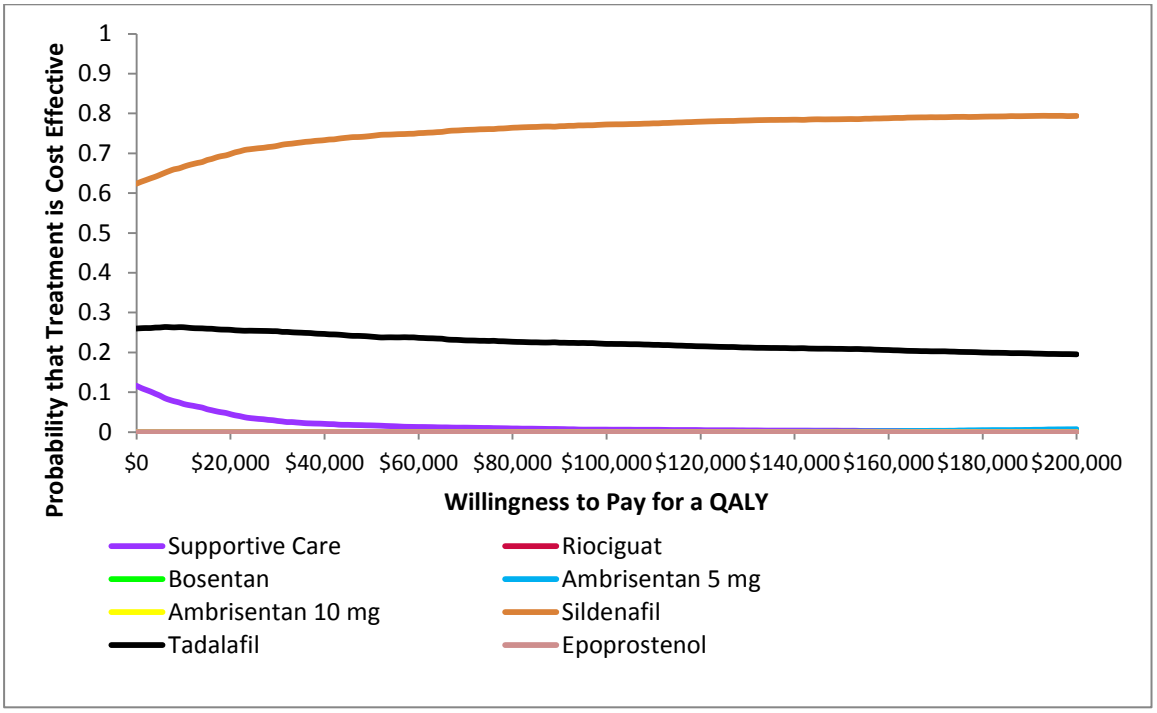
The results of the PSA for FC III were similar for those for FC II, in that the estimated costs and QALYs were slightly higher than those of the deterministic analysis; however, as in the deterministic analysis, sildenafil dominated all other therapies, being both less costly and more effective. Results are presented in Table 120. The cost-effectiveness frontier consisted solely of sildenafil at values of willingness to pay for a QALY ranging from $0 to $200,000. Sildenafil was the most cost-effective treatment in 60% to 80% of replications at willingness to pay values of $0 to $200,000 per QALY. At a willingness to pay of $50,000 per QALY, supportive care was the most cost-effective in 32% of replications, whereas tadalafil was most cost-effective in only 16% of replications (Figure 24).

As is evident from the confidence ellipses, there is significant uncertainty regarding the estimates of costs and effects for each treatment versus supportive care; however, the greater part of the confidence ellipses for sildenafil and tadalafil lie below a threshold willingness to pay of $50,000 per QALY (Figure 25).

Table 120: Results of Probabilistic Sensitivity Analysis for Monotherapy in Functional Class III					
Treatment	**Total Costs**	**Total QALYs**	**Versus sildenafil**		
			Incremental Costs	**Incremental QALYs**	**ICUR**
Sildenafil	$190,237 ($69,865 to $403,802)	3.392 (1.635 to 5.605)	Ref	Ref	Dominates all treatments
Dominated Treatments					
Tadalafil	$213,459 ($72,535 to $446,178)	3.047 (1.431 to 5.067)	$23,222 (–$68,465 to $142,993)	0.344 (–1.198 to –0.330)	Dominated by sildenafil
Supportive care	$223,528 ($67,026 to $447,621)	2.642 (1,186 to 4.619)	$33,291 (–$36,527 to $143,913)	–0.750 (–1.615 to –0.176)	Dominated by sildenafil
Ambrisentan 5 mg	$366,368 ($161.551 to $655,020)	3.299 (1.540 to 5.521)	$176,131 ($77,261 to $333,400)	–0.093 (–0.872 to –0.645)	Dominated by sildenafil
Ambrisentan 10 mg	$394,070 ($164,560 to $728,440)	3.105 (1.446 to 5.234)	$203,833 ($87,155 to $405,373)	–0.286 (–1.096 to –0.393)	Dominated by sildenafil
Riociguat	$395,773 ($169,365 to $713,549)	3.193 (1.488 to 5.392)	$205,536 ($91,069 to $399,012)	–0.199 (–1.006 to –0.572)	Dominated by sildenafil
Bosentan	$437,768 ($172,616 to $817,936)	2.900 (1.344 to 4.904)	$247,531 ($99,903 to $491,023)	–0.492 (–1.389 to –0.269)	Dominated by sildenafil
Epoprostenol	$445,672 ($220,285 to $739,567)	3.191 (1.715 to 4.942)	$255,435 ($144,058 to $419,183)	–0.200 (–1.043 to 0.433)	Dominated by sildenafil

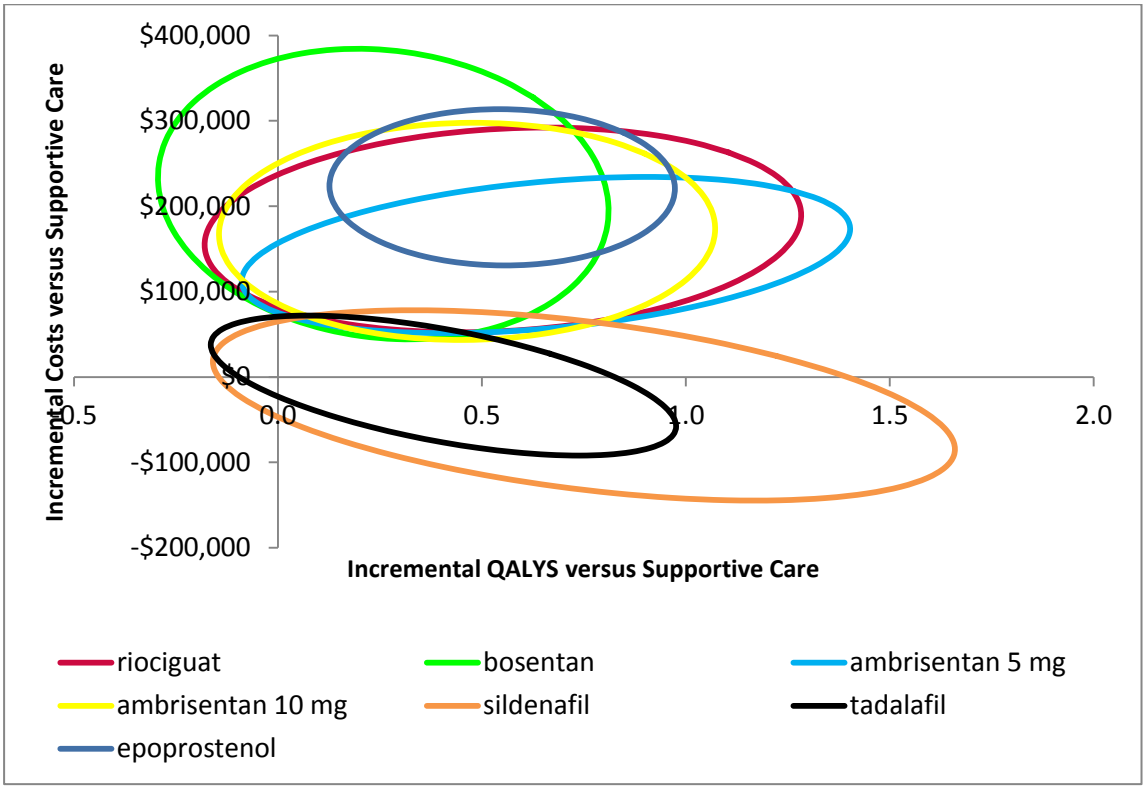
ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Figure 24: Cost-Effectiveness Acceptability Curve for Monotherapy in Pulmonary Arterial Hypertension Functional Class III



QALY = quality-adjusted life-year.

Figure 25: Confidence Ellipses for PSA Results in PAH Functional Class III — Incremental Costs Versus Incremental QALYs Versus Supportive Care



PAH = pulmonary arterial hypertension; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

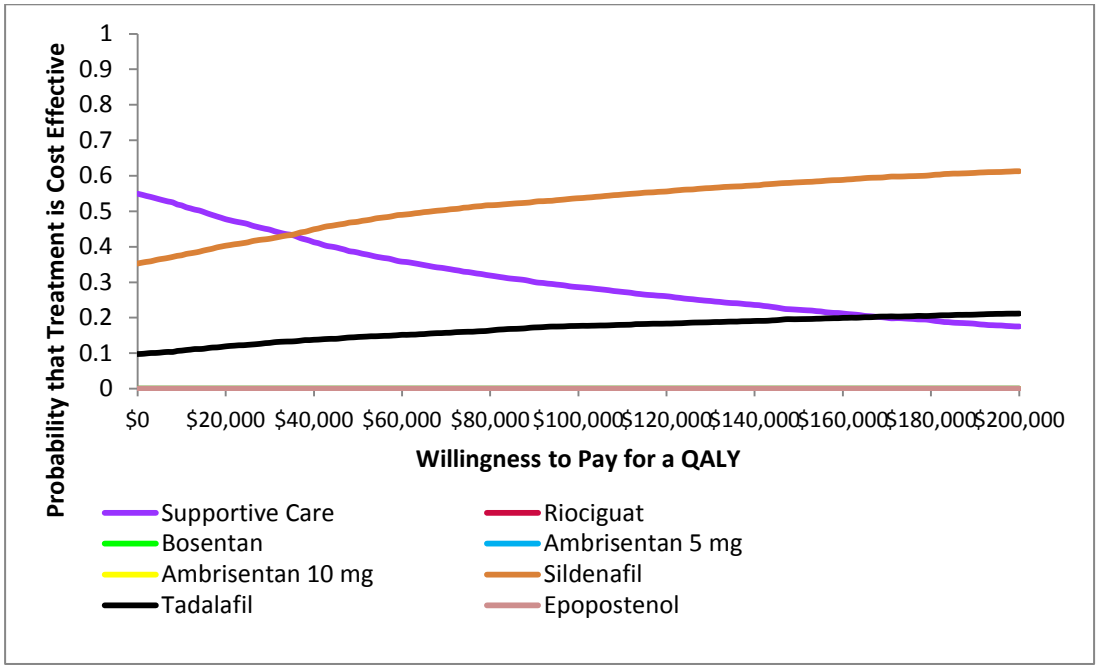
Probabilistic Sensitivity Analysis for Monotherapy Versus Supportive Care in Pulmonary Arterial Hypertension Functional Class IV:

As per the base-case analysis, supportive care was the least costly therapy in PAH FC IV. All other treatments were dominated by sildenafil, which was the next most costly therapy to supportive care; however, it also produced greater QALYs. The ICUR for sildenafil versus supportive care was slightly higher within the PSA at $31,224 per QALY. From the CEAC presented in Figure 26, sildenafil had the greatest probability of being cost-effective at willingness to pay values of greater than approximately $35,000 per QALY; however, the probability that sildenafil is the most cost-effective therapy did not exceed 60% at willingness to pay values up to $200,000 per QALY. As is evidenced by the confidence ellipses plotted in Figure 27, there is a great deal of uncertainty surrounding the estimates.

Table 121: Results of Probabilistic Sensitivity Analysis for Single Therapies in Functional Class IV						
Treatment	**Total Costs**	**Total QALYs**	**Versus Supportive Care**			**Incremental ICUR**
			Incremental Costs	**Incremental QALYs**	**ICUR**	
Supportive care	$273,421 ($106,528 to $505,181)	2.461 (0.990 to 4.453)	Ref	Ref	Ref	Ref
Sildenafil	$279,637 ($104,062 to $531,593)	2.661 (1.120 to 4.696)	$6,216 (–$65,119 to $62,764)	0.199 (0.006 to 0.612)	$31,224	$31,224
Dominated Treatments						
Tadalafil	$292,880 ($112,804 to $550,284)	2.560 (1.067 to 4.565)	$19,459 (–$19,175 to $58,050)	0.098 (0.001 to 0.321)	$197,637	Dominated by sildenafil
Epoprostenol	$427,300 ($180,646 to $757,034)	2.536 (1.072 to 4.445)	$153,879 ($75,081 to $257,028)	0.075 (–0.297 to 0.515)	$2,048,712	Dominated by sildenafil
Ambrisentan 5 mg	$479,676 ($195,803 to $867,216)	2.536 (1.030 to 4.544)	$206,254 ($88,019 to $368,530)	0.075 (–0.003 to 0.280)	$2,756,463	Dominated by sildenafil
Ambrisentan 10 mg	$483,151 ($195,976 to $882,823)	2.519 (1.032 to 4.514)	$209,730 ($88,978 to $378,055)	0.058 (–0.004 to 0.214)	$3,641,580	Dominated by sildenafil
Riociguat	$488,950 ($198,314 to $886,394)	2.538 (1.048 to 4.563)	$215,529 ($91,408 to $392,714)	0.077 (–0.013 to 0.350)	$2,798,125	Dominated by sildenafil
Bosentan	$497,562 ($200,244 to $911,253)	2.507 (1.023 to 4.507)	$224,141 ($91,924 to $408,263)	0.046 (–0.030 to 0.317)	$4,900,304	Dominated by sildenafil

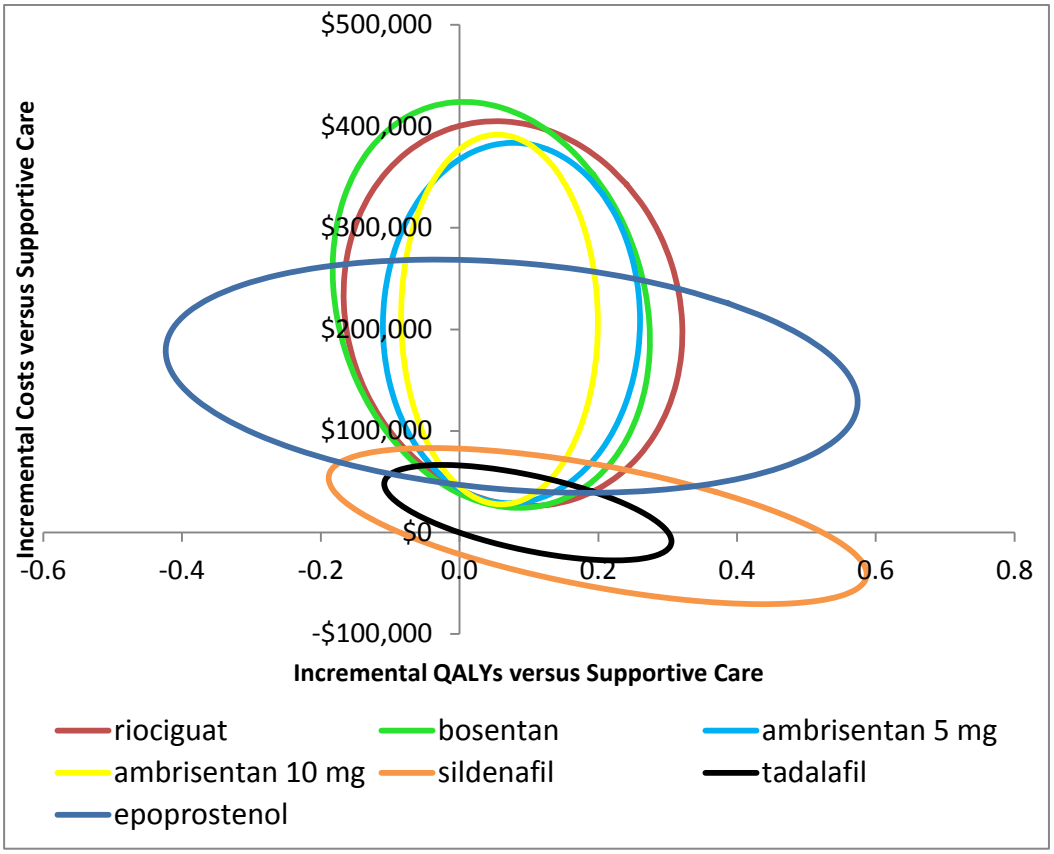
ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Figure 26: Cost-Effectiveness Acceptability Curve for Monotherapy in Pulmonary Arterial Hypertension Functional Class IV



QALY = quality-adjusted life-year.

Figure 27: Confidence Ellipses for Probabilistic Sensitivity Analysis Results in PAH Functional Class IV — Incremental Costs Versus Incremental QALYs versus Supportive Care



PAH = pulmonary arterial hypertension; QALY = quality-adjusted life-year.

b) Probabilistic Sensitivity Analysis for Add-on Therapies Versus Single Therapy

Probabilistic Sensitivity Analysis for Add-on Therapies Versus Single Therapy in Pulmonary Arterial Hypertension Functional Class II:

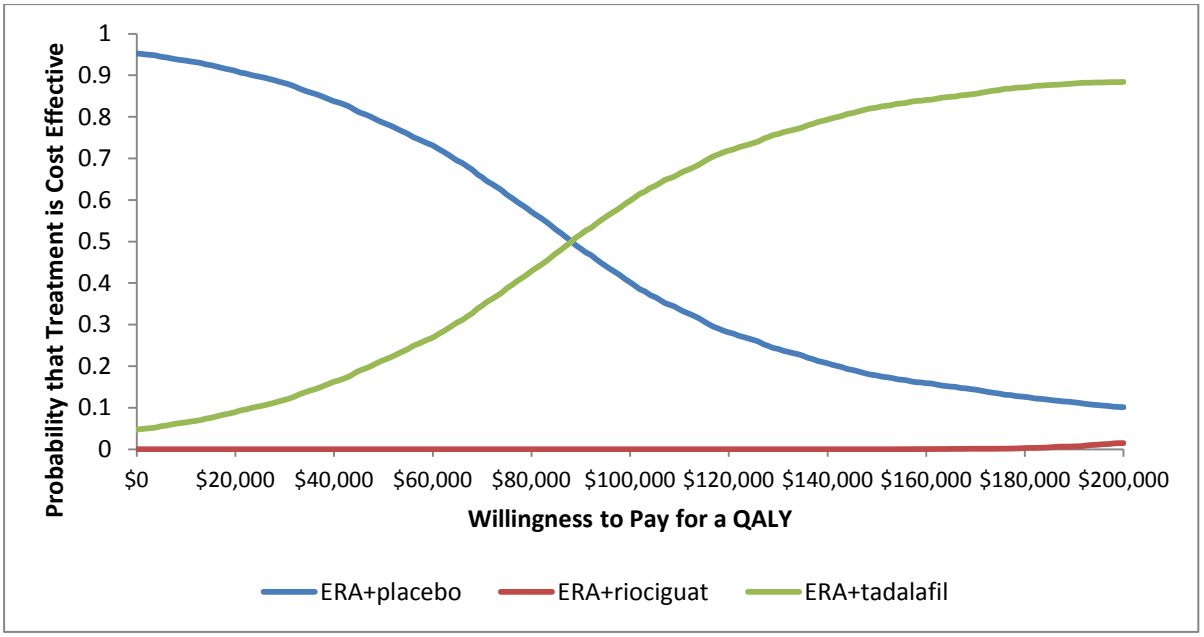
The estimates of mean cost and QALYs associated with each of the treatments within the PSA analysis differed slightly from those of the deterministic; however, the ICURs led to the same conclusions. Single therapy with an ERA is less costly than add-on therapy; however, add-on therapy results in greater efficacy. As in the deterministic sensitivity analysis, the estimated costs of ERA plus riociguat are greater than those of ERA plus tadalafil; however, ERA plus riociguat also produced greater QALYs. Based on the CEAC, at values below approximately $90,000 per QALY, single therapy with an ERA had the greatest probability of being the most cost-effective, and at values greater than $90,000 per QALY, an ERA plus tadalafil had the greatest probability. At a willingness to pay threshold of $50,000 per QALY, an ERA alone was the most cost-effective in 78% of replications, whereas ERA plus tadalafil was most cost-effective in 21% of replications.

As is evident within the confidence ellipses plotted in Figure 29, there is a great deal of uncertainty surrounding the estimates of costs and QALYs for both add-on therapies.

Table 122: Results of Probabilistic Sensitivity Analysis for Add-on Therapies Versus Single Therapy in Functional Class II						
Treatment	**Total Costs**	**Total QALYs**	**Versus ERA alone**			**Incremental ICUR**
			Incremental Costs	**Incremental QALYs**	**ICUR**	
ERA plus placebo	$448,964 ($199,831 to $819,000)	3.188 (1.840 to 5.035)	Ref	Ref	Ref	Ref
ERA plus tadalafil	$489,415 ($247,830 to $830,929)	3.698 (2.176 to 5.608)	$40,451 (–$11,962 to $76,320)	0.510 (0.091 to 1.101)	$79,374	$79,374
ERA plus riociguat	$760,870 ($434,926 to $1,181,481)	4.244 (2.560 to 6.189)	$311,906 ($209,977 to $414,910)	1.056 (0.321 to 2.038)	$295,385	$496,895

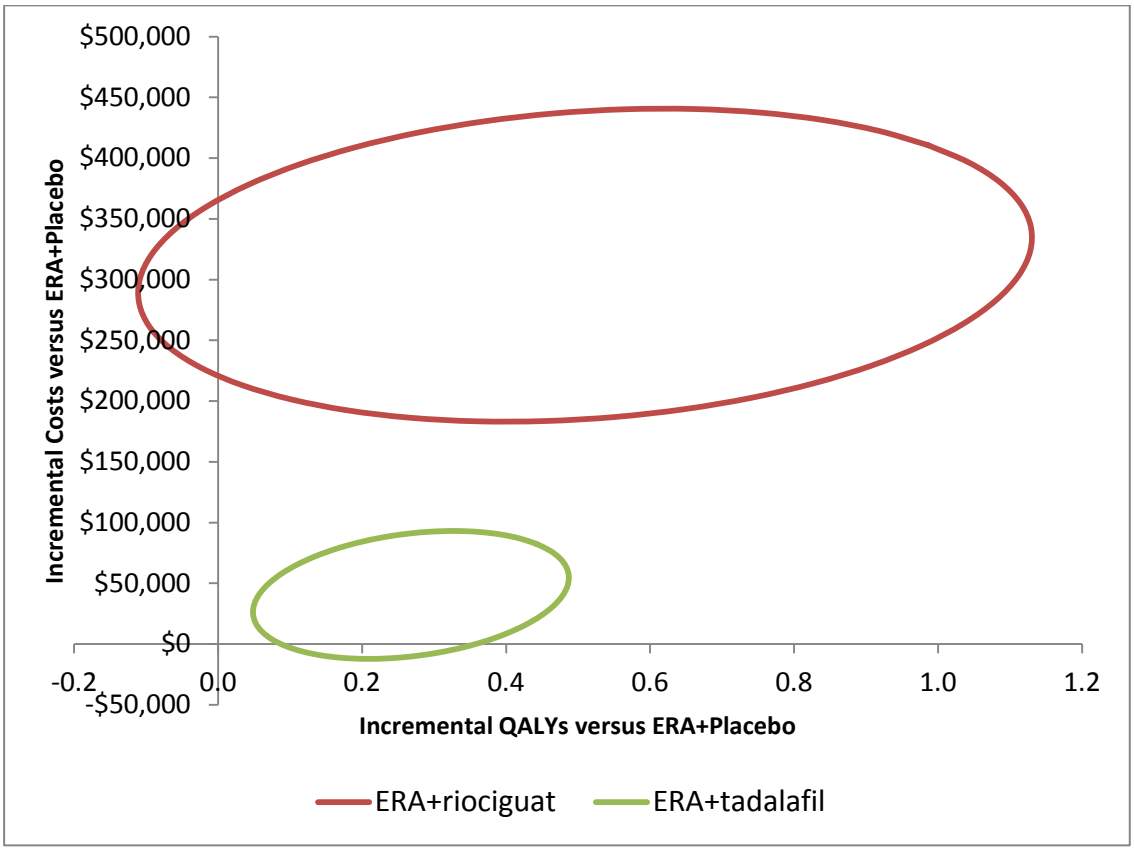
ERA = endothelin receptor antagonist; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; ref = reference.

Figure 28: Cost-Effectiveness Acceptability Curve for Add-on Therapies Versus Monotherapy in Pulmonary Arterial Hypertension Functional Class II



QALY = quality-adjusted life-year.

Figure 29: Confidence Ellipses for PSA Results in PAH Functional Class II — Incremental Costs Versus Incremental QALYs Add-on Therapy Versus Single Therapy



ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Probabilistic Sensitivity Analysis for Add-on Therapies Versus Single Therapy in PAH Functional Class III:

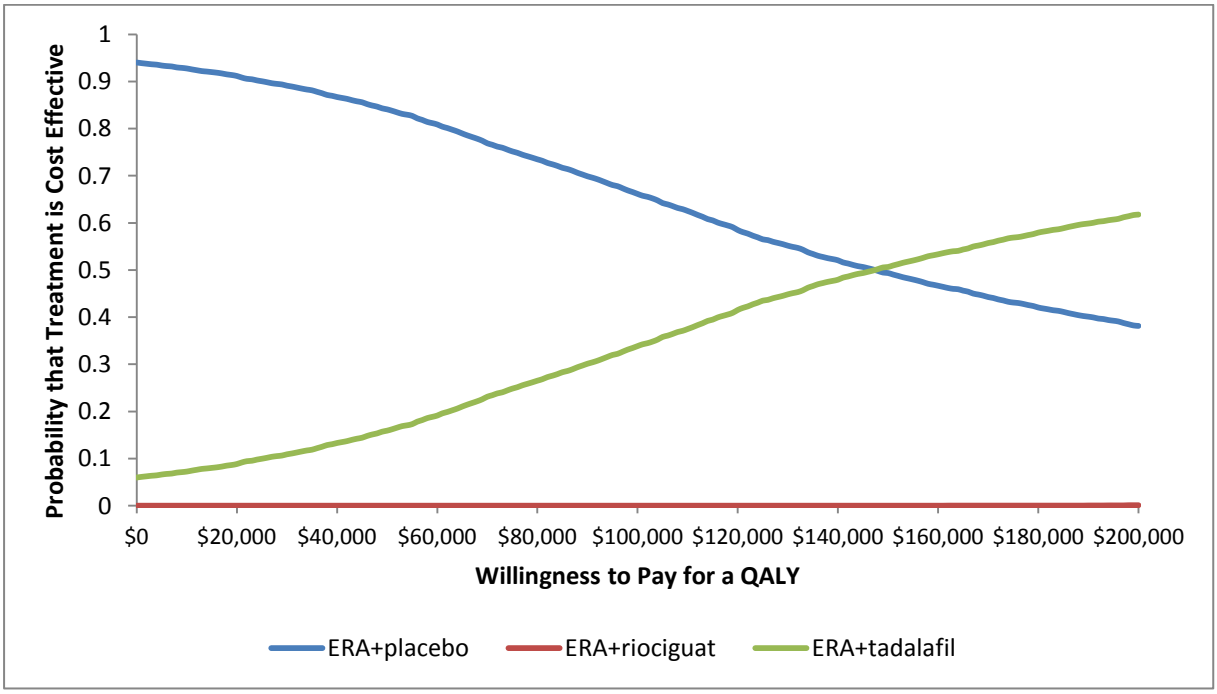
The results for the PSA for PAH FC III produced similar results to those of the base-case analysis. Based on the CEAC, an ERA alone is the optimal therapy at willingness to pay values of less than approximately $150,000, whereas an ERA plus tadalafil is the optimal therapy above this value.

Again, there is a great deal of uncertainty surrounding the estimates of costs and QALYs, as is evident in Figure 31, which is a plot of the confidence ellipses for the estimates.

Table 123: Results of PSA for Add-on Therapies in Functional Class III						
Treatment	**Total Costs**	**Total QALYs**	**Versus ERA alone**			**Incremental ICUR**
			Incremental Costs	**Incremental QALYs**	**ICUR**	
ERA plus placebo	$470,287 ($178,486 to, $875,123)	2.669 (1.215 to 4.640)	Ref	Ref	Ref	Ref
ERA plus tadalafil	$498,585 ($200,500 to $920,311)	2.868 (1.339 to 4.847)	$28,298 (–$14,013 to $65,838)	0.200 (0.005 to 0.494)	$141,666	$141,666
ERA plus riociguat	$699,432 ($313,177 to $1,225,148)	3.124 (1.528 to 5.215)	$229,145 ($126,947 to $364,627)	0.455 (0.098 to 0.980)	$503,695	$787,095

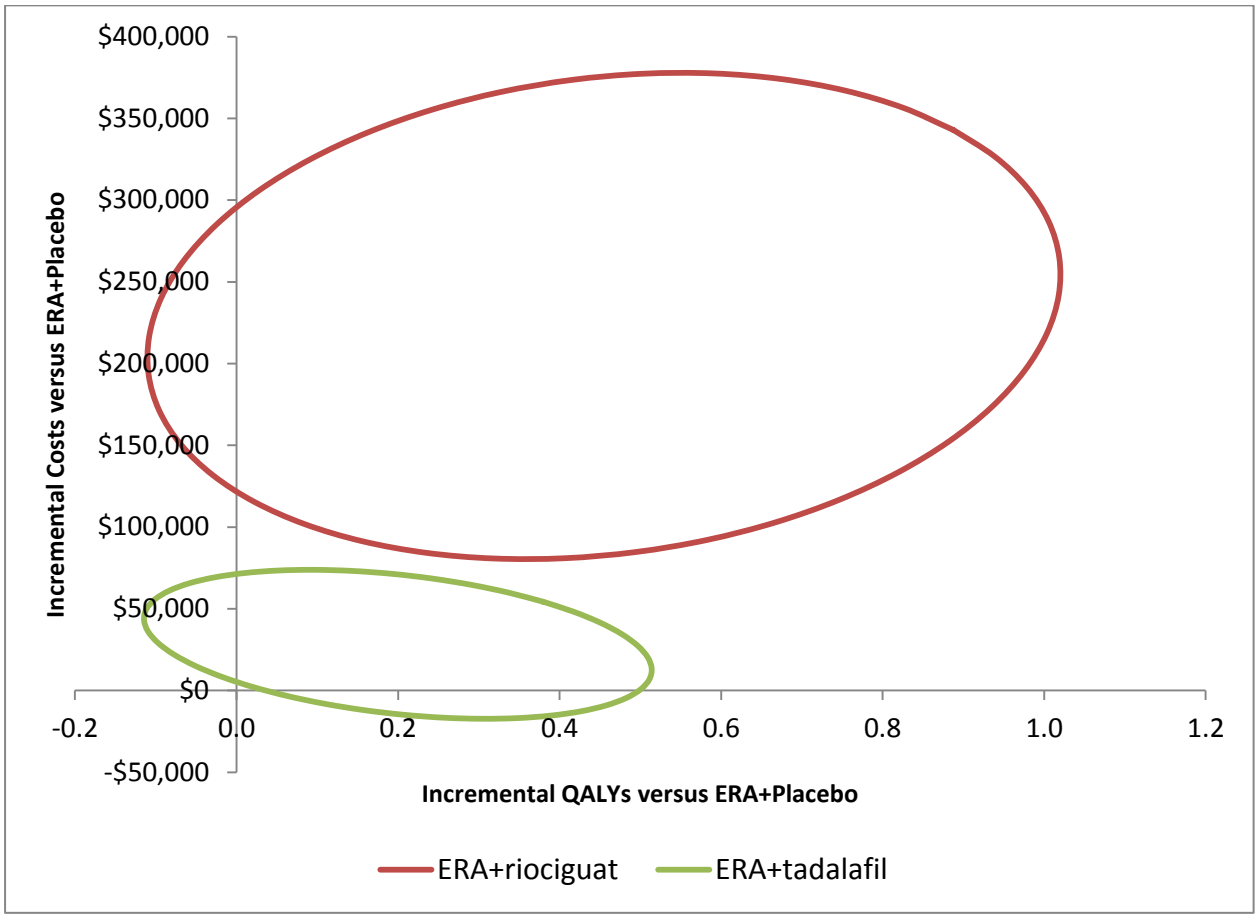
ERA = endothelin receptor antagonist; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; PSA = probabilistic sensitivity analysis; ref = reference.

Figure 30: Cost-Effectiveness Acceptability Curve for Add-on Therapies Versus Monotherapy in Pulmonary Arterial Hypertension Functional Class III



ERA = endothelin receptor antagonist; QALY = quality-adjusted life-year.

Figure 31: Confidence Ellipses for PSA Results in PAH Functional Class III — Incremental Costs Versus Incremental QALYs Add-on Therapy Versus Single Therapy



ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

Probabilistic Sensitivity Analysis for Add-on Therapies Versus Single Therapy in PAH Functional Class IV:

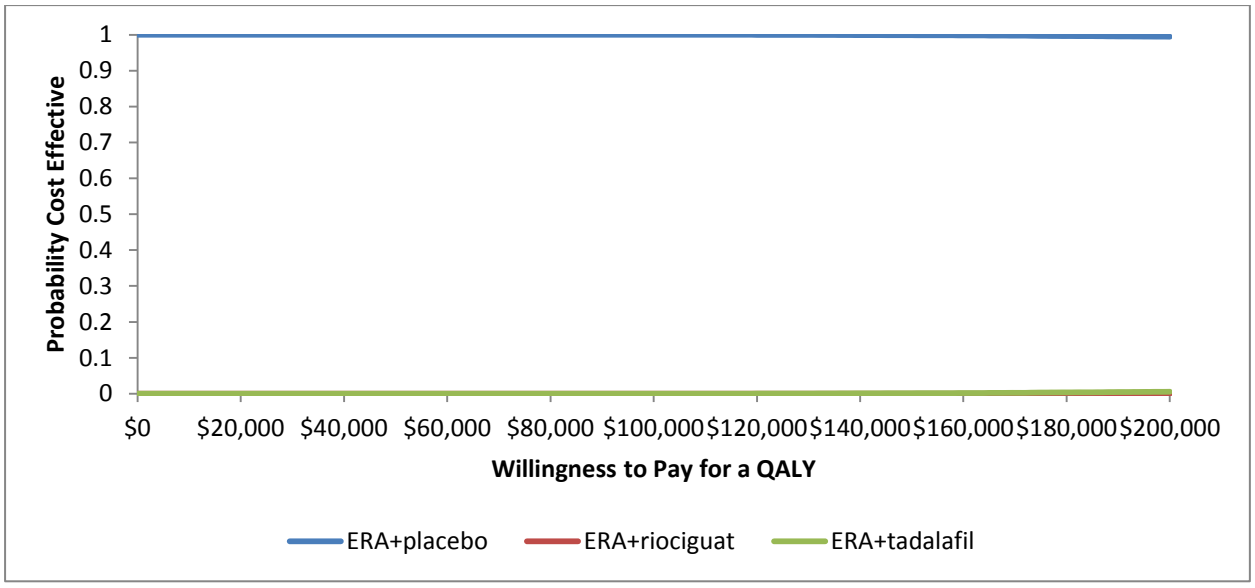
The estimated ICUR for add-on therapies versus ERA alone was greater than $1 million per QALY in PAH FC IV (Table 124). In values ranging from $0 to $200,000 per QALY, ERA alone therapy was optimal in 100% of replications (ERA = endothelin receptor antagonist; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Figure 32, Figure 33).

Table 124: Results of PSA for Add-on Therapies in Functional Class IV						
Treatment	**Total Costs**	**Total QALYs**	**Versus ERA alone**			**Incremental ICUR**
			Incremental Costs	**Incremental QALYs**	**ICUR**	
ERA plus placebo	$502,293 ($210,614 to $920,060)	2.476 (1.009 to 4.451)	Ref	Ref	Ref	Ref
ERA plus tadalafil	$546,231 ($222,373 to $995,213)	2.504 (1.027 to 4.490)	$43,939 ($18,223 to $81,012)	0.029 (–0.012 to 0.112)	$1,528,750	$1,528,750
ERA plus riociguat	$711,224 ($300,468 to $1,306,216)	2.587 (1.095 to 4.577)	$219,932 ($95,705 to $389,951)	0.111 (0.001 to 0.335)	$1,974,958	$2,130,186

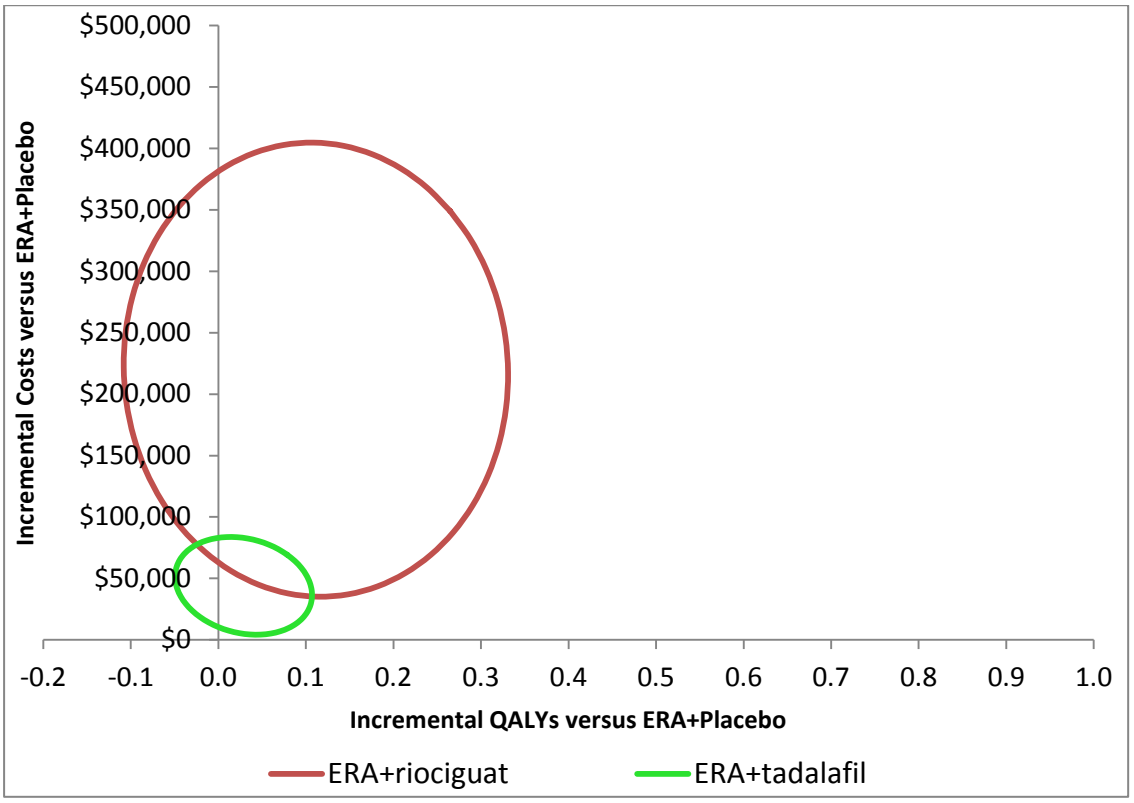
ERA = endothelin receptor antagonist; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Figure 32: Cost-Effectiveness Acceptability Curve for Add-on Therapies Versus Monotherapy in Pulmonary Arterial Hypertension Functional Class IV



ERA = endothelin receptor antagonist; QALY = quality-adjusted life-year.

Figure 33: Confidence Ellipses for PSA Results in PAH Functional Class IV — Incremental Costs Versus Incremental QALYs Add-on Therapy Versus Single Therapy



ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year.

6 DISCUSSION

6.1 Summary of the Clinical Evidence

The systematic review included 20 RCTs that reported the efficacy and safety of pharmacological therapies in patients with PAH. There were 19 studies[18-35] that provided comparisons of treatments in naive populations and four studies[33-36] that provided comparisons of treatments in populations that had been pre-treated with PAH drugs (add-on combination therapy). Evaluated interventions included the oral ERAs (ambrisentan 5 mg once daily, ambrisentan 10 mg once daily, bosentan 125 mg twice daily, macitentan 10 mg once daily), the sGC stimulator (riociguat max 1.5 mg three times daily and max 2.5 mg three times daily), the PDE-5 inhibitors (sildenafil 20 mg three times daily, tadalafil 40 mg once daily), and the prostanoids (epoprostenol i.v., and treprostinil s.c. or i.v.).

For add-on therapy trials, PATENT-1 (riociguat)[33] included patients who had been pre-treated with ERA or prostanoids, SERAPHIN (macitentan)[35] included patients who had been pre-treated with PDE-5 inhibitors or prostanoids, PHIRST (tadalafil)[34] included patients who had been pre-treated with bosentan, and Zhuang et al. (tadalafil)[36] included patients who had been pre-treated with ambrisentan. Those patients were receiving stable doses of background treatment in addition to the study medication. Patients had to be on stable background treatment for at least 90 days before randomization. Given that a common strategy in clinical practice is to wait for eight to 12 weeks before determining the effect of a new drug for a particular patient, it may be assumed that the first drug prescribed had reached its maximum effect at the time the second drug was added.

Data available for efficacy and safety outcomes were analyzed by direct pairwise meta-analyses. NMAs were conducted for four efficacy outcomes (clinical worsening, FC improvement, FC worsening, and 6MWD) to estimate the comparative efficacies between all studied interventions.

6.2 Interpretation of the Results

6.2.1 Summary of results of each PAH treatment

Table 174 and Table 175 provide an overview of the results of the clinical efficacy, safety, and quality of life of each PAH treatment strategy in the total, naive, and add-on populations.

a) Ambrisentan

ARIES-1 and ARIES-2 trials[18] included patients of both IPAH/FPAH (65%) and APAH (35%), who were predominantly WHO FC II (39%) and III (55%), and were naive to specific PAH drugs. At the end of the 12-week treatment, ambrisentan 5 mg and 10 mg showed reduction in clinical worsening, FC worsening, improvement in 6MWD, and reduction in BDI, compared with placebo. There were no differences in FC improvement, hospitalization, and death between ambrisentan and placebo. Results of hemodynamic parameters were not available in ARIES-1 and ARIES-2 trials. For safety, ambrisentan significantly lowered SAEs, which included ventricular failure and PH worsening. Total withdrawal was also lower in the ambrisentan than in placebo groups. For treatment-related AEs, ambrisentan was frequently associated with peripheral edema and anemia. In ARIES-1,[18] ambrisentan (both 5 mg and 10 mg) showed no differences in physical functioning and other items of SF-36 scales compared with placebo. In

ARIES-2,[18] ambrisentan 5 mg showed improvement in several items including physical functioning of the SF-36 health survey.

b) Bosentan

Of the five bosentan studies, BREATHE-5[22] enrolled all patients with Eisenmenger syndrome, PAH associated with congenital heart disease, who were at WHO FC III. The other four studies[21,23,29,32] included patients of both IPAH/FPAH (59% to 86%) and APAH (14% to 41%), who were predominantly WHO FC II (37% to100%)[29,32] and III (59% to100%).[21,23,29] Four studies[21-23,29] included patients who were naive to PAH-specific drugs, and one study (EARLY)[32] included 15% of patients who were on sildenafil background. Treatment durations were 12 to 18 weeks.

When all studies were included in the analysis (total population), bosentan showed statistically significant reduction in clinical worsening and FC worsening, compared with placebo. When the EARLY study was excluded from the analysis (naive population), bosentan also showed reduction in clinical worsening and FC worsening, but statistically significant differences were not reached. Bosentan also showed improvement in 6MWD and BDI, and in hemodynamic parameters including PVR, PAP, and cardiac index in both total and naive populations. There was no difference in death. For safety, there were no differences in SAEs, discontinuation of treatment due to AEs, and total withdrawal between bosentan and placebo groups. However, bosentan was associated with higher incidence of liver toxicity (increase in aminotransferases, ALT or AST) and peripheral edema. For quality of life, there were no differences between bosentan and placebo for any of the eight components of the SF-36 health survey.

When 6MWD was analyzed based on patient subgroups, bosentan showed improvement in 6MWD irrespective of gender, age, baseline WHO FC, baseline 6MWD, or PAH etiology.

c) Macitentan

The SERAPHIN trial[18] included patients of both IPAH/FPAH (57%) and APAH (43%), who were predominantly WHO FC II (52%) and III (46%). The patient population consisted of both patients who were naive to PAH therapy (36%) and who were previously treated with PDE-5 inhibitors (61%) or prostanoids (5%). Clinical worsening and death were reported at median follow-up of 115 weeks and 129 weeks, respectively, while other outcomes were reported at six months.

In the total population, macitentan 10 mg showed significant reduction in clinical worsening, FC worsening, hospitalization, BDI, and significant increase in FC improvement and 6MWD, compared with placebo. There was no difference in death. Changes in hemodynamic parameters such as PVR and cardiac index were also in favour of macitentan compared with placebo. In the naive population, macitentan also showed significant reduction in clinical worsening, but did not show any significant difference in 6MWD. Other outcomes were not available for the naive population. For safety, there were no differences in discontinuation of treatment due to AEs, and total withdrawal between macitentan and placebo groups. SAEs were significantly less frequent with macitentan than with placebo, typically PAH worsening and right ventricular failure. However, macitentan was frequently associated with anemia. For quality of life, macitentan showed significant improvements in seven out of eight domains of the SF-36 health survey, compared with placebo.

Addition of macitentan 10 mg to PDE-5 inhibitors or prostanoids showed significant reduction of clinical worsening and significant improvement in 6MWD. Results for other outcomes were not available.

The effect of macitentan in clinical worsening and 6MWD was observed in patient subgroups based on gender, PAH etiology, and background PAH therapies.

d) Riociguat

The PATENT-1 trial[33] included patients of both IPAH/FPAH (63%) and APAH (37%), who were predominantly WHO FC II (42%) and III (53%). The patient population consisted of both patients who were naive to PAH therapy (50%) and who had been previously treated with ERA (44%) or prostanoids (6%). Treatment duration was 12 weeks.

In the total population, riociguat max 2.5 mg showed significant reduction in clinical worsening, FC worsening, BDI, and significant improvement in 6MWD compared with placebo. The lower dose, max 1.5 mg, showed improvement only in 6MWD. Both doses did not show any significant change in FC improvement or hospitalization. For hemodynamic parameters, both doses of riociguat showed significant reduction in PVR, PAP, and significant improvement in cardiac index. For safety, there were no differences in death, SAEs, treatment discontinuation due to AEs, and total withdrawal between riociguat (both doses) and placebo. However, riociguat was associated with higher incidence of peripheral edema, anemia, and hypotension. Both doses of riociguat showed improvement in quality of life when assessed by EQ-5D and the LPH questionnaires.

In the naive population, riociguat max 2.5 mg did not show any significant reduction in clinical worsening. It only showed significant reduction in FC worsening, significant improvement in 6MWD, and significant improvement in hemodynamic parameters including PVR, PAP, and cardiac index compared with placebo.

For add-on therapy, addition of riociguat max 2.5 mg to the overall background therapy (ERA and prostanoids) resulted in significant reduction in clinical worsening, FC worsening, and significant improvement 6MWD compared with placebo. The hemodynamic parameters were also improved in the overall population. When ERA background was analyzed separately, statistical significance could not be reached for any of the clinical outcomes, although significant improvement in hemodynamic parameters was still observed. To the prostanoid background therapy, addition of riociguat max 2.5 mg only showed significant improvement in 6MWD and hemodynamic parameters.

In subgroup analyses, riociguat showed improvement in 6MWD irrespective of gender, age, baseline WHO FC, baseline 6MWD, or PAH etiology.

e) Sildenafil

The SUPER trial[30] included patients of both IPAH/FPAH (63%) and APAH (37%), who were predominantly WHO FC II (39%) and III (58%), and were naive to PAH-specific drugs. At the end of the 12-week treatment, sildenafil 20 mg had significantly increased FC improvement, 6MWD, and BDI, but did not show any significant change in clinical worsening, FC worsening, or hospitalization compared with placebo. Sildenafil 20 mg showed significant improvement in hemodynamic parameters such as PVR and PAP, but not cardiac index. There were no significant differences between sildenafil and placebo in all safety outcomes, as well as treatment-specific outcomes. Sildenafil showed improvement in quality of life when assessed by SF-36 and EQ-5D instruments.

Sildenafil significantly improved 6MWD in all patient subgroups including gender, age, baseline WHO FC, baseline 6MWD, and PAH etiology.

f) Tadalafil

The PHIRST trial[34] included patients of both IPAH/FPAH (63%) and APAH (37%), who were predominantly WHO FC II (32%) and III (65%). The patient population consisted of both patients who were naive to PAH therapy (46%) and who had been previously treated with bosentan (54%). Treatment duration was 16 weeks.

In the total population, tadalafil 40 mg showed significant reduction in clinical worsening, and significant increase in FC improvement and 6MWD compared with placebo. There were no significant differences in FC worsening, BDI, hospitalization, hemodynamic parameters, safety outcomes, and treatment-specific AEs between tadalafil and placebo. Tadalafil showed improvement in quality of life when assessed by SF-36 and EQ-5D instruments.

In the naive population, tadalafil showed significant increase only in FC improvement and 6MWD compared with placebo. Results for hospitalization, BDI, and hemodynamic parameters were not available.

In the add-on therapy population, addition of tadalafil 40 mg to bosentan background therapy showed significant reduction in clinical worsening and significant improvement in 6MWD. There were no significant differences between tadalafil and placebo in other clinical outcomes and hemodynamic parameters.

Tadalafil improved 6MWD in all patient subgroups including gender, age, baseline WHO FC, baseline 6MWD, and PAH etiology.

g) Epoprostenol

Of the three epoprostenol studies, two (Barst et al. [1996][20] and Rubin et al. [1990][27]) enrolled all patients with IPAH/FPAH, while Badesch et al. (2000)[19] included all patients who had secondary PH (PAH associated with connective tissue disease). All patients in the three studies were naive to PAH drugs, and mostly of WHO or NYHA FC III (65% to 79%) and IV (17% to 26%). Treatment duration was 12 weeks in two studies[19,20] and eight weeks in one study.[27]

At the end of treatment, epoprostenol showed significant increase in FC improvement and 6MWD, and significant reduction in BDI compared with placebo. Clinical worsening was not reported in epoprostenol studies. Epoprostenol also lowered FC worsening, but a significant difference could not be reached. There was also significant improvement in hemodynamic parameters that were in favour of epoprostenol compared with placebo. For safety, there were no differences in death and SAEs between epoprostenol and placebo. Epoprostenol was associated with higher incidence of hypotension. Epoprostenol showed improvement in quality of life, which was assessed using the following instruments: Chronic Heart Failure Questionnaire, Nottingham Health Profile, and Dyspnea-Fatigue Rating.

Subgroup analyses were not available for any of the outcomes in the epoprostenol trials.

h) Treprostinil

Of the four treprostinil studies, three (McLaughlin et al. [2003],[25] Rubenfire et al. [2007],[26] and Simonneau et al. [2002][28]) administered the drug subcutaneously, and one (TRUST [2010][31]) intravenously. Patient populations were naive to treprostinil, and were either mostly IPAH/FPAH (98%),[25,31] or a mixture of both IPAH/FPAH (66%) and APAH (43%). Three studies had patients of WHO or NYHA FC mostly FC III (82% to 96%). Because not all studies reported the same outcomes, and there was substantial statistical heterogeneity among studies, treatment effects are reported separately for certain outcomes.

Overall, treprostinil showed significant improvement in 6MWD and BDI compared with placebo, without having significant changes in FC worsening, FC improvement, or hospitalization. Clinical worsening was not reported in treprostinil studies. Treprostinil also showed significant improvement in hemodynamic parameters (PVR, PAP, and cardiac index). For safety, the largest study (N = 469) on treprostinil, by Simonneau et al. (2002),[28] showed that treprostinil was frequently associated with SAEs, leading to higher incidence of withdrawal due to AEs compared with placebo. Frequent SAEs associated with treprostinil included injection site pain, injection site reaction, injection site bleed or bruise, rash, headache, edema, hypoxia, and hypotension. For quality of life, treprostinil showed significant improvement in physical dimension of the Minnesota Living with Heart Failure instrument.

Subgroup analyses were not available for any of the outcomes in the treprostinil trials.

6.2.2 Comparisons Among Pulmonary Arterial Hypertension Treatments

a) Total and Naive Populations

Comparisons were made for diverse treatment strategies that differed in chemical structures, mechanisms of action, mode of administration, dosage, and treatment-related AEs. The different modes of administration included i.v. infusion (epoprostenol, treprostinil), s.c. injection (treprostinil), and oral (ambrisentan, bosentan, macitentan, riociguat, sildenafil, tadalafil). NMA was conducted for selected clinical outcomes including clinical worsening, FC improvement, FC worsening, and 6MWD. The results of NMA on those outcomes are consistent with those of pairwise meta-analysis, which in part suggests robustness of the NMA findings.

For clinical worsening, all treatments showed improvement compared with placebo at the individual RCT level. However, statistically significant differences could not be reached for certain treatments (i.e., ambrisentan 10 mg and sildenafil 20 mg) or for certain subpopulations (bosentan [naive], riociguat max 2.5 mg [naive], and tadalafil 40 mg [naive]). This could be due to the fact that the studies for these were either short in duration (and therefore few events could occur), or they were underpowered to detect a significant difference between groups for a secondary outcome. In the comparison between active treatments, the NMA results showed that none of the treatment strategies — including macitentan, riociguat, bosentan, ambrisentan, sildenafil, and tadalafil — showed superiority in either total or naive populations for reduced clinical worsening. Because the SERAPHIN trial had a longer treatment duration (median follow-up of 115 weeks) compared with the 12 to 16 weeks of other trials, a sensitivity analysis was conducted by omitting macitentan from the NMA. Removing macitentan did not have a substantial effect on the results. Further sensitivity analyses that were conducted by adjusting for covariates such as PAH etiology and WHO FC also did not change the magnitude and direction of the relative treatment effect from the results of the unadjusted base case. Clinical worsening was not reported in trials of epoprostenol and treprostinil; therefore, the relative treatment effect of prostanoids compared with other treatment strategies for clinical worsening remains unknown.

For FC improvement, the treatment effects significantly favoured macitentan (total), sildenafil (naive), tadalafil (naive), and epoprostenol (naive), while there were no significant differences in other treatments compared with placebo at the individual RCT level. In the comparison between active treatments using NMA, epoprostenol had the highest activity compared with all other treatments in both total and naive populations. The treatment effect of epoprostenol was over nine-fold higher than placebo. The results from the NMA showed that the treatment effects significantly favoured epoprostenol compared with the remaining treatments (ambrisentan, bosentan, macitentan, riociguat, sildenafil, tadalafil, and treprostinil). There were no significant

differences in FC improvement between the remaining treatment strategies, except that sildenafil 20 mg was superior to ambrisentan 5 mg. When sensitivity analyses were performed by omitting macitentan, or by adjusting covariates such as PAH etiology and WHO FC, the treatment effects of the remaining strategies were not affected in either magnitude or direction compared with those of the unadjusted base case.

For FC worsening, the results were similar to those observed for clinical worsening at the individual RCT level, in that all treatments showed a trend in the reduction of FC worsening although statistically significant differences could not be reached for certain treatments or subpopulations. Between treatments, the NMA results showed that none of the treatment strategies provided a significant difference to each other in both the total and naive populations. FC worsening results for macitentan compared with placebo were not available for naive populations. When sensitivity analyses were performed by omitting macitentan (in total populations), or by adjusting covariates such as PAH etiology and WHO FC (in total and naive populations), the treatment effects of the remaining strategies were not affected in either magnitude or direction compared with those of the unadjusted base case.

For 6MWD, all treatments showed statistically significant improvement compared with placebo. Of note, 6MWD was the primary outcome in most studies, which were powered to detect a significant difference versus placebo for this outcome. NMA results showed that epoprostenol had the highest activity compared with all other treatments in both the total and naive populations. In the total populations, improvement in 6MWD significantly favoured epoprostenol compared with treprostinil, macitentan, bosentan, and tadalafil. In the naive populations, epoprostenol was shown to be significantly better than macitentan and treprostinil. There were no significant differences in 6MWD between the remaining treatment strategies, except that ambrisentan 10 mg was significantly better than macitentan and treprostinil. Sensitivity analyses were not conducted for change in 6MWD because it is a surrogate outcome that has not been clearly shown to reflect benefit in clinical outcomes such as all-cause death, hospitalization, and initiation of PAH rescue therapy.[38]

In summary, of the four outcomes analyzed using NMA, there were no significant differences in clinical worsening and FC worsening among treatment strategies. For FC improvement and 6MWD, epoprostenol had the highest activity in both the total and naive populations, while there were no apparent differences among the remaining treatments. Acknowledging the limitations in the available evidence, these findings suggest that there may not be statistically or clinically meaningful differences between PAH drugs currently available in Canada when used in the PAH population as a whole. There is, however, an exception with epoprostenol, which appears to be the most effective in improving clinical status, as measured by FC improvement and 6MWD. Results of sensitivity analyses showed the robustness of the findings in the base-case analysis of the NMA.

b) Treatment-Experienced Populations (Add-on Therapy)

NMA could be conducted only to compare between treatment effects of riociguat max 2.5 mg three times a day (PATENT-1) and tadalafil 40 mg once a day (PHIRST, Zhuang) in patients with ERA (ambrisentan or bosentan) background therapy. Macitentan was not included in the comparison because SERAPHIN was a long-term trial and its patients had different treatment background (PDE-5 inhibitors or prostanoids).

The addition of macitentan 10 mg to PDE-5 inhibitor or prostanoid background therapy statistically significantly reduced clinical worsening compared with background therapy alone. Likewise, the addition of tadalafil 40 mg to ERA background therapy statistically significantly

reduced clinical worsening versus ERA monotherapy. However, the addition of riociguat max 2.5 mg to ERA background therapy non-significantly reduced clinical worsening versus ERA monotherapy. For FC improvement, there were no statistically significant differences between combination therapy of riociguat max 2.5 mg plus ERA or of tadalafil 40 mg plus ERA versus ERA alone. The addition of riociguat max 2.5 mg or tadalafil 40 mg to ERA background therapy reduced FC worsening versus ERA alone; however, neither combination resulted in a statistically significant difference versus monotherapy.

The addition of macitentan 10 mg, riociguat max 2.5 mg, or tadalafil 40 mg to corresponding background therapy numerically improved 6MWD compared with background therapy alone. Statistically significant differences were reached for macitentan and tadalafil, but not for riociguat.

The NMA results showed that there were no differences between riociguat and tadalafil in clinical worsening, FC improvement, FC worsening, or 6MWD when given in addition to ERA (ambrisentan or bosentan). Of note, the clinical conditions of patients in those studies were stable, with ERA background for at least three months before randomization. Thus, the effect of the second active treatment could be masked and less apparent due to the presence of the background treatment. However, the lack of differences between riociguat and tadalafil in the experienced populations was consistent with the results in the total and naive populations, where the two treatments showed no significant differences for all four outcomes of interest.

6.2.3 Combination Therapy Studies Not Included in the Analysis

This section provides a summary of evidence from studies on the combination therapy that did not meet the selection criteria of the therapeutic review. Articles were selected from a 10-year literature search (2004 to 2014). We considered systematic reviews (with or without meta-analysis), RCTs, and observational studies, except case reports and case series. The characteristics of the studies are presented in Table 230 of APPENDIX 14. A total of nine studies were evaluated:

- One systematic review / meta-analysis of six double-blind placebo-controlled trials.[93] The meta-analysis compared the efficacy of combination therapy with monotherapy in PAH Group I patients having FC varying from II to IV. The baseline therapy was bosentan, sildenafil, or epoprostenol. The second therapy was tadalafil, treprostinil, sildenafil, iloprost, or bosentan.
- Three combination therapy studies on newly diagnosed PAH patients:
  - One retrospective study[94] on upfront dual or triple therapy of epoprostenol plus ERA and/or PDI-5 inhibitors. This study also had another group of add-on therapy of ERA and/or PDI-5 inhibitors prior to epoprostenol.
  - One retrospective study[95] on upfront triple therapy (epoprostenol i.v., bosentan, and sildenafil).
  - One retrospective study[96] on upfront dual therapy of epoprostenol and bosentan.
- Five combination therapy studies on PAH patients who deteriorated or were nonresponsive on first PAH treatment.
  - One prospective uncontrolled study[97] on add-on dual therapy. The first drug was bosentan, sildenafil, ambrisentan, or sitaxsentan (note: sitaxsentan was withdrawn from the Canadian market in 2010/11 due to hepatotoxicity). The second drug was sildenafil, iloprost (note: iloprost is a prostanoid that is not available in Canada), bosentan, or ambrisentan.
  - One prospective uncontrolled study[98] on add-on therapy of sildenafil in patients who deteriorated while on bosentan.

- One retrospective study[99] on add-on therapy of prostanoids in patients who failed on oral therapy of bosentan or bosentan or sildenafil.
- One retrospective study[100] on add-on therapy of bosentan in patients who had long-term treatment with treprostinil and remained WHO FC III or II.
- One retrospective study[101] on add-on therapy of sildenafil as rescue therapy in patients who had long-term treatment with prostanoids and who started to deteriorate.

Patients in the RCTs included in the meta-analysis were either treatment-naive or had been on long-term treatment or on stable doses of an initial PAH therapy. The included RCTs were PHIRST-1b, TRIUMPH-1, PACES, STEP, COMBI, and BREATHE-2. Of note, PACES was excluded from the CADTH review because the sildenafil dose used in the study (80 mg three times a day) was four times higher than the Health Canada–approved dose (20 mg twice a day). Other studies were excluded for various reasons, as indicated in APPENDIX 6. Follow-up durations ranged from 12 to 16 weeks. Several limitations of this systematic review/meta-analysis were noted, including:

- The authors pooled data from studies comparing different combinations of PAH therapy.
- There is between-study heterogeneity in patient baseline characteristics.
- There was a small sample size in four of the six RCTs.
- There was between-study heterogeneity in “escalation” of PAH therapy.
- There was publication bias in the combination therapy literature.

Patients in the observational studies were adults with severe PAH with WHO FC of III and IV. Follow-up periods ranged from four months to two years. The observational studies had several limitations in their respective design. They lacked an appropriate comparator group. Many were retrospective in nature and had small sample sizes. Only patients who survived underwent follow-up assessment and not all patients had the same treatment background prior to treatment initiation. Results on survival were not adjusted for potential differences in demographic, functional, and hemodynamic differences. There is a high risk of selection bias in the studies. The results should therefore be interpreted with caution.

A summary of the findings is presented in Table 231 of APPENDIX 14. Of the RCTs on combination therapy included in the systematic review by Fox et al. 2011,[93] the addition of sildenafil up-titrated to 80 mg onto long-term intravenous epoprostenol therapy in the PACES trial improved 6MWD, time to clinical worsening, hemodynamic parameters, and quality of life. However, the pooled results in the systematic review and meta-analysis[93] showed that combination therapy resulted only in a modest increase in 6MWD compared with monotherapy. Combination therapy did not show a statistically significant difference in FC improvement, FC worsening, mortality, hospital admissions for worsening of PAH, need for escalation therapy, premature study discontinuation, and clinical worsening compared with monotherapy.

In contrast, retrospective studies[94-96] from the French PAH registry showed that upfront dual or triple therapy involving epoprostenol and ERA and/or sildenafil result in improvement in clinical and hemodynamic status; it is also associated with favourable survival estimates in patients with severe PAH. The remaining five combination therapy studies,[97-101] in which a second rescue PAH therapy was used in patients who had failed or were nonresponsive to the initial treatment, also suggested improvement in clinical status, exercise capacity, and hemodynamics.

During the scoping phase of this therapeutic review, two studies on combination therapy (COMPASS-2 and AMBITION) were identified and initial results of both studies have been

made public, but are not yet published, toward the end of this review. CADTH could therefore not include these studies in the analyses. Below are brief summaries of these new trials.

COMPASS-2 was a phase 4, prospective, randomized, double-blind, placebo-controlled, event-driven study evaluating the effect of bosentan on the time to first morbidity or mortality event in patients with symptomatic PAH already treated with sildenafil. The trial did not meet the primary end point of the time to first morbidity or mortality event; the addition of bosentan to sildenafil showed a nonsignificant risk reduction of 17% compared with sildenafil alone (*P* = 0.25). The combination (add-on) therapy of bosentan and sildenafil improved 6MWD at week 16 (mean difference 21.8 m, *P* = 0.01). Liver enzyme elevation (15.4%) was a common adverse event observed in the bosentan group compared with placebo.

AMBITION was a randomized, double-blind, phase 3b/4 study of first-line combination therapy with ambrisentan and tadalafil in patients with WHO FC II and III PAH. The primary end point was time to first clinical failure event, defined as time from randomization to the first occurrence of death (all-cause), hospitalization for worsening of PAH, disease progression, or unsatisfactory long-term clinical response. The combination of ambrisentan 10 mg and tadalafil 40 mg reduced the risk of clinical failure by 50% compared with the pooled monotherapy groups of ambrisentan and tadalafil (HR = 0.502; 95% CI, 0.348 to 0.724; *P* = 0.002). The treatment effect was mainly driven by a reduction in hospitalizations. There was no difference between groups in the change from baseline to week 24 for WHO FC. Combination therapy improved 6MWD, but not BDI. Adverse events frequently associated with combination therapy versus ambrisentan and tadalafil were peripheral edema (45% versus 33% and 28%), headache (42% versus 33% and 35%), nasal congestion (21% versus 15% and 12%), and anemia (15% versus 6% and 12%).

Therefore, a limited number of RCTs and lower-quality observational studies on combination therapy have demonstrated a modest improvement in certain PAH outcomes. High-quality studies are still needed to ascertain whether combination therapy shows improvement in outcomes including mortality, morbidity, FC improvement, and FC worsening compared with monotherapy, or which combination therapy is more effective in the treatment of PAH patients who deteriorated or became nonresponsive while on the initial therapy.

6.2.4 Pharmacoeconomic Considerations

a) Monotherapy Versus Supportive Care

The results of the base case show that sildenafil would be considered the most cost-effective therapy for PAH in patients with FC II, III or IV. CDR economic analysis used the listed price of brand name sildenafil.

In patients with FC II and III, sildenafil was both less costly and more effective than all comparator treatments including supportive care, making it the dominant therapy. Of note, generic sildenafil is reimbursed by some of the drug plans. Using the generic cost would not change the conclusions of the analysis, as sildenafil would remain the most cost-effective option for adult patients with FC II and III PAH.

In FC IV, supportive care was less costly than treatment with sildenafil; however, provided a payer's willingness to pay per QALY was greater than $19,188, sildenafil would be the optimal therapy. Although sildenafil was found to be the cost-effective PAH therapy in FC IV based on the economic analysis, its role as monotherapy in FC IV has been questioned.

Although sildenafil dominated treatment with tadalafil, being both more effective and less costly, when compared with supportive care, tadalafil was dominant compared with supportive care in patients with FC II and III PAH. In FC IV, the ICUR for tadalafil versus supportive care was $211,923 per QALY. All other treatments in comparison with supportive care produced ICURs of greater than $1,000,000 per QALY.

Extensive sensitivity analyses were conducted to examine the impact of changes in the input parameters and structural assumptions on the results. In almost all cases, the results were robust to changes, with sildenafil remaining the optimal therapy. The only three assumptions that affected the results were with respect to the time horizon for FC II and IV, the percentage of patients initiating epoprostenol upon deteriorating to FC IV, and the incorporation of unadjusted relative risks of improvement and worsening in FC from the NMA.

If the time horizon was reduced to two years, in FC II sildenafil no longer dominated supportive care, but resulted in an ICUR of $132,643 versus supportive care. In FC IV, reducing the time horizon to two years resulted in sildenafil dominating all other therapies.

In FC II and III, reducing the percentage of patients initiating epoprostenol upon deteriorating to FC IV to 0% resulted in sildenafil no longer dominating the other therapies. However, even in these cases the ICUR for sildenafil versus supportive care remained below $40,000 per QALY. In FC IV, the ICUR for sildenafil versus supportive care exceeded $50,000 per QALY in this same scenario in which no patients initiating epoprostenol.

Incorporation of unadjusted relative risks for improvement and worsening in FC did not change the results in FC II or III, with sildenafil remaining the dominant treatment. In FC IV, the ICER for sildenafil versus supportive care rose from $19,188 per QALY in the base case to $93,756 per QALY. Sildenafil continued to dominate all other treatments except epoprostenol, which would only be considered cost-effective at willingness to pay values greater than $13 million per QALY.

Incorporating lower survival estimates based on the NIH registry within the model did not change the conclusions of the analysis, with sildenafil being the most cost-effective therapy versus supportive care in all FCs. The ICUR for other therapies versus supportive care were reduced somewhat by this change, primarily due to the fact that patients with reduced survival would be maintained on epoprostenol in FC IV for a shorter period of time. In no case was the ICUR for the other treatments apart from sildenafil and tadalafil less than $130,000 per QALY.

The PSA suggests that there is a great deal of uncertainty surrounding the estimates of costs and effectiveness associated with the PAH therapies under study. This primary source of this uncertainty is the estimates of treatment efficacy based on improvements and worsening in FC derived from the NMA, which is reflected in the wide credible intervals around the relative risk estimates for treatment versus placebo. Even given the uncertainty within the clinical inputs, apart from sildenafil and tadalafil, the other PAH therapies had negligible probability of being the most cost-effective.

b) Add-on Therapy Versus Monotherapy

The studies examining the use of add-on therapy in PAH compared the combination of an ERA plus tadalafil and an ERA plus riociguat with that of an ERA plus placebo. They are therefore helpful in answering the question: Is it cost-effective to add therapy with either tadalafil or riociguat in a patient treated with an ERA alone? The answer to this question should be put into context with the results of the monotherapy analysis, which did not find that ERAs alone were

cost-effective at a willingness to pay of $50,000 per QALY as compared with supportive care in any PAH FC.

At a decision-maker's willingness to pay of $50,000 per QALY, neither add-on therapy with an ERA plus tadalafil nor add-on therapy with an ERA plus riociguat would be considered cost-effective in PAH patients with FC II, III, or IV disease relative to an ERA alone. The ICUR for an ERA plus tadalafil versus an ERA alone in FC II patients was the lowest at $88,506 per QALY, followed by FC III at $156,513 per QALY and significantly higher in FC IV at $1,568,400 per QALY. An ERA plus riociguat was both more costly and more efficacious than an ERA plus tadalafil, resulting in comparative cost-effectiveness ratios of more than $500,000 per QALY in all three PAH FCs.

Extensive sensitivity analyses around the input parameters to the model were conducted and the structural uncertainty was tested. The only scenario in which the ICUR was below $50,000 per QALY was with respect to patients starting in FC II or III and assuming that 100% of patients initiated epoprostenol therapy upon deteriorating to FC IV. Generic pricing of bosentan also lowered the ICUR for an ERA plus tadalafil versus and ERA alone to $51,771 in patients starting in FC II.

As in the analysis of monotherapies, the PSA revealed that there is a great deal of uncertainty surrounding the estimates of costs and effectiveness. The primary source of the uncertainty was the estimates of FC improvement and worsening derived from the NMA.

c) Exploratory Analysis With Macitentan

Macitentan was compared with supportive care, assuming that 61% of patients also received treatment with a PDE-5 inhibitor, as per the macitentan clinical trial. For all PAH FCs, the ICUR was greater than $200,000 per QALY, making it unlikely that it would be considered cost-effective.

6.3 Strengths and Limitations of the Systematic Review

6.3.1 Strengths

This systematic review was conducted according to a pre-specified protocol, using standard approaches for collecting evidence, performing data extraction, quality assessment, and analysis. This review includes two new drugs (macitentan and riociguat) recently approved for the treatment of PAH in Canada; these were not yet approved, however, at the time the project was initiated. It also includes six other drugs that have been available in Canada for some time (ambrisentan, bosentan, sildenafil, tadalafil, epoprostenol, and treprostinil); these come from different drug classes. The evidence was analyzed and presented using both direct pairwise meta-analysis and NMA. The robustness of the NMA findings is supported by the similarity between the results of the indirect comparison and those of the pairwise comparison. Selected sensitivity analyses, which were conducted to explore heterogeneity with respect to WHO FC at baseline and PAH etiology, further demonstrated the robustness of the findings in the reference case analysis. A comprehensive economic evaluation was conducted using available cost data and the results of the NMAs.

A comprehensive economic analysis was conducted using available cost data and the results of the NMA.

6.3.2 Limitations

a) Clinical Findings

Key limitations of the review are related to the degree of availability of data in the public domain and the suitability of available data for statistical pooling. As previously noted, we did not identify any head-to-head RCTs comparing the efficacy and safety of any of the drugs. We also did not identify trials specifically designed to assess comparative efficacy and safety of new treatments in patients who had failed or were intolerant to previous treatments. A further limitation is the inability to estimate the comparative treatment effects of PAH therapies among specific subpopulations with respect to age, gender, baseline 6MWD, baseline PAH etiology, baseline WHO FC, and background PAH therapy, because data were not reported in published articles. We were therefore unable to include these subgroup analyses in the review to identify which treatment is better for specific subgroups and to account for related potential sources of bias.

None of the four research questions in this review could be fully answered. For instance, there were no studies which met the inclusion criteria that compared the efficacy and safety of dual combination therapies (question 3) or triple combination therapy versus dual combination therapy (question 4). For the comparative efficacy of dual combination therapy versus monotherapy (question 2), data were available only for macitentan, riociguat, and tadalafil. However, NMA could be conducted only between riociguat max 2.5 mg and tadalafil 40 mg (both with ERA background therapy) because the macitentan study used a different treatment background (PDE-5 inhibitor or prostanoid). For question 1, NMA was conducted to explore the comparative efficacy of monotherapy (naive populations) between treatments. However, data for macitentan for naive populations were available in the published article only for clinical worsening and 6MWD, but not for FC improvement or FC worsening. Safety data (and data on hemodynamics) were largely reported from whole populations without stratifying into naive or experienced populations in trials having mixed populations such as those of macitentan, riociguat, tadalafil, and bosentan. NMA was therefore not conducted for any of the safety (or hemodynamic) outcomes. Likewise, sub-questions in question 1 were partly answered, and none of the sub-questions of questions 2 to 4 could be answered due to lack of available data.

As indicated, evidence for add-on therapy was very limited; few RCTs and no comparative observational studies were identified for inclusion in the systematic review. Of those that were included, only two were appropriate for including in a NMA. Patients who received add-on therapy in the studies were prevalent cases of PAH and had been stable on background therapy for at least three months. In studies that included both treatment-naive and treatment-experienced (i.e., add-on therapy) patients, combining naive and experienced patients makes interpreting the outcomes difficult. Although the numbers of naive and experienced patients appeared to be balanced between treatment groups in the studies, the presence of experienced patients in the total population might dilute the observed treatment effect. Also, there were no trials specifically designed to assess the comparative efficacy and safety of new treatments in patients who had failed or were intolerant to previous treatments; thus, it is uncertain to what extent the results of the current review are applicable to this patient population. According to the clinical experts involved in this review, in the clinical practice setting, the decision to intensify therapy by adding a new therapy to the existing one is proactive, occurring when patients fail to meet specific targets of response rather than waiting for a bad outcome to occur. Several studies on combination therapy did not meet the review inclusion criteria and were therefore excluded from data analysis. The results of those studies (one systematic review and eight single-group observational studies) were presented in Section 6.2.3. Most studies showed that combination therapy resulted in only modest increase in 6MWD, with mixed evidence regarding the clinical improvement of the combination therapy compared with monotherapy. Therefore, a

limited number of RCTs and lower-quality observational studies have demonstrated a modest improvement in certain PAH outcomes only.

Performing NMA involves pooling of trials. To avoid the introduction of bias, it is important that clinical and methodological variation across studies is minimized. If variability does exist, the assessment of its effects on NMA results is required. We observed between-trial variability in both study characteristics (definition of outcome) and baseline patient characteristics (WHO FC at baseline and PAH etiology). The resultant between-trial differences in patient characteristics may be important predictors of treatment effect. To address this heterogeneity, we performed meta-regression and subgroup analyses using patient characteristics as covariates. However, the small number of studies in relation to the number of treatment strategies may not allow for complete control of confounding.
Similarly, the inclusion of a long-term study of macitentan (median 115 weeks' duration) together with shorter-term studies (range: 12 to 16 weeks duration) in the NMA is a potential source of bias. To examine the effect of this potential source of heterogeneity, sensitivity analyses were performed by excluding the study of macitentan from the NMA, and the results did not show any changes in the magnitude and direction of the effect sizes of the remaining treatments.

Another limitation is that the impact of treatment on long-term efficacy and safety could not be studied in this review using largely short-term data; only the aforementioned macitentan trial provided longer-term evidence. In fact, NMA could not be conducted for mortality, an important outcome of the disease, due to lack of controlled long-term data. Long-term data on efficacy and safety of most PAH therapies were mainly from uncontrolled extension studies, which did not meet the inclusion criteria of the review. Results from those studies suggested that many PAH therapies including epoprostenol, bosentan, ambrisentan, riociguat, and tadalafil could maintain their clinical efficacy and safety at the approved doses. In contrast, there is a lack of evidence to suggest the long-term clinical benefit of sildenafil 20 mg three times daily as most patients who completed the extension study SUPER-2 were on sildenafil 80 mg three times daily, which is not a Health Canada–approved dose. In general, however, although extension studies may be helpful in assessing the safety of medications, they are of uncertain value in assessing the efficacy of treatments. The lack of a comparator group and the potential for selection bias make the interpretation of the results unclear. Hence, there is a need for long-term RCT data to evaluate the potential long-term benefits of these therapies.

In addition to uncertainty with respect to the long-term efficacy of sildenafil 20 mg three times daily, there may be concerns regarding the long-term safety. The US FDA issued a warning in 2012 regarding the potential association between increasing sildenafil dose and increased risk of death with long-term use in pediatrics.[39] FDA is requiring the manufacturer of sildenafil to evaluate its effect on the risk of death in pediatrics and adults with PAH.
The definition of clinical worsening as a secondary outcome differed between the trials, with the main difference being Channick defining clinical worsening as "*right ventricular heart failure or aggravated pulmonary hypertension,*"[23] whereas in other trials, clinical worsening was generally defined as "*time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal because of the addition of other PAH medications, or early escape criteria*".[18,21,23,24,29-34] For that reason, the proportion of patients experiencing clinical worsening was expected to vary across trials. We combined data for this outcome across all trials despite the difference in definition, based on the expectation that the relative differences between treatments would be unaffected. However, this is a potential source of heterogeneity. To examine the effect of this potential source of heterogeneity, we did a sensitivity analysis of clinical worsening excluding a study having

different outcome definition, i.e., Channick et al. (2001).[23] This analysis did not show any changes in the magnitude and direction of the effect sizes of all treatments (data not shown); this observation adds to our sentiment that our findings are robust. In addition, clinical worsening in the macitentan study (SERAPHIN) was adjudicated by an independent Clinical Event Committee, and the impact of adjudication on the results was not investigated in this review. It was unclear whether the adjudication process was applied in other studies. Despite this limitation, subgroup analyses by excluding macitentan did not show any change in the magnitude and direction of the effect sizes of other treatments.

b) Economic Limitations

The NMA produced large credible intervals surrounding the estimates of the relative risks of improvement and worsening of FC for epoprostenol. This made the implementation of the PSA challenging, as when applied within the model, there was the potential for the transition probabilities to exceed 1. This was not a concern within PAH FC II, as epoprostenol was not included within the analysis, nor was it a concern for epoprostenol comparator group within the PAH FC IV analysis, as patients could only improve from this state. It does, however, affect the estimates for patients entering the model in FC III and receiving epoprostenol therapy. To address this issue, the relative risks for improvement and worsening of FC were not varied within the first cycle of the PSA for PAH FC III for epoprostenol, which will somewhat underestimate the uncertainty surrounding the estimate of cost-effectiveness of epoprostenol within this patient population. With an ICER of more than $400,000 per QALY, it is unlikely that epoprostenol would be cost-effective within this population. The relative risk for improvement and worsening with epoprostenol was also not varied for patients with PAH FC IV receiving oral therapies who initiate epoprostenol therapy. Given the same assumption was consistent across all therapies, this should have minimal impact upon the results of the analysis.

Economic modelling requires a number of assumptions to be made as a result of limitations in data availability. This was the case also within the model for this analysis, which required the use of a clinical marker, specifically functional class, in order to model disease progression and required that short-term clinical trial data be extrapolated to predict longer-term outcomes. The assumptions incorporated within the model have been explicitly laid out within this document and where possible, they have been tested within sensitivity analyses.

With respect to transition probabilities within the model, the available data within published clinical trials for PAH therapies did not allow for a stratified analysis by FC and therefore the overall relative risk of improving or worsening FC was assumed to apply regardless of the initial class. In addition, the probability of improvement and worsening in FC with supportive care was derived from the NMA analysis based on the placebo groups of the clinical trials. Again, the analyses based on the overall probably of improvement and worsening was assumed to apply to each FC transition.

The lack of long-term clinical data meant that a number of assumptions were required regarding the duration of benefits produced by PAH therapies. As the majority of clinical trials provided estimates of efficacy at 12 weeks and there are limited data to support further improvement beyond this initial benefit, the relative risks of improvement with treatment were applied only to the first cycle within the model. Similar difficulties arise when determining the impact of treatment on the rate of worsening of disease relative to supportive care. Estimates from the clinical trials found that treatments reduce the probability of worsening to a more severe FC when measured over the period of the clinical trial. The decision was made, based on expert clinical guidance, to continue to apply the effect of treatment on the rate of worsening disease for the duration of the analysis.

The model assumed the same dosage of therapies as was studied within the clinical trials that were incorporated within the NMA. Consequently, both the estimates of efficacy and cost for therapies were based on the RCT dosages. Although alternate dosage regimens may be employed in clinical practice, the lack of RCT data supporting their effectiveness precluded their inclusion within the economic analysis.

Improvements and deterioration in illness must be modelled based on a chosen objective measure that has been used across clinical trials of PAH drugs. The most common measure within clinical trials is the 6MWD. This would probably be the best measure on which to base the efficacy within the economic model; however, there are no studies associating 6MWD and utility values, and therefore it would not allow for a cost-utility analysis. There are, however, studies associating PAH FC with utility values, and therefore this measure was used to define the states within the model.

There are limited clinical data available regarding sequential treatments in PAH, which makes modelling a sequential treatment approach challenging. It was therefore decided to conduct an analysis comparing monotherapies and a separate analysis comparing add-on therapies versus monotherapies, when available. Unfortunately, there were no clinical trials comparing the use of the PDE-5 inhibitors alone versus in combination with additional therapies, which would have been most relevant to the question of the cost-effectiveness of adding therapy, as sildenafil and tadalafil were the optimal monotherapies.

Correlation between parameters (specifically between the relative risks of improvement and worsening) is not accounted for within the NMA nor within the economic analysis.

7 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING

The objective of this therapeutic review was to assess the comparative efficacy and safety and to determine the cost-effectiveness of drug therapies for the treatment of PAH in adults.

Results from the systematic review and NMA suggest that there were no significant differences in clinical worsening and FC worsening between drugs used to treat PAH as monotherapy. For FC improvement and 6MWD, epoprostenol appeared to be the most effective treatment option in improving clinical status, while there were no apparent differences among other treatments.

The addition of macitentan to PDE-5 inhibitor or prostanoids background therapy and addition of riociguat or tadalafil onto ERA background therapy produce improvement in clinical worsening, FC improvement, FC worsening, and/or 6MWD compared with monotherapy. There were no differences between combination therapy of riociguat plus ERA and tadalafil plus ERA for all four clinical outcomes.

All drugs showed improvement in pulmonary hemodynamics and HRQoL compared with placebo. Adverse events were treatment specific and may be an important consideration in treatment selection.

Key limitations of the review are related to the poor availability of data in the public domain and the suitability of available data for statistical pooling due to clinical and methodological heterogeneity. None of the four therapeutic review research questions could be fully answered.

Patient-group input suggests that patient experience with current available therapy is generally positive and the majority reporting taking combination therapy. Patients are hopeful that new drugs will reduce symptoms of PAH, will have fewer adverse effects, and offer better quality of life than currently available medications.

Based on the economic analysis comparing the cost-effectiveness of single therapies for PAH, with efficacy of treatments assessed via relative improvements and reductions in worsening of FC, sildenafil would be considered the optimal therapy as it was dominant over other therapies in patients with FC II and III and dominated all therapies except supportive care in FC IV, in which case it resulted in an ICUR of less than $20,000 versus supportive care. Although sildenafil was found to be the most cost-effective PAH therapy in FC IV, its role as monotherapy in FC IV has been questioned. Tadalafil was also less costly and more effective than supportive care in patients with FC II and III PAH; however, sildenafil was dominant over tadalafil, being both less costly and more effective. All other therapies were more costly than sildenafil, tadalafil, and supportive care and resulted in ICURs compared with supportive care of greater than $140,000 per QALY. Extensive sensitivity analyses found the results to be relatively robust to changes in assumptions. The only scenarios that affected the results were reducing the time horizon to two years, reducing the percentage of patients initiating epoprostenol upon deteriorating to FC IV to 0, and incorporating unadjusted relative risks of improvement and worsening in FC from the NMA.

With respect to dual (add-on) therapy for PAH, unfortunately there were no comparisons examining the addition of treatments to either sildenafil or tadalafil, but rather, studies have examined the addition of tadalafil and riociguat to existing ERA therapy. ERA monotherapy was not cost-effective as compared with either sildenafil or supportive care; it is therefore challenging to draw conclusions from this analysis. ERA monotherapy was the most cost-effective strategy versus the combination of ERA plus tadalafil and versus ERA plus riociguat. The ICUR for ERA plus tadalafil ranged from $88,000 in FC II to $1.5 million in FC IV versus an ERA alone. The sequential ICUR for ERA plus riociguat versus ERA plus tadalafil was greater than $500,000 per QALY in all FCs. These results were robust to changes implemented within the sensitivity analysis, except in the case when the percentage of patients initiating epoprostenol upon deteriorating to FC IV was increased to 100%. In this case, for patients in FC II and III, the ICUR was below $40,000 per QALY for an ERA plus tadalafil versus an ERA alone.

A separate analysis specific to macitentan in a cohort of patients with a proportion receiving additional therapy with a PDE-5 inhibitor, macitentan was not cost-effective unless a decision-maker's willingness to pay for a QALY exceeded $200,000.

PSA revealed that there was a great deal of uncertainty surrounding the estimates of costs and QALYs for each of the therapies. Estimates of cost-effectiveness would be better informed by more head-to-head trials comparing therapies for PAH and longer-term follow-up of outcomes.

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APPENDIX 1: PATIENT INPUT INFORMATION

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Pulmonary Hypertension Association of Canada (PHA Canada) is a charitable organization established by patients, caregivers, parents and family members collectively referred to as "Canadians living with PH". PHA Canada aims to end isolation, provide education, support PH patients and their caregivers, raise awareness, and create a united Canadian PH community.

Actelion Pharmaceuticals, Bayer Inc., GlaxoSmithKline, McKesson Specialty Pharmacy, Pfizer Canada, Shoppers Drug Mart Specialty Health and Unither Biotech are members of the PHA Canada Corporate Committee and provide unrestricted grants. The submission was reviewed and approved by the Chair of the Board of Directors who has received consulting and speaking fees, research grant support and investigator fees from various pharmaceutical companies.

The Edmonton PAH (Pulmonary Arterial Hypertension) Society (EPAHS) is a charitable organization formed by patients and caregivers. EPAHS' vision is to enhance the life of patients and caregivers affected by pulmonary hypertension. The EPAHS declared no conflict of interest with respect to funding or assistance in preparation of the submission.

The British Columbia Pulmonary Hypertension Society (BCPHS) is a charitable foundation that was founded by PH patient Elizabeth McCall in 2001. The mission of the Society is to advocate for those living with pulmonary hypertension, to promote public awareness through education, to provide support to patients and caregivers, to support research and education of healthcare professionals, and to raise funds to meet the objectives set by the Society. The BCPHS declared no conflict of interest with respect to funding or assistance in preparation of the submission.

The Scleroderma Society of Canada is the national organization representing all scleroderma organizations and groups in Canada; providing information, raising awareness, supporting research, fostering growth and development of Canadian scleroderma organizations, providing a communication service, and serving as an advocate for scleroderma in Canada. In the last five years, the Society has received unrestricted funding from Actelion, Pfizer, AstraZeneca, GlaxoSmithKline, Bayer and Shoppers Drug Mart. It declares no conflict of interest in the preparation of the submission.

2. Condition and Current-Therapy Related Information

Depending on the submitting organization information for the patient-group input was gathered via: requests to patients and caregivers to provide details on the condition, its current therapy, and any information on the drugs being reviewed; a survey disseminated through websites, social media, and support groups; an organization's history of working with the PH community and the stories of patients and caregivers that have been gathered over that time; patient registry data for health-related quality of life information; focus groups; or from one-to-one conversations with patients and caregivers.

Pulmonary hypertension has a significant impact on the lives of patients. PH is most often a disease never before heard of by the newly diagnosed patient. It is a shocking and life-changing

experience to learn that one has a rare, usually progressive and typically terminal illness. Patients and their caregivers often go through abrupt life changes as a result.

The condition-related symptoms and problems that impact the day-to-day life of a patient are difficulty breathing with or without exertion, palpitations or pounding of the chest, chest pain, ankle, leg, and abdomen swelling due to fluid retention, dizziness, syncope (fainting), tingling of hands and feet due to low oxygen levels. Patients commonly experience depressed mood, anxiety, feelings of helplessness and hopelessness as they are faced with a high risk of death within a few years. The following aspects are reported as the most important to control: breathing ability, peripheral edema, dizziness and syncope.

Patients continually struggle with these symptoms that may fluctuate in severity day-to-day. Shortness of breath, fatigue, headaches, sleep disturbances, and a low tolerance for physical exertion of any kind make regular household chores and activities of daily living difficult. As PH affects people of all ages from children to older adults, patients are affected in different ways. Children may be prevented from attending school, and adults may not be able to work – even part time. Adults with PH struggle with simple day-to-day activities such as climbing stairs, walking short distances, carrying things (groceries, children, etc.). Pursuit of leisure activities can be challenging due to low energy and stamina.

People with PH live with much uncertainty in the short and long term — from how they will feel each day to what the future holds for them. Frequent medical appointments, tests, and hospitalizations are burdensome for patients and their caregivers. Because PH is an invisible disease and the public is largely unaware of PH, patients can spend a lot of time explaining their illness and they can sometimes be mislabelled as being lazy or abusing the system.

While not a cure, experience with currently available therapy, six approved drugs on the Canadian market*, is generally positive, with a majority of responders reporting taking combination therapy. The main benefits of treatment were reducing lung pressures, decreasing the workload demand on the heart, and delay of disease progression – but in general current therapies do not offer the opportunity to live a normal life. Most patients on therapy see an increased ability for light physical activity. The medications (particularly IV therapies) help to keep PH stable and do play a role in increasing the quality of life. However, the effectiveness of therapy varies drastically from patient to patient based on many factors: a patient's age, gender, type of PH, severity of PH, and underlying medical conditions. Most patients with PH who are treated with current PH therapies remain quite ill with moderate-severe PH and significant ongoing right ventricular heart failure. In addition to the PH-specific treatments, most patients also take diuretics and blood thinners as well as anti-nausea medication in order to control one of the many reported side effects of PH treatment. In addition to nausea, other common side effects include: gastrointestinal discomfort and pain, diarrhea (particularly with IV epoprostenol), fatigue, insomnia, bruising, weight gain, early onset menopause, osteopenia, headaches, cataracts, skin flushing, redness, spots on the skin and site infections due to IVs. Many patients believe that despite currently available therapies they will one day require a double lung or double lung and heart transplant.

Caring for a person living with PH is life-changing for caregivers. Many find themselves needing to fulfill roles to which they were not accustomed or were used to sharing such as: household chores, childcare responsibilities, being the wage earners for their household, and often times needing to mix complicated medications. In addition, they face the very grave reality that there is no cure for PH and that at some point they will likely lose their loved one to this disease. Caregivers often face burnout and need many reminders to also care for themselves. Without

the caregiver most patients would have difficulty living on their own. The effects on children of PH patients are also significant. Their parent's limited ability to interact in family activities is often resented. Children's fears and concerns over their parent's situation and prognosis add tremendous emotional strain to both the patient and the caregiver.

3. Related Information About the Drugs Being Reviewed

Patients that have not had any experience with new drugs for PAH* such as macitentan, riociguat, selexipag, vardenafil, and imatinib are hopeful that they will reduce the symptoms of PAH and result in fewer side effects than currently available medications, resulting in an improved quality of life. New IV drugs with longer half-lives will allow patients more freedom since they will not be required to mix their medications daily and medications won't need to be kept refrigerated or on ice. Oral drugs replacing IV therapies will also make patients' lives easier. Increased quality and quantity of life, fewer hospital visits, the ability to return to work and family/childcare responsibilities are other results that patients are looking for with the new drugs. An important expectation that patients have with the availability of new drugs is that they will have more treatment choices. Being able to work with their specialists to find the right drug or combination of drugs is considered very important; treatment options are often equated with hope by PAH patients.

Feedback from several patients who had been or were currently taking part in clinical trials involving the new PAH drugs was provided. Often these patients had been treated with available drugs for PAH with minimal or transient response. Patients taking the new drugs felt that they were helping to decrease PAP, improve heart function, and delay progression of the disease. They reported an increased ability to perform daily tasks and an increased ability to undertake light physical activity. Adverse events were rated from mild (nasal congestion, skin flushing) to more severe such as nausea and loss of appetite. Generally the mild adverse events are tolerable, while the more severe discomfort and physical reactions are not. Patients who experienced severe adverse events often discontinued treatment or opted for another drug. The new drugs are generally thought of as being easier to use because they were either in oral form or provided other benefits (such as requiring no ice packs and not needing to mix twice a day).

* At the time input from patient groups was received for this project (i.e. fall of 2013), macitentan and riociguat had not yet been approved for PAH in Canada. These drugs have since been approved. Selexipag, vardenafil, and imatinib are not currently approved for PAH in Canada.

APPENDIX 2: VALIDITY OF OUTCOMES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

1. Objective

To describe outcomes measures used in trials of drugs for pulmonary arterial hypertension and report minimal clinically important difference (MCID) estimates where available.

2. Findings

A summary of the scales and other outcome measures from included studies is presented in **Table 125**.

Table 125: Summary of Outcomes Used in Included Studies

Instrument	Description	Validated in PAH	MCID	Comments
6MWD[20,102-111]	Total distance walked in 6 minutes Submaximal test to assess exercise capacity Widely used in studies and clinical practice; accepted by regulatory agencies	Yes	33.0 m (range: 25.1 to 38.6 m)	Baseline 6MWD correlated with outcomes in PAH[112] Absolute 6MWD during treatment is correlated with outcomes in PAH Change in 6MWD moderately to poorly correlated with outcomes in PAH[38,112,113] Ceiling effect in patients with less severe disease[114]
Clinical worsening[85,115]	Composite outcome includes various components designed to measure PH morbidity and mortality. May also be reported as time to clinical worsening.	No[a]	Unknown	Recommended as a key outcome for use in PAH studies by 2008 Dana Point and 2013 NICE clinical trial design task forces.[116] Rescue PEA performed due to PH persistent worsening component not a relevant intervention in the context of Canadian clinical practice.
Borg dyspnea score[117-119]	CR10 – open scale (ranges 0 [no dyspnea] to 10 [max dyspnea] points) with ability for subject to assign scores above 10 Modified Borg Scale - 11-point scale	No	Unknown	Although it is a subjective assessment scale for assessing the intensity of breathlessness, it has been shown to be reliable for quantifying dyspnea in trial patients with COPD who have undergone a 6-minute treadmill walk test.[117-119]

Table 125: Summary of Outcomes Used in Included Studies				
Instrument	**Description**	**Validated in PAH**	**MCID**	**Comments**
	(ranges 0 [no dyspnea] to 10 [max dyspnea] points)			
EQ-5D[120]	Generic HRQoL instrument applied to wide range of health conditions and treatments 2 parts: health states and VAS Index score generated using multi-attribute utility function to the descriptive system	No	General: ranges 0.033 to 0.074[121]	Different utility functions for US and UK. Scores < 0 represent health states that are valued by society as being worse than dead; scores 0 and 1.00 are assigned to the health states 'dead' and 'perfect health', respectively. Well validated in different diseases
WHO functional class[122]	PH severity classification system based on NYHA HF classification	No	Unknown	
Living with PH questionnaire[102]	PH-specific HRQoL scale derived from MLHFQ. 6-point Likert scale (21 items) range: 0 (no) to 5 (very much). Total score range: 0 to 105; higher score indicates worse HRQoL	Yes	Physical and emotional subscales: change of 3 points Total score: change of 7 points	
SF-36	Generic HRQoL instrument applied to wide range of health conditions and treatment. 8 subscales are scored separately and transformed to a zero to 100 scale; higher score indicates better HRQoL	No	Between three and five points for any given domain	

6MWD = six-minute walk distance; COPD = chronic obstructive pulmonary disease; EQ-5D = EuroQol Questionnaire; HF = heart failure; HRQoL = health-related quality of life; MCID = minimal clinically important difference; PAH = pulmonary arterial hypertension; PEA = pulmonary endarterectemy; PH = pulmonary hypertension; pts = points; SF-36 = Short-Form Health Survey 36-item; UK = United Kingdom; US = United States.

[a] Clinical worsening has not been formally validated, but it has been recommended as an outcome for use in PAH studies by the 2008 Dana Point and the 2013 NICE clinical trial design task forces to more accurately reflect disease progression.

Six-Minute Walk Distance (6MWD)

The 6MWD measures the distance a patient can walk in six minutes. Change in 6MWD is the most widely used test to assess exercise capacity in PH and is used in most PAH trials as a primary outcome.[103,105,123-125] 6MWD is also used in clinical practice and is widely accepted by regulatory agencies. The main advantage of the 6MWD is its ease of administration; it is a submaximal exercise test that can be performed by a patient who is unable to tolerate maximal cardiopulmonary exercise testing (CPET).[103] Baseline 6MWD in PAH treatment studies has been shown to correlate with long-term outcomes such as morbidity and mortality, as has the absolute 6MWD during treatment for PAH.[112] However, change in 6MWD is a surrogate outcome and has demonstrated moderate to poor correlation with key clinical outcomes in PAH.[38,112,113] Performance on the six-minute walk distance may be influenced by patient age, sex, height, weight, lung function, and ethnicity, and it may be susceptible to motivational factors and a training effect.[106-108] Furthermore, in multi-centre trials experience and technical skills may vary between sites, and the correlations between the 6MWD and CPET might improve over time with increasing experience.[109] There is also evidence of a ceiling effect on the 6MWD, whereby the effect of the treatment on the test is diminished due to the inclusion of patients with milder disease (NYHA/WHO functional class II, baseline 6MWD > 450 m).[126] Despite these limitations, improvement in function, as reflected by 6MWD, remains clinically valuable in PH.

Clinical Worsening

The composite outcome of clinical worsening – combining the events of death, heart and/or lung transplantation, rescue PEA due to persistent worsening of PH, initiation of new PH medications, hospitalization, persistent decrease of > 15 % from baseline or > 30% compared with the last measurement in 6MWD due to worsening PH, and persistent worsening of WHO FC due to deterioration of PH as a single outcome – may improve precision (increased statistical power would make it easier to detect a therapeutic benefit) and offer a more global assessment of the patient and his/her clinical state by including nonfatal but important morbid events in the course of disease.[115] Therefore, it is likely a clinically relevant outcome. However, there are limitations using composite outcomes in PH studies:[115]

- confounding may occur if a component outcomes occurs at a different rate versus others in the composite outcome, especially during a trial of short duration;
- including outcomes such as hospitalization in a composite outcomes may be a problem because they may, at least partially, be driven by social or nonmedical factors, which may disproportionately influence a composite also containing more direct measures of disease progression (death);
- a composite outcome driven by individual outcomes with centre-specific availability (lung transplantation and atrial septostomy) may pose difficulty in multi-centre trials;
- in a composite outcome, each of the components has equal clinical implications;
- there is no standardized definition for clinical worsening and the component end points vary across PAH trials.

In a recent assessment of survival in an observational study, Frost et al. suggested that clinical worsening was highly predictive of subsequent mortality and was meaningful as a primary endpoint in clinical trials of PAH.[85]

Borg Dyspnea Score and Borg CR10

The CR10 is a categorical scale with a score from zero to ten where zero represents normal breathing and 10 represents maximum dyspnea.[127] However, the patient may report a score greater than 10 to describe their own sensation of dyspnea with greater precision than a 10 point score would allow, thus making this an open scale. The modified Borg dyspnea score is a

version of the CR10.[127] The modified Borg dyspnea score is a scale from zero to 10, where zero represents no dyspnea and 10 represents maximal dyspnea. It is obtained at the end of the 6MWD test and reflects the maximum degree of dyspnea at any time during the walk test. Although it is a subjective assessment scale for assessing the intensity of breathlessness, it has been shown to be reliable for quantifying dyspnea in trial patients with chronic obstructive pulmonary disease (COPD) who have undergone a six-minute treadmill walk test.[117-119] No studies have clearly addressed the MCID of the score.

EuroQol Questionnaire

The European Quality of Life Scale (EQ-5D)[120,128] is a generic quality of life (QoL) instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing 'no problems', 'some problems', and 'extreme problems', respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[120,128] The second part is a 20 cm visual analog scale (EQ-VAS) that has endpoints labeled 0 and 100, with respective anchors of 'worst imaginable health state' and 'best imaginable health state'. Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS which best represents their health on that day.

Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g. -0.59 for the UK algorithm and -0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states 'dead' and 'perfect health', respectively. The EQ-5D demonstrated convergent validity with the MRC Dyspnoea Scale in both primary and specialist care settings within the UK and USA and across five EU countries.[129] The MCID for the EQ-5D ranges from 0.033 to 0.074.[121]

WHO Functional Classification for Pulmonary Hypertension

The WHO FC system for PH was adapted from the New York Heart Association (NYHA) classification.

The WHO FC system is used widely in clinical practice and as an outcome in clinical trials. One study reported clinicians' assessment of functional class varied widely in PAH, especially when classifying patients as functional class II or III.[122] The intraclass correlation coefficient was approximately 0.6. In one instance, 53% of clinicians classified a patient as functional class II and 47% classified the patient as functional class III. Thus, despite wide use of the WHO classification system, inter-rater agreement may be poor.

Living With Pulmonary Hypertension Questionnaire

The LPH was derived from the Minnesota Living with Heart Failure Questionnaire for use in PH populations. The instrument comprises 21 items, responded to on a 6-point Likert scale ranging from 0 “No” to 5 “Very much.” The responses to all 21 questions are summed for a total score ranging from 0 to 105. A physical dimension score (range 0–40, 8 items) and an emotional dimension score (range 0–25, 5 items) can also be calculated. A higher score on all LPH scores indicates that patients are more affected by their PH.[102] In terms of clinical validity, the LPH Physical and total scores were able to differentiate between patients of different severity levels, based on WHO functional class or 6MWD. The LPH emotional score did not demonstrate the same differentiation. There was high correlation between the Borg scores and the LPH Physical score. A change of 3 points for the subscales (range: 1.48 to 4.71) and 7 points (range: 4.41 to 11.02) for the total score were indicated as the MCID values for PAH.

Short-Form Health Survey 36-Item

The Short-Form Health Survey 36-Item (SF-36) is one of the most commonly used measures of quality of life.[130] The SF-36 was designed to understand the burden of chronic disease and the effect of treatments on general health status. It has eight dimensions measuring physical functioning, role functioning (work or other activities) affected by both physical and emotional symptoms, pain, general health, vitality, social functioning and mental health. These eight subscales may be collapsed into two domain scores reflecting physical and mental components of quality of life. The SF-36 dimensions are scored separately and transformed to a zero to 100 scale. Each scale is scored positively, which means that higher scores indicate better health-related quality of life (HRQoL) and lower scores indicate worse HRQoL. Among patients with PAH, SF-36 correlates moderately well with the six-minute walk distance, NYHA/WHO functional class, and Borg dyspnea score.[131,132] The MCID for the SF-36 is has been suggested to be between three and five points for any given domain.[133,134] However, Gilbert et al. recently used three distribution-based methods of estimating MCID specifically in the context of pulmonary arterial hypertension. Gilbert reported a mean (range) minimal important difference of 13 (5.8 to 25), 25 (12 to 46), 21 (7.9 to 43), and 15 (6.9 to 27) points for the SF-36 physical functioning, role-physical, social functioning, and vitality domains, respectively, in patients with PAH.[110] A limitation of the methodology used to generate these MCID estimates is that Gilbert et al did not use an anchor-based approach (i.e., patient or clinician input, correlation to other scoring systems).

APPENDIX 3: LITERATURE SEARCH STRATEGY

See Section 5.1 Literature Search Strategy for more details on literature search methods.

Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 12, 2013
Alerts:	Weekly search updates until finalization of project
Study Types:	HTA/SR/MA, all clinical trials, observational studies
Limits:	Date limit: None Language limit: None Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.nm	Name of Substance Word
.ot	Original title
.pt	Publication type
.rn	CAS registry number
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

#	Searches
1	exp hypertension, pulmonary/ use pmez
2	pulmonary veno-occlusive disease/ use pmez
3	exp pulmonary hypertension/ use oemezd
4	((pulmonary$ adj4 hypertens$) or (ayerza$ adj2 syndrome)).ti,ab.
5	(Lung hypertens* or lung arterial hypertens* or lung artery hypertens* or PAH or iPAH or hPAH).ti,ab.
6	((hemangiomatosis adj3 pulmonary$) or (pulmonary$ adj2 "veno occlusive")).ti,ab.
7	1 or 2 or 3 or 4 or 5 or 6
8	(epoprostenol or Flolan or Caripul or Veletri or treprostinil or Remodulin or Tyvaso or bosentan or Tracleer or Usenta or ambrisentan or Volibris or Letairis or sildenafil or Viagra or Revatio or Adonix or Andros or Aphrodil or Edegra or Ejertol or Elonza or Emposil or Erectol or Erilin or Eroton or Eroxim or "Neo Up" or Patrex or Penegra or Rigix or Ripol or Sildefil or Supra or Tigerfil or Vimax or Xex or Zilden or Zwagra or tadalafil or Adcirca or Cialis or "36 Horas" or Forzest or Pasport or Xpandyl or Zydalis or macitentan or Opsumit or riociguat or Adempas).ti,ot,ab,sh,hw,nm.
9	(35121-78-9 or 81846-19-7 or 147536-97-8 or 157212-55-0 or 177036-94-1 or 139755-83-2 or 171596-29-5 or 625115-55-1 or 441798-33-0).rn,nm.
10	8 or 9
11	7 and 10
12	11 use pmez
13	*treprostinil/ or *bosentan/ or *ambrisentan/ or *sildenafil/ or *tadalafil/ or *riociguat/ or *macitentan/
14	(epoprostenol or Flolan or Caripul or Veletri or treprostinil or Remodulin or Tyvaso or bosentan or Tracleer or Usenta or ambrisentan or Volibris or Letairis or sildenafil or Viagra or Revatio or Adonix or Andros or Aphrodil or Edegra or Ejertol or Elonza or Emposil or Erectol or Erilin or Eroton or Eroxim or "Neo Up" or Patrex or Penegra or Rigix or Ripol or Sildefil or Supra or Tigerfil or Vimax or Xex or Zilden or Zwagra or tadalafil or Adcirca or Cialis or "36 Horas" or Forzest or Pasport or Xpandyl or Zydalis or macitentan or Opsumit or riociguat or Adempas).ti,ab.
15	13 or 14
16	7 and 15
17	16 not conference abstract.pt.
18	17 use oemezd
19	12 or 18
20	meta-analysis.pt.
21	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
22	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
23	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
24	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
25	(data synthes* or data extraction* or data abstraction*).ti,ab.
26	(handsearch* or hand search*).ti,ab.
27	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.

#	Searches
28	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
29	(meta regression* or metaregression*).ti,ab.
30	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
31	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
32	(cochrane or (health adj2 technology assessment) or evidence report).jw.
33	(meta-analysis or systematic review).md.
34	(comparative adj3 (efficacy or effectiveness)).ti,ab.
35	(outcomes research or relative effectiveness).ti,ab.
36	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
37	or/20-36
38	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
39	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
40	Multicenter Study.pt.
41	Randomized Controlled Trial/
42	Randomized Controlled Trials as Topic/
43	"Randomized Controlled Trial (topic)"/
44	Controlled Clinical Trial/
45	Controlled Clinical Trials as Topic/
46	"Controlled Clinical Trial (topic)"/
47	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/
48	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/
49	"Clinical Trial (topic)"/ or "Phase 2 Clinical Trial (topic)"/ or "Phase 3 Clinical Trial (topic)"/ or "Phase 4 Clinical Trial (topic)"/
50	Multicenter Study/ or Multicenter Study as Topic/ or "Multicenter Study (topic)"/
51	Randomization/
52	Random Allocation/
53	Double-Blind Method/
54	Double Blind Procedure/
55	Double-Blind Studies/
56	Single-Blind Method/
57	Single Blind Procedure/
58	Single-Blind Studies/
59	Placebos/
60	Placebo/
61	Control Groups/
62	Control Group/
63	Cross-Over Studies/ or Crossover Procedure/
64	(random* or sham or placebo*).ti,ab,hw.
65	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
66	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
67	(control* adj3 (study or studies or trial*)).ti,ab,hw.

#	Searches
68	(clinical adj3 (study or studies or trial*)).ti,ab,hw.
69	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
70	(phase adj3 (study or studies or trial*)).ti,ab,hw.
71	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.
72	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.
73	allocated.ti,ab,hw.
74	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
75	trial.ti.
76	or/38-75
77	exp animals/
78	exp animal experimentation/
79	exp models animal/
80	exp animal experiment/
81	nonhuman/
82	exp vertebrate/
83	animal.po.
84	or/77-83
85	exp humans/
86	exp human experiment/
87	human.po.
88	or/85-87
89	84 not 88
90	76 not 89
91	epidemiologic methods.sh.
92	epidemiologic studies.sh.
93	cohort studies/
94	cohort analysis/
95	longitudinal studies/
96	longitudinal study/
97	prospective studies/
98	prospective study/
99	follow-up studies/
100	follow up/
101	followup studies/
102	retrospective studies/
103	retrospective study/
104	case-control studies/
105	exp case control study/
106	cross-sectional study/
107	observational study/
108	quasi experimental methods/
109	quasi experimental study/
110	validation studies.pt.
111	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab.
112	cohort*.ti,ab.

#	Searches
113	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti,ab.
114	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab.
115	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti,ab.
116	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti,ab.
117	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab.
118	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab.
119	(population adj3 (study or studies or analysis or analyses)).ti,ab.
120	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab.
121	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab.
122	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab.
123	((natural adj experiment) or (natural adj experiments)).ti,ab.
124	(quasi adj (experiment or experiments or experimental)).ti,ab.
125	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab.
126	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab.
127	or/91-126
128	37 or 90 or 127
129	19 and 128
130	((endothelin adj3 antagonist*) or ERA* or prostaglandin* or prostanoid* or Phosphodiesterase* Enzyme Inhibitor* or PDE5 inhibitor* or PDE 5 Inhibitor* or Phosphodiesterase Type 5 Inhibitor*).ti.
131	((soluble guanylate cyclase or SGC) adj3 (stimulator* or activator*)).ti.
132	exp Prostaglandins/ use pmez
133	Phosphodiesterase 5 Inhibitors/ use pmez
134	exp *prostanoid/ use oemezd
135	exp *endothelin receptor antagonist/ use oemezd
136	exp *phosphodiesterase V inhibitor/ use oemezd
137	130 or 131 or 132 or 133 or 134 or 135 or 136
138	7 and 137
139	138 and 37
140	129 or 139
141	exp animals/
142	exp animal experimentation/ or exp animal experiment/
143	exp models animal/
144	nonhuman/
145	exp vertebrate/ or exp vertebrates/
146	animal.po.
147	or/141-146
148	exp humans/
149	exp human experimentation/ or exp human experiment/
150	human.po.
151	or/148-150

#	Searches
152	147 not 151
153	140 not 152
154	153 not conference abstract.pt.
155	limit 154 to english language
156	remove duplicates from 155

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

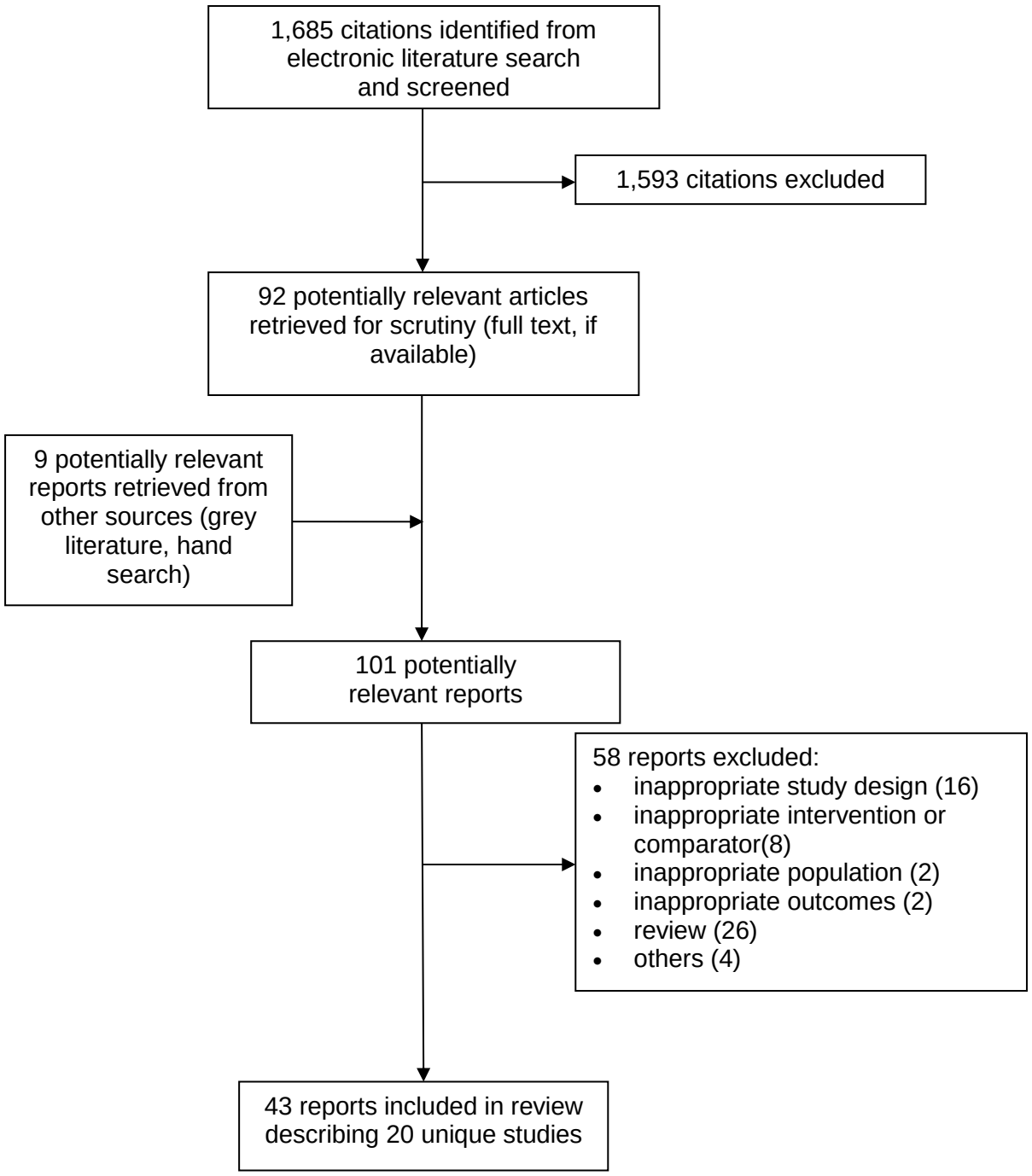
Grey Literature

Date of Search:	October, 2013
Keywords:	pulmonary arterial hypertension and riociguat, macitentan, epoprostenol, treprostinil, bosentan, ambrisentan, sildenafil, and tadalafil.
Limits:	no date limit, English only

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Listing
- Databases (free).

APPENDIX 4: SELECTION OF INCLUDED STUDIES



APPENDIX 5: INCLUDED STUDY LIST

Monotherapy

ARIES-1 (2008)
Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation [Internet]. 2008 Jun 10 [cited 2013 Oct 9];117(23):3010-9. Available from: http://circ.ahajournals.org/cgi/reprint/117/23/3010

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APPENDIX 7: CHARACTERISTICS OF INCLUDED STUDIES

ARIES-1 (2008)[18]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized, placebo-controlled trial.
Participants	201 patients (mean age: 48–53 years) were enrolled at 46 centres in the USA, Mexico, South America, Australia, and Europe. Inclusion criteria: PAH (idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use); WHO FC I to IV. Exclusion criteria: treatment with bosentan, sitaxsentan, sildenafil, epoprostenol, iloprost, or treprostinil; 6MWD < 150 or > 450 m.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo or ambrisentan 5 or 10 mg q.d. for 12 weeks. **Ambrisentan oral 5 mg q.d.** (n = 67) **Ambrisentan oral 10 mg q.d.** (n = 67) **Placebo** (n = 67)
Outcomes	Primary end point: 6MWD Secondary end points: Time to clinical worsening; WHO FC (improved, unchanged, worsened); QoL (SF-36 Health Survey); Borg dyspnea score; and plasma B-type natriuretic peptide. Safety: Death, hospitalization, withdrawal because of other PAH treatment, and AEs.
Definitions	Time to clinical worsening: Time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal because of the addition of other PAH medications, or early escape criteria.
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; PAH = pulmonary arterial hypertension; q.d. = once a day; SF-36 = Short-Form 36-Item Health Survey; WHO = World Health Organization.

ARIES-2 (2008)[18]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	192 patients (mean age: 50–51 years) were enrolled at 41 centres in Europe, Israel, and South America. Inclusion criteria: PAH (idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use); WHO FC I to IV. Exclusion criteria: Treatment with bosentan, sitaxsentan, sildenafil, epoprostenol, iloprost, or treprostinil; 6MWD < 150 or > 450 m.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo or ambrisentan 2.5 or 5 mg q.d. for 12 weeks. ~~**Ambrisentan oral 2.5 mg q.d.** (n = 64)~~ **Ambrisentan oral 5 mg q.d.** (n = 63) **Placebo** (n = 65)
Outcomes	Primary end point: 6MWD Secondary end points: Time to clinical worsening; WHO FC (improved, unchanged, worsened); QoL (SF-36 Health Survey); Borg dyspnea score; and plasma B-type natriuretic peptide. Safety: Death, hospitalization, withdrawal because of other PAH treatment, and AEs.
Definitions	Time to clinical worsening: Time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal because of the addition of other PAH medications, or early escape criteria.
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; PAH = pulmonary arterial hypertension; q.d. = once a day; SF-36 = Short-Form 36-Item Health Survey; WHO = World Health Organization.

Badesch et al. (2000)[19]

Methods	Multi-centre, open-label, randomized trial
Participants	111 patients (mean age: 53-57 years) were enrolled at 17 centres Inclusion criteria: Secondary PH (PAH associated with connective tissue disease); NYHA FC II to IV; 6MWD ≥ 50 m; mean PAP ≥ 35 mm Hg; PVR ≥ 3 mm Hg/L per minute; right atrial pressure ≤ 20 mm Hg; absence of CHD; pulmonary capillary wedge pressure or left ventricular end diastolic pressure ≤ 15 mm Hg. Exclusion criteria: any new long-term therapy for PH or the scleroderma spectrum of disease added within the past month; any medication used to treat PH or the scleroderma spectrum of disease discontinued within the last week, except anticoagulant agents; any type of current prostaglandin therapy.
Interventions	Patients were randomly assigned (1:1) to receive conventional therapy or epoprostenol + conventional therapy for 12 weeks. Epoprostenol initiated at ≤ 2 ng/kg per minute, dose were then adjusted on the basis of signs and symptoms up to 11.2 ng/kg per minute at week 12. **Epoprostenol + conventional therapy** (n = 56) **Conventional therapy** (n = 55)
Outcomes	Primary end point: 6MWD Secondary end points: Cardiopulmonary hemodynamics, Borg dyspnea score; Dyspnea-Fatigue Rating; NYHA FC (improved, unchanged, worsened); digital ulcer count; severity of Raynaud phenomenon. Safety: Death; AEs; laboratory tests.
Definitions	None
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance.

Barst et al. (1996)[20]

Methods	Multi-centre, open-label, randomized trial
Participants	81 patients (mean age: 40 years) Inclusion criteria: Primary PH (IPAH); NYHA FC III or IV; under conventional therapy (anticoagulants, oral vasodilators, diuretic agents, and supplemental O_2) Exclusion criteria: Not reported
Interventions	Patients were randomly assigned (1:1) to receive conventional therapy or epoprostenol + conventional therapy for 12 weeks. Epoprostenol initiated at 4 ng/kg per minute, dose was then adjusted on the basis of signs and symptoms up to 9.2 ng/kg per minute at week 12. **Epoprostenol + conventional therapy** (n = 41) **Conventional therapy** (n = 40)
Outcomes	Primary end point: 6MWD Secondary end points: QoL (Chronic Heart Failure Questionnaire); NYHA FC (improved, worsened, unchanged); cardiopulmonary hemodynamics. Safety: Death; lung transplantation; AEs.
Definitions	None
Treatment history	Unclear (inadequate information to characterize)

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association; PH = pulmonary hypertension; QoL = quality of life.

BREATHE-1 (2002)[21]

Methods	Multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	213 patients (mean age: 47 to 50 years) were enrolled at 27 centres in Europe, North America, Israel, and Australia. Inclusion criteria: Primary PH (IPAH), or PAH associated with connective tissue disease; WHO FC III or IV; under conventional therapy (anticoagulants, vasodilators, diuretics, cardiac glycosides, or supplemental O_2); 6MWD between 150 and 450 m; resting mean PAP > 25 mm Hg; pulmonary capillary wedge pressure < 15 mm Hg; PVR > 240 dyn.sec.cm^{-5}. Exclusion criteria: Any therapy for PAH within one month before screening; received long-term treatment with epoprostenol within three months before screening.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo or bosentan 62.5 mg b.i.d. for 4 weeks followed by 125 or 250 mg b.i.d. for 12 weeks (total 16 weeks) **Bosentan oral 125 mg b.i.d.** (n = 74) ~~**Bosentan oral 250 mg b.i.d.** (n = 70)~~ **Placebo** (n = 69)
Outcomes	Primary end point: 6MWD Secondary end points: Borg dyspnea index; WHO FC (improved, unchanged, worsened); time to clinical worsening. Safety: Death; AEs; laboratory measures; and electrocardiography.
Definitions	Time to clinical worsening: Time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy.
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; b.i.d. = twice a day; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WHO = World Health Organization.

BREATHE-5 (2006)[22]

Methods	Multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	54 patients (mean age: 37 to 44 years) were enrolled at 15 centres in Europe, North America, Israel, and Australia. Inclusion criteria: Eisenmenger syndrome — PAH associated with congenital heart disease; WHO FC III; under conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides, or supplemental O_2); 6MWD between 150 and 450 m; resting mean PAP > 25 mm Hg; pulmonary capillary wedge pressure < 15 mm Hg; PVR > 240 dyn.sec.cm^{-5}. Medical therapy and clinical conditions had to be stable within 3 months of screening. Exclusion criteria: patent ductus arteriosus; complex congenital heart defect; left ventricular dysfunction; obstructive lung disease; treatment with prostanoids, phosphodiesterase type-5 inhibitors, and endothelin receptor antagonists during the study or within one month before screening, treatment with glibenclamide or cyclosporine within one month of enrolment (to avoid potential drug interaction).
Interventions	Patients were randomly assigned (1:2) to receive placebo or bosentan 62.5 mg b.i.d. for 4 weeks followed by 125 mg b.i.d. for 12 weeks (total 16 weeks) **Bosentan oral 125 mg b.i.d.** (n = 37) **Placebo** (n = 17)
Outcomes	Primary end point: change in SpO_2 (non-inferiority test to compare bosentan with placebo); change in PVR from baseline to week 16 (if null hypothesis for SpO_2 was rejected). Secondary end points: 6MWD; WHO FC (improved, unchanged, worsened); cardiopulmonary hemodynamics. Safety: AEs.
Definitions	None
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; b.i.d. = twice a day; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; SpO_2 = systemic pulse oximetry; WHO = World Health Organization.

Channick et al. (2001)[23]

Methods	Multi-centre, double-blind, randomized, placebo-controlled trial
Participants	32 patients (mean age: 47 to 52 years) were enrolled at five centres in the USA and one in France. Inclusion criteria: Primary PH (IPAH) or PH due to scleroderma (PAH associated with connective tissue disease); WHO FC III and IV; under conventional therapy (anticoagulants, vasodilators, diuretics, cardiac glycosides, or supplemental O_2); 6MWD between 150 m and 500 m; mean PAP > 25 mm Hg; pulmonary capillary wedge pressure < 15 mm Hg; PVR > 240 dyn.sec.cm^{-5}. Exclusion criteria: Unstable WHO FC IV; chronic treatment with epoprostenol; treatment with glibenclamide or 204yclosporine within one month of enrolment (to avoid potential drug interaction).
Interventions	Patients were randomly assigned (1:2) to receive placebo or bosentan 62.5 mg b.i.d. for 4 weeks followed by 125 mg b.i.d. for 8 weeks (total 12 weeks) **Bosentan oral 125 mg b.i.d.** (n = 21) **Placebo** (n = 11)
Outcomes	Primary end point: 6MWD. Secondary end points: Cardiopulmonary hemodynamics; Borg dyspnea index; WHO FC (improved, unchanged, worsened); clinical worsening. Safety: AEs; laboratory tests.
Definitions	Clinical worsening: Right ventricular heart failure or aggravated pulmonary hypertension.
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; b.i.d. = twice a day; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WHO = World Health Organization.

EARLY (2008)[32]

Methods	Multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	185 patients (mean age: 44 to 45 years) were enrolled at 52 centres in 21 countries. Inclusion criteria: PAH (idiopathic, familial, or associated with HIV, anorexigen use, atrial septal defect of < 1 cm in diameter, ventricular septal defect of < 1 cm in diameter, patent ductus arteriosus, or connective tissue or autoimmune diseases); WHO FC II; under conventional therapy (anticoagulants, vasodilators, diuretics, cardiac glycosides, or supplemental O_2); 6MWD < 80% of normal predicted value or < 500 m; mean PAP > 25 mm Hg; pulmonary capillary wedge pressure < 15 mm Hg; PVR > 240 dyn.sec.cm^{-5}. Exclusion criteria: Unstable WHO FC IV; chronic treatment with epoprostenol; treatment with glibenclamide or 204yclosporine within 1 month of enrolment (to avoid potential drug interaction).
Interventions	Patients were randomly assigned (1:2) to receive placebo or bosentan 62.5 mg b.i.d. for 4 weeks followed by 125 mg b.i.d. for 8 weeks (total 12 weeks) **Bosentan oral 125 mg b.i.d.** (n = 92) **Placebo** (n = 93)
Outcomes	Primary end point: 6MWD. Secondary end points: Cardiopulmonary hemodynamics; Borg dyspnea index; WHO FC (worsened); time to clinical worsening; QoL (SF-36). Safety: Death; AEs.
Definitions	Time to clinical worsening: First occurrence of death of any cause (during the treatment period or as the outcome of a TEAE that led to permanent discontinuation of study treatment), hospitalization due to PAH complications, or symptomatic progression of PAH. Symptomatic progression of PAH: presence of one of the following: appearance or worsening of right heart failure (as assessed by the investigator); decrease of 10% or more from baseline in two 6-min walk tests done 2 weeks or more apart; or 5% greater decrease from baseline in two 6-min walk tests done 2 weeks or more apart associated with a 2-point or greater increase in Borg dyspnea index.
Treatment history	Mixed (15% to 16% of patients were on background sildenafil)

6MWD = six-minute walk distance; AE = adverse event; b.i.d. = twice a day; FC = functional class; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; SF-36 = Short-Form 36-Item Health Survey; TEAE = treatment-emergent adverse event; WHO = World Health Organization.

Galiè et al. (2005)[24]

Methods	Multi-centre, multi-country, double-blind, randomized, dose-controlled trial
Participants	64 patients (mean age: 48 to 53 years) were enrolled at 20 centres in the USA, Europe, and Australia. Inclusion criteria: PAH (idiopathic or associated with collagen vascular disease, anorexigen use, or HIV infection); WHO FC II and III; 6MWD between 150 and 500 m; mean PAP ≥ 25 mm Hg; pulmonary capillary wedge pressure < 15 mm Hg; PVR > 240 dyn.sec.cm^{-5}. Exclusion criteria: Congenital heart defects; left-sided myocardial disease, chronic thromboembolic pulmonary hypertension, or portal hypertension; had received chronic prostanoid or ERA therapy within 4 weeks before study entry; or had serum aminotransferase concentrations > 1.5 times the upper limit of normal.
Interventions	Patients were randomly assigned (1:1:1:1) to receive 1, 2.5, 5, or 10 mg ambrisentan orally q.d. for 12 weeks. ~~**Ambrisentan oral 1 mg** (n = 16)~~ ~~**Ambrisentan oral 2.5 mg** (n = 19)~~ **Ambrisentan oral 5 mg q.d.** (n = 16) **Ambrisentan oral 10 mg q.d.** (n = 13)
Outcomes	Primary end point: 6MWD. Secondary end points: Borg dyspnea index; WHO FC (improved); QoL (subject global assessment); time to clinical worsening; cardiopulmonary hemodynamics. Safety: Death; AEs, laboratory tests. [Note: Only combined data from all dose groups were given for Borg dyspnea score, WHO FC, QoL, clinical worsening, and AEs]
Definitions	Time to clinical worsening: First occurrence of death, all-cause hospitalizations, the addition of new diuretic or a doubling of the dose of diuretic, or study withdrawal because of a need for other PAH therapeutic agents (defined as prostanoids, ERAs, or sildenafil).
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; ERA = endothelin receptor antagonist; FC = functional class; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; q.d. = once a day; QoL = quality of life; WHO = World Health Organization.

McLaughlin et al. (2002)[25]

Methods	Multi-centre, double-blind, randomized, placebo-controlled trial
Participants	26 patients (mean age: 37 years). Inclusion criteria: Primary PH (IPAH); WHO FC III and IV; mean PAP ≥ 25 mm Hg; pulmonary capillary wedge pressure or left ventricular end diastolic pressure ≤ 15 mm Hg; PVR > 3 Wood units. Exclusion criteria: Not reported.
Interventions	Patients were randomly assigned (1:2) to receive placebo or Treprostinil subcutaneous (initiated at 2.5 to 5.0 ng/kg/min, and adjusted in increments of 2.5 to 5.0 ng/kg/min every 24 hours based on response to therapy and side effects to a maximum dose of 20 ng/kg/min) for 8 weeks. **Treprostinil s.c.** (n = 17) **Placebo** (n = 9)
Outcomes	AEs; cardiopulmonary hemodynamics; 6MWD; Borg dyspnea scale.
Definitions	None
Treatment history	Unclear (inadequate information to characterize)

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; s.c. = subcutaneous; WHO = World Health Organization.

PATENT-1 (2013)[33]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	443 patients (mean age: 49 to 51 years) were enrolled at 124 centres in 30 countries. Inclusion criteria: PAH (idiopathic, familial, or associated with connective tissue disease, congenital heart disease, portal hypertension with liver cirrhosis, or anorexigen use); WHO FC I to IV; 6MWD between 150 and 450 m; mean PAP ≥ 25 mm Hg; PVR > 300 dyn.sec.cm^{-5}; naive patients or patients who were receiving treatment with ERAs or prostanoids (excluding intravenous prostanoids) at does that had been stable for ≥ 90 days; oral anticoagulant agents, diuretics, and supplemental O_2 at stable doses were permitted. Exclusion criteria: treatment with phosphodiesterase type-5 inhibitors.
Interventions	Patients were randomly assigned (2:1:4) to receive placebo, 1.5 mg, or 2.5 mg Riociguat oral t.i.d for 12 weeks. **Riociguat oral 1.5 mg t.i.d** (n = 63) **Riociguat oral 2.5 mg t.i.d** (n = 254) **Placebo** (n = 126)
Outcomes	Primary end point: 6MWD. Secondary end points: Cardiopulmonary hemodynamics; WHO FC (improved, unchanged, worsened); time to clinical worsening; Borg dyspnea score; QoL (EQ-5D, LPH questionnaire). Safety: Death; AEs.
Definitions	Time to clinical worsening: First occurrence of all-cause death; heart/lung transplantation; hospitalization due to persistent worsening of PAH; start new specific PAH treatment (ERAs, prostanoids, or phosphodiesterase type-5 inhibitors), or modification of a pre-existing prostanoid treatment, or start an intravenous prostanoid; persistent decrease of > 15% from baseline or > 30% compared with the last study related measurement in 6MWD; or persistent worsening of WHO FC.
Treatment history	Mixed (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; EQ-5D = EuroQol 5-Dimensions Questionnaire; ERA = endothelin receptor antagonist; FC = functional class; LPH = Living with Pulmonary Hypertension questionnaire; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; SF-36 = Short-Form 36-Item Health Survey; t.i.d. = three times a day; WHO = World Health Organization.

PHIRST (2009)[34]

Methods	Multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	405 patients (mean age: 53 to 55 years) were enrolled at 84 centres in Canada, USA, Europe and Japan. Inclusion criteria: PAH (idiopathic, familial, or associated with anorexigen use, connective tissue disease, HIV infection, or congenital systemic-to-pulmonary shunts); WHO FC I to IV; 6MWD between 150 and 450 m; mean PAP ≥ 25 mm Hg; pulmonary wedge pressure ≤ 15 mm Hg; PVR ≥ 3 Wood units; naive patients or patients who were taking a maximum dose of 125 mg bosentan b.i.d for a minimum of 12 weeks at the time of screening continued on bosentan in addition of the study medication. Exclusion criteria: treatment with intravenous epoprostenol, intravenous or inhaled iloprost, or subcutaneous treprostinil.
Interventions	Patients were randomly assigned (1:1:1:1:1) to receive placebo, 2.5 mg, 10 mg, 20 mg, or 40 mg Tadalafil oral q.d. for 16 weeks. ~~**Tadalafil oral 2.5 mg q.d** (n = 82)~~ ~~**Tadalafil oral 10 mg q.d** (n = 80)~~ ~~**Tadalafil oral 20 mg q.d** (n = 82)~~ **Tadalafil oral 40 mg q.d** (n = 79) **Placebo** (n = 82)
Outcomes	Primary end point: 6MWD. Secondary end points: WHO FC (improved, unchanged, worsened); time to clinical worsening; Borg dyspnea score; QoL (SF-36, EQ-5D); cardiopulmonary hemodynamics. Safety: Death; AEs; laboratory tests.
Definitions	Time to clinical worsening: Time from randomization to the first occurrence of death; lung or heart-lung transplantation; atrial septostomy; hospitalization due to worsening PAH; initiation of new PAH-approved therapy; worsening WHO FC.
Treatment history	Mixed (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; EQ-5D = EuroQol 5-Dimensions Questionnaire; FC = functional class; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; q.d. = once a day; QoL = quality of life; SF-36 = Short-Form 36-Item Health Survey; WHO = World Health Organization.

Rubenfire et al. (2007)[26]

Methods	Multi-centre, open-label, randomized, placebo-controlled trial
Participants	22 patients (mean age: 42 to 47 years) were enrolled at different centres in the USA. Inclusion criteria: PAH (idiopathic, familial, or associated with scleroderma, congenital systemic-to-pulmonary shunts, HIV or portal hypertension); WHO FC II or III; 6MWD ≥ 250m; stable on epoprostenol therapy for ≥ 3 months, with no dose change within 15 days, and a current dose of 10 to 75 ng/kg/min. Exclusion criteria: not reported.
Interventions	Patients were randomly assigned (1:2) to receive placebo, or Treprostinil subcutaneous (mean dose at transition was 25.3 mg/kg/min; mean maximum study drug dose was 32.2 ng/kg/min) for 8 weeks. **Treprostinil s.c.** (n = 14) **Placebo** (n = 8)
Outcomes	Primary end point: Clinical deterioration. Secondary end points: 6MWD; Borg dyspnea score; dyspnea fatigue index; symptoms of PAH; cardiovascular hospitalizations. Safety: AEs.
Definitions	Time to clinical deterioration: not reported.
Treatment history	Naive to Treprostinil (pre-treated with epoprostenol)

6MWD = six-minute walk distance; AE = adverse event; ERA = endothelin receptor antagonist; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; q.d. = once a day; s.c. = subcutaneous; SF-36 = Short-Form 36-Item Health Survey; WHO = World Health Organization.

Rubin et al. (1990)[27]

Methods	Multi-centre, open-label, randomized, placebo-controlled trial
Participants	23 patients (age: 15 to 66 years) were enrolled at different centres in the USA. Inclusion criteria: Primary PH (IPAH); NYHA FC II to IV; unresponsive to or unable to tolerate one or more of the vasodilators. Exclusion criteria: thromboembolic disease.
Interventions	Patients were randomly assigned (1:1) to receive conventional therapy (oral vasodilators, anticoagulants, cardiac glycoside, diuretics, and supplemental O_2), or prostacyclin intravenous (epoprostenol – initiated at 1 to 2 ng/kg/min, increased by increments of 1 to 2 ng/kg/min every 5 to 15 min) for 8 weeks. **Epoprostenol i.v.** (n = 11) **Conventional therapy** (n = 12)
Outcomes	Cardiopulmonary hemodynamics; 6MWD; NYHA FC (improved). Safety: Death; AEs.
Definitions	None
Treatment history	Naive (based on date of the study)

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; i.v. = intravenous; NYHA = New York Heart Association; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; q.d. = once a day; SF-36 = Short-Form 36-Item Health Survey.

SERAPHIN (2013)[35]

Methods	Phase 3, multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	742 patients (mean age: 46 years) were enrolled at 151 centres in 39 countries. Inclusion criteria: PAH (idiopathic, familial, or associated with connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, or drug use or toxin exposure); WHO FC II to IV; 6MWD ≥ 50m; naive patients or patients who were on stable treatment (at least 3 months before randomization) with oral phosphodiesterase type-5 inhibitors, oral or inhaled prostanoids, calcium channel blockers, or L-arginine. Exclusion criteria: treatment with intravenous or subcutaneous prostanoids.
Interventions	Patients were randomly assigned (1:1:1) to receive placebo, 3 mg, or 10 mg Macitentan oral q.d. for 36 months. ~~**Macitentan oral 3 mg q.d** (n = 250)~~ **Macitentan oral 10 mg q.d** (n = 242) **Placebo** (n = 250)
Outcomes	Primary end point: Time to clinical worsening. Secondary end points: 6MWD; WHO FC (improved); cardiopulmonary hemodynamics. Safety: Death; AEs.
Definitions	Time to clinical worsening: Time from randomization to the first event related to PAH (worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause up to the end of treatment. Worsening of PAH: Occurrence of all three of the following: a decrease in the 6MWD of ≥ 15% from baseline, confirmed by a second 6MWD performed on a different day within 2 weeks; worsening of symptoms of PAH; and the need for additional treatment of PAH. Worsening of symptoms of PAH: included ≥ one of the following: a change from baseline to a higher WHO FC (or no change in patients who were in WHO FC IV at baseline) and the appearance or worsening of signs of right heart failure that did not respond to oral diuretic therapy.
Treatment history	Mixed (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; EQ-5D = EuroQol 5-Dimensions Questionnaire; FC = functional class; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; q.d. = once a day; WHO = World Health Organization.

Simonneau et al. (2002)[28]

Methods	Multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	470 patients (mean age: 45 years) were enrolled at 24 centres in North America (Canada, Mexico, USA), and at 16 centres in the rest of the world (Australia, Austria, Belgium, France, Germany, Israel, Italy, Poland, Spain, UK). Inclusion criteria: Primary PH (IPAH) or secondary PH (PAH associated with connective tissue diseases or with congenital systemic-to-pulmonary shunts); NYHA FC II to IV; mean PAP ≥ 25 mm Hg; pulmonary wedge pressure ≤ 15 mm Hg; PVR > 3 mm Hg/L/min. Exclusion criteria: Significant parenchymal pulmonary disease as evidenced by pulmonary function tests or high resolution CT scan; portopulmonary hypertension, or HIV-associated pulmonary hypertension; uncontrolled sleep apnea; history of left-side heart disease; other disease associated with PH (i.e., sickle cell anemia, schistosomiasis); baseline 6MWD < 50 m or > 450 m; any new type of chronic therapy for PH added within the last month; any PH medication discontinued with the last week except anticoagulants; any use of prostaglandin derivatives with the past 30 days.
Interventions	Patients were randomly assigned (1:1) to receive conventional therapy (oral vasodilators, oral anticoagulants, diuretics, and/or digitalis), or Treprostinil subcutaneous plus conventional therapy for 12 weeks. **Treprostinil + conventional therapy** (n = 233) **Placebo + conventional therapy** (n = 236)
Outcomes	Primary end point: 6MWD Principal reinforcing end points: Signs and symptoms of PAH; Dyspnea-Fatigue Rating; death, lung transplantation, or discontinuation due to clinical deterioration. Secondary end points: Borg dyspnea score; cardiopulmonary hemodynamics; QoL (Minnesota Living with Heart Failure Questionnaire) Safety: Death; AEs.
Definitions	None
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; QoL = quality of life.

STRIDE-2 (2006)[29]

Methods	Multi-centre, multi-country, open-label (bosentan group), randomized, placebo-controlled trial
Participants	245 patients (mean age: 54 years) were enrolled at 55 centres around the world. Inclusion criteria: PAH (idiopathic or associated with connective tissue diseases, repaired atrial septal defect, ventricular septal defect, or patent ductus arteriosus at least one year before enrolment); WHO FC II to IV; 6MWD between 150 and 450 m; mean PAP ≥ 25 mm Hg; pulmonary wedge pressure ≤ 15 mm Hg; PVR ≥ 3 Wood units. Exclusion criteria: Significant parenchymal lung disease; porto hypertension; chronic liver disease; HIV infection; hepatic dysfunction; renal insufficiency; history of left-side heart disease; history of obstructive sleep apnea; previously failed bosentan; were on prostaglandin, phosphodiesterase inhibitor, or an endothelin receptor antagonist; or had received any new type of PAH treatment within 30 days before study entry.
Interventions	Patients were randomly assigned (1:1:1:1) to receive placebo, sitaxsentan 50 mg, sitaxsentan 100 mg, or bosentan (62.5 mg b.i.d. for 4 weeks followed by 125 mg b.i.d.) for a total of 18 weeks. ~~**Sitaxsentan oral 50 mg** (n = 62)~~ ~~**Sitaxsentan oral 100 mg** (n = 61)~~ **Bosentan oral 125 mg b.i.d.** (n = 60) **Placebo** (n = 62)
Outcomes	Primary end point: 6MWD Secondary end points: WHO FC (worsened); time to clinical worsening; Borg dyspnea score. Safety: AEs.
Definitions	Time to clinical worsening: First occurrence of death, transplantation, hospitalization for PAH, initiation of new chronic PAH treatment, or worsening of WHO FC and decreasing at least 15% in 6MWD.
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; b.i.d. = twice a day; AE = adverse event; FC = functional class; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; WHO = World Health Organization.

SUPER (2005)[30]

Methods	Multi-centre, multi-country, double-blind, randomized, placebo-controlled trial
Participants	278 patients (mean age: 47 to 51 years) were enrolled at 53 centres in the USA, Mexico, South America, and Israel. Inclusion criteria: PAH (idiopathic or associated with connective tissue diseases, or occurring after surgical repair of congenital systemic-to-pulmonary shunts that had been performed at least 5 years previously); WHO FC II to IV; 6MWD between 100 m and 450 m; mean PAP ≥ 25 mm Hg. Exclusion criteria: Treatment with intravenous epoprostenol, oral bosentan, intravenous or inhaled iloprost, or subcutaneous treprostinil and supplementation with L-arginine.
Interventions	Patients were randomly assigned (1:1:1:1) to receive placebo, sildenafil oral 20 mg, 40 mg, or 80 mg for 12 weeks. **Sildenafil oral 20 mg t.i.d.** (n = 69) ~~**Sildenafil oral 40 mg** (n = 67)~~ ~~**Sildenafil oral 80 mg** (n = 71)~~ **Placebo** (n = 70)
Outcomes	Primary end point: 6MWD Secondary end points: Cardiopulmonary hemodynamics; Borg dyspnea score; WHO FC (improved, unchanged, worsened); time to clinical worsening; QoL (SF-36, EQ-5D). Safety: Death; AEs.
Definitions	Time to clinical worsening: Time from randomization to first occurrence of death, transplantation, hospitalization for PAH, or initiation of additional therapies for PAH, such as intravenous epoprostenol or oral bosentan.
Treatment history	Naive (based on inclusion and exclusion criteria)

6MWD = six-minute walk distance; AE = adverse event; EQ-5D = EuroQol 5-Dimensions Questionnaire; FC = functional class; PAH = pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; QoL = quality of life; SF-36 = Short-Form 36-Item Health Survey; t.i.d. = three times a day; WHO = World Health Organization.

TRUST (2010)[31]

Methods	Multi-centre, double-blind, randomized, placebo-controlled trial
Participants	44 patients (mean age: 32 years) were enrolled at 14 centres in India. Inclusion criteria: PAH (idiopathic – sporadic or familial, or associated with HIV infection, or collagen vascular disease); stable NYHA FC III or IV; on conventional therapy (anticoagulants, diuretics, digoxin, oxygen); 6MWD between 50 and 325 m; mean PAP > 35 mm Hg; pulmonary capillary wedge pressure < 16 mm Hg; PVR > 5 mm Hg/L/min. Exclusion criteria: Not reported.
Interventions	Patients were randomly assigned (1:2) to receive placebo, or treprostinil intravenous (initiated at 4 ng/kg/min, increased to a maximum of 100 ng/kg/min) for 12 weeks. **Treprostinil i.v.** (n = 30) **Placebo** (n = 14)
Outcomes	Primary end point: 6MWD Secondary end points: Borg dyspnea score; dyspnea fatigue index; NYHA FC (improved, unchanged, worsened); clinical worsening (no data; only *P* value was provided). Safety: Death; AEs.
Definitions	Clinical worsening: Death, lung transplant, hospitalization, unblinding for rescue or too-ill-to-walk.
Treatment history	Naive (based on patient baseline characteristics)

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; i.v. = intravenous; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance.

Zhuang et al. (2014)[36]

Methods	Double-blind, randomized, placebo-controlled trial
Participants	124 patients (mean age: 52 years) from China. Inclusion criteria: PAH receiving ambrisentan for 4 months or more; mPAH ≥ 25 mm Hg, pulmonary wedge pressure ≤ 15 mm Hg and PVR ≥ 3 Wood units, 6MWD between 150 m and 400 m (stable for at least 1 month), stable WHO FC for at least 1 month. Exclusion criteria: thromboembolic disease, untreated obstructive sleep apnea, portal hypertension, chronic liver disease, renal insufficiency, left-side or unrepaired congenital heart disease, or substantial obstructive or restrictive lung disease.
Interventions	Patients were randomly assigned (1:1) to receive placebo, or tadalafil 40 mg q.d. for 16 weeks. **Tadalafil oral 40 mg q.d** (n = 60) **Placebo** (n = 64)
Outcomes	Primary end point: 6MWD Secondary end points: NYHA FC (improved, unchanged, worsened); clinical worsening, hemodynamic parameters (mPAP, PVR, CO). Safety: Death; AEs.
Definitions	Clinical worsening: Death, transplantation, arterial septostomy, hospitalization due to worsening PAH, initiation of new therapy or worsening FC by week 16.
Treatment history	Experienced (ambrisentan)

6MWD = six-minute walk distance; AE = adverse event; FC = functional class; mPAH = mean pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; q.d. = once a day; WHO = World Health Organization.

APPENDIX 8: CRITICAL APPRAISAL OF INCLUDED STUDIES

Table 126: Assessment of Individual Study Quality

Study	Interventions	Randomization	Allocation Concealment	Double-Blinding	Powered for Primary Analysis	Baseline Characteristics Similarity[a]	Total WDs (%)	ITT	Funding from Industry
ARIES-1, (2008)[18]	**Ambrisentan oral 5 mg q.d.** (n = 67) **Ambrisentan oral 10 mg q.d.** (n = 67) **Placebo** (n = 67)	Y	Y	Y	Y	Y	9%	Y	Y
ARIES-2, 2008[18]	**Ambrisentan oral 5 mg q.d.** (n = 63) **Placebo** (n = 65)	Y	Y	Y	Y	Y	11%	Y	Y
Badesch, 2000[19]	**Epoprostenol + conventional therapy** (n = 56) **Conventional therapy** (n = 55)	Y	Y	N	Y	Y, but intervention group had higher 6MWD	8%	Y	Y
Barst, 1996[20]	**Epoprostenol + conventional therapy** (n = 41) **Conventional therapy** (n = 40)	Y	Y	N	NR	Y, but intervention group had higher 6MWD	12%	Y	Y
BREATHE-1, 2002[21]	**Bosentan oral 125 mg b.i.d.** (n = 74) **Placebo** (n = 69)	Y	NR	Y	Y	Y	9%	Y	Y
BREATHE-5, 2006[22]	**Bosentan oral 125 mg b.i.d.** (n = 37) **Placebo** (n = 17)	Y	Y	Y	Y	Y	7%	PP	Y
Channick, 2001[23]	**Bosentan oral 125 mg b.i.d.** (n = 21) **Placebo** (n = 11)	Y	Y	Y	Y	Y, but placebo group had longer time since diagnosis	6%	Y	Y
EARLY, 2008[32]	**Bosentan oral 125 mg b.i.d.** (n = 92) **Placebo** (n = 93)	Y	Y	Y	Y	Y, but higher percentage of women in intervention group	12%	Y	Y
Galiè, 2005[24]	**Ambrisentan oral 5 mg** (n = 16)	Y	NR	Y	Y	Y	9%	Y	Y

Table 126: Assessment of Individual Study Quality									
Study	**Interventions**	**Randomization**	**Allocation Concealment**	**Double-Blinding**	**Powered for Primary Analysis**	**Baseline Characteristics Similarity[a]**	**Total WDs (%)**	**ITT**	**Funding from Industry**
	Ambrisentan oral 10 mg (n = 13)								
McLaughlin, 2003[25]	**Treprostinil s.c.** (n = 17) **Placebo** (n = 9)	Y	NR	Y	NR	Y	8%	NR	Y
PATENT-1, 2013[33]	**Riociguat oral max 1.5 mg t.i.d** (n = 63) **Riociguat oral max 2.5 mg t.i.d** (n = 254) **Placebo** (n = 126)	Y	Y	Y	Y	Y	9%	Y	Y
PHIRST, 2009[34]	**Tadalafil oral 40 mg q.d** (n = 79) **Placebo** (n = 82)	Y	NR	Y	Y	Y	16%	Y	Y
Rubenfire, 2007[26]	**Treprostinil s.c.** (n = 14) **Placebo** (n = 8)	Y	NR	N	Y	Y	41%	Y	NR
Rubin, 1990[27]	**Epoprostenol i.v.** (n = 11) **Conventional therapy** (n = 12)	Y	NR	N	NR	Y, but intervention group had higher 6MDW	17%	PP	Y
SERAPHIN, 2013[35]	**Macitentan oral 3 mg q.d** (n = 250) **Macitentan oral 10 mg q.d** (n = 242) **Placebo** (n = 250)	Y	Y	Y	Y	Y	21%	Y	Y
Simonneau, 2002[28]	**Treprostinil + conventional therapy** (n = 233) **Placebo + conventional therapy** (n = 236)	Y	NR	Y	NR	Y	10%	Y	Y
STRIDE-2, 2006[29]	**Bosentan oral 125 mg b.i.d.** (n = 60) **Placebo** (n = 62)	Y	Y	N	NR	Y	13%	Y	Y
SUPER, 2005[30]	**Sildenafil oral 20**	Y	Y	Y	Y	Y	4%	Y	Y

Table 126: Assessment of Individual Study Quality									
Study	**Interventions**	**Randomization**	**Allocation Concealment**	**Double-Blinding**	**Powered for Primary Analysis**	**Baseline Characteristics Similarity[a]**	**Total WDs (%)**	**ITT**	**Funding from Industry**
	mg t.i.d. (n = 69) **Placebo** (n = 70)								
TRUST, 2010[31]	**Treprostinil i.v.** (n = 30) **Placebo** (n = 14)	Y	NR	Y	N	Y	30%	Y	Y
Zhuang et al. 2014[36]	**Tadalafil oral 40 mg q.d** (n = 60) **Placebo** (n = 64)	Y	NR	Y	NR	Y	9%	Y	NR

6MWD = six-minute walk distance; b.i.d. = twice a day; ITT = intention to treat; i.v. = intravenous; MDW = mean distance walked; NR = not reported; PVRI = pulmonary vascular resistance index; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day;
[a] No differences in baseline characteristics were reported to be statistically significant.

APPENDIX 9: DETAILED DATA OF MONOTHERAPY AND ADD-ON THERAPY TRIALS

Table 127: Data of 6MWD, Mean Change From Baseline (Total)

Study	Treatment			1		2		3	
	1	2	3	Mean	SD	Mean	SD	Mean	SD
ARIES-1, (2008)[18]	Placebo (N = 67)	Ambrisentan oral 5 mg q.d. (N = 67)	Ambrisentan oral 10 mg q.d. (N = 67)	–7.8[a]	78.9	22.8[a]	83	46.3[a]	65.9
ARIES-2, 2008[18]	Placebo (N = 65)	Ambrisentan oral 5 mg q.d. (N = 63)	NA	–10.1[a]	93.8	49.4[a]	75.4	NA	NA
Badesch, 2000[19]	Placebo (N = 55)	Epoprostenol i.v. (N = 56)	NA	–36[b]	107.3	63.5[b]	133	NA	NA
Barst, 1996[20]	Placebo (N = 40)	Epoprostenol i.v. (N = 41)	NA	–15	112.1[b]	32	148.7[b]	NA	NA
BREATHE-1, 2002[21]	Placebo (N = 69)	Bosentan oral 125 mg b.i.d. (N = 74)	NA	–8[b]	100	27[b]	77	NA	NA
BREATHE-5, 2006[22]	Placebo (N = 17)	Bosentan oral 125 mg b.i.d. (N = 37)	NA	–9.7	91.9[c]	43.3	19.3[c]	NA	NA
Channick, 2001[23]	Placebo (N = 11)	Bosentan oral 125 mg b.i.d. (N = 21)	NA	–6	120.5[b]	70	56.1[b]	NA	NA
EARLY, 2008[32]	Placebo (N = 92)	Bosentan oral 125 mg b.i.d. (N = 93)	NA	–7.9	79.2[d]	11.2	76.7[d]	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5 mg q.d. (N = 16)	Ambrisentan oral 10 mg q.d. (N = 13)	NA	38.1	52.7[e]	35.1	39.9[e]	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	–6	84[c]	37	70[c]	NA	NA
PATENT-1, 2013[33]	Placebo (N = 126)	Riociguat oral max 1.5 mg t.i.d. (N = 63)	Riociguat oral max 2.5 mg t.i.d. (N = 254)	–6	86	31	79	30	66
PHIRST, 2009[34]	Placebo (N = 79[a])	Tadalafil oral 40 mg q.d. (N = 76[a])	NA	9.2[a]	60	41.1[a]	49.4	NA	NA
Rubenfire, 2007[26]	Placebo (N = 8)	Treprostinil s.c. (N = 14)	NA	–357	195	–35.2	40.1	NA	NA
Rubin, 1990[27]	Placebo (N = 12)	Epoprostenol i.v. (N = 11)	NA	87	74.2	132	113.8	NA	NA
SERAPHIN, 2013[35]	Placebo (N = 250)	Macitentan oral 10 mg q.d. (N = 242)	NA	–9.4	100.6	12.5	83.5	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	–22[a]	92	–2[a]	76	NA	NA
STRIDE-2, 2006[29]	Placebo (N = 62)	Bosentan oral 125 mg b.i.d. (N = 60)	NA	–6.5	84.4[b]	23	76.4[b]	NA	NA
SUPER, 2005[30]	Placebo (n = 70)	Sildenafil oral 20 mg t.i.d. (N = 69)	NA	–3.7[a]	52.8	41.4[a]	54.8	NA	NA
TRUST, 2010[31]	Placebo (N = 14)	Treprostinil i.v. (N = 30)	NA	–25.5	137.3	67.2	126	NA	NA

6MWD = six-minute walk distance; b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; SE = standard error; t.i.d. = three times a day.
[a] Data from FDA Clinical Review. [b] Data from Chen 2009 (Cochrane Review). [c] Estimated from SE.
[d] Estimated from 95% CI. [e] Estimated from *P* value.

Table 128: Data of 6MWD, Mean Change From Baseline (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
ARIES-1, (2008)[18]	Placebo (N = 67)	Ambrisentan oral 5 mg q.d. (N = 67)	Ambrisentan oral 10 mg q.d. (N = 67)	–7.8[a]	78.9	22.8[a]	83	46.3[a]	65.9
ARIES-2, 2008[18]	Placebo (N = 65)	Ambrisentan oral 5 mg q.d. (N = 63)	NA	–10.1[a]	93.8	49.4[a]	75.4	NA	NA
Badesch, 2000[19]	Placebo (N = 55)	Epoprostenol i.v. (N = 56)	NA	–36[b]	107.3	63.5[b]	133	NA	NA
Barst, 1996[20]	Placebo (N = 40)	Epoprostenol i.v. (N = 41)	NA	–15	112.1[b]	32	148.7[b]	NA	NA
BREATHE-1, 2002[21]	Placebo (N = 69)	Bosentan oral 125 mg b.i.d. (N = 74)	NA	–8[b]	100	27[b]	77	NA	NA
BREATHE-5, 2006[22]	Placebo (N = 17)	Bosentan oral 125 mg b.i.d. (N = 37)	NA	–9.7	91.9[c]	43.3	19.3[c]	NA	NA
Channick, 2001[23]	Placebo (N = 11)	Bosentan oral 125 mg b.i.d. (N = 21)	NA	–6	120.5[b]	70	56.1[b]	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5 mg q.d. (N = 16)	Ambrisentan oral 10 mg q.d. (N = 13)	NA	38.1	52.7[e]	35.1	39.9[e]	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	–6	84[c]	37	70[c]	NA	NA
PATENT-1, 2013[33]	Placebo (N = 66)	Riociguat oral max 1.5 mg t.i.d. (N = 32)	Riociguat oral max 2.5 mg t.i.d. (N = 123)	–6	88	49.4	79	32	74
PHIRST, 2009[34]	Placebo (N = 35[a])	Tadalafil oral 40 mg q.d. (N = 37[a])	NA	–6[a]	60[f]	38.4[a]	49.4[f]	NA	NA
Rubenfire, 2007[26]	Placebo (N = 8)	Treprostinil s.c. (N = 14)	NA	–357	195	–35.2	40.1	NA	NA
Rubin, 1990[27]	Placebo (N = 12)	Epoprostenol i.v. (N = 11)	NA	87	74.2	132	113.8	NA	NA
SERAPHIN, 2013[35]	Placebo (N = 95)	Macitentan oral 10 mg q.d. (N = 88)	NA	–12.2	122.4	3.1	85.4	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	–22[a]	92	–2[a]	76	NA	NA
STRIDE-2, 2006[29]	Placebo (N = 62)	Bosentan oral 125 mg b.i.d. (N = 60)	NA	–6.5	84.4[b]	23	76.4[b]	NA	NA
SUPER, 2005[30]	Placebo (n = 70)	Sildenafil oral 20 mg t.i.d. (N = 69)	NA	–3.7[a]	52.8	40[a]	54.8	NA	NA
TRUST, 2010[31]	Placebo (N = 14)	Treprostinil i.v. (N = 30)	NA	–25.5	137.3	67.2	126	NA	NA

6MWD = six-minute walk distance; b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; SE = standard error; t.i.d. = three times a day.

[a] Data from FDA Clinical Review.

[b] Data from Chen 2009 (Cochrane Review). [c] Estimated from SE. [d] Estimated from 95% CI. [e] Estimated from *P* value.

[f] Estimated from that of total population.

Table 129: Data of 6MWD, Mean Change From Baseline (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
PATENT-1, 2013;[33] overall	Placebo (N = 60)	Riociguat oral max 1.5 mg t.i.d. (N = 31)	Riociguat oral max 2.5 mg t.i.d. (N = 131)	–5.3	83	12.3[a]	79	27[b]	58
PATENT-1, 2013;[33] ERA background	Placebo (N = 54)	Riociguat oral max 2.5 mg t.i.d. (N = 113)	NA	–0.4	83	23	51	NA	NA
PATENT-1, 2013;[33] prostanoids background	Placebo (N = 6)	Riociguat oral max 2.5 mg t.i.d. (N = 18)	NA	–49	82	56	88	NA	NA
PHIRST, 2009;[34] bosentan background	Placebo (N = 44[a])	Tadalafil oral 40 mg q.d. (N = 39[a])	NA	18[a]	60[b]	40.7[a]	49.4[b]	NA	NA
SERAPHIN, 2013;[35] overall	Placebo (N = 154)	Macitentan oral 10 mg q.d. (N = 154)	NA	–7.8	84.8	17.9	82.3	NA	NA
Zhuang, 2014;[36] Ambrisentan background	Placebo (N = 64)	Tadalafil (N = 60)	NA	18.3	7.63	54.4	12.46	NA	NA

6MWD = six-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.

[a] Data from FDA Clinical Review.

[b] Estimated from that of total population.

Table 130: Data of Clinical Worsening (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	6	67	3	67	3	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	14	65	3	63	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	14	69	5	74	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	3	11	0	21	NA	NA
EARLY, 2008[32]	Placebo	Bosentan oral 125 mg b.i.d.	NA	13	92	3	93	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	8[a]	126	2[a]	63	3[a]	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	13	82	4	79	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	116	250	76	242	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	10	62	9	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	7	70	3	69	NA	NA

b.i.d. = twice a day; NA = not applicable; q.d. = once a day; SD = standard deviation; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 131: Data of Clinical Worsening (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d. (N = 67)	6	67	3	67	3	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	14	65	3	63	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	14	69	5	74	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	3	11	0	21	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	4	66	2	123	NA	NA
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	8	37	2	37	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	48	96	26	88	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	10	62	9	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	7	70	3	69	NA	NA

b.i.d. = twice a day; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.

Table 132: Data of Clinical Worsening (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
PATENT-1, 2013;[33] overall	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	4[a]	60	1[a]	131	NA	NA
PATENT-1, 2013;[33] ERA background	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	3[a]	54	1[a]	113	NA	NA
PATENT-1, 2013;[33] Prostanoids background	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	1[a]	7	0[a]	20	NA	NA
PHIRST, 2009;[34] Bosentan background	Placebo	Tadalafil oral 40 mg q.d.	NA	5	45	2	42	NA	NA
SERAPHIN, 2013;[35] overall	Placebo	Macitentan oral 10 mg q.d.	NA	68	154	50	154	NA	NA
Zhuang, 2014;[36] Ambrisentan background	Placebo	Tadalafil oral 40 mg q.d.	NA	14	64	5	60	NA	NA

ERA = endothelin receptor antagonist; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from abstract by Humbert et al.[135]

Table 133: Data of Hospitalization (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	2	67	2	67	2	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	9	65	2	63	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	9	69	3	74	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	4[a]	126	0[a]	63	1[a]	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	2	82	1	79	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	79	250	45	242	NA	NA
Simonneau, 2002[28]	Placebo	Treprostinil s.c.	NA	40[a]	236	38[a]	233	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	4	62	3	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	7	70	2	69	NA	NA
Zhuang, 2014[36]	Placebo	Tadalafil oral 40 mg q.d.	NA	2	64	0	60	NA	NA

b.i.d. = twice a day; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 134: Data of Functional Class, Improved (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5mg q.d.	Ambrisentan oral 10 mg q.d.	16[a]	67	19[a]	67	20[a]	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5mg q.d.	NA	11[a]	65	9[a]	63	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	0	55	21	56	NA	NA
Barst, 1996[20]	Placebo	Epoprostenol i.v.	NA	1	40	16	41	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	21[a]	69	32[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	17	13	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	1	11	9	21	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	18	125	15	63	53	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	17	82	18	79	NA	NA
Rubin, 1990[27]	Placebo	Epoprostenol i.v.	NA	2	9	10	10	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.		33	250	53	242	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	5[a]	70	19[a]	68	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	3	14	15	30	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 135: Data of Functional Class, Improved (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	16[a]	67	19[a]	67	20[a]	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	11[a]	65	9[a]	63	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	0	55	21	56	NA	NA
Barst, 1996[20]	Placebo	Epoprostenol i.v.	NA	1	40	16	41	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	21[a]	69	32[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	17	13	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	1	11	9	21	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	10	66	18	123	NA	NA
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	6	37	14	37	NA	NA
Rubin, 1990[27]	Placebo	Epoprostenol i.v.	NA	2	9	10	10	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	5[a]	70	19[a]	68	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	3	14	15	30	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 136: Data of Functional Class, Improved (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
PATENT-1, 2013;[33] overall	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	8[a]	59	34[a]	131	NA	NA
PATENT-1, 2013;[33] ERA background	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	7[a]	53	29[a]	113	NA	NA
PATENT-1, 2013;[33] Prostanoids background	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	1[a]	7	6[a]	20	NA	NA
PHIRST, 2009;[34] Bosentan background	Placebo	Tadalafil oral 40 mg q.d.	NA	11	45	4	42	NA	NA
Zhuang, 2014;[36] Ambrisentan background	Placebo	Tadalafil oral 40 mg q.d.	NA	20	64	26	60	NA	NA

NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from abstract by Humbert et al.[135]

Table 137: Data of Functional Class, Unchanged (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	40[a]	67	47[a]	67	44[a]	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	42[a]	65	52[a]	63	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	42[b]	55	33[b]	56	NA	NA
Barst, 1996[20]	Placebo	Epoprostenol i.v.	NA	27	40	19	41	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	44[a]	69	41[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	14	17	23	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	8	11	12	21	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	89	125	43	63	192	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	52	82	53	79	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	164[a]	249	171[a]	242	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	58[c]	70	47[c]	68	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	9	14	15	30	NA	NA

b.i.d. = twice a day; FC = functional class; i.v. = intravenous; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.

[a] Data from FDA Clinical Review.

[b] Estimated from percent FC improved and worsened.

[c] Data from FDA Clinical Review, estimated from numbers of FC improved and worsened.

Table 138: Data of Functional Class, Unchanged (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	40[a]	67	47[a]	67	44[a]	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	42[a]	65	52[a]	63	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	42[b]	55	33[b]	56	NA	NA
Barst, 1996[20]	Placebo	Epoprostenol i.v.	NA	27	40	19	41	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	44[a]	69	41[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	14	17	23	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	8	11	12	21	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	45	66	98	123	NA	NA
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	23	37	19	37	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	58[c]	70	47[c]	68	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	9	14	15	30	NA	NA

b.i.d. = twice a day; FC = functional class; i.v. = intravenous; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.

[a] Data from FDA Clinical Review.

[b] Estimated from percent FC improved and worsened.

[c] Data from FDA Clinical Review, estimated from numbers of FC improved and worsened.

Table 139: Data of Functional Class, Unchanged (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
PATENT-1, 2013;[33] overall	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	44[a]	59	93[a]	131	NA	NA
PATENT-1, 2013;[33] ERA background	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	40[a]	53	80[a]	113	NA	NA
PATENT-1, 2013;[33] Prostanoids background	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	5[a]	7	14[a]	20	NA	NA
PHIRST, 2009;[34] Bosentan background	Placebo	Tadalafil oral 40 mg q.d.	NA	29	45	34	42	NA	NA
Zhuang, 2014;[36] Ambrisentan background	Placebo	Tadalafil oral 40 mg q.d.	NA	32	64	29	60	NA	NA

ERA = endothelin receptor antagonist; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from abstract by Humbert et al.[135]

Table 140: Data of Functional Class, Worsened (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	11[a]	67	1[a]	67	3[a]	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	12[a]	65	2[a]	63	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	13[a]	55	2[a]	56	NA	NA
Barst, 1996[20]	Placebo	Epoprostenol i.v.	NA	3	40	5	41	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	4[a]	69	2[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	1	17	1	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	11	0	21	NA	NA
EARLY, 2008[32]	Placebo	Bosentan oral 125 mg b.i.d.	NA	12	92	3	93	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	18	125	5	63	9	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	13	82	8	79	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	53[a]	249	17[a]	242	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	8	62	5	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	7[a]	70	2[a]	68	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	2	14	0	30	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 141: Data of Functional Class, Worsened (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	11[a]	67	1[a]	67	3[a]	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	12[a]	65	2[a]	63	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	13[a]	55	2[a]	56	NA	NA
Barst, 1996[20]	Placebo	Epoprostenol i.v.	NA	3	40	5	41	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	4[a]	69	2[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	1	17	1	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	11	0	21	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	11	66	5	123	NA	NA
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	8	37	4	37	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	8	62	5	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	7[a]	70	2[a]	68	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	2	14	0	30	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 142: Data of Functional Class, Worsened (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
PATENT-1, 2013;[33] overall	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	7[a]	59	4[a]	131	NA	NA
PATENT-1, 2013;[33] ERA background	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	6[a]	53	5[a]	113	NA	NA
PATENT-1, 2013;[33] Prostanoids background	Placebo	Riociguat oral max 2.5 mg t.i.d.	NA	1[a]	7	0[a]	20	NA	NA
PHIRST, 2009;[34] Bosentan background	Placebo	Tadalafil oral 40 mg q.d.	NA	5	45	4	42	NA	NA
Zhuang, 2014;[36] Ambrisentan background	Placebo	Tadalafil oral 40 mg q.d.	NA	12	64	5	60	NA	NA

NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from abstract by Humbert et al.[135]

Table 143: Data of Borg Dyspnea Index, Mean Change From Baseline (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
ARIES-1, (2008)[18]	Placebo (N = 67)	Ambrisentan oral 5 mg q.d. (N = 67)	Ambrisentan oral 10 mg q.d. (N = 67)	0[a]	2.22	–0.3[a]	1.93	–0.9[a]	1.93
ARIES-2, 2008[18]	Placebo (N = 65)	Ambrisentan oral 5 mg q.d. (N = 63)	NA	0.8[a]	2.63	–0.4[a]	1.99	NA	NA
Badesch, 2000[19]	Placebo (N = 42[a])	Epoprostenol i.v. (N = 49[a])	NA	0.62[a]	3.21[b]	–1.79[a]	3.78[b]	NA	NA
BREATHE-1, 2002[21]	Placebo (N = 69)	Bosentan oral 125 mg b.i.d. (N = 74)	NA	0.3[a]	2.0	–0.1[a]	2.1	NA	NA
Channick, 2001[23]	Placebo (N = 11)	Bosentan oral 125 mg b.i.d. (N = 21)	NA	1.3[a]	2.7	–0.3[a]	1.8	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	1.0	2.4	0.0	1.5	NA	NA
PATENT-1, 2013[33]	Placebo (N = 126)	Riociguat oral max 1.5 mg t.i.d. (N = 63)	Riociguat oral max 2.5 mg t.i.d. (N = 254)	0.1	2.1	–0.3	1.0	–0.4	1.7
PHIRST, 2009[34]	Placebo (N = 79[a])	Tadalafil oral 40 mg q.d. (N = 76[a])	NA	0.4[a]	3.8[c]	–0.7[a]	3.8[c]	NA	NA
Rubenfire, 2007[26]	Placebo (N = 8)	Treprostinil s.c. (N = 14)	NA	5.63	2.66[d]	0.61	2.24[d]	NA	NA
SERAPHIN, 2013[35]	Placebo (N = 250)	Macitentan oral 10 mg q.d. (N = 242)		0.4[a]	2.1	–0.1[a]	2.02	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	–0.2[e]	3.1	–1.1[e]	3.1	NA	NA
SUPER, 2005[30]	Placebo (n = 66[a])	Sildenafil oral 20 mg t.i.d. (N = 67[a])	NA	0[a]	2.0[f]	–0.8[a]	2.0[f]	NA	NA
TRUST, 2010[31]	Placebo (N = 14)	Treprostinil i.v. (N = 30)	NA	0.4	0.6	–1.7	0.4	NA	NA

b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; SE = standard error; t.i.d. = three times a day.

[a] Data from FDA Clinical Review.

[b] Estimated from 95% CI.

[c] Estimated from *P* value.

[d] Estimated from SE.

[e] Estimated from baseline and end-treatment values.

[f] Estimated using imputation approach.

Table 144: Data of Borg Dyspnea Index, Mean Change From Baseline (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
ARIES-1, (2008)[18]	Placebo (N = 67)	Ambrisentan oral 5 mg q.d. (N = 67)	Ambrisentan oral 10 mg q.d. (N = 67)	0[a]	2.22	–0.3[a]	1.93	–0.9[a]	1.93
ARIES-2, 2008[18]	Placebo (N = 65)	Ambrisentan oral 5 mg q.d. (N = 63)	NA	0.8[a]	2.63	–0.4[a]	1.99	NA	NA
Badesch, 2000[19]	Placebo (N = 42[a])	Epoprostenol i.v. (N = 49[a])	NA	0.62[a]	3.21[b]	–1.79[a]	3.78[b]	NA	NA
BREATHE-1, 2002[21]	Placebo (N = 69)	Bosentan oral 125 mg b.i.d. (N = 74)	NA	0.3[a]	2.0	–0.1[a]	2.1	NA	NA
Channick, 2001[23]	Placebo (N = 11)	Bosentan oral 125 mg b.i.d. (N = 21)	NA	1.3[a]	2.7	–0.3[a]	1.8	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	1.0	2.4	0.0	1.5	NA	NA
PATENT-1, 2013[33]	Placebo (N = 66)	Riociguat oral max 2.5 mg t.i.d. (N = 123)	NA	0.02	2.2	–0.4	1.6	NA	NA
Rubenfire, 2007[26]	Placebo (N = 8)	Treprostinil s.c. (N = 14)	NA	5.63	2.66[c]	0.61	2.24[c]	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	–0.2[d]	3.1	–1.1[d]	3.1	NA	NA
SUPER, 2005[30]	Placebo (n = 66[a])	Sildenafil oral 20 mg t.i.d. (N = 67[a])	NA	0[a]	2.0[e]	–0.8[a]	2.0[e]	NA	NA
TRUST, 2010[31]	Placebo (N = 14)	Treprostinil i.v. (N = 30)	NA	0.4	0.6	–1.7	0.4	NA	NA

b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; SE = standard error; t.i.d. = three times a day.

[a] Data from FDA Clinical Review.

[b] Estimated from 95% CI.

[c] Estimated from SE.

[d] Estimated from baseline and end-treatment values.

[e] Estimated using imputation approach.

Table 145: Data of Borg Dyspnea Index, Mean Change From Baseline (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
PATENT-1, 2013;[33] overall	Placebo (N = 60)	Riociguat oral max 2.5 mg t.i.d. (N = 131)	NA	0.2[a]	2.0	–0.5[a]	1.9	NA	NA
PATENT-1, 2013;[33] ERA background	Placebo (N = 54)	Riociguat oral max 2.5 mg t.i.d. (N = 113)	NA	0.2[a]	2.0	–0.4[a]	1.9	NA	NA
PATENT-1, 2013;[33] Prostanoids background	Placebo (N = 7)	Riociguat oral max 2.5 mg t.i.d. (N = 20)	NA	–0.4[a]	1.4	–0.8[a]	1.7	NA	NA

ERA = endothelin receptor antagonist; SD = standard deviation; t.i.d. = three times a day.
[a] Data from abstract by Humbert et al.[135]

Table 146: Data of Pulmonary Vascular Resistance, mean change from baseline (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Badesch, 2000[19]	Placebo (N = 55)	Epoprostenol i.v. (N = 56)	NA	74	332	–366	455	NA	NA
Barst, 1996[20]	Placebo (N = 40)	Epoprostenol i.v. (N = 41)	NA	120	607	–272	359	NA	NA
BREATHE-5, 2006[22]	Placebo (N = 17)	Bosentan oral 125 mg b.i.d.(N = 37)	NA	155	552	–317	841	NA	NA
Channick, 2001[23]	Placebo (N = 10)	Bosentan oral 125 mg b.i.d. (N = 19)	NA	191	234	–223	244	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5 mg q.d. (N = 16)	Ambrisentan oral 10 mg q.d. (N = 13)	NA	–277	261	–345	226	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	16	456	–384	434	NA	NA
PATENT-1, 2013[33]	Placebo (N = 126)	Riociguat oral max 1.5 mg t.i.d. (N = 63)	Riociguat oral max 2.5 mg t.i.d. (N = 254)	–9	317	–168	320	–223	260
PHIRST, 2009[34]	Placebo (N = 16[a])	Tadalafil oral 40 mg q.d. (N = 18[a])	NA	11[a]	321[b]	–209[a]	395[b]	NA	NA
Rubin, 1990[27]	Placebo (N = 9)	Epoprostenol i.v. (N = 10)	NA	–16	630[b]	–616	609[b]	NA	NA
SERAPHIN, 2013[35]	Placebo (N = 67[a])	Macitentan oral 10 mg q.d. (N = 57[a])	NA	504[a]	919	–25[a]	688	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	96	737	–280	733	NA	NA
SUPER, 2005[30]	Placebo (n = 65)	Sildenafil oral 20 mg t.i.d. (N = 65)	NA	49	418	-122	383	NA	NA

b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.
[a] Data from FDA Clinical Review. [b] Estimated from 95% CI.

Table 147: Data of Pulmonary Vascular Resistance, Mean Change From Baseline (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Badesch, 2000[19]	Placebo (N = 55)	Epoprostenol i.v. (N = 56)	NA	74	332	–366	455	NA	NA
Barst, 1996[20]	Placebo (N = 40)	Epoprostenol i.v. (N = 41)	NA	120	607	–272	359	NA	NA
BREATHE-5, 2006[22]	Placebo (N = 17)	Bosentan oral 125 mg b.i.d.(N = 37)	NA	155	552	–317	841	NA	NA
Channick, 2001[23]	Placebo (N = 10)	Bosentan oral 125 mg b.i.d. (N = 19)	NA	191	234	–223	244	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5mg q.d. (N = 16)	Ambrisentan oral 10 mg q.d. (N = 13)	NA	–277	261	–345	226	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	16	456	–384	434	NA	NA
PATENT-1, 2013[33]	Placebo (N = 55)	Riociguat oral max 2.5 mg t.i.d. (N = 115)	NA	17	361	–259	296	NA	NA
Rubin, 1990[27]	Placebo (N = 9)	Epoprostenol i.v. (N = 10)	NA	–16	630[a]	–616	609[a]	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	96	737	–280	733	NA	NA
SUPER, 2005[30]	Placebo (n = 65)	Sildenafil oral 20 mg t.i.d. (N = 65)	NA	49	418	–122	383	NA	NA

b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.
[a] Estimated from 95% CI.

Table 148: Data of Pulmonary Vascular Resistance, Mean Change From Baseline (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
PATENT-1, 2013;[33] overall	Placebo (N = 52)	Riociguat oral max 2.5 mg t.i.d. (N = 117)	NA	–36[a]	263	–188[a]	215	NA	NA
PATENT-1, 2013;[33] ERA background	Placebo (N = 48)	Riociguat oral max 2.5 mg t.i.d. (N = 100)	NA	–46[a]	266	–174[a]	202	NA	NA
PATENT-1, 2013;[33] Prostanoids background	Placebo (N = 5)	Riociguat oral max 2.5 mg t.i.d. (N = 19)	NA	61[a]	198	–259[a]	260	NA	NA
Zhuang, 2014;[36] Ambrisentan background	Placebo (N = 64)	Tadalafil oral 40 mg q.d. (N = 60)	NA	–108	506	–214	1223	NA	NA

NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.
[a] Data from abstract by Humbert et al.[135]

Table 149: Data of Pulmonary Artery Pressure, Mean Change From Baseline (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Badesch, 2000[19]	Placebo (N = 55)	Epoprostenol i.v. (N = 56)	NA	0.94	8.16	–5.03	8.16	NA	NA
Barst, 1996[20]	Placebo (N = 40)	Epoprostenol i.v. (N = 41)	NA	1.9	10.1	–4.8	8.3	NA	NA
BREATHE-5, 2006[22]	Placebo (N = 17)	Bosentan oral 125 mg b.i.d.(N = 37)	NA	0.5	5.8[c]	–5.0	9.7[c]	NA	NA
Channick, 2001[23]	Placebo (N = 10)	Bosentan oral 125 mg b.i.d. (N = 20)	NA	5.1	8.9	–1.6	5.4	NA	NA
EARLY, 2008[32]	Placebo (N = 92)	Bosentan oral 125 mg b.i.d. (N = 93)	NA	3.0	14.7[b]	–2.7	18.2[b]	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5 mg q.d. (N = 16)	Ambrisentan oral 10 mg q.d. (N = 13)	NA	–4.3	4.8	–13.3	5.1	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	–2.0	3.0	0.0	11.6	NA	NA
PATENT-1, 2013[33]	Placebo (N = 126)	Riociguat oral max 1.5 mg t.i.d. (N = 63)	Riociguat oral max 2.5 mg t.i.d. (N = 254)	–0.5	9.4	–4.0	7.0	–4.0	8.0
PHIRST, 2009[34]	Placebo (N = 16[a])	Tadalafil oral 40 mg q.d. (N = 18[a])	NA	–2.21[a]	9.44[b]	–4.27[a]	6.56[b]	NA	NA
Rubin, 1990[27]	Placebo (N = 9)	Epoprostenol i.v. (N = 10)	NA	0.0	11.6[b]	–9.3	13[b]	NA	NA
SERAPHIN, 2013[35]	Placebo (N = 67[a])	Macitentan oral 10 mg q.d. (N = 57[a])	NA	6.6[a]	14.37	3.9[a]	28.39	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	0.7	9.2	–2.3	7.6	NA	NA
SUPER, 2005[30]	Placebo (n = 65)	Sildenafil oral 20 mg t.i.d. (N = 65)	NA	0.6	5.7[b]	–2.1	8.7[b]	NA	NA

b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; SE = standard error; t.i.d. = three times a day.

[a] Data from FDA Clinical Review.

[b] Estimated from 95% CI.

[c] Estimated from SE.

Table 150: Data of Pulmonary Artery Pressure, Mean Change From Baseline (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Badesch, 2000[19]	Placebo (N = 55)	Epoprostenol i.v. (N = 56)	NA	0.94	8.16	–5.03	8.16	NA	NA
Barst, 1996[20]	Placebo (N = 40)	Epoprostenol i.v. (N = 41)	NA	1.9	10.1	–4.8	8.3	NA	NA
BREATHE-5, 2006[22]	Placebo (N=17)	Bosentan oral 125 mg b.i.d. (N = 37)	NA	0.5	5.8[a]	–5.0	9.7[a]	NA	NA
Channick, 2001[23]	Placebo (N = 10)	Bosentan oral 125 mg b.i.d. (N = 20)	NA	5.1	8.9	–1.6	5.4	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5mg q.d. (N = 16)	Ambrisentan oral 10 mg q.d. (N = 13)	NA	–4.3	4.8	–13.3	5.1	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	–2.0	3.0	0.0	11.6	NA	NA
PATENT-1, 2013[33]	Placebo (N = 56)	Riociguat oral max 2.5 mg t.i.d. (N = 116)	NA	–0.3	11.8	–4.4	8.0	NA	NA
Rubin, 1990[27]	Placebo (N = 9)	Epoprostenol i.v. (N = 10)	NA	0.0	11.6[b]	–9.3	13[b]	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	0.7	9.2	–2.3	7.6	NA	NA
SUPER, 2005[30]	Placebo (n = 65)	Sildenafil oral 20 mg t.i.d. (N = 65)	NA	0.6	5.7[b]	–2.1	8.7[b]	NA	NA

b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; SE = standard error; t.i.d. = three times a day.

[a] Estimated from SE.

[b] Estimated from 95% CI.

Table 151: Data of Pulmonary Artery Pressure, Mean Change From Baseline (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
PATENT-1, 2013;[33] ERA background	Placebo (N = 48)	Riociguat oral max 2.5 mg t.i.d. (N = 101)	NA	–1.1[a]	6.2	–3.5[a]	7.1	NA	NA
PATENT-1, 2013;[33] Prostanoids background	Placebo (N = 6)	Riociguat oral max 2.5 mg t.i.d. (N = 20)	NA	3.1[a]	3.8	–2.9[a]	9.5	NA	NA
Zhuang, 2014;[36] Ambrisentan background	Placebo (N = 64)	Tadalafil oral 40 mg q.d. (N = 60)	NA	–3.0	11.6	–7.0	37.0	NA	NA

ERA = endothelin receptor antagonist; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.

[a] Data from abstract by Jing et al.[136]

Table 152: Data of Cardiac Index, Mean Change From Baseline (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Badesch, 2000[19]	Placebo (N = 55)	Epoprostenol i.v. (N = 56)	NA	–0.1	0.59	0.5	0.6	NA	NA
Barst, 1996[20]	Placebo (N = 40)	Epoprostenol i.v. (N = 41)	NA	–0.2	1.3	0.3	0.6	NA	NA
BREATHE-1, 2002[21]	Placebo (N = 26)	Bosentan oral 125 mg b.i.d. (N = 28)	NA	–0.18	0.56	0.18	0.48		
BREATHE-5, 2006[22]	Placebo (N = 17)	Bosentan oral 125 mg b.i.d.(N = 37)	NA	–0.2	0.4[c]	0.9	4.9[c]	NA	NA
Channick, 2001[23]	Placebo (N = 10)	Bosentan oral 125 mg b.i.d. (N = 20)	NA	–0.5	0.3	0.5	0.4	NA	NA
EARLY, 2008[32]	Placebo (N = 92)	Bosentan oral 125 mg b.i.d. (N = 93)	NA	–0.15	0.7	0.09	0.78	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5 mg q.d. (N = 16)	Ambrisentan oral 10 mg q.d. (N = 13)	NA	0.47	0.62	0.37	0.16	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	0.0	0.6	0.4	0.2	NA	NA
PATENT-1, 2013[33]	Placebo (N = 126)	Riociguat oral max 1.5 mg t.i.d. (N = 63)	Riociguat oral max 2.5 mg t.i.d. (N = 254)	–0.02[a]	0.3[d]	0.25[a]	0.3[d]	0.54[a]	1.0[d]
PHIRST, 2009[34]	Placebo (N = 16[a])	Tadalafil oral 40 mg q.d. (N = 18[a])	NA	–0.01[a]	0.8[b]	0.36[a]	0.54[b]	NA	NA
SERAPHIN, 2013[35]	Placebo (N = 67[a])	Macitentan oral 10 mg q.d. (N = 57[a])		–0.48[a]	0.701	0.13[a]	0.887	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	–0.06	0.61	0.12	0.61	NA	NA
SUPER, 2005[30]	Placebo (n = 65)	Sildenafil oral 20 mg t.i.d. (N=65)	NA	–0.02	0.61	0.21	1.53	NA	NA

b.i.d. = twice a day; CI = confidence interval; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; SE = standard error; t.i.d. = three times a day.

[a] Data from FDA Clinical Review.

[b] Estimated from 95% CI.

[c] Estimated from SE.

[d] Estimated from imputation based on SD of difference.

Table 153: Data of Cardiac Index, Mean Change From Baseline (Naive)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Badesch, 2000[19]	Placebo (N = 55)	Epoprostenol i.v. (N = 56)	NA	–0.1	0.59	0.5	0.6	NA	NA
Barst, 1996[20]	Placebo (N = 40)	Epoprostenol i.v. (N = 41)	NA	–0.2	1.3	0.3	0.6	NA	NA
BREATHE-1, 2002[21]	Placebo (N = 26)	Bosentan oral 125 mg b.i.d. (N = 28)	NA	–0.18	0.56	0.18	0.48		
BREATHE-5, 2006[22]	Placebo (N = 17)	Bosentan oral 125 mg b.i.d.(N = 37)	NA	–0.2	0.4[a]	0.9	4.9[a]	NA	NA
Channick, 2001[23]	Placebo (N = 10)	Bosentan oral 125 mg b.i.d. (N = 20)	NA	–0.5	0.3	0.5	0.4	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5mg q.d. (N = 16)	Ambrisentan oral 10 mg q.d. (N = 13)	NA	0.47	0.62	0.37	0.16	NA	NA
McLaughlin, 2003[25]	Placebo (N = 9)	Treprostinil s.c. (N = 17)	NA	0.0	0.6	0.4	0.2	NA	NA
PATENT-1, 2013[33]	Placebo (N = 55)	Riociguat oral max 2.5 mg t.i.d. (N = 115)	NA	–0.1	0.7	0.6	0.6	NA	NA
Simonneau, 2002[28]	Placebo (N = 236)	Treprostinil s.c. (N = 233)	NA	–0.06	0.61	0.12	0.61	NA	NA
SUPER, 2005[30]	Placebo (n = 65)	Sildenafil oral 20 mg t.i.d. (N = 65)	NA	–0.02	0.61	0.21	1.53	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; SE = standard error; t.i.d. = three times a day.
[a] Estimated from SE.

Table 154: Data of Cardiac Index, Mean Change From Baseline (Add-on)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
PATENT-1, 2013;[33] ERA background	Placebo (N = 48)	Riociguat oral max 2.5 mg t.i.d. (N = 100)	NA	0.1[a]	0.5	0.5[a]	0.6	NA	NA
PATENT-1, 2013;[33] Prostanoids background	Placebo (N = 6)	Riociguat oral max 2.5 mg t.i.d. (N = 20)	NA	0.0[a]	0.5	0.5[a]	0.5	NA	NA
Zhuang, 2014;[36] Ambrisentan background	Placebo (N = 64)	Tadalafil oral 40 mg q.d. (N = 60)	NA	0.17	0.7	0.34	2.1	NA	NA

ERA = endothelin receptor antagonist; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.
[a] Data from abstract by Jing et al[136]

Table 155: Data of Mortality (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	2	67	1	67	1	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	3	65	0	63	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	5	55	4	56	NA	NA
Barst, 1996[20]	Placebo	Epoprostenol i.v.	NA	8	40	0	41	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	69	1	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	0	17	0	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	0	11	0	21	NA	NA
EARLY, 2008[32]	Placebo	Bosentan oral 125 mg b.i.d.	NA	1	92	1	93	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5mg q.d.	Ambrisentan oral 10 mg q.d.	NA	0	16	1	13	NA	NA
McLaughlin, 2003[25]	Placebo	Treprostinil s.c.	NA	0	9	0	17	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	2	126	1	63	0	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	1[a]	79[a]	0[a]	76[a]	NA	NA
Rubenfire, 2007[26]	Placebo	Treprostinil s.c.	NA	0	8	0	14	NA	NA
Rubin, 1990[27]	Placebo	Epoprostenol i.v.	NA	3	12	1	11	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	44	250	34	242	NA	NA
Simonneau, 2002[28]	Placebo	Treprostinil s.c.	NA	10	236	9	233	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	62	0	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	1	70	1	69	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	5	14	3	30	NA	NA
Zhuang, 2014[36]	Placebo	Tadalafil oral 40 mg q.d.	NA	1	64	0	60	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 156: Data of Serious Adverse Events (Other Than Death) (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1 & ARIES-2 (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d. & 10 mg q.d.	NA	21[a]	132	23[a]	261	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	36[a]	55	35[a]	56	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	13[a]	69	12[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	3	17	5	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	1[a]	11	1[a]	21	NA	NA
EARLY, 2008[32]	Placebo	Bosentan oral 125 mg b.i.d.	NA	8	92	12	93	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	23[a]	126	11[a]	63	29[a]	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	12[a]	82	7[a]	79	NA	NA
Rubenfire, 2007[26]	Placebo	Treprostinil s.c.	NA	3	8	1	14	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	137	249	109	242	NA	NA
Simonneau, 2002[28]	Placebo	Treprostinil s.c.	NA	47[a]	236	146[a]	233	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	12[a]	70	13[a]	69	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	9	14	11	30	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 157: Data of Drug Discontinuation Due to Adverse Events (Other Than Death) (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1 & ARIES-2 (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d. & 10 mg q.d.	NA	4[a]	132	5[a]	197	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	0[a]	55	0[a]	56	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	5[a]	69	3[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	17	2	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	3[a]	11	0[a]	21	NA	NA
EARLY, 2008[32]	Placebo	Bosentan oral 125 mg b.i.d.	NA	8	92	8	93	NA	NA
McLaughlin, 2003[25]	Placebo	Treprostinil s.c.	NA	0	9	2	17	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	7	126	1	63	8	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	12	82	7	79	NA	NA
Rubenfire, 2007[26]	Placebo	Treprostinil s.c.	NA	7	8	2	14	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	31	250	26	242	NA	NA
Simonneau, 2002[28]	Placebo	Treprostinil s.c.	NA	1	236	18	233	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	6	62	6	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	0[a]	70	1[a]	69	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	2	14	1	30	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; SD = standard deviation; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 158: Data of Total Withdrawal (Including Death) (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1 & ARIES-2 (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d. & 10 mg q.d.	NA	21[a]	132	14[a]	197	NA	NA
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	2[a]	55	1[a]	56	NA	NA
Barst, 1996[20]	Placebo	Epoprostenol i.v.	NA	10	40	3	41	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	6[a]	69	3[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	17	2	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	3	11	0	21	NA	NA
EARLY, 2008[32]	Placebo	Bosentan oral 125 mg b.i.d.	NA	10	92	12	93	NA	NA
McLaughlin, 2003[25]	Placebo	Treprostinil s.c.	NA	0	9	2	17	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	15	126	6	63	17	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	13	82	8	79	NA	NA
Rubenfire, 2007[26]	Placebo	Treprostinil s.c.	NA	7	8	2	14	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	55	250	41	242	NA	NA
Simonneau, 2002[28]	Placebo	Treprostinil s.c.	NA	15[a]	236	33[a]	233	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	11	62	8	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	2[a]	70	2[a]	69	NA	NA
TRUST, 2010[31]	Placebo	Treprostinil i.v.	NA	6	14	7	30	NA	NA
Zhuang, 2014[36]	Placebo	Tadalafil oral 40 mg q.d.	NA	5	64	6	60	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 159: Data of Liver Toxicity* (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1 & ARIES-2 (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d. & 10 mg q.d.	NA	3	132	0	261	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	0[a]	68	10[a]	73	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	0	17	1	37	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	0[a]	11	3[a]	21	NA	NA
EARLY, 2008[32]	Placebo	Bosentan oral 125 mg b.i.d.	NA	2	92	12	93	NA	NA
Galiè, 2005[24]	Ambrisentan oral 5mg q.d.	Ambrisentan oral 10 mg q.d.	NA	2	16	0	13	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	0	126	0	63	1	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	2[a]	82	1[a]	79	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	11	244	8	236	NA	NA
Simonneau, 2002[28]	Placebo	Treprostinil s.c.	NA	1[a]	236	0[a]	233	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	4	62	7	60	NA	NA
SUPER, 2005[30]	Placebo	Sildenafil oral 20 mg t.i.d.	NA	0	70	1	69	NA	NA

ALT = alanine transaminase; AST = aspartate transaminase; b.i.d. = twice a day; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.
*ALT or AST: > 3 × upper limit of normal.

Table 160: Data of Edema (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1, (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	7	67	18	67	19	67
ARIES-2, 2008[18]	Placebo	Ambrisentan oral 5 mg q.d.	NA	7	65	6	63	NA	NA
ARIES-1 & ARIES-2 (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	14	132	24	130	19	67
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	48[a]	55	44[a]	56	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	6[a]	69	13[a]	74	NA	NA
BREATHE-5, 2006[22]	Placebo	Bosentan oral 125 mg b.i.d.	NA	1	17	7	37	NA	NA
EARLY, 2008[32]	Placebo	Bosentan oral 125 mg b.i.d.	NA	7	92	6	93	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	14	126	14	63	44	254
PHIRST, 2009[34]	Placebo	Tadalafil oral 40 mg q.d.	NA	1	82	4	79	NA	NA
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	45	249	44	242	NA	NA
Simonneau, 2002[28]	Placebo	Treprostinil s.c.	NA	6	236	21	233	NA	NA
STRIDE-2, 2006[29]	Placebo	Bosentan oral 125 mg b.i.d.	NA	5	62	9	60	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 161: Data of Anemia (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
ARIES-1 & ARIES-2 (2008)[18]	Placebo	Ambrisentan oral 5 mg q.d.	Ambrisentan oral 10 mg q.d.	23[a]	132	83[a]	130	49[a]	67
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	0[a]	69	5[a]	74	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	3	126	1	63	21	254
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	8	249	32	242	NA	NA

b.i.d. = twice a day; NA = not applicable; q.d. = once a day; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

Table 162: Data of Hypotension (Total)									
Study	**Treatment**			**1**		**2**		**3**	
	1	**2**	**3**	**n**	**N**	**n**	**N**	**n**	**N**
Badesch, 2000[19]	Placebo	Epoprostenol i.v.	NA	0[a]	55	7[a]	56	NA	NA
BREATHE-1, 2002[21]	Placebo	Bosentan oral 125 mg b.i.d.	NA	3[a]	69	5[a]	74	NA	NA
Channick, 2001[23]	Placebo	Bosentan oral 125 mg b.i.d.	NA	0	11	0	21	NA	NA
McLaughlin, 2003[25]	Placebo	Treprostinil s.c.	NA	0	9	4	17	NA	NA
PATENT-1, 2013[33]	Placebo	Riociguat oral max 1.5 mg t.i.d.	Riociguat oral max 2.5 mg t.i.d.	3	126	2	63	25	254
SERAPHIN, 2013[35]	Placebo	Macitentan oral 10 mg q.d.	NA	11[a]	249	15[a]	242	NA	NA
Simonneau, 2002[28]	Placebo	Treprostinil s.c.	NA	5	236	9	233	NA	NA

b.i.d. = twice a day; i.v. = intravenous; NA = not applicable; q.d. = once a day; s.c. = subcutaneous; t.i.d. = three times a day.
[a] Data from FDA Clinical Review.

APPENDIX 10: PAIRWISE META-ANALYSES

Table 163: Meta-analysis Results: Ambrisentan 5 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Naive	RR	262[18]	0%; 0.52	NA	0.31 (0.05 to 1.96)
Clinical worsening	Naive	RR	262[18]	0%; 0.37	NA	**0.32 (0.13 to 0.78)**
FC improved	Naive	RR	262[18]	0%; 0.50	NA	1.06 (0.66 to 1.69)
FC unchanged	Naive	RR	262[18]	0%; 0.62	NA	**1.23 (1.04 to 1.45)**
FC worsened	Naive	RR	262[18]	0%; 0.61	NA	**0.14 (0.04 to 0.45)**
Hospitalization	Naive	RR	262[18]	29.2%; 0.23	NA	0.42 (0.10 to 1.75)
6MWD (m)	Naive	WMD	262[18]	49.6%; 0.16	NA	**44.53 (16.23 to 72.84)**
BDI	Naive	WMD	262[18]	63.2%; 0.10	NA	–0.73 (–1.61 to 0.15)
Hemodynamics						
PVR (dyn s/cm^5)	Naive	WMD	NR		NA	NR
PAP (mm Hg)	Naive	WMD	NR		NA	NR
Cardiac index (L/min/m^2)	Naive	WMD	NR		NA	NR
Safety						
Serious AEs[a]	Naive	RR	393[86]	NA	NA	**0.55 (0.32, 0.96)**
Withdrawal due to AEs[a]	Naive	RR	329[86]	NA	NA	0.84 (0.23, 3.06)
Total withdrawal[a]	Naive	RR	329[86]	NA	NA	**0.45 (0.24, 0.85)**

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; No. = number; NA = not applicable; NR = not reported; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.
[a] For the combined ambrisentan group (5 mg and 10 mg)
Bold numbers indicate statistical significance.

Table 164: Meta-analysis Results: Ambrisentan 10 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Naive	RR	134[18]	NA	NA	0.50 (0.05 to 5.38)
Clinical worsening	Naive	RR	134[18]	NA	NA	0.50 (0.13 to 1.92)
FC improved	Naive	RR	134[18]	NA	NA	1.25 (0.71 to 2.20)
FC unchanged	Naive	RR	134[18]	NA	NA	1.10 (0.85 to 1.43)
FC worsened	Naive	RR	134[18]	NA	NA	**0.27 (0.08 to 0.93)**
Hospitalization	Naive	RR	134[18]	NA	NA	1.00 (0.15 to 6.89)
6MWD (m)	Naive	WMD	134[18]	NA	NA	**54.10 (29.48 to 78.72)**
BDI	Naive	WMD	134[18]	NA	NA	**–0.90 (–1.60 to –0.20)**
Hemodynamics						
PVR (dyn s/cm^5)	Naive	WMD	NR		NA	NR
PAP (mm Hg)	Naive	WMD	NR		NA	NR
Cardiac index (L/min/m^2)	Naive	WMD	NR		NA	NR
Safety						
Serious AEs[a]	Naive	RR	393[86]	NA	NA	**0.55 (0.32 to 0.96)**
Withdrawal due to AEs[a]	Naive	RR	329[86]	NA	NA	0.84 (0.23 to 3.06)
Total withdrawal[a]	Naive	RR	329[86]	NA	NA	**0.45 (0.24 to 0.85)**

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; No. = number; NA = not applicable; NR = not reported; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.

[a] For the combined ambrisentan group (5 mg and 10 mg).

Bold numbers indicate statistical significance.

Table 165: Meta-analysis Results: Bosentan 125 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Total	RR	536[21-23,29,32]	0%; 0.75	NA	0.48 (0.10 to 2.24)
	Naive	RR	351[21-23,29]	0%; 0.68	NA	0.34 (0.05 to 2.21)
Clinical worsening	Total	RR	482[21,23,29,32]	50.7%; 0.11	NA	**0.39 (0.16 to 0.92)**
	Naive	RR	297[21,23,29]	55.1%; 0.11	NA	0.46 (0.16 to 1.32)
FC improved	Naive	RR	229[21-23]	18.6%; 0.29	NA	1.81 (0.98 to 3.34)
FC unchanged	Naive	RR	229[21-23]	0%; 0.80	NA	**0.82 (0.67 to 0.99)**
FC worsened	Total	RR	536[21-23,29,32]	0%; 0.70	NA	**0.41 (0.21 to 0.80)**
	Naive	RR	351[21-23,29]	0%; 0.74	NA	0.51 (0.22 to 1.14)
Hospitalization	Naive	RR	265[21,29]	0%; 0.35	NA	0.46 (0.18 to 1.20)
6MWD (m)	Total	WMD	536[21-23,29,32]	0%; 0.48	NA	**30.70 (16.64 to 44.77)**
	Naive	WMD	351[21-23,29]	0%; 0.61	NA	**38.17 (20.14 to 56.21)**
BDI	Naive	WMD	175[21,23]	35.1%; 0.21	NA	–0.71 (–1.74 to 0.32)
Hemodynamics						
PVR (dyn s/cm^5)	Naive	WMD	83[22,23]	0%; 0.79	NA	**–424.94 (–588.75 to –261.13)**
PAP (mm Hg)	Total	WMD	269[22,23,32]	0%; 0.95	NA	**–5.83 (–8.61 to –3.05)**
	Naive		84[22,23]	0%, 0.75	NA	**–5.89 (–9.31 to –2.47)**
Cardiac index (L/min/m^2)	Total	WMD	323[21-23,32]	86.3%; < 0.0001	Results from each study are presented separately below	No pooling
	Naive	WMD	54[21]	NA	NA	**0.36 (0.08 to 0.64)**
	Naive	WMD	54[22]	NA	NA	1.10 (–0.49 to 2.69)
	Naive	WMD	30[23]	NA	NA	1.00 (0.74 to 1.26)
	Total	WMD	185[32]	NA	NA	**0.24 (0.03 to 0.45)**
Safety					NA	
Serious AEs	Total	RR	414[21-23,32]	0%; 0.71	NA	1.00 (0.61 to 1.64)
Withdrawal due to AEs	Total	RR	536[21-23,29,32]	0%; 0.47	NA	0.76 (0.42 to 1.36)
Total withdrawal	Total	RR	536[21-23,29,32]	10.7%; 0.34	NA	0.74 (0.42 to 1.28)

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; No. = number; NA = not applicable; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.
Bold numbers indicate statistical significance.

Table 166: Meta-analysis Results: Macitentan 10 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Total	RR	492[35]	NA	NA	0.80 (0.53 to 1.20)
Clinical worsening	Total	RR	492[35]	NA	NA	**0.68 (0.54 to 0.85)**
	Naive	RR	184[35]	NA	NA	**0.59 (0.40 to 0.86)**
	Add-on (overall)	RR	308[35]	NA	NA	**0.74 (0.55 to 0.98)**
FC improved	Total	RR	492[35]	NA	NA	**1.66 (1.12 to 2.47)**
FC unchanged	Total	RR	491[35]	NA	NA	1.07 (0.95 to 1.21)
FC worsened	Total	RR	491[35]	NA	NA	**0.33 (0.20 to 0.55)**
Hospitalization	Total	RR	492[35]	NA	NA	**0.59 (0.43 to 0.81)**
6MWD (m)	Total	WMD	492[35]	NA	NA	**21.90 (5.58 to 38.22)**
	Naive	WMD	183[35]	NA	NA	15.30 (–15.10 to 45.70)
	Add-on (overall)	WMD	308[35]	NA	NA	**25.70 (7.04 to 44.36)**
BDI	Total	WMD	492[35]	NA	NA	**–0.50 (–0.86 to –0.14)**
Hemodynamics						
PVR (dyn s/cm^5)	Total	WMD	124[35]	NA	NA	**–529.00 (–812.41 to –245.59)**
PAP (mm Hg)	Total	WMD	124[35]	NA	NA	–2.70 (–10.83 to 5.43)
Cardiac index (L/min/m^2)	Total	WMD	124[35]	NA	NA	**0.61 (0.32 to 0.90)**
Safety						
Serious AEs	Total	RR	491[35]	NA	NA	**0.82 (0.68 to 0.98)**
Withdrawal due to AEs	Total	RR	492[35]	NA	NA	0.87 (0.53 to 1.41)
Total withdrawal	Total	RR	492[35]	NA	NA	0.77 (0.54 to 1.11)

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; No. = number; NA = not applicable; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.
Bold numbers indicate statistical significance.

Table 167: Meta-analysis Results: Riociguat Max 1.5 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Total	RR	189[33]	NA	NA	1.00 (0.09 to 10.82)
Clinical worsening	Total	RR	189[33]	NA	NA	0.50 (0.11 to 2.29)
FC improved	Total	RR	188[33]	NA	NA	1.65 (0.89, 3.06)
FC unchanged	Total	RR	188[33]	NA	NA	0.96 (0.78 to 1.17)
FC worsened	Total	RR	188[33]	NA	NA	0.55 (0.21 to 1.42)
Hospitalization	Total	RR	189[33]	NA	NA	0.22 (0.01 to 4.03)
6MWD (m)	Total	WMD	189[33]	NA	NA	**37.00 (12.38 to 61.62)**
	Naive	WMD	98[33]	NA	NA	**55.40 (20.76 to 90.04)**
	Add-on (overall)	WMD	91[33]	NA	NA	17.60 (–17.25 to 52.45)
BDI	Total	WMD	189[33]	NA	NA	–0.40 (–0.84 to 0.04)
Hemodynamics						
PVR (dyn s/cm^5)	Total	WMD	189[33]	NA	NA	**–159.00 (–255.48 to –62.52)**
PAP (mm Hg)	Total	WMD	189[33]	NA	NA	**–3.50 (–5.88 to –1.12)**
Cardiac index (L/min/m^2)	Total	WMD	189[33]	NA	NA	**0.27 (0.18 to 0.36)**
Safety						
Serious AEs	Total	RR	189[33]	NA	NA	0.96 (0.50 to 1.84)
Withdrawal due to AEs	Total	RR	189[33]	NA	NA	0.29 (0.04 to 2.27)
Total withdrawal	Total	RR	189[33]	NA	NA	0.80 (0.33 to 1.96)

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; No. = number; NA = not applicable; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.
Bold numbers indicate statistical significance.

Table 168: Meta-analysis Results: Riociguat Max 2.5 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Total	RR	380[33]	NA	NA	0.10 (0.00 to 2.06)
Clinical worsening	Total	RR	380[33]	NA	NA	**0.19 (0.05 to 0.69)**
	Naive	RR	189[135]	NA	NA	0.27 (0.05 to 1.43)
	Add-on (overall)	RR	191[135]	NA	NA	0.11 (0.01 to 1.00)
	Add-on (ERA)	RR	167[135]	NA	NA	0.16 (0.02 to 1.50)
	Add-on (prostanoids)	RR	27[135]	NA	NA	0.13 (0.01 to 2.81)
FC improved	Total	RR	379[33]	NA	NA	1.45 (0.89 to 2.37)
	Naive	RR	189[135]	NA	NA	0.97 (0.47 to 1.97)
	Add-on (overall)	RR	190[135]	NA	NA	1.91 (0.94 to 3.88)

Table 168: Meta-analysis Results: Riociguat Max 2.5 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
	Add-on (ERA)	RR	166[135]	NA	NA	1.94 (0.91 to 4.15)
	Add-on (prostanoids)	RR	27[135]	NA	NA	2.10 (0.30 to 14.53)
FC unchanged	Total	RR	379[33]	NA	NA	1.06 (0.93 to 1.21)
	Naive	RR	189[135]	NA	NA	1.17 (0.97 to 1.41)
	Add-on (overall)	RR	190[135]	NA	NA	0.95 (0.79 to 1.15)
	Add-on (ERA)	RR	166[135]	NA	NA	0.94 (0.77 to 1.14)
	Add-on (prostanoids)	RR	27[135]	NA	NA	0.98 (0.57 to 1.70)
FC worsened	Total	RR	379[33]	NA	NA	**0.25 (0.11 to 0.53)**
	Naive	RR	189[135]	NA	NA	**0.24 (0.09 to 0.67)**
	Add-on (overall)	RR	190[135]	NA	NA	**0.26 (0.08 to 0.85)**
	Add-on (ERA)	RR	166[135]	NA	NA	0.39 (0.12 to 1.22)
	Add-on (prostanoids)	RR	27[135]	NA	NA	0.13 (0.01 to 2.81)
Hospitalization	Total	RR	380[33]	NA	NA	0.12 (0.01 to 1.10)
6MWD (m)	Total	WMD	380[33]	NA	NA	**36.00 (18.93 to 53.07)**
	Naive	WMD	189[33]	NA	NA	**38.00 (13.07 to 62.94)**
	Add-on (overall)	WMD	191[33]	NA	NA	**32.30 (9.07 to 55.53)**
	Add-on (ERA)	WMD	167[33]	NA	NA	23.40 (–0.65 to 47.45)
	Add-on (prostanoids)	WMD	24[33]	NA	NA	**105.00 (27.81 to 182.19)**
BDI	Total	WMD	380[33]	NA	NA	**–0.50 (–0.92 to –0.08)**
	Naive	WMD	189[135]	NA	NA	–0.42 (–1.02 to 0.18)
	Add-on (overall)	WMD	191[135]	NA	NA	**–0.70 (–1.30 to –0.10)**
	Add-on (ERA)	WMD	167[135]	NA	NA	–0.60 (–1.24 to 0.04)
	Add-on (prostanoids)	WMD	27[135]	NA	NA	–0.40 (–1.68 to 0.88)
Hemodynamics						
PVR (dyn s/cm^5)	Total	WMD	380[33]	NA	NA	**–214.00 (–277.92 to –150.08)**
	Naive	WMD	170[135]	NA	NA	**–276.00 (–385.68 to –166.32)**
	Add-on (overall)	WMD	169[135]	NA	NA	**–152.00 (–233.41 to –70.59)**
	Add-on (ERA)	WMD	148[135]	NA	NA	**–128.00 (–213.00 to –42.97)**
	Add-on (prostanoids)	WMD	24[135]	NA	NA	**–320.00 (–529.25 to –110.75)**
PAP (mm Hg)	Total	WMD	380[33]	NA	NA	**–3.50 (–5.41 to –1.59)**
	Naive	WMD	172[136]	NA	NA	**–4.10 (–7.52 to –0.68)**
	Add-on (ERA)	WMD	149[136]	NA	NA	**–2.40 (–4.63 to –0.17)**
	Add-on (prostanoids)	WMD	26[136]	NA	NA	**–6.00 (–11.16 to –0.84)**
Cardiac index (L/min/m^2)	Total	WMD	380[33]	NA	NA	**0.56 (0.43 to 0.69)**
	Naive	WMD	170[136]	NA	NA	**0.70 (0.48 to 0.92)**

Table 168: Meta-analysis Results: Riociguat Max 2.5 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
	Add-on (ERA)	WMD	148[136]	NA	NA	**0.40 (0.22 to 0.58)**
	Add-on (prostanoids)	WMD	26[136]	NA	NA	**0.50 (0.04 to 0.96)**
Safety						
Serious AEs	Total	RR	380[33]	NA	NA	0.63 (0.38 to 1.04)
Withdrawal due to AEs	Total	RR	380[33]	NA	NA	0.57 (0.21 to 1.53)
Total withdrawal	Total	RR	380[33]	NA	NA	0.56 (0.29 to 1.09)

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; No. = number; NA = not applicable; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.
Bold numbers indicate statistical significance.

Table 169: Meta-analysis Results: Sildenafil 20 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Naive	RR	139	NA	NA	1.01 (0.06 to 15.90)
Clinical worsening	Naive	RR	139	NA	NA	0.43 (0.12 to 1.61)
FC improved	Naive	RR	138	NA	NA	**3.91 (1.55 to 9.88)**
FC unchanged	Naive	RR	138	NA	NA	0.83 (0.69 to 1.01)
FC worsened	Naive	RR	138	NA	NA	0.29 (0.06 to 1.37)
Hospitalization	Naive	RR	139	NA	NA	0.29 (0.06 to 1.35)
6MWD (m)	Naive	WMD	139	NA	NA	**43.70 (25.81 to 61.59)**
BDI	Naive	WMD	133	NA	NA	**–0.80 (–1.48 to –0.12)**
Hemodynamics						
PVR (dyn s/cm^5)	Naive	WMD	130	NA	NA	**–171.00 (–308.82 to –33.18)**
PAP (mm Hg)	Naive	WMD	130	NA	NA	**–2.70 (–5.23 to –0.17)**
Cardiac index (L/min/m^2)	Naive	WMD	130	NA	NA	0.23 (–0.17 to 0.63)
Safety						
Serious AEs	Naive	RR	139	NA	NA	1.10 (0.54 to 2.24)
Withdrawal due to AEs	Naive	RR	139	NA	NA	3.04 (0.13 to 73.43)
Total withdrawal	Naive	RR	139	NA	NA	1.01 (0.15 to 7.00)

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; No. = number of patients; NA = not applicable; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference
Bold numbers indicate statistical significance.

Table 170: Meta-analysis Results: Tadalafil 40 mg Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**N**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Total	RR	279[34,36]	0%; 0.99	NA	0.35 (0.04 to 3.33)
Clinical worsening	Total	RR	161[34]	NA	NA	**0.32 (0.11 to 0.94)**
	Naive	RR	74[34]	NA	NA	0.25 (0.06 to 1.10)
	Add-on (bosentan, ambrisentan)	RR	211[34,36]	0%; 0.90	NA	**0.39 (0.17 to 0.89)**
FC improved	Total	RR	161[34]	NA	NA	1.10 (0.61 to 1.98)
	Naive	RR	74[34]	NA	NA	**2.33 (1.01 to 5.41)**
	Add-on (bosentan, ambrisentan)	RR	211[34,36]	79.0%; 0.03	Results from each study are presented separately below	No pooling
	PHIRST (2009)	RR	87	NA	NA	0.39 (0.13 to 1.13)
	Zhuang (2014)	RR	124	NA	NA	1.39 (0.87 to 2.21)
FC unchanged	Total	RR	161[34]	NA	NA	1.06 (0.84 to 1.33)
	Naive	RR	74[34]	NA	NA	0.83 (0.55 to 1.23)
	Add-on (bosentan, ambrisentan)	RR	211[34,36]	31.5%; 0.23	NA	1.13 (0.87 to 1.47)
FC worsened	Total	RR	161[34]	NA	NA	0.64 (0.28 to 1.46)
	Naive	RR	74[34]	NA	NA	0.50 (0.16 to 1.52)
	Add-on (bosentan, ambrisentan)	RR	211[34,36]	0%; 0.42	NA	0.57 (0.26 to 1.24)
Hospitalization	Total	RR	285[34,36]	0%; 0.65	NA	0.37 (0.06 to 2.39)
6MWD (m)	Total	WMD	155[34]	NA	NA	**31.90 (14.63 to 49.17)**
	Naive	WMD	72[34]	NA	NA	**44.40 (18.93 to 69.87)**
	Add-on (bosentan, ambrisentan)	WMD	207[34,36]	17.6%; 0.27	NA	**34.66 (26.52 to 42.80)**
BDI	Total	WMD	155[34]	NA	NA	–1.10 (–2.30 to 0.10)
Hemodynamics						
PVR (dyn s/cm^5)	Total	WMD	158[34,36]	0%; 0.59	NA	–180.89 (–376.15 to 14.37)
	Add-on	WMD	124[36]	NA	NA	–106.00 (–439.36 to 227.36)
PAP (mm Hg)	Total	WMD	158[34,36]	0%; 0.74	NA	–2.53 (–7.34 to 2.28)
	Add-on	WMD	124[36]	NA	NA	–4.00 (–13.78 to 5.78)
Cardiac index (L/min/m^2)	Total	WMD	158[34,36]	0%; 0.59	NA	0.29 (–0.07 to 0.65)
	Add-on	WMD	124[36]	NA	NA	0.17 (–0.39 to 0.73)
Safety						
Serious AEs	Total	RR	161[34]	NA	NA	0.61 (0.25 to 1.46)
Withdrawal due to AEs	Total	RR	161[34]	NA	NA	0.61 (0.25 to 1.46)
Total withdrawal	Total	RR	285[34,36]	0%; 0.33	NA	0.82 (0.42 to 1.57)

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; N = number of patients; NA = not applicable; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.
Bold numbers indicate statistical significance.

Table 171: Meta-analysis Results: Epoprostenol Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Naive	RR	215[19,20,27]	39.0%; 0.19	NA	0.37 (0.09 to 1.57)
Clinical worsening	Naive	RR	NR	NA	NA	NR
FC improved	Naive	RR	211[19,20,27]	59.0%; 0.09	NA	**10.18 (1.91 to 54.24)**
FC unchanged	Naive	RR	192[19,20]	0%; 0.62	NA	**0.74 (0.60 to 0.93)**
FC worsened	Naive	RR	192[19,20]	82.4%; 0.02	Results from each study are presented separately below	No pooling
	Naive	RR	81[20]	NA	NA	1.63 (0.42 to 6.36)
	Naive	RR	111[19]	NA	NA	**0.15 (0.04 to 0.64)**
Hospitalization	Naive	RR	NR	NA	NA	NR
6MWD (m)	Naive	WMD	215[19,20,27]	23.3%; 0.27	NA	**71.30 (33.35 to 109.25)**
BDI	Naive	WMD	91[19]	NA	NA	**–2.41 (–3.85 to –0.97)**
Hemodynamics						
PVR (dyn s/cm^5)	Naive	WMD	211[19,20,27]	0%, 0.78	NA	**–432.87 (–552.45 to –313.30)**
PAP (mm Hg)	Naive	WMD	211[19,20,27]	0%; 0.85	NA	**–6.13 (–8.50 to –3.76)**
Cardiac index (L/min/m^2)	Naive	WMD	192[19,20]	0%; 0.69	NA	**0.58 (0.38 to 0.78)**
Safety						
Serious AEs	Naive	RR	111[19]	NA	NA	0.95 (0.72 to 1.26)
Withdrawal due to AEs	Naive	RR	111[19]	NA	NA	Not estimable
Total withdrawal	Naive	RR	192[19,20]	0%; 0.70	NA	**0.33 (0.11 to 0.96)**

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; No. = number of patients; NA = not applicable; NR = not reported; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.
Bold numbers indicate statistical significance.

Table 172: Meta-analysis Results: Treprostinil Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
Efficacy						
Death	Naive	RR	561[25,26,28,31]	55.0%; 0.14	NA	0.56 (0.18 to 1.75)
Clinical worsening	Naive	RR	NR	NA	NA	NR
FC improved	Naive	RR	44[31]	NA	NA	2.33 (0.80 to 6.77)
FC unchanged	Naive	RR	44[31]	NA	NA	0.78 (0.46 to 1.32)
FC worsened	Naive	RR	44[31]	NA	NA	0.10 (0.00 to 1.89)
Hospitalization	Naive	RR	469[28]	NA	NA	0.96 (0.64 to 1.44)
6MWD (m)	Naive	WMD	561[25,26,28,31]	85.8%; < 0.0001	--	No pooling
	Naive	WMD	539[25,28,31]	35.7%; 0.21	Excluding Rubenfire[26]	**34.52 (0.24 to 68.80)**
BDI	Naive	WMD	561[25,26,28,31]	86.3%; < 0.0001	Results from each study are presented separately below	No pooling
	Naive	WMD	22[26]	NA	NA	**–5.02 (–7.21 to –2.83)**
	Naive	WMD	469[28]	NA	NA	**–0.90 (–1.46 to –0.34)**
	Naive	WMD	26[25]	NA	NA	–1.00 (–2.72 to 0.72)
	Naive	WMD	44[31]	NA	NA	**–2.10 (–2.45 to –1.75)**
Hemodynamics						
PVR (dyn s/cm^5)	Naive	WMD	495[25,28]	0%, 0.90	NA	**–378.85 (–503.74 to –253.96)**
PAP (mm Hg)	Naive	WMD	495[25,28]	61.9%; 0.11	--	–1.33 (–5.95 to 3.29)
			469[28]	NA	Excluding McLaughlin[25]	**–3.00 (–4.53 to –1.47)**
Cardiac index (L/min/m^2)	Naive	WMD	495[25,28]	5.9%; 0.30	NA	**0.20 (0.07 to 0.33)**
Safety						
Serious AEs	Naive	RR	535[26,28,31]	93.5%; < 0.00001	Results from each study are presented separately below	No pooling
	Naive	RR	469[28]	NA	NA	**3.15 (2.39 to 4.14)**
	Naive	RR	22[26]	NA	NA	0.19 (0.02 to 1.54)
	Naive	RR	44[31]	NA	NA	0.57 (0.31 to 1.05)
Withdrawal due to AEs	Naive	RR	561[25,26,28,31]	85.3%; 0.0001	Results from each study are presented separately below	No pooling

Table 172: Meta-analysis Results: Treprostinil Versus Placebo						
Outcomes	**Background**	**Statistics (Random)**	**No. of Patients**	**Heterogeneity (I^2, *P* Value)**	**Sensitivity Analysis**	**Effect Size (95% CI)**
	Naive	RR	469[28]	NA	NA	**18.23 (2.45 to 135.46)**
	Naive	RR	26[25]	NA	NA	2.78 (0.15 to 52.35)
	Naive	RR	22[26]	NA	NA	**0.16 (0.04 to 0.60)**
	Naive	RR	44[31]	NA	NA	0.23 (0.02 to 2.36)
Total withdrawal	Naive	RR	561[25,26,28,31]	47.2%; 0.13	NA	0.54 (0.25 to 1.19)

6MWD = six-minute walk distance; AEs = adverse events; BDI = Borg dyspnea index; CI = confidence interval; FC = functional class; No. = number of patients; NA = not applicable; NR = not reported; PAP = pulmonary artery pressure; PVR = pulmonary ventricular resistance; RR = relative risk; WMD = weighted mean difference.
Bold numbers indicate statistical significance.

Table 173: Treatment-Related Adverse Events, n (%)										
Study	**Intervention**	**Peripheral Edema**	**Anemia[b]**	**Liver Toxicity[c]**	**Hypotension**	**Nausea**	**Diarrhea**	**Jaw Pain**	**Headache**	**Injection site reaction**
ARIES-1 & 2, 2008[18]	**Placebo** (N = 132)	14 (11)[a]	23 (17)[a]	3 (2)	--	--	--	--	--	--
	Combined ambrisentan (n = 261)	45 (17)[a]	171 (66)[a]	0 (0)	--	--	--	--	--	--
Badesch, 2000[19]	**Placebo** (n = 55)	48 (87)[a]	--	--	0 (0.0)[a]	9 (16)	3 (5)	0 (0)	3 (5)[a]	0 (0)[a]
	Epoprostenol (n = 56)	44 (79)[a]	--	--	7 (13.0)[a]	23 (41)	28 (50)	42 (75)	26 (46)[a]	8 (14)[a]
BREATHE-1, 2002[21]	**Placebo** (n = 69)	6 (9)[a]	0 (0)[a]	0 (0)[a]	3 (4)[a]	--	--	--	13 (19)	--
	Bosentan (n = 74)	13 (18)[a]	5 (7)[a]	10 (14)[a]	5 (7)[a]	--	--	--	14 (19)	--
BREATHE-5, 2006[22]	**Placebo** (n = 17)	1 (6)	--	0 (0)	--	--	--	--	2 (12)	--
	Bosentan (n = 37)	7 (19)	--	1 (3)	--	--	--	--	5 (14)	--
Channick, 2001[23]	**Placebo** (n = 11)	--	--	0 (0)	0 (0)	3 (27)	1 (9)	--	3 (27)	--
	Bosentan (n = 21)	--	--	3 (14)	0 (0)	2 (10)	1 (5)	--	6 (29)	--
EARLY, 2008[32]	**Placebo** (n = 93)	7 (8)	--	2 (2)	--	8 (9)	7 (8)	--	9 (10)	--
	Bosentan (n = 92)	6 (6)	--	12 (13)	--	5 (5)	2 (2)	--	4 (4)	--
McLaughlin, 2003[25]	**Placebo** (n = 9)	--	--	--	0 (0)	--	--	--	--	2 (22)
	Treprostinil s.c. (n = 17)	--	--	--	4 (24)	--	--	--	--	16 (94)
PATENT-1, 2013[33]	**Placebo** (n = 126)	14 (11)	3 (2)	0 (0)	3 (2)	16 (13)	13 (10)	--	25 (20)	--
	Riociguat max 1.5 mg (n = 63)	14 (22)	1 (2)	0 (0)	2 (3)	10 (16)	6 (10)	--	20 (32)	--
	Riociguat max 2.5 mg (n = 254)	44 (17)	21 (8)	1 (0)	25 (10)	40 (16)	35 (14)	--	69 (27)	--
PHIRST, 2009[34]	**Placebo** (n = 82)	1 (1)	--	2 (2)	--	5 (6)	8 (10)	--	12 (15)	--
	Tadalafil (n = 79)	4 (5)	--	1 (1)	--	9 (11)	9 (11)	--	33 (42)	--
Rubenfire, 2007[26]	**Placebo** (n = 8)	--	--	--	--	6 (75)	3 (37)	1 (13)	5 (63)	0 (0)
	Treprostinil s.c. (n = 14)	--	--	--	--	6 (43)	7 (50)	4 (29)	6 (43)	10 (71)
SERAPHIN, 2013[35]	**Placebo** (n = 249)	45 (18)	8 (3)	11 (5)	11 (4)	13 (5)[a]	17 (7)[a]	--	22 (9)	--
	Macitentan 10 mg (n = 242)	44 (18)	32 (13)	8 (3)	15 (6)	12 (5)[a]	22 (9)[a]	--	33 (14)	--
Simonneau, 2002[28]	**Placebo** (n = 236)	6 (3)	--	1 (0)	5 (2)	41 (18)	36 (16)	11 (5)	54 (23)	62 (27)

Table 173: Treatment-Related Adverse Events, n (%)										
Study	**Intervention**	**Peripheral Edema**	**Anemia**[b]	**Liver Toxicity**[c]	**Hypotension**	**Nausea**	**Diarrhea**	**Jaw Pain**	**Headache**	**Injection site reaction**
	Treprostinil s.c. (n = 233)	21 (9)	--	0 (0)	9 (4)	52 (22)	58 (25)	31 (13)	64 (27)	196 (83)
STRIDE-2, 2006[29]	**Placebo** (n = 62)	5 (8)	--	4 (6)	--	0 (0)	--	--	5 (8)	--
	Bosentan (n = 60)	9 (15)	--	7 (12)	--	4 (7)	--	--	6 (10)	--
SUPER, 2005[30]	**Placebo** (n = 70)	--	--	0 (0)	--	--	4 (6)	--	27 (39)	--
	Sildenafil (n = 69)	--	--	1 (1)	--	--	6 (9)	--	32 (46)	--
TRUST, 2010[31]	**Placebo** (n = 14)	--	--	--	--	4 (29)	1 (7)	0 (0)	4 (14)	--
	Treprostinil i.v. (n = 30)	--	--	--	--	9 (30)	10 (33)	8 (27)	15 (50)	--
Zhuang, 2014[36]	**Placebo** (n = 64)	--	--	--	--	2 (3)	6 (9)	--	13 (20)	--
	Tadalafil (n = 60)	--	--	--	--	3 (5)	4 (7)	--	36 (60)	--

ALT = alanine transaminase; AST = aspartate transaminase; i.v. = intravenous; s.c. = subcutaneous.
[a] Data from FDA Clinical Review.
[b] Decreases in hemoglobin ≥1 g/dL.
[c] ALT or AST > 3 x upper limit of normal.

Table 174: Summary of Results From Direct Pairwise Meta-Analysis (Total & Naive Populations)										
Outcome	**Amb 5 mg**	**Amb 10 mg**	**Bos 125 mg**	**Mac 10 mg**	**Rio 1.5 mg**	**Rio 2.5 mg**	**Sil 20 mg**	**Tad 40 mg**	**Epo i.v.**	**Tre s.c. or i.v.**
Efficacy										
Clinical worsening										
Total	--	--	↓	↓	↔	↓	--	↓	--	--
Naive	↓	↔	↔	↓	--	↔	↔	↔	--	--
FC improvement										
Total	--	--	--	↑	↔	↔	--	↔	--	--
Naive	↔	↔	↔	--	--	↔	↑	↑	↑	↔
FC worsening										
Total	--	--	↓	↓	↔	↓	--	↔	--	--
Naive	↓	↓	↔	--	--	↓	↔	↔	↔/↓	↔
FC unchanged										
Total	--	--	--	↔	↔	↔	--	↔	--	
Naive	↑	↔	↓	--	--	↔	↔	↔	↓	
6MWD										
Total	--	--	↑	↑	↑	↑	--	↑	--	--
Naive	↑	↑	↑	↔	↑	↑	↑	↑	↑	↑
Hospitalization										
Total	--	--	--	↓	↔	↔	--	↔	--	--
Naive	↔	↔	↔	--	--	--	↔	--	--	↔
BDI										
Total	--	--	--	↓	↔	↓	--	↔	--	--
Naive	↔	↓	↓	--	--	↔	↓	--	↓	↓
PVR										
Total	--	--	--	↓	↓	↓	--	↔	--	--
Naive	--	--	↓	--	--	↓	↓	--	↓	↓
PAP										
Total	--	--	↓	↔	↓	↓	--	↔	--	--
Naive	--	--	↓	--	--	↓	↓	--	↓	↔/↓
Cardiac index										
Total	--	--	↔/↑	↑	↑	↑	--	↔	--	--
Naive	--	--	↔/↑	--	--	↑	↔	--	↑	↑
Safety										
Death										
Total	--	--	↔	↔	↔	↔	--	↔	--	--
Naive	↔	↔	--	--	--	--	↔	--	↔	↔
SAEs										
Total	--	--	↔	↓	↔	↔	--	↔	--	--
Naive	↓	↓	--	--	--	--	↔	--	↔	↔/↑
Discontinuation due to AEs										
Total	--	--	↔	↔	↔	↔	--	↔	--	--
Naive	↔	↔	--	--	--	--	↔	--	--	↔/↑
Total withdrawal										
Total	--	--	↔	↔	↔	↔	--	↔	--	--
Naive	↓	↓	--	--	--	--	↔	--	↓	↔/↑
Liver toxicity	--	--	higher	↔	↔	↔	↔	↔	↔	↔
Peripheral edema	higher	higher	higher	↔	higher	higher	↔	↔	↔	higher
Anemia	higher	higher	↔	higher	--	higher	--	--	--	--
Hypotension	↔	↔	↔	↔	--	higher	--	--	higher	higher
Quality of life										
SF-36	↔/↑	↔	↔	↑			↑	↑		
EQ-5D					higher	higher	↑	↑		
LPHQ					↑	↑				
CHFQ / NHP / DFR									↑	
MLHFQ										↑

↑ significantly higher; ↓ significantly lower; ↔ no significant difference; -- not reported; 6MWD = six-minute walk distance; AEs = adverse events; Amb = ambrisentan; BDI = Borg Dyspnea Index; Bos = bosentan, CHFG = Chronic Heart Failure Questionnaire; DFR = Dyspnea-Fatigue Rating; Epo = epoprostenol; EQ-5D = EuroQol Group 5-Dimension Self-Report Questionnaire; FC = functional class; i.v. = intravenous; LPHQ = Living with Pulmonary Hypertension Questionnaire; Mac = macitentan; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NHP = Nottingham Health Profile; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; Rio = riociguat; SAEs = serious adverse events; s.c. = subcutaneous; SF-36 = Short-Form (36-Item) Health Survey; Sil = sildenafil; Tad = tadalafil; Tre = treprostinil.

Table 175: Summary of Results From Direct Pairwise Meta-Analysis (Add-On Therapy)					
Outcome	**Macitentan 10 mg**	**Riociguat 2.5 mg**			**Tadalafil 40 mg**
	Overall	**Overall**	**ERA**	**Prostanoids**	**ERA**
Clinical worsening	↓	↓	↔	↔	↓
FC improvement	--	↔	↔	↔	↔
FC worsening	--	↓	↔	↔	↔
FC unchanged	--	↔	↔	↔	↔
6MWD	↑	↑	↔	↑	↑
BDI	--	↓	↔	↔	--
PVR	--	↓	↓	↓	↔
PAP	--	--	↓	↓	↔
Cardiac index	--	--	↑	↑	↔

↑ significantly higher; ↓ significantly lower; ↔ no significant difference; -- not reported; 6MWD = six-minute walk distance; BDI = Borg Dyspnea Index; ERA = endothelin receptor antagonist; FC = functional class; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance.

APPENDIX 11: COMPARISONS OF PAIRWISE META-ANALYSES AND NETWORK META-ANALYSES

Table 176: Meta-analysis Results of Clinical Worsening, Total Populations of All Studies

Treatment vs. Placebo	Pairwise		NMA	
	RR (95% CI)) (Random)	RR (95% CI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)
Macitentan 10 mg	**0.68 (0.54 to 0.85)**	**0.68 (0.54 to 0.85)**	0.57 (0.17 to 1.65)	**0.57 (0.40 to 0.79)**
Riociguat max 1.5 mg	0.50 (0.11 to 2.29)	0.50 (0.11 to 2.29)	0.46 (0.05 to 2.20)	0.47 (0.06 to 1.66)
Riociguat max 2.5 mg	**0.19 (0.05 to 0.69)**	**0.19 (0.05 to 0.69)**	**0.19 (0.03 to 0.93)**	**0.19 (0.04 to 0.64)**
Bosentan 125 mg	**0.39 (0.16 to 0.92)**	**0.41 (0.24 to 0.70)**	**0.36 (0.14 to 0.74)**	**0.39 (0.22 to 0.67)**
Ambrisentan 5 mg	**0.32 (0.13 to 0.78)**	**0.31 (0.13 to 0.74)**	**0.29 (0.08 to 0.92)**	**0.29 (0.10 to 0.68)**
Ambrisentan 10 mg	0.50 (0.13 to 1.92)	0.50 (0.13 to 1.92)	0.40 (0.06 to 1.73)	0.41 (0.09 to 1.32)
Sildenafil 20 mg	0.43 (0.12 to 1.61)	0.43 (0.12 to 1.61)	0.42 (0.06 to 1.92)	0.42 (0.09 to 1.40)
Tadalafil 40 mg	**0.32 (0.11 to 0.94)**	**0.32 (0.11 to 0.94)**	0.30 (0.05 to 1.27)	**0.30 (0.08 to 0.83)**

CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; RR = relative risk.
Bold numbers indicate statistical significance.

Table 177: Meta-analysis Results of Clinical Worsening, Naive Populations of All Studies

Treatment vs. Placebo	Pairwise		NMA	
	RR (95% CI) (Random)	RR (95% CI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)
Macitentan 10 mg	**0.59 (0.40 to 0.86)**	**0.59 (0.40 to 0.86)**	0.46 (0.11 to 1.55)	**0.46 (0.26 to 0.79)**
Riociguat max 2.5 mg	0.27 (0.05 to 1.43)	0.27 (0.05 to 1.43)	0.26 (0.02 to 1.75)	0.27 (0.03 to 1.26)
Bosentan 125 mg	0.46 (0.16 to 1.32)	**0.50 (0.28 to 0.89)**	**0.42 (0.12 to 0.98)**	**0.47 (0.24 to 0.86)**
Ambrisentan 5 mg	**0.32 (0.13 to 0.78)**	**0.31 (0.13 to 0.74)**	**0.30 (0.08 to 0.96)**	**0.29 (0.10 to 0.68)**
Ambrisentan 10 mg	0.50 (0.13 to 1.92)	0.50 (0.13 to 1.92)	0.41 (0.06 to 1.82)	0.42 (0.09 to 1.32)
Sildenafil 20 mg	0.43 (0.12 to 1.61)	0.43 (0.12 to 1.61)	0.42 (0.06 to 1.99)	0.42 (0.09 to 1.39)
Tadalafil 40 mg	0.25 (0.06 to 1.10)	0.25 (0.06 to 1.10)	0.21 (0.02 to 1.24)	**0.21 (0.03 to 0.86)**

CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; RR = relative risk.
Bold numbers indicate statistical significance.

Table 178: Meta-analysis Results of Clinical Worsening, Total Populations of All Studies; No Macitentan				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
Riociguat max 1.5 mg	0.50 (0.11 to 2.29)	0.50 (0.11 to 2.29)	0.45 (0.05 to 2.25)	0.46 (0.06 to 1.69)
Riociguat max 2.5 mg	**0.19 (0.05 to 0.69)**	**0.19 (0.05 to 0.69)**	**0.18 (0.03 to 0.94)**	**0.18 (0.04 to 0.63)**
Bosentan 125 mg	**0.39 (0.16 to 0.92)**	**0.41 (0.24 to 0.70)**	**0.35 (0.13 to 0.73)**	**0.38 (0.21 to 0.66)**
Ambrisentan 5 mg	**0.32 (0.13 to 0.78)**	**0.31 (0.13 to 0.74)**	**0.29 (0.08 to 0.93)**	**0.28 (0.10 to 0.67)**
Ambrisentan 10 mg	0.50 (0.13 to 1.92)	0.50 (0.13 to 1.92)	0.40 (0.06 to 1.78)	0.41 (0.09 to 1.33)
Sildenafil 20 mg	0.43 (0.12 to 1.61)	0.43 (0.12 to 1.61)	0.41 (0.06 to 1.99)	0.42 (0.09 to 1.41)
Tadalafil 40 mg	**0.32 (0.11 to 0.94)**	**0.32 (0.11 to 0.94)**	0.29 (0.05 to 1.28)	**0.30 (0.08 to 0.83)**

CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; RR = relative risk.
Bold numbers indicate statistical significance.

Table 179: Meta-analysis Results of Clinical Worsening, Naive Populations of All Studies; No Macitentan				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
Riociguat max 2.5 mg	0.27 (0.05 to 1.43)	0.27 (0.05 to 1.43)	0.26 (0.02 to 1.76)	0.26 (0.03 to 1.27)
Bosentan 125 mg	0.46 (0.16 to 1.32)	**0.50 (0.28 to 0.89)**	**0.42 (0.12 to 0.98)**	**0.46 (0.23 to 0.86)**
Ambrisentan 5 mg	**0.32 (0.13 to 0.78)**	**0.31 (0.13 to 0.74)**	**0.29 (0.07 to 0.96)**	**0.29 (0.10 to 0.67)**
Ambrisentan 10 mg	0.50 (0.13 to 1.92)	0.50 (0.13 to 1.92)	0.40 (0.06 to 1.86)	0.41 (0.08 to 1.32)
Sildenafil 20 mg	0.43 (0.12 to 1.61)	0.43 (0.12 to 1.61)	0.41 (0.06 to 2.04)	0.42 (0.09 to 1.41)
Tadalafil 40 mg	0.25 (0.06 to 1.10)	0.25 (0.06 to 1.10)	0.20 (0.02 to 1.24)	**0.20 (0.03 to 0.85)**

CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; RR = relative risk.
Bold numbers indicate statistical significance.

Table 180: Results of Adjusted Analyses for Clinical Worsening, Total Populations of All Studies; No Macitentan			
Treatment vs. Placebo	**Base Case (NMA)**	**Covariate: Baseline FC**	**Covariate: Baseline PAH Etiology**
	RR (95% CrI) (Random)	**RR (95% CrI) (Random)**	**RR (95% CrI) (Random)**
Riociguat max 1.5 mg	0.45 (0.05 to 2.25)	0.45 (0.04 to 2.52)	0.43 (0.06 to 1.60)
Riociguat max 2.5 mg	**0.18 (0.03 to 0.94)**	0.18 (0.02 to 1.09)	**0.17 (0.04 to 0.59)**
Bosentan 125 mg	**0.35 (0.13 to 0.73)**	**0.34 (0.11 to 0.76)**	**0.42 (0.22 to 0.74)**
Ambrisentan 5 mg	**0.29 (0.08 to 0.93)**	0.29 (0.07 to 1.04)	**0.28 (0.10 to 0.66)**
Ambrisentan 10 mg	0.40 (0.06 to 1.78)	0.40 (0.05 to 2.03)	0.39 (0.08 to 1.27)
Sildenafil 20 mg	0.41 (0.06 to 1.99)	0.41 (0.05 to 2.25)	0.39 (0.08 to 1.33)
Tadalafil 40 mg	0.29 (0.05 to 1.28)	0.29 (0.04 to 1.54)	**0.28 (0.07 to 0.78)**

CrI = credible interval; FC = functional class; NMA = network meta-analysis; PAH = pulmonary arterial hypertension; RR = relative risk.
Bold numbers indicate statistical significance.

Table 181: Results of Adjusted Analyses for Clinical Worsening, Naive Populations of All Studies; No Macitentan			
Treatment vs. Placebo	**Base Case (NMA)**	**Covariate: Baseline FC**	**Covariate: Baseline PAH Etiology**
	RR (95% CrI) (Random)	**RR (95% CrI) (Random)**	**RR (95% CrI) (Random)**
Riociguat max 2.5 mg	0.26 (0.02 to 1.76)	0.17 (0.01 to 1.31)	0.23 (0.03 to 1.15)
Bosentan 125 mg	**0.42 (0.12 to 0.98)**	0.76 (0.18 to 2.39)	0.58 (0.28 to 1.11)
Ambrisentan 5 mg	**0.29 (0.07 to 0.96)**	**0.22 (0.05 to 0.79)**	**0.30 (0.11 to 0.71)**
Ambrisentan 10 mg	0.40 (0.06 to 1.86)	0.37 (0.05 to 1.72)	0.38 (0.08 to 1.25)
Sildenafil 20 mg	0.41 (0.06 to 2.04)	0.35 (0.04 to 1.79)	0.37 (0.08 to 1.28)
Tadalafil 40 mg	0.20 (0.02 to 1.24)	0.21 (0.02 to 1.32)	**0.18 (0.02 to 0.77)**

CrI = credible interval; FC = functional class; NMA = network meta-analysis; PAH = pulmonary arterial hypertension; RR = relative risk.
Bold numbers indicate statistical significance.

Table 182: Meta-analysis Results of FC Improvement, Total Populations of All Studies				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
Macitentan 10 mg	**1.66 (1.12 to 2.47)**	**1.66 (1.12 to 2.47)**	1.70 (0.68 to 3.72)	**1.70 (1.14 to 2.51)**
Riociguat max 1.5 mg	1.65 (0.89 to 3.06)	1.65 (0.89 to 3.06)	1.71 (0.58 to 4.11)	1.71 (0.87 to 3.11)
Riociguat max 2.5 mg	1.45 (0.89 to 2.37)	1.45 (0.89 to 2.37)	1.49 (0.57 to 3.49)	1.49 (0.91 to 2.45)
Epoprostenol	**10.18 (1.91 to 54.24)**	**11.39 (4.40 to 29.46)**	**9.31 (5.71 to 16.87)**	**8.96 (5.60 to 15.92)**
Treprostinil s.c. or i.v.	2.33 (0.80 to 6.77)	2.33 (0.80 to 6.77)	3.06 (0.77 to 8.28)	3.04 (0.98 to 7.55)
Bosentan 125 mg	1.81 (0.98 to 3.34)	**1.75 (1.16 to 2.67)**	**2.23 (1.17 to 4.61)**	**2.04 (1.26 to 3.28)**
Ambrisentan 5 mg	1.06 (0.66 to 1.69)	1.05 (0.66 to 1.67)	1.04 (0.45 to 2.20)	1.06 (0.61 to 1.78)
Ambrisentan 10 mg	1.25 (0.71 to 2.20)	1.25 (0.71 to 2.20)	1.21 (0.43 to 2.98)	1.21 (0.63 to 2.21)
Sildenafil 20 mg	**3.91 (1.55 to 9.88)**	**3.91 (1.55 to 9.88)**	**3.69 (1.33 to 7.90)**	**3.66 (1.76 to 6.97)**
Tadalafil 40 mg	1.10 (0.61 to 1.98)	1.10 (0.61 to 1.98)	1.12 (0.37 to 2.93)	1.11 (0.56 to 2.12)

CI = confidence interval; CrI = credible interval; FC = functional class; i.v. = intravenous; NMA = network meta-analysis; RR = relative risk; s.c. = subcutaneous.
Bold numbers indicate statistical significance.

Table 183: Meta-analysis Results of FC Improvement, Naive Populations of All Studies				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
Riociguat max 2.5 mg	0.97 (0.47 to 1.97)	0.97 (0.47 to 1.97)	0.98 (0.31 to 2.78)	0.98 (0.45 to 2.08)
Epoprostenol	**10.18 (1.91 to 54.24)**	**11.39 (4.40 to 29.46)**	**9.72 (5.77 to 18.54)**	**9.42 (5.65 to 17.48)**
Treprostinil s.c. or i.v.	2.33 (0.80 to 6.77)	2.33 (0.80 to 6.77)	3.11 (0.78 to 8.67)	3.08 (0.98 to 7.93)
Bosentan 125 mg	1.81 (0.98 to 3.34)	**1.75 (1.16 to 2.67)**	**2.24 (1.17 to 4.70)**	**2.06 (1.25 to 3.32)**
Ambrisentan 5 mg	1.06 (0.66 to 1.69)	1.05 (0.66 to 1.67)	1.05 (0.46 to 2.20)	1.06 (0.61 to 1.79)
Ambrisentan 10 mg	1.25 (0.71 to 2.20)	1.25 (0.71 to 2.20)	1.21 (0.43 to 2.99)	1.21 (0.62 to 2.23)
Sildenafil 20 mg	**3.91 (1.55 to 9.88)**	**3.91 (1.55 to 9.88)**	**3.76 (1.34 to 8.29)**	**3.71 (1.76 to 7.29)**
Tadalafil 40 mg	**2.33 (1.01 to 5.41)**	**2.33 (1.01 to 5.41)**	2.67 (0.83 to 6.74)	**2.67 (1.11 to 5.76)**

CI = confidence interval; CrI = credible interval; FC = functional class; i.v. = intravenous; NMA = network meta-analysis; RR = relative risk; s.c. = subcutaneous.
Bold numbers indicate statistical significance.

Table 184: Meta-analysis Results of FC Improvement, Total Populations of All Studies; No Macitentan

Treatment vs. Placebo	Pairwise		NMA	
	RR (95% CI) (Random)	RR (95% CI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)
Riociguat max 1.5 mg	1.65 (0.89 to 3.06)	1.65 (0.89 to 3.06)	1.72 (0.60 to 4.11)	1.71 (0.86 to 3.12)
Riociguat max 2.5 mg	1.45 (0.89 to 2.37)	1.45 (0.89 to 2.37)	1.50 (0.57 to 3.49)	1.49 (0.90 to 2.46)
Epoprostenol	**10.18 (1.91 to 54.24)**	**11.39 (4.40 to 29.46)**	**9.43 (5.64 to 17.84)**	**9.16 (5.56 to 17.30)**
Treprostinil s.c. or i.v.	2.33 (0.80 to 6.77)	2.33 (0.80 to 6.77)	3.11 (0.79 to 8.62)	3.05 (0.97 to 7.76)
Bosentan 125 mg	1.81 (0.98 to 3.34)	**1.75 (1.16 to 2.67)**	**2.24 (1.17 to 4.63)**	**2.05 (1.26 to 3.31)**
Ambrisentan 5 mg	1.06 (0.66 to 1.69)	1.05 (0.66 to 1.67)	1.05 (0.46 to 2.22)	1.06 (0.61 to 1.79)
Ambrisentan 10 mg	1.25 (0.71 to 2.20)	1.25 (0.71 to 2.20)	1.21 (0.43 to 2.99)	1.21 (0.63 to 2.23)
Sildenafil 20 mg	**3.91 (1.55 to 9.88)**	**3.91 (1.55 to 9.88)**	**3.74 (1.34 to 8.08)**	**3.68 (1.76 to 7.22)**
Tadalafil 40 mg	1.10 (0.61 to 1.98)	1.10 (0.61 to 1.98)	1.12 (0.37 to 2.93)	1.11 (0.56 to 2.12)

CI = confidence interval; CrI = credible interval; FC = functional class; i.v. = intravenous; NMA = network meta-analysis; RR = relative risk; s.c. = subcutaneous.
Bold numbers indicate statistical significance.

Table 185: Results of Adjusted Analyses for FC Improved, Total Populations of All Studies; No Macitentan

Treatment vs. Placebo	Base Case (NMA)		Covariate: Baseline FC		Covariate: Baseline PAH Etiology	
	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)
Riociguat max 1.5 mg	1.72 (0.60 to 4.11)	1.71 (0.86 to 3.12)	1.93 (0.06 to 8.70)	2.32 (0.43 to 7.07)	1.74 (0.57 to 4.37)	1.74 (0.88 to 3.21)
Riociguat max 2.5 mg	1.50 (0.57 to 3.49)	1.49 (0.90 to 2.46)	1.71 (0.05 to 8.21)	2.06 (0.40 to 6.48)	1.52 (0.55 to 3.70)	1.52 (0.91 to 2.52)
Epoprostenol	**9.43 (5.64 to 17.84)**	**9.16 (5.56 to 17.30)**	**9.02 (1.59 to 18.70)**	**8.59 (2.22 to 17.47)**	**10.31 (5.97 to 21.55)**	**10.00 (5.84 to 19.28)**
Treprostinil s.c. or i.v.	3.11 (0.79 to 8.62)	3.05 (0.97 to 7.76)	2.57 (0.03 to 13.35)	1.85 (0.06 to 9.80)	4.03 (0.86 to 11.32)	**4.01 (1.16 to 10.35)**
Bosentan 125 mg	**2.24 (1.17 to 4.63)**	**2.05 (1.26 to 3.31)**	1.83 (0.02 to 12.83)	1.13 (0.04 to 7.93)	**2.27 (1.14 to 4.89)**	**2.11 (1.27 to 3.49)**
Ambrisentan 5 mg	1.05 (0.46 to 2.22)	1.06 (0.61 to 1.79)	1.14 (0.09 to 4.77)	1.31 (0.41 to 3.55)	1.06 (0.45 to 2.30)	1.08 (0.62 to 1.83)
Ambrisentan 10 mg	1.21 (0.43 to 2.99)	1.21 (0.63 to 2.23)	1.29 (0.15 to 4.77)	1.43 (0.52 to 3.52)	1.22 (0.42 to 3.14)	1.23 (0.64 to 2.28)
Sildenafil 20 mg	**3.74 (1.34 to 8.08)**	**3.68 (1.76 to 7.22)**	3.99 (0.45 to 10.13)	**4.26 (1.45 to 8.98)**	**3.83 (1.32 to 8.90)**	**3.82 (1.80 to 7.61)**
Tadalafil 40 mg	1.12 (0.37 to 2.93)	1.11 (0.56 to 2.12)	1.15 (0.25 to 3.53)	1.21 (0.55 to 2.48)	1.13 (0.36 to 3.09)	1.13 (0.56 to 2.17)

CrI = credible interval; FC = functional class; i.v. = intravenous; NMA = network meta-analysis; PAH = pulmonary arterial hypertension; RR = relative risk; s.c. = subcutaneous.
Bold numbers indicate statistical significance.

Table 186: Results of Adjusted Analyses for FC Improved, Naive Populations of All Studies; No Macitentan						
Treatment vs. Placebo	**Base Case (NMA)**		**Covariate: Baseline FC**		**Covariate: Baseline PAH Etiology**	
	RR (95% CrI) (Random)	**RR (95% CrI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
Riociguat max 2.5 mg	0.98 (0.31 to 2.78)	0.98 (0.45 to 2.08)	1.33 (0.06 to 8.27)	1.40 (0.23 to 5.51)	0.98 (0.30 to 2.96)	0.99 (0.45 to 2.12)
Epoprostenol	**9.72 (5.77 to 18.54)**	**9.42 (5.65 to 17.48)**	9.02 (0.99 to 18.62)	**8.67 (2.20 to 17.22)**	**10.51 (6.06 to 20.3)**	**10.14 (5.95 to 19.60)**
Treprostinil s.c. or i.v.	3.11 (0.78 to 8.67)	3.08 (0.98 to 7.93)	1.94 (0.01 to 12.62)	1.77 (0.06 to 9.83)	4.04 (0.87 to 11.47)	**4.00 (1.16 to 10.47)**
Bosentan 125 mg	**2.24 (1.17 to 4.70)**	**2.06 (1.25 to 3.32)**	1.35 (0.01 to 11.90)	1.09 (0.04 to 7.94)	**2.27 (1.14 to 4.89)**	**2.10 (1.27 to 3.50)**
Ambrisentan 5 mg	1.05 (0.46 to 2.20)	1.06 (0.61 to 1.79)	1.28 (0.15 to 5.61)	1.32 (0.41 to 3.62)	1.07 (0.45 to 2.31)	1.08 (0.62 to 1.84)
Ambrisentan 10 mg	1.21 (0.43 to 2.99)	1.21 (0.62 to 2.23)	1.41 (0.22 to 5.43)	1.44 (0.52 to 3.59)	1.23 (0.41 to 3.17)	1.23 (0.63 to 2.28)
Sildenafil 20 mg	**3.76 (1.34 to 8.29)**	**3.71 (1.76 to 7.29)**	4.30 (0.67 to 10.78)	**4.31 (1.46 to 9.11)**	**3.86 (1.30 to 8.75)**	**3.81 (1.80 to 7.65)**
Tadalafil 40 mg	2.67 (0.83 to 6.74)	**2.67 (1.11 to 5.76)**	2.87 (0.68 to 7.68)	**2.85 (1.12 to 6.26)**	2.74 (0.81 to 7.11)	**2.72 (1.11 to 5.99)**

CrI = credible interval; FC = functional class; i.v. = intravenous; NMA = network meta-analysis; PAH = pulmonary arterial hypertension; RR = relative risk; s.c. = subcutaneous.
Bold numbers indicate statistical significance.

Table 187: Meta-analysis Results of FC Worsening, Total Populations of All Studies*				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
Macitentan 10 mg	**0.33 (0.20 to 0.55)**	**0.33 (0.20 to 0.55)**	0.30 (0.08 to 1.09)	**0.30 (0.17 to 0.52)**
Riociguat max 1.5 mg	0.55 (0.21 to 1.42)	0.55 (0.21 to 1.42)	0.52 (0.10 to 2.01)	0.52 (0.17 to 1.27)
Riociguat max 2.5 mg	**0.25 (0.11 to 0.53)**	**0.25 (0.11 to 0.53)**	**0.24 (0.05 to 0.95)**	**0.24 (0.10 to 0.52)**
Epoprostenol	0.50 (0.05 to 5.34)	0.43 (0.18 to 1.01)	0.43 (0.12 to 1.41)	**0.40 (0.15 to 0.94)**
Bosentan 125 mg	**0.41 (0.21 to 0.80)**	**0.38 (0.20 to 0.74)**	**0.35 (0.13 to 0.82)**	**0.37 (0.17 to 0.71)**
Ambrisentan 5 mg	**0.14 (0.04 to 0.45)**	**0.13 (0.04 to 0.43)**	**0.11 (0.02 to 0.43)**	**0.11 (0.02 to 0.34)**
Ambrisentan 10 mg	**0.27 (0.08 to 0.93)**	**0.27 (0.08 to 0.93)**	0.26 (0.04 to 1.27)	**0.25 (0.05 to 0.81)**
Sildenafil 20 mg	0.29 (0.06 to 1.37)	0.29 (0.06 to 1.37)	0.26 (0.03 to 1.58)	0.27 (0.04 to 1.09)
Tadalafil 40 mg	0.64 (0.28 to 1.46)	0.64 (0.28 to 1.46)	0.62 (0.14 to 2.28)	0.62 (0.24 to 1.42)

CI = confidence interval; CrI = credible interval; FC = functional class; NMA = network meta-analysis; PAH = pulmonary arterial hypertension; RR = relative risk.
* Except treprostinil.
Bold numbers indicate statistical significance.

Table 188: Meta-analysis Results of FC Worsening, Naive Populations of All Studies*				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
Riociguat max 2.5 mg	**0.24 (0.09 to 0.67)**	**0.24 (0.09 to 0.67)**	**0.22 (0.04 to 1.11)**	**0.23 (0.07 to 0.63)**
Epoprostenol	0.50 (0.05 to 5.34)	0.43 (0.18 to 1.01)	0.43 (0.11 to 1.48)	**0.40 (0.15 to 0.93)**
Bosentan 125 mg	0.51 (0.22 to 1.14)	0.48 (0.22 to 1.06)	0.42 (0.12 to 1.17)	0.46 (0.18 to 1.04)
Ambrisentan 5 mg	**0.14 (0.04 to 0.45)**	**0.13 (0.04 to 0.43)**	**0.11 (0.02 to 0.44)**	**0.11 (0.03 to 0.34)**
Ambrisentan 10 mg	**0.27 (0.08 to 0.93)**	**0.27 (0.08 to 0.93)**	0.25 (0.04 to 1.35)	**0.25 (0.05 to 0.81)**
Sildenafil 20 mg	0.29 (0.06 to 1.37)	0.29 (0.06 to 1.37)	0.26 (0.02 to 1.64)	0.27 (0.04 to 1.10)
Tadalafil 40 mg	0.50 (0.16 to 1.52)	0.50 (0.16 to 1.52)	0.45 (0.07 to 2.23)	0.45 (0.11 to 1.44)

CI = confidence interval; CrI = credible interval; FC = functional class; NMA = network meta-analysis; RR = relative risk.
* Except treprostinil.
Bold numbers indicate statistical significance.

Table 189: Meta-analysis Results of FC Worsening, Total Populations of All Studies*; No Macitentan				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
Riociguat max 1.5 mg	0.55 (0.21 to 1.42)	0.55 (0.21 to 1.42)	0.52 (0.10 to 2.07)	0.52 (0.17 to 1.28)
Riociguat max 2.5 mg	**0.25 (0.11 to 0.53)**	**0.25 (0.11 to 0.53)**	**0.23 (0.05 to 0.96)**	**0.24 (0.10 to 0.51)**
Epoprostenol	0.50 (0.05 to 5.34)	0.43 (0.18 to 1.01)	0.43 (0.12 to 1.42)	**0.40 (0.15 to 0.94)**
Bosentan 125 mg	**0.41 (0.21 to 0.80)**	**0.38 (0.20 to 0.74)**	**0.35 (0.13 to 0.82)**	**0.36 (0.17 to 0.71)**
Ambrisentan 5 mg	**0.14 (0.04 to 0.45)**	**0.13 (0.04 to 0.43)**	**0.11 (0.02 to 0.42)**	**0.11 (0.02 to 0.34)**
Ambrisentan 10 mg	**0.27 (0.08 to 0.93)**	**0.27 (0.08 to 0.93)**	0.25 (0.04 to 1.26)	**0.25 (0.05 to 0.81)**
Sildenafil 20 mg	0.29 (0.06 to 1.37)	0.29 (0.06 to 1.37)	0.26 (0.02 to 1.57)	0.26 (0.03 to 1.09)
Tadalafil 40 mg	0.64 (0.28 to 1.46)	0.64 (0.28 to 1.46)	0.62 (0.14 to 2.31)	0.62 (0.24 to 1.42)

CI = confidence interval; CrI = credible interval; FC = functional class; NMA = network meta-analysis; RR = relative risk.
* Except treprostinil.
Bold numbers indicate statistical significance.

Table 190: Results of Adjusted Analyses for FC Worsening, Total Populations of All Studies; No Macitentan

Treatment vs. Placebo	Base Case (NMA)		Covariate: Baseline FC		Covariate: Baseline PAH Etiology	
	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)
Riociguat max 1.5 mg	0.52 (0.10 to 2.07)	0.52 (0.17 to 1.28)	0.53 (0.09 to 2.27)	0.55 (0.17 to 1.35)	0.50 (0.12 to 1.68)	0.50 (0.16 to 1.22)
Riociguat max 2.5 mg	**0.23 (0.05 to 0.96)**	**0.24 (0.10 to 0.51)**	0.24 (0.05 to 1.08)	**0.25 (0.10 to 0.55)**	**0.22 (0.06 to 0.73)**	**0.22 (0.09 to 0.49)**
Epoprostenol	0.43 (0.12 to 1.42)	**0.40 (0.15 to 0.94)**	0.37 (0.08 to 1.71)	**0.33 (0.10 to 0.93)**	0.56 (0.16 to 1.71)	0.56 (0.19 to 1.49)
Bosentan 125 mg	**0.35 (0.13 to 0.82)**	**0.36 (0.17 to 0.71)**	**0.35 (0.12 to 0.87)**	**0.38 (0.17 to 0.77)**	**0.36 (0.14 to 0.79)**	**0.36 (0.17 to 0.71)**
Ambrisentan 5 mg	**0.11 (0.02 to 0.42)**	**0.11 (0.02 to 0.37)**	**0.11 (0.02 to 0.45)**	**0.11 (0.03 to 0.35)**	**0.10 (0.02 to 0.37)**	**0.10 (0.02 to 0.32)**
Ambrisentan 10 mg	0.25 (0.04 to 1.26)	**0.25 (0.05 to 0.81)**	0.26 (0.03 to 1.38)	**0.25 (0.05 to 0.81)**	0.24 (0.04 to 1.04)	**0.24 (0.05 to 0.77)**
Sildenafil 20 mg	0.26 (0.02 to 1.57)	0.26 (0.03 to 1.09)	0.26 (0.02 to 1.70)	0.27 (0.04 to 1.11)	0.25 (0.03 to 1.32)	0.25 (0.03 to 1.04)
Tadalafil 40 mg	0.62 (0.14 to 2.31)	0.62 (0.24 to 1.42)	0.61 (0.12 to 2.49)	0.61 (0.23 to 1.40)	0.59 (0.16 to 1.86)	0.59 (0.23 to 1.36)

CrI = credible interval; FC = functional class; NMA = network meta-analysis; PAH = pulmonary arterial hypertension; RR = relative risk.
Bold numbers indicate statistical significance.

Table 191: Results of Adjusted Analyses for FC Worsening, Naive Populations of All Studies; No Macitentan

Treatment vs. Placebo	Base Case (NMA)		Covariate: Baseline FC		Covariate: Baseline PAH Etiology	
	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)	RR (95% CrI) (Random)	RR (95% CrI) (Fixed)
Riociguat max 2.5 mg	**0.22 (0.04 to 1.11)**	**0.23 (0.07 to 0.63)**	0.17 (0.02 to 1.20)	**0.18 (0.05 to 0.62)**	**0.21 (0.05 to 0.87)**	**0.21 (0.06 to 0.60)**
Epoprostenol	0.43 (0.11 to 1.48)	**0.40 (0.15 to 0.93)**	0.69 (0.07 to 4.44)	0.60 (0.12 to 2.42)	0.56 (0.15 to 1.75)	0.56 (0.19 to 1.49)
Bosentan 125 mg	0.42 (0.12 to 1.17)	0.46 (0.18 to 1.04)	0.51 (0.10 to 1.99)	0.52 (0.18 to 1.30)	0.44 (0.14 to 1.13)	0.46 (0.18 to 1.06)
Ambrisentan 5 mg	**0.11 (0.02 to 0.44)**	**0.11 (0.03 to 0.34)**	**0.09 (0.01 to 0.44)**	**0.10 (0.02 to 0.32)**	**0.10 (0.02 to 0.37)**	**0.10 (0.02 to 0.31)**
Ambrisentan 10 mg	0.25 (0.04 to 1.35)	**0.25 (0.05 to 0.81)**	0.23 (0.03 to 1.44)	**0.23 (0.05 to 0.78)**	0.24 (0.04 to 1.08)	**0.24 (0.05 to 0.77)**
Sildenafil 20 mg	0.26 (0.02 to 1.64)	0.27 (0.04 to 1.10)	0.22 (0.02 to 1.69)	0.23 (0.03 to 1.02)	0.25 (0.03 to 1.36)	0.25 (0.03 to 1.04)
Tadalafil 40 mg	0.45 (0.07 to 2.23)	0.45 (0.11 to 1.44)	0.43 (0.05 to 2.42)	0.44 (0.11 to 1.39)	0.43 (0.08 to 1.84)	0.43 (0.10 to 1.36)

CrI = credible interval; FC = functional class; NMA = network meta-analysis; PAH = pulmonary arterial hypertension; RR = relative risk.
Bold numbers indicate statistical significance.

Table 192: Meta-analysis Results of 6MWD, Total Populations of All Studies*				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	WMD (95% CI) (Random)	**WMD (95% CI) (Fixed)**	**WMD (95% CrI) (Random)**	**WMD (95% CrI) (Fixed)**
Macitentan 10 mg	**21.90 (5.58 to 38.22)**	**21.90 (5.58 to 38.22)**	**21.79 (5.04 to 39.33)**	**21.64 (5.54 to 37.93)**
Riociguat max 1.5 mg	**37.00 (12.38 to 61.62)**	**37.00 (12.38 to 61.62)**	**36.14 (10.26 to 60.96)**	**36.16 (11.74 to 60.52)**
Riociguat max 2.5 mg	**36.00 (18.93 to 53.07)**	**36.00 (18.93 to 53.07)**	**35.17 (17.40 to 53.15)**	**35.50 (18.61 to 52.43)**
Epoprostenol	**71.30 (33.35 to 109.25)**	**73.78 (41.50 to 106.06)**	**71.50 (39.88 to 102.60)**	**71.87 (40.18 to 103.70)**
Treprostinil	**34.52 (0.24 to 68.80)**	**23.35 (8.73 to 37.98)**	**23.61 (7.58 to 38.99)**	**23.34 (8.82 to 37.85)**
Bosentan 125 mg	**30.70 (16.64 to 44.77)**	**30.70 (16.64 to 44.77)**	**30.51 (16.87 to 44.36)**	**30.43 (16.38 to 44.36)**
Ambrisentan 5 mg	**44.53 (16.23 to 72.84)**	**44.03 (23.96 to 64.09)**	**44.96 (24.51 to 63.70)**	**45.16 (25.99 to 64.37)**
Ambrisentan 10 mg	**54.10 (29.48 to 78.72)**	**54.10 (29.48 to 78.72)**	**53.07 (31.30 to 74.58)**	**53.48 (32.29 to 74.86)**
Sildenafil 20 mg	**43.70 (25.81 to 61.59)**	**45.10 (27.21 to 62.99)**	**43.08 (24.38 to 62.39)**	**43.41 (25.50 to 61.22)**
Tadalafil 40 mg	**31.90 (14.63 to 49.17)**	**31.90 (14.63 to 49.17)**	**31.40 (13.61 to 49.26)**	**31.69 (14.48 to 49.05)**

6MWD = six-minute walk distance; CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; WMD = weighted mean difference.
* Excluding Rubenfire 2007.
Bold numbers indicate statistical significance.

Table 193: Meta-analysis Results of 6MWD, Naive Populations of All Studies*				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	WMD (95% CI) (Random)	**WMD (95% CI) (Fixed)**	**WMD (95% CrI) (Random)**	**WMD (95% CrI) (Fixed)**
Macitentan 10 mg	15.30 (–15.10 to 45.70)	15.30 (–15.10 to 45.70)	15.19 (–15.17 to 46.20)	14.70 (–15.23 to 44.47)
Riociguat max 1.5 mg	**55.40 (20.76 to 90.04)**	**55.40 (20.76 to 90.04)**	**53.38 (18.49 to 86.88)**	**53.29 (19.19 to 87.30)**
Riociguat max 2.5 mg	**38.00 (13.07 to 62.94)**	**38.00 (13.07 to 62.94)**	**36.94 (12.01 to 62.67)**	**36.66 (12.14 to 61.19)**
Epoprostenol	**71.30 (33.35 to 109.25)**	**73.78 (41.50 to 106.06)**	**71.65 (40.98 to 103.10)**	**71.95 (40.39 to 103.70)**
Treprostinil	**34.52 (0.24 to 68.80)**	**23.35 (8.73 to 37.98)**	**23.66 (8.03 to 38.86)**	**23.25 (8.69 to 37.82)**
Bosentan 125 mg	**38.17 (20.14 to 56.21)**	**38.17 (20.14 to 56.21)**	**37.73 (19.41 to 56.03)**	**37.65 (19.86 to 55.48)**
Ambrisentan 5 mg	**44.53 (16.23 to 72.84)**	**44.03 (23.96 to 64.09)**	**44.97 (25.43 to 65.08)**	**45.15 (26.00 to 64.26)**
Ambrisentan 10 mg	**54.10 (29.48 to 78.72)**	**54.10 (29.48 to 78.72)**	**53.18 (31.48 to 75.26)**	**53.58 (32.12 to 74.81)**
Sildenafil 20 mg	**43.70 (25.81 to 61.59)**	**43.70 (25.81 to 61.59)**	**43.39 (24.57 to 61.67)**	**43.37 (25.46 to 61.12)**
Tadalafil 40 mg	**44.40 (18.93 to 69.87)**	**44.40 (18.93 to 69.87)**	**43.67 (18.06 to 69.39)**	**43.56 (18.37 to 68.77)**

6MWD = six-minute walk distance; CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; WMD = weighted mean difference.
* Excluding Rubenfire 2007.
Bold numbers indicate statistical significance.

Table 194: Meta-analysis Results of Clinical Worsening, Add-on to ERA Pre-treated Populations				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
ERA + Riociguat max 2.5 mg	0.16 (0.02 to 1.50)	0.16 (0.02 to 1.50)	0.13 (0.004 to 1.35)	0.13 (0.004 to 1.10)
ERA + Tadalafil 40 mg	0.39 (0.17 to 0.89)	0.39 (0.17 to 0.89)	0.36 (0.11 to 1.05)	0.36 (0.14 to 0.82)

CI = confidence interval; CrI = credible interval; ERA = endothelin receptor antagonist; NMA = network meta-analysis; RR = relative risk.

Table 195: Meta-analysis Results of FC Improvement, Add-on to ERA Pre-treated Populations				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
ERA + Riociguat max 2.5 mg	1.94 (0.91 to 4.15)	1.94 (0.91 to 4.15)	1.83 (0.47 to 4.10)	1.84 (0.99 to 3.40)
ERA + Tadalafil 40 mg	0.80 (0.23 to 2.82)	1.03 (0.68 to 1.57)	0.93 (0.27 to 2.10)	1.04 (0.63 to 1.67)

CI = confidence interval; CrI = credible interval; ERA = endothelin receptor antagonist; FC = functional class; NMA = network meta-analysis; RR = relative risk.

Table 196: Meta-analysis Results of FC Worsening, Add-on to ERA Pre-treated Populations				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	RR (95% CI) (Random)	**RR (95% CI) (Fixed)**	**RR (95% CrI) (Random)**	**RR (95% CrI) (Fixed)**
ERA + Riociguat max 2.5 mg	0.39 (0.12 to 1.22)	0.39 (0.12 to 1.22)	0.39 (0.08 to 1.68)	0.39 (0.11 to 1.24)
ERA + Tadalafil 40 mg	0.57 (0.26 to 1.24)	0.57 (0.26 to 1.21)	0.56 (0.19 to 1.52)	0.55 (0.24 to 1.17)

CI = confidence interval; CrI = credible interval; ERA = endothelin receptor antagonist; FC = functional class; NMA = network meta-analysis; RR = relative risk.

Table 197: Meta-analysis Results of 6MWD, Add-on to ERA Pre-treated Populations				
Treatment vs. Placebo	**Pairwise**		**NMA**	
	WMD (95% CI) (Random)	**WMD (95% CI) (Fixed)**	**WMD (95% CrI) (Random)**	**WMD (95% CrI) (Fixed)**
ERA + Riociguat max 2.5 mg	23.40 (–0.65 to 47.45)	23.40 (–0.65 to 47.45)	22.86 (–2.17 to 47.24)	22.94 (–0.58 to 46.63)
ERA + Tadalafil 40 mg	**34.66 (26.52 to 42.80)**	**35.78 (32.16 to 39.40)**	22.68 (–1.20 to 46.07)	22.49 (–0.66 to 45.97)

6MWD = six-minute walk distance; CI = confidence interval; CrI = credible interval; ERA = endothelin receptor antagonist; NMA = network meta-analysis; WMD = weighted mean difference.
Bold numbers indicate statistical significance.

APPENDIX 12: COMPLETE RESULTS OF NETWORK META-ANALYSIS

Table 198: Meta-analysis Results of Clinical Worsening, Total Populations of All Studies (Random)

	Placebo	Macitentan 10 mg	Riociguat max 1.5 mg	Riociguat max 2.5 mg	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	1.76 (0.61, 5.80)	2.18 (0.45, 21.41)	**5.37 (1.07, 37.36)**	**2.78 (1.35, 7.38)**	**3.41 (1.09, 12.48)**	2.47 (0.58, 16.14)	2.37 (0.52, 16.75)	3.38 (0.79, 19.23)
Macitentan 10 mg	0.57 (0.17, 1.65)	1	1.25 (0.18, 14.91)	3.06 (0.42, 27.06)	1.57 (0.43, 6.95)	1.94 (0.38, 9.96)	1.41 (0.22, 11.73)	1.35 (0.20, 12.07)	1.92 (0.30, 14.28)
Riociguat max 1.5 mg	0.46 (0.05, 2.20)	0.80 (0.07, 5.60)	1	2.42 (0.23, 19.73)	1.28 (0.12, 8.33)	1.55 (0.12, 11.71)	1.12 (0.08, 13.26)	1.07 (0.07, 13.35)	1.54 (0.11, 16.14)
Riociguat max 2.5 mg	**0.19 (0.03, 0.93)**	0.33 (0.04, 2.39)	0.41 (0.05, 4.29)	1	0.52 (0.07, 3.58)	0.64 (0.07, 4.96)	0.46 (0.04, 5.46)	0.44 (0.04, 5.53)	0.63 (0.06, 6.77)
Bosentan 125 mg	**0.36 (0.14, 0.74)**	0.64 (0.14, 2.32)	0.78 (0.12, 8.19)	1.93 (0.28, 14.61)	1	1.22 (0.26, 5.22)	0.89 (0.15, 6.35)	0.85 (0.13, 6.57)	1.21 (0.20, 7.63)
Ambrisentan 5 mg	**0.29 (0.08, 0.92)**	0.52 (0.10, 2.65)	0.65 (0.09, 8.13)	1.57 (0.20, 14.78)	0.82 (0.19, 3.85)	1	0.73 (0.13, 5.12)	0.70 (0.09, 6.71)	0.99 (0.14, 7.86)
Ambrisentan 10 mg	0.40 (0.06, 1.73)	0.71 (0.09, 4.52)	0.89 (0.08, 12.90)	2.15 (0.18, 24.30)	1.13 (0.16, 6.65)	1.38 (0.20, 7.55)	1	0.96 (0.09, 10.94)	1.36 (0.13, 13.04)
Sildenafil 20 mg	0.42 (0.06, 1.92)	0.74 (0.08, 4.96)	0.93 (0.07, 13.73)	2.25 (0.18, 26.70)	1.18 (0.15, 7.41)	1.43 (0.15, 10.57)	1.05 (0.09, 11.58)	1	1.42 (0.13, 14.33)
Tadalafil 40 mg	0.30 (0.05, 1.27)	0.52 (0.07, 3.31)	0.65 (0.06, 9.35)	1.59 (0.15, 17.68)	0.83 (0.13, 4.96)	1.01 (0.13, 7.00)	0.73 (0.08, 7.84)	0.70 (0.07, 7.92)	1

Table 199: Meta-analysis Results of Clinical Worsening, Total Populations of All Studies (Fixed)

	Placebo	Macitentan 10 mg	Riociguat max 1.5 mg	Riociguat max 2.5 mg	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	**1.76 (1.26, 2.47)**	2.15 (0.60, 15.44)	**5.32 (1.57, 25.56)**	**2.57 (1.50, 4.65)**	**3.46 (1.48, 9.62)**	2.41 (0.76, 11.40)	2.36 (0.71, 11.37)	**3.34 (1.20, 12.32)**
Macitentan 10 mg	**0.57 (0.40, 0.79)**	1	1.23 (0.33, 9.00)	3.03 (0.84, 15.01)	1.47 (0.77, 2.89)	1.97 (0.79, 5.78)	1.38 [0.41, 6.70	1.35 (0.39, 6.70)	1.90 (0.64, 7.30)
Riociguat max 1.5 mg	0.47 (0.06, 1.66)	0.82 (0.11, 3.07)	1	2.46 (0.31, 14.88)	1.19 (0.16, 4.94)	1.60 (0.19, 8.32)	1.11 (0.12, 8.50)	1.09 (0.11, 8.38)	1.54 (0.17, 9.70)
Riociguat max 2.5 mg	**0.19 (0.04, 0.64)**	0.33 (0.07, 1.19)	0.41 (0.07, 0.41)	1	0.48 (0.09, 1.89)	0.65 (0.11, 3.22)	0.45 (0.06, 3.26)	0.44 (0.06, 3.26)	0.63 (0.10, 3.76)
Bosentan 125 mg	**0.39 (0.22, 0.67)**	0.68 (0.35, 1.30)	0.84 (0.20, 6.42)	2.07 (0.53, 10.85)	1	1.35 (0.47, 4.28)	0.94 (0.25, 4.82)	0.92 (0.24, 4.87)	1.30 (0.39, 5.31)
Ambrisentan 5 mg	**0.29 (0.10, 0.68)**	0.51 (0.17, 1.27)	0.63 (0.12, 5.27)	1.54 (0.31, 9.15)	0.74 (0.23, 2.12)	1	0.70 (0.17, 3.64)	0.68 (0.14, 4.07)	0.97 (0.23, 4.57)
Ambrisentan 10 mg	0.41 (0.09, 1.32)	0.73 (0.15, 2.44)	0.90 (0.12, 8.65)	2.20 (0.31, 15.39)	1.06 (0.21, 3.94)	1.43 (0.27, 5.96)	1	0.98 (0.14, 6.86)	1.38 (0.22, 7.94)
Sildenafil 20 mg	0.42 (0.09, 1.40)	0.74 (0.15, 2.60)	0.92 (0.12, 9.02)	2.25 (0.31, 16.18)	1.09 (0.21, 4.17)	1.46 (0.25, 7.08)	1.02 (0.15, 7.26)	1	1.42 (0.22, 8.33)
Tadalafil 40 mg	**0.30 (0.08, 0.83)**	0.53 (0.14, 1.56)	0.65 (0.10, 5.83)	1.59 (0.27, 10.34)	0.77 (0.19, 2.54)	1.04 (0.22, 4.44)	0.72 (0.13, 4.65)	0.71 (0.12, 4.63)	1

Table 200: Meta-analysis Results of Clinical Worsening, Naive Populations of All Studies (Random)

	Placebo	Macitentan 10 mg	Riociguat max 2.5 mg	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	2.18 (0.65, 8.76)	3.80 (0.57, 42.83)	**2.37 (1.02, 8.12)**	**3.37 (1.04, 12.93)**	2.45 (0.55, 17.52)	2.38 (0.50, 17.40)	4.84 (0.81, 51.52)
Macitentan 10 mg	0.46 (0.11, 1.55)	1	1.74 (0.17, 24.87)	1.08 (0.24, 6.43)	1.55 (0.25, 9.17)	1.13 (0.15, 11.05)	1.09 (0.14, 10.90)	2.22 (0.23, 30.53)
Riociguat max 2.5 mg	0.26 (0.02, 1.75)	0.57 (0.04, 5.84)	1	0.63 (0.05, 6.20)	0.89 (0.06, 8.89)	0.65 (0.04, 9.84)	0.63 (0.04, 9.65)	1.29 (0.06, 25.91)
Bosentan 125 mg	**0.42 (0.12, 0.98)**	0.93 (0.16, 4.21)	1.60 (0.16, 19.66)	1	1.42 (0.24, 6.67)	1.04 (0.15, 8.33)	1.00 (0.13, 8.18)	2.03 (0.22, 24.00)
Ambrisentan 5 mg	**0.30 (0.08, 0.96)**	0.64 (0.11, 4.01)	1.12 (0.11, 16.39)	0.70 (0.15, 4.08)	1	0.73 (0.13, 5.49)	0.70 (0.09, 7.15)	1.43 (0.15, 19.81)
Ambrisentan 10 mg	0.41 (0.06, 1.82)	0.89 (0.09, 6.66)	1.53 (0.10, 26.53)	0.97 (0.12, 6.90)	1.37 (0.18, 7.91)	1	0.97 (0.08, 11.61)	1.96 (0.14, 32.06)
Sildenafil 20 mg	0.42 (0.06, 1.99)	0.91 (0.09, 7.25)	1.59 (0.10, 27.85)	1.00 (0.12, 7.47)	1.42 (0.14, 10.88)	1.03 (0.09, 12.56)	1	2.02 (0.14, 33.92)
Tadalafil 40 mg	0.21 (0.02, 1.24)	0.45 (0.03, 4.27)	0.78 (0.04, 15.93)	0.49 (0.04, 4.51)	0.70 (0.05, 6.59)	0.51 (0.03, 7.22)	0.49 (0.03, 7.05)	1

Table 201: Meta-analysis Results of Clinical Worsening, Naive Populations of All Studies (Fixed)

	Placebo	Macitentan 10 mg	Riociguat max 2.5 mg	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	**2.18 (1.27, 3.90)**	3.76 (0.79, 30.04)	**2.14 (1.16, 4.20)**	**3.43 (1.48, 9.58)**	2.40 (0.76, 11.32)	2.36 (0.72, 11.33)	**4.85 (1.17, 37.36)**
Macitentan 10 mg	**0.46 (0.26, 0.79)**	1	1.73 (0.32, 14.77)	0.98 (0.42, 2.35)	1.58 (0.56, 5.00)	1.11 (0.30, 5.66)	1.09 (0.29, 5.69)	2.24 (0.47, 18.30)
Riociguat max 2.5 mg	0.27 (0.03, 1.26)	0.58 (0.07, 3.09)	1	0.57 (0.07, 3.16)	0.92 (0.10, 5.95)	0.64 (0.06, 5.73)	0.63 (0.06, 5.75)	1.30 (0.10, 16.63)
Bosentan 125 mg	**0.47 (0.24, 0.86)**	1.02 (0.43, 2.39)	1.76 (0.32, 15.32)	1	1.61 (0.54, 5.31)	1.13 (0.29, 5.94)	1.11 (0.28, 5.95)	2.27 (0.46, 19.05)
Ambrisentan 5 mg	**0.29 (0.10, 0.68)**	0.63 (0.20, 1.78)	1.09 (0.17, 10.15)	0.62 (0.19, 1.86)	1	0.70 (0.17, 3.61)	0.69 (0.14, 4.06)	1.41 (0.24, 12.72)
Ambrisentan 10 mg	0.42 (0.09, 1.32)	0.90 (0.18, 3.32)	1.56 (0.17, 16.56)	0.89 (0.17, 3.41)	1.43 (0.28, 5.94)	1	0.98 (0.14, 6.84)	2.02 (0.25, 20.77)
Sildenafil 20 mg	0.42 (0.09, 1.39)	0.92 (0.18, 3.49)	1.59 (0.17, 17.27)	0.90 (0.17, 3.58)	1.46 (0.25, 7.04)	1.02 (0.15, 7.13)	1	2.06 (0.24, 21.57)
Tadalafil 40 mg	**0.21 (0.03, 0.86)**	0.45 (0.05, 2.11)	0.77 (0.06, 9.60)	0.44 (0.05, 2.17)	0.71 (0.08, 4.16)	0.50 (0.05, 4.06)	0.49 (0.05, 4.11)	1

Table 202: Meta-analysis Results of Clinical Worsening, Total Populations of All Studies; No Macitentan (Random)

	Placebo	Riociguat max 1.5 mg	Riociguat max 2.5 mg	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	2.20 (0.45, 21.73)	**5.49 (1.06, 37.47)**	**2.83 (1.36, 7.67)**	**3.48 (1.08, 12.85)**	2.52 (0.56, 17.46)	2.42 (0.50, 17.13)	3.42 (0.78, 19.64)
Riociguat max 1.5 mg	0.45 (0.05, 2.25)	1	2.43 (0.23, 19.63)	1.29 (0.12, 8.64)	1.56 (0.12, 12.46)	1.13 (0.07, 14.18)	1.08 (0.07, 13.55)	1.53 (0.10, 16.67)
Riociguat max 2.5 mg	**0.18 (0.03, 0.94)**	0.41 (0.05, 4.37)	1	0.52 (0.07, 3.65)	0.64 (0.07, 5.18)	0.46 (0.04, 5.69)	0.44 (0.04, 5.60)	0.63 (0.05, 6.87)
Bosentan 125 mg	**0.35 (0.13, 0.73)**	0.78 (0.12, 8.21)	1.92 (0.27, 14.31)	1	1.23 (0.26, 5.34)	0.88 (0.14, 6.76)	0.85 (0.13, 6.63)	1.21 (0.19, 7.69)
Ambrisentan 5 mg	**0.29 (0.08, 0.93)**	0.64 (0.08, 8.17)	1.57 (0.19, 14.83)	0.82 (0.19, 3.92)	1	0.72 (0.13, 5.39)	0.69 (0.09, 6.82)	0.98 (0.14, 8.08)
Ambrisentan 10 mg	0.40 (0.06, 1.78)	0.89 (0.07, 13.39)	2.15 (0.18, 25.07)	1.13 (0.15, 7.02)	1.38 (0.19, 7.71)	1	0.96 (0.08, 11.25)	1.35 (0.12, 13.24)
Sildenafil 20 mg	0.41 (0.06, 1.99)	0.93 (0.07, 14.22)	2.25 (0.18, 27.00)	1.18 (0.15, 7.72)	1.44 (0.15, 11.07)	1.04 (0.09, 12.48)	1	1.42 (0.12, 14.66)
Tadalafil 40 mg	0.29 (0.05, 1.28)	0.65 (0.06, 9.70)	1.59 (0.15, 18.21)	0.83 (0.13, 5.17)	1.02 (0.12, 7.33)	0.74 (0.08, 8.19)	0.71 (0.07, 8.18)	1

Table 203: Meta-analysis Results of Clinical Worsening, Total Populations of All Studies; No Macitentan (Fixed)

	Placebo	Riociguat max 1.5 mg	Riociguat max 2.5 mg	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	2.18 (0.59, 15.66)	**5.43 (1.58, 26.50)**	**2.61 (1.51, 4.76)**	**3.51 (1.49, 9.90)**	2.44 (0.75, 11.74)	2.40 (0.71, 11.74)	**3.39 (1.20, 12.64)**
Riociguat max 1.5 mg	0.46 (0.06, 1.69)	1	2.48 (0.31, 15.26)	1.20 (0.16, 5.08)	1.61 (0.19, 8.59)	1.12 (0.11, 8.69)	1.10 (0.11, 8.59)	1.55 (0.17, 10.00)
Riociguat max 2.5 mg	**0.18 (0.04, 0.63)**	0.40 (0.07, 3.26)	1	0.48 (0.09, 1.91)	0.65 (0.11, 3.24)	0.45 (0.06, 3.30)	0.44 (0.06, 3.28)	0.63 (0.09, 3.76)
Bosentan 125 mg	**0.38 (0.21, 0.66)**	0.84 (0.20, 6.44)	2.08 (0.25, 11.04)	1	1.35 (0.47, 4.33)	0.94 (0.25, 4.92)	0.92 (0.23, 4.91)	1.30 (0.39, 5.39)
Ambrisentan 5 mg	**0.28 (0.10, 0.67)**	0.62 (0.12, 5.28)	1.54 (0.31, 9.27)	0.74 (0.23, 2.14)	1	0.69 (0.16, 3.68)	0.68 (0.14, 4.11)	0.96 (0.22, 4.60)
Ambrisentan 10 mg	0.41 (0.09, 1.33)	0.90 (0.12, 8.76)	2.21 (0.30, 15.84)	1.07 (0.20, 4.05)	1.44 (0.27, 6.09)	1	0.98 (0.14, 7.06)	1.39 (0.21, 8.08)
Sildenafil 20 mg	0.42 (0.09, 1.41)	0.91 (0.12, 9.04)	2.26 (0.30, 16.59)	1.09 (0.20, 4.26)	1.47 (0.24, 7.23)	1.02 (0.14, 7.38)	1	1.41 (0.21, 8.45)
Tadalafil 40 mg	**0.30 (0.08, 0.83)**	0.65 (0.10, 5.85)	1.60 (0.27, 10.61)	0.77 (0.19, 2.58)	1.04 (0.22, 4.49)	0.72 (0.12, 4.73)	0.71 (0.12, 4.70)	1

Table 204: Meta-analysis Results of Clinical Worsening, Naive Populations of All Studies; No Macitentan (Random)

	Placebo	Riociguat max 2.5 mg	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	3.90 (0.57, 45.05)	**2.40 (1.02, 8.33)**	**3.45 (1.04, 13.41)**	2.50 (0.54, 17.75)	2.44 (0.49, 18.11)	5.05 (0.81, 54.29)
Riociguat max 2.5 mg	0.26 (0.02, 1.76)	1	0.62 (0.05, 6.33)	0.89 (0.06, 9.34)	0.65 (0.04, 9.93)	0.63 (0.03, 10.06)	1.30 (0.06, 26.93)
Bosentan 125 mg	**0.42 (0.12, 0.98)**	1.61 (0.16, 20.34)	1	1.44 (0.24, 6.78)	1.04 (0.14, 8.30)	1.01 (0.13, 8.37)	2.10 (0.22, 24.81)
Ambrisentan 5 mg	**0.29 (0.07, 0.96)**	1.13 (0.11, 16.89)	0.70 (0.15, 4.12)	1	0.73 (0.12, 5.48)	0.71 (0.09, 7.32)	1.47 (0.15, 20.57)
Ambrisentan 10 mg	0.40 (0.06, 1.86)	1.54 (0.10, 27.83)	0.96 (0.12, 7.21)	1.38 (0.18, 8.10)	1	0.97 (0.08, 12.12)	2.01 (0.14, 33.24)
Sildenafil 20 mg	0.41 (0.06, 2.04)	1.58 (0.10, 29.32)	0.99 (0.12, 7.84)	1.40 (0.14, 11.56)	1.03 (0.08, 12.86)	1	2.07 (0.14, 35.63)
Tadalafil 40 mg	0.20 (0.02, 1.24)	0.77 (0.04, 15.98)	0.48 (0.04, 4.58)	0.68 (0.05, 6.71)	0.50 (0.03, 7.21)	0.48 (0.03, 7.20)	1

Table 205: Meta-analysis Results of Clinical Worsening, Naive Populations of All Studies; No Macitentan (Fixed)

	Placebo	Riociguat max 2.5 mg	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	3.84 (0.79, 30.99)	**2.18 (1.17, 4.31)**	**3.50 (1.49, 9.83)**	2.45 (0.76, 11.77)	2.39 (0.71, 11.58)	**4.94 (1.17, 38.51)**
Riociguat max 2.5 mg	0.26 (0.03, 1.27)	1	0.57 (0.06, 3.22)	0.92 (0.10, 6.09)	0.65 (0.06, 5.93)	0.63 (0.06, 5.80)	1.30 (0.10, 17.04)
Bosentan 125 mg	**0.46 (0.23, 0.86)**	1.77 (0.31, 15.64)	1	1.61 (0.54, 5.39)	1.13 (0.29, 6.06)	1.10 (0.27, 5.98)	2.28 (0.46, 19.42)
Ambrisentan 5 mg	**0.29 (0.10, 0.67)**	1.09 (0.16, 10.49)	0.62 (0.19, 1.86)	1	0.70 (0.16, 3.69)	0.68 (0.14, 4.10)	1.42 (0.24, 12.87)
Ambrisentan 10 mg	0.41 (0.08, 1.32)	1.55 (0.17, 17.14)	0.88 (0.17, 3.50)	1.43 (0.27, 6.09)	1	0.97 (0.13, 6.98)	2.02 (0.24, 21.15)
Sildenafil 20 mg	0.42 (0.09, 1.41)	1.59 (0.17, 17.87)	0.91 (0.17, 3.70)	1.47 (0.24, 7.26)	1.03 (0.14, 7.41)	1	2.08 (0.24, 22.05)
Tadalafil 40 mg	**0.20 (0.03, 0.85)**	0.77 (0.06, 9.85)	0.44 (0.05, 2.19)	0.71 (0.08, 4.19)	0.50 (0.05, 4.16)	0.48 (0.05, 4.12)	1

Table 206: Meta-analysis Results of Functional Class Improvement, Total Populations of All Studies (Random)											
	Placebo	**Macitentan 10 mg**	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Treprostinil s.c. or i.v.**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	0.59 (0.27, 1.47)	0.59 (0.24, 1.71)	0.67 (0.29, 1.77)	**0.11 (0.06, 0.18)**	0.33 (0.12, 1.30)	0.45 (0.22, 0.86)	0.96 (0.46, 2.21)	0.83 (0.34, 2.33)	0.27 (0.13, 0.75)	0.90 (0.34, 2.71)
Macitentan 10 mg	1.70 (0.68, 3.72)	1	1.00 (0.28, 3.74)	1.14 (0.33, 3.93)	**0.18 (0.06, 0.43)**	0.56 (0.15, 2.65)	0.77 (0.23, 1.98)	1.62 (0.51, 5.09)	1.40 (0.39, 5.09)	0.46 (0.14, 1.62)	1.52 (0.41, 5.88)
Riociguat max 1.5 mg	1.71 (0.58, 4.11)	1.00 (0.27, 3.52)	1	1.14 (0.44, 2.80)	**0.18 (0.05, 0.46)**	0.56 (0.13, 2.82)	0.77 (0.20, 2.16)	1.63 (0.45, 5.48)	1.41 (0.35, 5.45)	0.46 (0.13, 1.75)	1.53 (0.37, 6.25)
Riociguat max 2.5 mg	1.49 (0.57, 3.49)	0.88 (0.25, 3.04)	0.88 (0.36, 2.28)	1	**0.16 (0.05, 0.40)**	0.49 (0.12, 2.43)	0.68 (0.19, 1.83)	1.43 (0.43, 4.69)	1.24 (0.33, 4.66)	0.41 (0.12, 1.49)	1.34 (0.35, 5.35)
Epoprostenol	**9.31 (5.71, 16.87)**	**5.46 (2.35, 16.29)**	**5.45 (2.17, 18.69)**	**6.21 (2.53, 19.47)**	1	**3.03 (1.20, 13.04)**	**4.16 (2.02, 9.12)**	**8.94 (3.82, 24.93)**	**7.72 (2.92, 25.67)**	**2.50 (1.22, 7.85)**	**8.37 (2.98, 29.57)**
Treprostinil subcutaneous or intravenous	3.06 (0.77, 8.28)	1.79 (0.38, 6.89)	1.78 (0.35, 7.74)	2.03 (0.41, 8.19)	**0.33 (0.08, 0.84)**	1	1.36 (0.29, 4.32)	2.91 (0.62, 10.89)	2.51 (0.50, 10.71)	0.83 (0.18, 3.35)	2.70 (0.52, 12.28)
Bosentan 125 mg	**2.23 (1.17, 4.61)**	1.30 (0.51, 4.43)	1.31 (0.46, 4.94)	1.48 (0.55, 5.24)	**0.24 (0.11, 0.50)**	0.73 (0.23, 3.45)	1	2.13 (0.83, 6.65)	1.84 (0.64, 6.80)	0.61 (0.23, 2.13)	1.99 (0.66, 7.86)
Ambrisentan 5 mg	1.04 (0.45, 2.20)	0.62 (0.20, 1.97)	0.61 (0.18, 2.24)	0.70 (0.21, 2.34)	**0.11 (0.04, 0.26)**	0.34 (0.09, 1.62)	0.47 (0.15, 1.20)	1	0.87 (0.33, 2.32)	**0.29 (0.09, 0.98)**	0.93 (0.26, 3.54)
Ambrisentan 10 mg	1.21 (0.43, 2.98)	0.71 (0.20, 2.53)	0.71 (0.18, 2.85)	0.81 (0.21, 3.00)	**0.13 (0.04, 0.34)**	0.40 (0.09, 2.02)	0.54 (0.15, 1.56)	1.15 (0.43, 2.99)	1	0.33 (0.09, 1.25)	1.08 (0.27, 4.48)
Sildenafil 20 mg	**3.69 (1.33, 7.90)**	2.15 (0.62, 7.07)	2.15 (0.57, 7.98)	2.45 (0.67, 8.39)	**0.40 (0.13, 0.82)**	1.20 (0.30, 5.65)	1.65 (0.47, 4.29)	**3.51 (1.02, 10.96)**	3.03 (0.80, 11.03)	1	3.27 (0.83, 12.62)
Tadalafil 40 mg	1.12 (0.37, 2.93)	0.66 (0.17, 2.45)	0.66 (0.16, 2.74)	0.75 (0.19, 2.89)	**0.12 (0.03, 0.34)**	0.37 (0.08, 1.94)	0.50 (0.13, 1.52)	1.07 (0.28, 3.84)	0.92 (0.22, 3.75)	0.31 (0.08, 1.21)	1

Table 207: Meta-analysis Results of Functional Class Improvement, Total Populations of All Studies (Fixed)											
	Placebo	**Macitentan 10 mg**	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Treprostinil s.c. or i.v.**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	**0.59 (0.40, 0.88)**	0.59 (0.32, 1.15)	0.67 (0.41, 1.10)	**0.11 (0.06, 0.18)**	0.33 (0.13, 1.02)	0.49 (0.30, 0.80)	0.95 (0.56, 1.64)	0.82 (0.45, 1.59)	**0.27 (0.14, 0.57)**	0.90 (0.47, 1.80)
Macitentan 10 mg	**1.70 (1.14, 2.51)**	1	1.00 (0.49, 2.17)	1.14 (0.60, 2.13)	**0.19 (0.10, 0.33)**	0.56 (0.21, 1.84)	0.83 (0.45, 1.54)	1.61 (0.83, 3.16)	1.40 (0.68, 3.01)	0.47 (0.22, 1.05)	1.52 (0.72, 3.37)
Riociguat max 1.5 mg	1.71 (0.87, 3.11)	1.00 (0.46, 2.06)	1	1.14 (0.64, 1.91)	**0.19 (0.08, 0.39)**	0.56 (0.18, 2.00)	0.83 (0.37, 1.79)	1.61 (0.69, 3.64)	1.41 (0.57, 3.42)	0.47 (0.19, 1.18)	1.53 (0.60, 3.83)
Riociguat max 2.5 mg	1.49 (0.91, 2.45)	0.88 (0.47, 1.66)	0.88 (0.52, 1.57)	1	**0.17 (0.08, 0.31)**	0.49 (0.17, 1.68)	0.73 (0.37, 1.45)	1.42 (0.69, 2.96)	1.24 (0.56, 2.81)	**0.41 (0.18, 0.98)**	1.34 (0.59, 3.14)
Epoprostenol	**8.96 (5.60, 15.92)**	**5.28 (3.00, 10.28)**	**5.28 (2.59, 12.38)**	**6.00 (3.18, 12.48)**	1	**2.94 (1.25, 9.67)**	**4.40 (2.48, 8.56)**	**8.51 (4.35, 18.32)**	**7.43 (3.58, 17.27)**	**2.44 (1.31, 5.65)**	**8.08 (3.74, 19.44)**
Treprostinil subcutaneous or intravenous	3.04 (0.98, 7.55)	1.79 (0.54, 4.78)	1.78 (0.50, 5.51)	2.02 (0.60, 5.73)	**0.34 (0.10, 0.80)**	1	1.49 (0.44, 4.06)	2.87 (0.83, 8.35)	2.50 (0.70, 7.72)	0.83 (0.23, 2.57)	2.72 (0.75, 8.58)
Bosentan 125 mg	**2.04 (1.26, 3.28)**	1.20 (0.65, 2.22)	1.20 (0.56, 2.71)	1.37 (0.69, 2.70)	**0.23 (0.12, 0.40)**	0.67 (0.25, 2.27)	1	1.93 (0.95, 3.98)	1.69 (0.78, 3.77)	0.56 (0.26, 1.31)	1.83 (0.82, 4.24)
Ambrisentan 5 mg	1.06 (0.61, 1.78)	0.62 (0.32, 1.20)	0.62 (0.27, 1.45)	0.71 (0.34, 1.45)	**0.12 (0.05, 0.23)**	0.35 (0.12, 1.21)	0.52 (0.25, 1.05)	1	0.87 (0.47, 1.66)	**0.29 (0.12, 0.70)**	0.95]0.41, 2.25]
Ambrisentan 10 mg	1.21 (0.63, 2.21)	0.71 (0.33, 1.47)	0.71 (0.29, 1.75)	0.81 (0.36, 1.77)	**0.13 (0.06, 0.28)**	0.40 (0.13, 1.43)	0.59 (0.27, 1.28)	1.15 (0.60, 2.14)	1	**0.33 (0.13, 0.85)**	1.09 (0.43, 2.72)
Sildenafil 20 mg	**3.66 (1.76, 6.97)**	2.15 (0.96, 4.55)	2.14 (0.84, 5.40)	**2.44 (1.02, 5.50)**	**0.41 (0.18, 0.76)**	1.20 (0.39, 4.29)	1.79 (0.76, 3.88)	**3.46 (1.42, 8.05)**	**3.01 (1.18, 7.54)**	1	**3.27 (1.26, 8.47)**
Tadalafil 40 mg	1.11 (0.56, 2.12)	0.66 (0.30, 1.40)	0.65 (0.26, 1.65)	0.74 (0.32, 1.68)	**0.12 (0.05, 0.27)**	0.37 (0.12, 1.33)	0.55 (0.24, 1.22)	1.05 (0.44, 2.45)	0.92 (0.37, 2.31)	**0.31 (0.12, 0.79)**	1

Table 208: Meta-analysis Results of Functional Class Improvement, Naive Populations of All Studies (Random)									
	Placebo	**Riociguat max 2.5 mg**	**Epoprostenol**	**Treprostinil s.c. or i.v.**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	1.03 (0.36, 3.22)	**0.10 (0.05, 0.17)**	0.32 (0.12, 1.28)	**0.45 (0.21, 0.85)**	0.96 (0.46, 2.20)	0.83 (0.33, 2.33)	0.27 (0.12, 0.75)	0.37 (0.15, 1.21)
Riociguat max 2.5 mg	0.98 (0.31, 2.78)	1	**0.10 (0.03, 0.31)**	0.32 (0.07, 1.72)	0.44 (0.11, 1.43)	0.93 (0.24, 3.55)	0.81 (0.19, 3.51)	0.26 (0.06, 1.11)	0.37 (0.08, 1.73)
Epoprostenol	**9.72 (5.77, 18.54)**	**10.00 (3.27, 37.29)**	1	**3.11 (1.21, 13.56)**	**4.33 (2.05, 9.89)**	**9.31 (3.98, 26.64)**	**8.07 (3.02, 27.33)**	**2.57 (1.23, 8.17)**	**3.64 (1.46, 13.39)**
Treprostinil subcutaneous or intravenous	3.11 (0.78, 8.67)	3.14 (0.58, 14.80)	**0.32 (0.07, 0.83)**	1	1.38 (0.29, 4.47)	2.96 (0.63, 11.16)	2.55 (0.50, 11.08)	0.83 (0.17, 3.43)	1.16 (0.22, 5.49)
Bosentan 125 mg	**2.24 (4.70, 1.17)**	2.28 (0.70, 9.33)	**0.23 (0.10, 0.49)**	0.72 (0.22, 3.46)	1	2.14 (0.83, 6.73)	1.85 (0.64, 6.86)	0.60 (0.23, 2.12)	0.84 (0.29, 3.40)
Ambrisentan 5 mg	1.05 (0.46, 2.20)	1.07 (0.28, 4.18)	**0.11 (0.04, 0.25)**	0.34 (0.09, 1.59)	0.47 (0.15, 1.21)	1	0.87 (0.33, 2.33)	**0.28 (0.09, 0.97)**	0.39 (0.11, 1.55)
Ambrisentan 10 mg	1.21 (0.43, 2.99)	1.23 (0.28, 5.30)	**0.12 (0.04, 0.33)**	0.39 (0.09, 2.00)	0.54 (0.15, 1.57)	1.15 (0.43, 3.00)	1	0.32 (0.09, 1.24)	0.46 (0.11, 1.95)
Sildenafil 20 mg	**3.76 (1.34, 8.29)**	3.80 (0.90, 15.48)	**0.39 (0.12, 0.81)**	1.20 (0.29, 5.77)	1.67 (0.47, 4.42)	**3.57 (1.03, 11.28)**	3.08 (0.80, 11.39)	1	1.40 (0.36, 5.64)
Tadalafil 40 mg	2.67 (0.83, 6.74)	2.70 (0.58, 11.85)	**0.27 (0.07, 0.68)**	0.86 (0.18, 4.46)	1.19 (0.29, 3.50)	2.54 (0.65, 8.88)	2.20 (0.51, 8.79)	0.71 (0.18, 2.76)	1

Table 209: Meta-analysis Results of FC Improvement, Naive Populations of All Studies (Fixed)									
	Placebo	**Riociguat max 2.5 mg**	**Epoprostenol**	**Treprostinil s.c. or i.v.**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	1.02 (0.48, 2.21)	**0.11 (0.06, 0.18)**	0.32 (0.13, 1.02)	**0.49 (0.30, 0.80)**	0.95 (0.56, 1.65)	0.83 (0.45, 1.60)	**0.27 (0.14, 0.57)**	**0.37 (0.17, 0.90)**
Riociguat max 2.5 mg	0.98 (0.45, 2.08)	1	**0.10 (0.04, 0.25)**	0.32 (0.09, 1.24)	0.48 (0.19, 1.16)	0.93 (0.36, 2.36)	0.81 (0.30, 2.19)	**0.26 (0.10, 0.75)**	0.37 (0.12, 1.16)
Epoprostenol	**9.42 (5.65, 17.48)**	**9.70 (4.06, 25.29)**	1	**3.04 (1.27, 10.31)**	**4.60 (2.53, 9.22)**	**8.96 (4.44, 19.93)**	**7.82 (3.66, 18.77)**	**2.52 (1.32, 6.03)**	**3.53 (1.61, 9.71)**
Treprostinil subcutaneous or intravenous	3.08 (0.98, 7.93)	3.15 (0.81, 10.65)	**0.33 (0.10, 0.79)**	1	1.51 (0.44, 4.24)	2.92 (0.82, 8.74)	2.54 (0.70, 8.06)	0.83 (0.23, 2.64)	1.16 (0.30, 4.13)
Bosentan 125 mg	**2.06 (1.25, 3.32)**	2.10 (0.86, 5.21)	**0.22 (0.11, 0.39)**	0.66 (0.24, 2.28)	1	1.94 (0.95, 4.04)	1.70 (0.78, 3.83)	0.55 (0.25, 1.31)	0.77 (0.32, 2.08)
Ambrisentan 5 mg	1.06 (0.61, 1.79)	1.08 (0.42, 2.76)	**0.11 (0.05, 0.23)**	0.34 (0.11, 1.21)	0.51 (0.25, 1.05)	1	0.87 (0.47, 1.67)	**0.28 (0.12, 0.71)**	0.40 (0.15, 1.10)
Ambrisentan 10 mg	1.21 (0.62, 2.23)	1.24 (0.46, 3.31)	**0.13 (0.05, 0.27)**	0.39 (0.12, 1.44)	0.59 (0.26, 1.28)	1.15 (0.60, 2.15)	1	**0.33 (0.13, 0.85)**	0.45 (0.17, 1.32)
Sildenafil 20 mg	**3.71 (1.76, 7.29)**	**3.78 (1.34, 10.52)**	**0.40 (0.17, 0.76)**	1.20 (0.38, 4.39)	1.81 (0.76, 4.01)	**3.51 (1.42, 8.34)**	**3.06 (1.18, 7.81)**	1	1.39 (0.49, 4.09)
Tadalafil 40 mg	**2.67 (1.11, 5.76)**	2.72 (0.86, 8.11)	**0.28 (0.10, 0.62)**	0.86 (0.24, 3.34)	1.30 (0.48, 3.15)	2.52 (0.91, 6.52)	2.20 (0.76, 6.06)	0.72 (0.24, 2.04)	1

Table 210: Meta-analysis Results of Functional Class Improvement, Total Populations of All Studies; No Macitentan (Random)										
	Placebo	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Treprostinil s.c. or i.v.**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	0.58 (0.24, 1.68)	0.67 (0.29, 1.75)	**0.11 (0.06, 0.18)**	0.32 (0.12, 1.27)	**0.45 (0.22, 0.85)**	0.95 (0.45, 2.19)	0.83 (0.33, 2.30)	0.27 (0.12, 0.75)	0.89 (0.34, 2.67)
Riociguat max 1.5 mg	1.72 (0.60, 4.11)	1	1.14 (0.44, 2.80)	**0.18 (0.05, 0.46)**	0.55 (0.13, 2.76)	0.77 (0.21, 2.14)	1.63 (0.45, 5.44)	1.41 (0.35, 5.43)	0.46 (0.13, 1.73)	1.52 (0.37, 6.17)
Riociguat max 2.5 mg	1.50 (0.57, 3.94)	0.88 (0.36, 2.26)	1	**0.16 (0.05, 0.40)**	0.49 (0.12, 2.36)	0.67 (0.19, 1.81)	1.43 (0.43, 4.64)	1.24 (0.33, 4.65)	0.41 (0.12, 1.49)	1.34 (0.35, 5.31)
Epoprostenol	**9.43 (5.64, 17.84)**	**5.52 (2.16, 18.95)**	**6.29 (2.52, 20.02)**	1	**3.03 (1.18, 13.96)**	**4.20 (2.02, 9.48)**	**9.06 (3.83, 25.45)**	**7.84 (2.92, 25.94)**	**2.51 (1.21, 8.05)**	**8.46 (3.01, 30.18)**
Treprostinil subcutaneous or intravenous	3.11 (0.79, 8.62)	1.81 (0.36, 7.93)	2.05 (0.42, 8.39)	**0.33 (0.08, 0.85)**	1	1.38 (0.30, 4.44)	2.95 (0.63, 11.11)	2.55 (0.50, 10.97)	0.84 (0.18, 3.45)	2.75 (0.53, 12.45)
Bosentan 125 mg	**2.24 (1.17, 4.63)**	1.30 (0.47, 4.86)	1.49 (0.55, 5.17)	**0.24 (0.11, 0.50)**	0.72 (0.23, 3.39)	1	2.14 (0.83, 6.60)	1.84 (0.64, 6.72)	0.60 (0.23, 2.11)	1.99 (0.66, 7.76)
Ambrisentan 5 mg	1.05 (0.46, 2.22)	0.61 (0.18, 2.22)	0.70 (0.22, 2.33)	**0.11 (0.04, 0.26)**	0.34 (0.09, 1.59)	0.47 (0.15, 1.21)	1	0.87 (0.33, 2.33)	**0.28 (0.09, 0.99)**	0.94 (0.26, 3.50)
Ambrisentan 10 mg	1.21 (0.43, 2.99)	0.71 (0.18, 2.83)	0.81 (0.22, 3.00)	**0.13 (0.04, 0.34)**	0.39 (0.09, 2.01)	0.54 (0.15, 1.26)	1.16 (0.43, 2.99)	1	0.33 (0.09, 1.25)	1.08 (0.27, 4.48)
Sildenafil 20 mg	**3.74 (1.34, 8.08)**	2.16 (0.58, 8.00)	2.47 (0.67, 8.40)	**0.40 (0.12, 0.82)**	1.19 (0.29, 5.57)	1.66 (0.47, 4.34)	**3.54 (1.01, 11.02)**	3.05 (0.80, 11.00)	1	3.30 (0.83, 12.66)
Tadalafil 40 mg	1.12 (0.37, 2.93)	0.66 (0.16, 2.70)	0.75 (0.19, 2.88)	**0.12 (0.03, 0.33)**	0.36 (0.08, 1.90)	0.50 (0.13, 1.51)	1.07 (0.29, 3.79)	0.92 (0.22, 3.73)	0.30 (0.08, 1.20)	1

Table 211: Meta-analysis Results of Functional Class Improvement, Total Populations of All Studies; No Macitentan (Fixed)										
	Placebo	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Treprostinil s.c. or i.v.**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	0.59 (0.32, 1.16)	0.67 (0.41, 1.11)	**0.11 (0.06, 0.18)**	0.33 (0.13, 1.03)	0.49 (0.30, 0.80)	0.94 (0.56, 1.64)	0.82 (0.45, 1.60)	**0.27 (0.14, 0.57)**	0.90 (0.47, 1.80)
Riociguat max 1.5 mg	1.71 (0.86, 3.12)	1	1.14 (0.64, 1.92)	**0.18 (0.08, 0.38)**	0.56 (0.18, 2.02)	0.83 (0.36, 1.79)	1.61 (0.68, 3.65)	1.40 (0.56, 3.43)	0.46 (0.18, 1.18)	1.53 (0.60, 3.83)
Riociguat max 2.5 mg	1.49 (0.90, 2.46)	0.88 (0.52, 1.57)	1	**0.16 (0.08, 0.31)**	0.49 (0.17, 1.70)	0.73 (0.37, 1.44)	1.41 (0.68, 2.96)	1.23 (0.56, 2.80)	**0.41 (0.18, 0.97)**	1.34 (0.60, 3.15)
Epoprostenol	**9.16 (5.56, 17.30)**	**5.41 (2.61, 13.20)**	**6.16 (3.19, 13.31)**	1	**3.00 (1.27, 10.11)**	**4.48 (2.49, 9.07)**	**8.71 (4.35, 19.54)**	**7.60 (3.58, 18.36)**	**2.47 (1.31, 5.95)**	**8.29 (3.78, 20.59)**
Treprostinil subcutaneous or intravenous	3.05 (0.97, 7.76)	1.79 (0.50, 5.65)	2.04 (0.59, 5.86)	**0.33 (0.10, 0.79)**	1	1.49 (0.44, 4.12)	2.88 (0.82, 8.52)	2.51 (0.69, 7.86)	0.83 (0.23, 2.61)	2.73 (0.74, 8.78)
Bosentan 125 mg	**2.05 (1.26, 3.31)**	1.20 (0.56, 2.75)	1.37 (0.69, 2.72)	**0.22 (0.11, 0.40)**	0.67 (0.24, 2.30)	1	1.94 (0.95, 4.00)	1.69 (0.78, 3.79)	0.56 (0.25, 1.31)	1.84 (0.83, 4.25)
Ambrisentan 5 mg	1.06 (0.61, 1.79)	0.62 (0.27, 1.47)	0.71 (0.34, 1.46)	**0.11 (0.05, 0.23)**	0.35 (0.12, 1.22)	0.52 (0.25, 1.05)	1	0.87 (0.47, 1.67)	**0.29 (0.12, 0.70)**	0.95 (0.41, 2.26)
Ambrisentan 10 mg	1.21 (0.63, 2.23)	0.71 (0.29, 1.77)	0.81 (0.36, 1.79)	**0.13 (0.05, 0.28)**	0.40 (0.13, 1.45)	0.59 (0.26, 1.28)	1.15 (0.60, 2.14)	1	**0.33 (0.13, 0.84)**	1.09 (0.43, 2.73)
Sildenafil 20 mg	**3.68 (1.76, 7.22)**	2.16 (0.85, 5.54)	**2.46 (1.03, 5.61)**	**0.40 (0.17, 0.76)**	1.21 (0.38, 4.37)	1.80 (0.76, 3.97)	**3.48 (1.42, 8.24)**	**3.03 (1.19, 7.73)**	1	**3.30 (1.25, 8.63)**
Tadalafil 40 mg	1.11 (0.56, 2.12)	0.66 (0.26, 1.66)	0.75 (0.32, 1.68)	**0.12 (0.05, 0.26)**	0.37 (0.11, 1.35)	0.54 (0.24, 1.21)	1.05 (0.44, 2.46)	0.92 (0.37, 2.31)	**0.30 (0.12, 0.80)**	1

Table 212: Meta-analysis Results of Functional Class Worsening, Total Populations of All Studies (Random)										
	Placebo	**Macitentan 10 mg**	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	3.31 (0.92, 12.98)	1.93 (0.50, 9.82)	**4.24 (1.06, 18.78)**	2.35 (0.71, 8.30)	**2.89 (1.22, 7.97)**	**9.21 (2.32, 52.80)**	3.91 (0.79, 26.19)	3.82 (0.63, 39.94)	1.62 (0.44, 7.30)
Macitentan 10 mg	0.30 (0.08, 1.09)	1	0.59 (0.09, 4.56)	1.28 (0.18, 9.01)	0.71 (0.11, 4.09)	0.87 (0.18, 4.57)	2.79 (0.42, 24.32)	1.19 (0.14, 11.29)	1.16 (0.12, 16.44)	0.49 (0.07, 3.48)
Riociguat max 1.5 mg	0.52 (0.10, 2.01)	1.70 (0.22, 11.72)	1	2.18 (0.42, 10.12)	1.21 (0.16, 7.60)	1.49 (0.24, 8.32)	4.79 (0.58, 43.38)	2.03 (0.20, 20.59)	1.98 (0.18, 29.39)	0.83 (0.11, 6.44)
Riociguat max 2.5 mg	**0.24 (0.05, 0.95)**	0.78 (0.11, 5.49)	0.46 (0.10, 2.37)	1	0.56 (0.08, 3.56)	0.68 (0.13, 3.92)	2.19 (0.29, 20.12)	0.93 (0.10, 9.35)	0.91 (0.09, 13.50)	0.38 (0.05, 2.96)
Epoprostenol	0.43 (0.12, 1.41)	1.40 (0.24, 8.85)	0.83 (0.13, 6.30)	1.80 (0.28, 12.44)	1	1.23 (0.27, 6.17)	3.97 (0.62, 32.85)	1.68 (0.22, 15.56)	1.65 (0.18, 22.72)	0.69 (0.12, 4.81)
Bosentan 125 mg	**0.35 (0.13, 0.82)**	1.15 (0.22, 5.53)	0.67 (0.12, 4.12)	1.47 (0.25, 7.84)	0.81 (0.16, 3.71)	1	3.21 (0.57, 22.18)	1.36 (0.19, 10.68)	1.32 (0.16, 15.55)	0.56 (0.11, 3.09)
Ambrisentan 5 mg	**0.11 (0.02, 0.43)**	0.36 (0.04, 2.40)	0.21 (0.02, 1.74)	0.46 (0.05, 3.43)	0.25 (0.03, 1.63)	0.31 (0.05, 1.75)	1	0.42 (0.05, 3.48)	0.42 (0.03, 6.15)	0.17 (0.02, 1.34)
Ambrisentan 10 mg	0.26 (0.04, 1.27)	0.84 (0.09, 6.92)	0.49 (0.05, 4.93)	1.07 (0.11, 9.75)	0.60 (0.06, 4.51)	0.74 (0.09, 5.14)	2.36 (0.29, 20.30)	1	0.98 (0.07, 16.46)	0.41 (0.04, 3.78)
Sildenafil 20 mg	0.26 (0.03, 1.58)	0.86 (0.06, 8.16)	0.50 (0.03, 5.68)	1.10 (0.07, 11.49)	0.61 (0.04, 5.50)	0.76 (0.06, 6.08)	2.41 (0.16, 29.20)	1.02 (0.06, 13.90)	1	0.42 (0.03, 4.33)
Tadalafil 40 mg	0.62 (0.14, 2.28)	2.05 (0.29, 13.34)	1.20 (0.16, 9.44)	2.61 (0.34, 18.95)	1.46 (0.21, 8.63)	1.78 (0.32, 9.52)	5.74 (0.75, 50.29)	2.43 (0.26, 23.81)	2.37 (0.23, 33.80)	1

Table 213: Meta-analysis Results of Functional Class Worsening, Total Populations of All Studies (Fixed)										
	Placebo	**Macitentan 10 mg**	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	**3.31 (1.94, 5.96)**	1.92 (0.79, 5.92)	**4.23 (1.94, 10.11)**	**2.49 (1.07, 6.65)**	**2.73 (1.41, 5.76)**	**8.87 (2.96, 40.27)**	**3.97 (1.23, 18.80)**	3.77 (0.91, 28.42)	1.61 (0.71, 4.15)
Macitentan 10 mg	**0.30 (0.17, 0.52)**	1	0.58 (0.20, 2.01)	1.28 (0.48, 3.54)	0.75 (0.27, 2.30)	0.83 (0.34, 2.09)	2.68 (0.76, 13.25)	1.20 (0.32, 6.17)	1.14 (0.24, 9.18)	0.49 (0.18, 1.44)
Riociguat max 1.5 mg	0.52 (0.17, 1.27)	1.72 (0.50, 5.02)	1	2.20 (0.67, 6.33)	1.29 (0.32, 4.86)	1.42 (0.38, 4.57)	4.63 (0.96, 26.56)	2.07 (0.40, 12.23)	1.96 (0.32, 17.67)	0.84 (0.21, 3.09)
Riociguat max 2.5 mg	**0.24 (0.10, 0.52)**	0.78 (0.28, 2.08)	0.45 (0.16, 1.49)	1	0.59 (0.17, 2.05)	0.65 (0.21, 1.91)	2.11 (0.51, 11.38)	0.94 (0.22, 5.26)	0.89 (0.17, 7.69)	0.38 (0.11, 1.29)
Epoprostenol	**0.40 (0.15, 0.94)**	1.33 (0.43, 3.76)	0.78 (0.21, 3.14)	1.70 (0.49, 5.77)	1	1.10 (0.33, 3.42)	3.59 (0.81, 20.04)	1.60 (0.34, 9.32)	1.52 (0.27, 13.45)	0.65 (0.18, 2.32)
Bosentan 125 mg	**0.37 (0.17, 0.71)**	1.21 (0.48, 2.96)	0.70 (0.22, 2.60)	1.55 (0.52, 4.66)	0.91 (0.29, 2.99)	1	3.26 (0.85, 16.88)	1.45 (0.36, 7.86)	1.38 (0.28, 11.54)	0.59 (0.19, 1.88)
Ambrisentan 5 mg	**0.11 (0.02, 0.34)**	0.37 (0.08, 1.31)	0.22 (0.04, 1.05)	0.47 (0.09, 1.95)	0.28 (0.05, 1.24)	0.31 (0.06, 1.18)	1	0.45 (0.07, 2.69)	0.42 (0.05, 4.21)	**0.18 (0.03, 0.78)**
Ambrisentan 10 mg	**0.25 (0.05, 0.81)**	0.83 (0.16, 3.11)	0.48 (0.08, 2.47)	1.06 (0.19, 4.63)	0.63 (0.11, 2.93)	0.69 (0.13, 2.79)	2.24 (0.37, 13.65)	1	0.95 (0.12, 9.64)	0.40 (0.07, 1.84)
Sildenafil 20 mg	0.27 (0.04, 1.09)	0.88 (0.11, 4.11)	0.51 (0.06, 3.14)	1.12 (0.13, 5.99)	0.66 (0.07, 3.74)	0.72 (0.09, 3.64)	2.36 (0.24, 18.62)	1.05 (0.10, 8.61)	1	0.43 (0.05, 2.38)
Tadalafil 40 mg	0.62 (0.24, 1.42)	2.05 (0.69, 5.68)	1.20 (0.32, 4.80)	2.62 (0.77, 8.76)	1.55 (0.43, 5.57)	1.70 (0.53, 5.16)	**5.54 (1.27, 30.63)**	2.48 (0.54, 14.12)	2.34 (0.42, 20.58)	1

Table 214: Meta-analysis Results of Functional Class Worsening, Naive Populations of All Studies (Random)								
	Placebo	**Riociguat max 2.5 mg**	**Epoprostenol**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	`4.50 (0.90, 26.60)	2.34 (0.67, 8.80)	2.38 (0.85, 8.65)	**9.44 (2.28, 57.87)**	3.96 (0.74, 27.75)	3.88 (0.61, 41.96)	2.22 (0.45, 14.76)
Riociguat max 2.5 mg	0.22 (0.04, 1.11)	1	0.52 (0.06, 4.08)	0.53 (0.07, 4.29)	2.12 (0.22, 23.23)	0.88 (0.08, 10.74)	0.87 (0.07, 14.84)	0.50 (0.05, 5.81)
Epoprostenol	0.43 (0.11, 1.48)	1.91 (0.24, 16.90)	1	1.01 (0.19, 6.44)	4.04 (0.58, 36.22)	1.69 (0.20, 16.84)	1.67 (0.17, 24.04)	0.94 (0.12, 9.25)
Bosentan 125 mg	0.42 (0.12, 1.17)	1.89 (0.23, 14.09)	0.99 (0.16, 5.16)	1	3.98 (0.57, 30.39)	1.67 (0.19, 14.36)	1.63 (0.17, 21.22)	0.93 (0.12, 7.67)
Ambrisentan 5 mg	**0.11 (0.02, 0.44)**	0.47 (0.04, 4.54)	0.25 (0.03, 1.72)	0.25 (0.03, 1.76)	1	0.42 (0.04, 3.61)	0.41 (0.03, 6.52)	0.23 (0.02, 2.52)
Ambrisentan 10 mg	0.25 (0.04, 1.35)	1.13 (0.09, 13.08)	0.59 (0.06, 4.96)	0.60 (0.07, 5.27)	2.39 (0.28, 22.37)	1	0.99 (0.07, 17.78)	0.56 (0.05, 7.10)
Sildenafil 20 mg	0.26 (0.02, 1.64)	1.15 (0.07, 14.81)	0.60 (0.04, 5.86)	0.62 (0.05, 6.05)	2.44 (0.15, 32.87)	1.01 (0.06, 14.73)	1	0.57 (0.03, 8.09)
Tadalafil 40 mg	0.45 (0.07, 2.23)	2.02 (0.17, 21.96)	1.06 (0.11, 8.27)	1.08 (0.13, 8.49)	4.28 (0.40, 47.50)	1.79 (0.14, 21.52)	1.76 (0.12, 30.43)	1

Table 215: Meta-analysis Results of Functional Class Worsening, Naive Populations of All Studies (Fixed)								
	Placebo	**Riociguat max 2.5 mg**	**Epoprostenol**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	**4.44 (1.59, 14.66)**	**2.49 (1.07, 6.63)**	2.18 (0.96, 5.43)	**8.80 (2.95, 39.43)**	**3.96 (1.23, 18.57)**	3.75 (0.91, 27.70)	2.20 (0.70, 8.95)
Riociguat max 2.5 mg	**0.23 (0.07, 0.63)**	1	0.56 (0.13, 2.33)	0.49 (0.11, 1.95)	2.00 (0.39, 12.17)	0.90 (0.17, 5.67)	0.85 (0.13, 7.91)	0.50 (0.09, 2.83)
Epoprostenol	**0.40 (0.15, 0.93)**	1.78 (0.43, 7.72)	1	0.87 (0.24, 3.05)	3.55 (0.81, 19.66)	1.59 (0.34, 9.22)	1.51 (0.27, 13.11)	0.88 (0.20, 4.54)
Bosentan 125 mg	0.46 (0.18, 1.04)	2.04 (0.51, 8.70)	1.15 (0.33, 4.14)	1	4.07 (0.96, 22.25)	1.83 (0.41, 10.43)	1.73 (0.32, 14.79)	1.01 (0.23, 5.19)
Ambrisentan 5 mg	**0.11 (0.03, 0.34)**	0.50 (0.08, 2.56)	0.28 (0.05, 1.24)	0.25 (0.04, 1.04)	1	0.45 (0.07, 2.69)	0.42 (0.05, 4.12)	0.25 (0.04, 1.49)
Ambrisentan 10 mg	**0.25 (0.05, 0.81)**	1.12 (0.18, 6.02)	0.63 (0.11, 2.92)	0.55 (0.10, 2.44)	2.24 (0.37, 13.39)	1	0.95 (0.12, 9.45)	0.55 (0.08, 3.46)
Sildenafil 20 mg	0.27 (0.04, 1.10)	1.17 (0.13, 7.65)	0.66 (0.08, 3.75)	0.58 (0.07, 3.17)	2.36 (0.24, 18.38)	1.05 (0.11, 8.65)	1	0.58 (0.06, 4.34)
Tadalafil 40 mg	0.45 (0.11, 1.44)	2.01 (0.35, 10.62)	1.13 (0.22, 5.13)	0.99 (0.19, 4.31)	4.03 (0.67, 26.33)	1.80 (0.29, 12.32)	1.72 (0.23, 16.85)	1

Table 216: Meta-analysis Results of Functional Class Worsening, Total Populations of All Studies; No Macitentan (Random)									
	Placebo	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	1	1.94 (0.48, 9.78)	**4.26 (1.04, 18.85)**	2.34 (0.71, 8.41)	**2.85 (1.22, 7.87)**	**9.35 (2.36, 54.14)**	3.94 (0.79, 26.44)	3.88 (0.64, 40.32)	1.62 (0.43, 7.37)
Riociguat max 1.5 mg	0.52 (0.10, 2.07)	1	2.18 (0.42, 10.20)	1.21 (0.16, 7.71)	1.47 (0.24, 8.39)	4.82 (0.59, 44.96)	2.03 (0.21, 20.89)	2.00 (0.18, 29.74)	0.84 (0.10, 6.44)
Riociguat max 2.5 mg	**0.23 (0.05, 0.96)**	0.46 (0.10, 2.38)	1	0.55 (0.08, 3.60)	0.67 (0.13, 3.91)	2.21 (0.29, 20.84)	0.93 (0.10, 9.56)	0.92 (0.09, 13.65)	0.38 (0.05, 2.98)
Epoprostenol	0.43 (0.12, 1.42)	0.83 (0.13, 6.35)	1.80 (0.28, 12.46)	1	1.22 (0.27, 6.03)	4.01 (0.61, 33.30)	1.69 (0.22, 15.98)	1.67 (0.18, 22.95)	0.69 (0.11, 4.79)
Bosentan 125 mg	**0.35 (0.13, 0.82)**	0.68 (0.12, 4.11)	1.49 (0.26, 7.99)	0.82 (0.17, 3.74)	1	3.27 (0.59, 22.39)	1.38 (0.20, 11.10)	1.35 (0.17, 15.93)	0.57 (0.11, 3.12)
Ambrisentan 5 mg	**0.11 (0.02, 0.42)**	0.21 (0.02, 0.21)	0.45 (0.05, 3.41)	0.25 (0.03, 1.64)	0.31 (0.04, 1.70)	1	0.42 (0.05, 3.49)	0.42 (0.03, 6.16)	0.17 (0.02, 1.33)
Ambrisentan 10 mg	0.25 (0.04, 1.26)	0.49 (0.05, 4.78)	1.07 (0.10, 9.60)	0.59 (0.06, 4.58)	0.73 (0.09, 5.01)	2.37 (0.29, 20.96)	1	0.99 (0.07, 16.55)	0.41 (0.04, 3.72)
Sildenafil 20 mg	0.26 (0.02, 1.57)	0.50 (0.03, 5.69)	1.09 (0.07, 11.41)	0.60 (0.04, 5.48)	0.74 (0.06, 6.00)	2.40 (0.16, 29.68)	1.01 (0.06, 13.90)	1	0.42 (0.03, 4.40)
Tadalafil 40 mg	0.62 (0.14, 2.31)	1.20 (0.16, 9.52)	2.62 (0.34, 19.03)	1.44 (0.21, 8.85)	1.77 (0.32, 9.46)	5.78 (0.75, 51.51)	2.44 (0.27, 24.28)	2.40 (0.23, 35.01)	1

Table 217: Meta-analysis Results of Functional Class Worsening, Total Populations of All Studies; No Macitentan (Fixed)

	Placebo	Riociguat max 1.5 mg	Riociguat max 2.5 mg	Epoprostenol	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	1	1.92 (0.78, 5.98)	**4.25 (1.95, 10.15)**	**2.50 (1.07, 6.70)**	**2.75 (1.41, 5.81)**	**8.91 (2.97, 40.31)**	**3.99 (1.23, 18.96)**	3.78 (0.92, 28.84)	1.62 (0.71, 4.18)
Riociguat max 1.5 mg	0.52 (0.17, 1.28)	1	2.21 (0.67, 6.35)	1.30 (0.32, 4.94)	1.43 (0.38, 4.63)	4.65 (0.96, 26.74)	2.07 (0.41, 12.54)	1.97 (0.32, 17.94)	0.84 (0.21, 3.11)
Riociguat max 2.5 mg	**0.24 (0.10, 0.51)**	0.45 (0.16, 1.50)	1	0.59 (0.17, 2.07)	0.65 (0.21, 1.92)	2.12 (0.51, 11.41)	0.94 (0.22, 5.33)	0.90 (0.17, 7.75)	0.38 (0.11, 1.30)
Epoprostenol	**0.40 (0.15, 0.94)**	0.77 (0.20, 3.17)	1.70 (0.48, 5.74)	1	1.10 (0.33, 3.43)	3.59 (0.81, 20.10)	1.60 (0.34, 0.22)	1.52 (0.27, 13.57)	0.65 (0.18, 2.31)
Bosentan 125 mg	**0.36 (0.17, 0.71)**	0.70 (0.22, 2.61)	1.54 (0.52, 4.66)	0.91 (0.29, 3.01)	1	3.26 (0.85, 16.88)	1.46 (0.36, 7.84)	1.38 (0.27, 11.60)	0.59 (0.19, 1.88)
Ambrisentan 5 mg	**0.11 (0.02, 0.34)**	0.22 (0.04, 1.05)	0.47 (0.09, 1.95)	0.28 (0.05, 1.24)	0.31 (0.06, 1.18)	1	0.45 (0.07, 2.70)	0.42 (0.05, 4.22)	**0.18 (0.03, 0.78)**
Ambrisentan 10 mg	**0.25 (0.05, 0.81)**	0.48 (0.08, 2.47)	1.06 (0.19, 4.62)	0.62 (0.11, 2.94)	0.69 (0.13, 2.80)	2.24 (0.37, 13.65)	1	0.95 (0.12, 9.68)	0.40 (0.07, 1.85)
Sildenafil 20 mg	0.26 (0.03, 1.09)	0.51 (0.06, 3.13)	1.11 (0.13, 5.99)	0.66 (0.07, 3.77)	0.72 (0.09, 3.65)	2.37 (0.24, 18.74)	1.05 (0.10, 8.66)	1	0.43 (0.05, 2.37)
Tadalafil 40 mg	0.62 (0.24, 1.42)	1.19 (0.32, 4.80)	2.62 (0.77, 8.72)	1.54 (0.43, 5.57)	1.70 (0.53, 5.20)	**5.54 (1.28, 30.77)**	2.47 (0.54, 14.30)	2.35 (0.42, 20.61)	1

Table 218: Meta-analysis Results of Six-Minute Walk Distance, Total Populations of All Studies (Random)

	Placebo	Macitentan 10 mg	Riociguat max 1.5 mg	Riociguat max 2.5 mg	Epoprostenol	Treprostinil s.c. or i.v.	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	0										
Macitentan 10 mg	**21.8 (5.0, 39.3)**	0									
Riociguat max 1.5 mg	**36.1 (10.3, 61.0)**	14.4 (–17.3, 44.8)	0								
Riociguat max 2.5 mg	**35.2 (17.4, 53.2)**	13.3 (–11.6, 38.0)	–0.8 (–22.2, 20.8)	0							
Epoprostenol	**71.5 (39.9, 102.6)**	**49.8 (13.0, 86.1)**	35.4 (–4.7, 77.7)	36.3 (–0.3, 72.3)	0						
Treprostinil subcutaneous or intravenous	**23.6 (7.6, 39.0)**	1.6 (–21.9, 25.6)	–12.3 (–42.1, 17.6)	–11.7 (–35.2, 11.6)	**–47.9 (–82.7, –13.0)**	0					
Bosentan 125 mg	**30.5 (16.9, 44.4)**	8.7 (–13.1, 30.5)	–5.5 (–33.4, 24.0)	–4.8 (–26.8, 18.1)	**–41.2 (–75.2, –6.7)**	6.9 (–13.5, 27.8)	0				
Ambrisentan 5 mg	**45.0 (24.5, 63.7)**	23.2 (–3.3, 48.3)	8.7 (–23.2, 42.1)	9.5 (–17.6, 35.8)	–26.6 (–67.2, 10.0)	21.3 (–3.9, 46.4)	14.6 (–11.7, 37.4)	0			
Ambrisentan 10 mg	**53.1 (31.3, 74.6)**	**31.3 (3.5, 58.5)**	16.8 (–15.9, 50.5)	17.8 (–10.4, 45.9)	–18.5 (–58.1, 20.8)	**29.3 (3.4, 56.0)**	22.4 (–3.3, 48.1)	8.1 (–10.9, 28.4)	0		
Sildenafil 20 mg	**43.1 (24.4, 62.4)**	21.3 (–4.3, 46.8)	6.9 (–24.5, 39.5)	7.8 (–17.5, 34.3)	–28.6 (–65.8, 8.6)	19.4 (–4.7, 44.2)	12.8 (–11.1, 35.5)	–2.0 (–27.8, 25.1)	–10.0 (–38.3, 18.4)	0	
Tadalafil 40 mg	**31.4 (13.6, 49.3)**	9.9 (–15.0, 34.3)	–4.4 (–34.9, 26.6)	–3.4 (–29.1, 20.9)	**–40.3 (–75.7, –3.2)**	8.1 (–16.1, 31.5)	0.9 (–21.7, 23.5)	–13.3 (–39.2, 12.9)	–21.6 (–49.2, 6.4)	–11.5 (–37.6, 14.3)	0

Table 219: Meta-analysis Results of Six-Minute Walk Distance, Total Populations of All Studies (Fixed)

	Placebo	Macitentan 10 mg	Riociguat max 1.5 mg	Riociguat max 2.5 mg	Epoprostenol	Treprostinil s.c. or i.v.	Bosentan 125 mg	Ambrisentan 5 mg	Ambrisentan 10 mg	Sildenafil 20 mg	Tadalafil 40 mg
Placebo	0										
Macitentan 10 mg	**21.6 (5.5, 37.9)**	0									
Riociguat max 1.5 mg	**36.2 (11.7, 60.5)**	14.4 (–14.8, 43.8)	0								
Riociguat max 2.5 mg	**35.5 (18.6, 52.4)**	13.8 (–9.8, 37.4)	–0.7 (–21.7, 20.2)	0							
Epoprostenol	**71.9 (40.2, 103.7)**	**50.1 (14.6, 85.8)**	35.7 (–4.3, 75.9)	**36.4 (0.4, 72.4)**	0						
Treprostinil subcutaneous or intravenous	**23.3 (8.8, 37.9)**	1.7 (–20.1, 23.5)	–12.8 (–41.1, 15.5)	–12.2 (–34.4, 10.3)	**–48.6 (–83.5, –13.6)**	0					
Bosentan 125 mg	**30.4 (16.4, 44.4)**	8.8 (–12.9, 30.2)	–5.7 (–33.7, 22.3)	–5.1 (–26.9, 16.9)	**–41.5 (–76.2, –6.7)**	7.1 (–13.1, 27.3)	0				
Ambrisentan 5 mg	**45.2 (26.0, 64.4)**	23.5 (–1.7, 48.7)	9.0 (–21.9, 40.1)	9.7 (–15.9, 35.3)	–26.7 (–63.7, 10.4)	21.9 (–2.2, 46.0)	14.8 (–9.0, 38.6)	0			
Ambrisentan 10 mg	**53.5 (32.3, 74.9)**	**31.8 (5.0, 58.7)**	17.4 (–15.0, 49.6)	18.0 (–9.2, 45.0)	–18.4 (–56.5, 19.8)	**30.2 (4.5, 56.0)**	23.0 (–2.5, 48.7)	8.3 (–10.9, 27.4)	0		
Sildenafil 20 mg	**43.4 (25.5, 61.2)**	21.7 (–2.4, 45.8)	7.2 (–22.9, 37.4)	7.9 (–16.7, 32.4)	–28.5 (–65.0, 8.0)	20.1 (–2.9, 43.1)	13.0 (–9.7, 35.6)	–1.7 (–28.2, 24.4)	–10.1 (–37.7, 17.7)	0	
Tadalafil 40 mg	**31.7 (14.5, 49.1)**	10.0 (-13.6, 33.9)	-4.5 (-34.3, 25.3)	-3.8 (-28.0, 20.6)	**-40.1 (-76.4, -4.0)**	8.4 (-14.2, 30.9)	1.3 (-20.9, 23.6)	-13.5 (-39.3, 12.3)	-21.8 (-49.0, 5.6)	-11.7 (-36.7, 13.2)	0

Table 220: Meta-analysis Results of Six-Minute Walk Distance, Naive Populations of All Studies (Random)											
	Placebo	**Macitentan 10 mg**	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Treprostinil s.c. or i.v.**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	0										
Macitentan 10 mg	15.2 (–15.2, 46.2)	0									
Riociguat max 1.5 mg	**53.4 (18.5, 86.9)**	38.5 (–8.3, 83.2)	0								
Riociguat max 2.5 mg	**36.9 (12.0, 62.7)**	21.9 (–18.0, 60.4)	–16.3 (–47.4, 15.2)	0							
Epoprostenol	**71.7 (41.0, 103.1)**	**56.9 (12.9, 98.2)**	18.7 (–27.1, 65.6)	34.7 (–4.9, 75.1)	0						
Treprostinil subcutaneous or intravenous	**23.7 (8.0, 38.9)**	8.4 (–25.6, 42.8)	–29.7 (–65.6, 7.5)	–13.1 (–43.1, 16.1)	**–47.9 (–83.9, –14.0)**	0					
Bosentan 125 mg	**37.7 (19.4, 56.0)**	22.5 [–13.1, 58.4	–15.4 (–53.4, 23.2)	0.8 (–31.3, 31.8)	–34.0 (–70.0, 2.3)	14.2 (–9.9, 38.2)	0				
Ambrisentan 5 mg	**45.0 (25.4, 65.1)**	29.9 (–6.1, 66.6)	–8.4 (–46.5, 31.5)	8.2 (–23.7, 39.8)	–26.7 (–64.5, 11.1)	21.3 (–3.7, 47.8)	7.0 (–18.4, 34.5)	0			
Ambrisentan 10 mg	**53.2 (31.5, 75.3)**	**38.3 (0.7, 74.4)**	0.4 (–39.6, 39.5)	16.5 (–16.8, 49.1)	–18.3 (–56.7, 20.5)	**29.6 (2.9, 56.6)**	15.3 (–12.4, 43.8)	8.2 (–11.4, 27.8)	0		
Sildenafil 20 mg	**43.4 (24.6, 61.7)**	28.0 (–7.6, 64.0)	–10.1 (–48.2, 29.2)	6.5 (–26.1, 37.6)	–28.6 (–64.9, 7.8)	19.7 (–4.4, 43.3)	5.5 (–21.0, 31.8)	–1.9 (–29.3, 25.3)	–10.1 (–38.4, 18.6)	0	
Tadalafil 40 mg	**43.7 (18.1, 69.4)**	28.3 (–10.7, 67.8)	–9.7 (–51.9, 33.5)	6.8 (–29.1, 42.8)	–28.0 (–69.0, 11.6)	20.0 (–10.1, 50.4)	5.6 (–26.1, 38.0)	–1.4 (–34.1, 30.5)	–9.6 (–43.7, 24.8)	0.2 (–30.7, 32.7)	0

Table 221: Meta-analysis Results of Six-Minute Walk Distance, Naive Populations of All Studies (Fixed)											
	Placebo	**Macitentan 10 mg**	**Riociguat max 1.5 mg**	**Riociguat max 2.5 mg**	**Epoprostenol**	**Treprostinil s.c. or i.v.**	**Bosentan 125 mg**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil 20 mg**	**Tadalafil 40 mg**
Placebo	0										
Macitentan 10 mg	14.7 (–15.2, 44.5)	0									
Riociguat max 1.5 mg	**53.3 (19.2, 87.3)**	38.6 (–6.7, 83.9)	0								
Riociguat max 2.5 mg	**36.7 (12.1, 61.2)**	22.0 (–16.7, 60.5)	–16.6 (–46.9, 13.5)	0							
Epoprostenol	**72.0 (40.4, 103.7)**	**57.3 (13.7, 101.0)**	18.7 (–27.8, 65.3)	35.4 (–4.7, 75.2)	0						
Treprostinil subcutaneous or intravenous	**23.3 (8.7, 37.8)**	8.6 (–25.6, 42.8)	–30.0 (–67.0, 7.1)	–13.4 (–41.9, 15.0)	**–48.7 (–83.6, –13.7)**	0					
Bosentan 125 mg	**37.7 (19.9, 55.5)**	22.5 (–13.1, 58.4)	–15.6 (–54.0, 22.9)	1.0 (–29.4, 31.4)	–34.3 (–70.7, 2.1)	14.4 (–8.7, 37.4)	0				
Ambrisentan 5 mg	**45.2 (26.0, 64.3)**	29.9 (–6.1, 66.6)	–8.2 (–47.0, 31.0)	8.5 (–22.4, 39.6)	–26.7 (–63.7, 10.1)	21.9 (–2.1, 46.1)	7.6 (–18.8, 33.7)	0			
Ambrisentan 10 mg	**53.6 (32.1, 74.8)**	**38.9 (2.3, 75.5)**	0.3 (–39.6, 40.5)	16.9 (–15.5, 49.3)	–18.3 (–56.7, 19.6)	**30.3 (4.4, 56.1)**	15.9 (–12.0, 43.6)	8.4 (–10.8, 27.5)	0		
Sildenafil 20 mg	**43.4 (25.5, 61.1)**	28.6 (–5.8, 63.5)	–10.0 (–48.4, 28.5)	6.6 (–23.5, 37.0)	–28.6 (–65.0, 7.7)	20.1 (–3.0, 43.2)	5.7 (–19.4, 31.0)	–1.8 (–27.8, 24.3)	–10.2 (–37.8, 17.7)	0	
Tadalafil 40 mg	**43.6 (18.4, 68.8)**	28.9 (–9.6, 68.0)	–9.7 (–51.7, 32.9)	7.0 (–28.3, 42.2)	–28.4 (–69.1, 12.3)	20.4 (–8.8, 49.4)	5.9 (–24.9, 36.8)	–1.6 (–33.2, 30.1)	–10.0 (–42.8, 23.0)	0.2 (–30.8, 31.2)	0

Table 222: Meta-analysis Results of Clinical Worsening, Add-on to Endothelin Receptor Antagonist Pre-treated Populations (Random)			
	ERA + Placebo	**ERA + Riociguat max 1.5 mg**	**ERA + Tadalafil 40 mg**
ERA + Placebo	1	7.65 (0.74, 268.02)	2.79 (0.95, 9.33)
ERA + Riociguat max 1.5 mg	0.13 (0.004, 1.35)	1	0.36 (0.01, 5.15)
ERA + Tadalafil 40 mg	0.36 (0.11, 1.05)	2.75 (0.19, 112.80)	1

Table 223: Meta-analysis Results of Clinical Worsening, Add-on to Endothelin Receptor Antagonist Pre-treated Populations (Fixed)			
	ERA + Placebo	ERA + Riociguat max 1.5 mg	ERA + Tadalafil 40 mg
ERA + Placebo	1	7.66 (0.91, 230.52)	2.79 (1.22, 7.32)
ERA + Riociguat max 1.5 mg	0.13 (0.004, 1.10)	1	0.36 (0.01, 3.90)
ERA + Tadalafil 40 mg	0.36 (0.14, 0.82)	2.76 (0.26, 91.02)	1

Table 224: Meta-analysis Results of Functional Class Improvement, Add-on to Endothelin Receptor Antagonist Pre-treated Populations (Random)			
	ERA + Placebo	ERA + Riociguat max 1.5 mg	ERA + Tadalafil 40 mg
ERA + Placebo	1	0.55 (0.24, 2.12)	1.07 (0.48, 3.68)
ERA + Riociguat max 1.5 mg	1.83 (0.47, 4.10)	1	1.95 (0.44, 8.37)
ERA + Tadalafil 40 mg	0.93 (0.27, 2.10)	0.51 (0.12, 2.28)	1

Table 225: Meta-analysis Results of Functional Class Improvement, Add-on to Endothelin Receptor Antagonist Pre-treated Populations (Fixed)			
	ERA + Placebo	ERA + Riociguat max 1.5 mg	ERA + Tadalafil 40 mg
ERA + Placebo	1	0.54 (0.29, 1.01)	0.96 (0.60, 1.59)
ERA + Riociguat max 1.5 mg	1.84 (0.99, 3.40)	1	1.78 (0.83, 3.78)
ERA + Tadalafil 40 mg	1.04 (0.63, 1.67)	0.56 (0.26, 1.21)	1

Table 226: Meta-analysis Results of Functional Class Worsening, Add-on to Endothelin Receptor Antagonist Pre-treated Populations (Random)			
	ERA + Placebo	ERA + Riociguat max 1.5 mg	ERA + Tadalafil 40 mg
ERA + Placebo	1	2.57 (0.60, 12.77)	1.80 (0.66, 5.33)
ERA + Riociguat max 1.5 mg	0.39 (0.08, 1.68)	1	0.70 (0.10, 4.32)
ERA + Tadalafil 40 mg	0.56 (0.19, 1.52)	1.43 (0.23, 9.53)	1

Table 227: Meta-analysis Results of Functional Class Worsening, Add-on to Endothelin Receptor Antagonist Pre-treated Populations (Fixed)			
	ERA + Placebo	ERA + Riociguat max 1.5 mg	ERA + Tadalafil 40 mg
ERA + Placebo	1	2.56 (0.81, 8.98)	1.83 (0.85, 4.25)
ERA + Riociguat max 1.5 mg	0.39 (0.11, 1.24)	1	0.72 (0.16, 3.04)
ERA + Tadalafil 40 mg	0.55 (0.24, 1.17)	1.40 (0.33, 6.19)	1

Table 228: Meta-analysis Results Six-Minute Walk Distance, Add-on to Endothelin Receptor Antagonist Pre-treated Populations (Random)			
	ERA + Placebo	ERA + Riociguat max 1.5 mg	ERA + Tadalafil 40 mg
ERA + Placebo	0		
ERA + Riociguat max 1.5 mg	22.9 (–2.2, 47.2)	0	
ERA + Tadalafil 40 mg	22.7 (–1.2, 46.1)	–0.1 (–35.0, 34.0)	0

Table 229: Meta-analysis Results of Six-Minute Walk Distance, Add-on to Endothelin Receptor Antagonist Pre-treated Populations (Fixed)			
	ERA + Placebo	ERA + Riociguat max 1.5 mg	ERA + Tadalafil 40 mg
ERA + Placebo	0		
ERA + Riociguat max 1.5 mg	22.9 (–0.6, 46.6)	0	
ERA + Tadalafil 40 mg	22.5 (–0.7, 46.0)	–0.5 (–33.5, 32.6)	0

APPENDIX 13: QUALITY OF LIFE

<table>
<tr><th>Study</th><th>Instrument used</th><th>Findings</th></tr>
<tr><td>ARIES-1 (2008)[18]

Placebo
Ambrisentan 5 mg
Ambrisentan 10 mg</td><td>SF-36 Health Survey</td><td>
<table>
<tr><th>SF-36 scale</th><th>Treatment</th><th>Change from baseline, mean (SD)*</th><th>P value</th></tr>
<tr><td rowspan="3">Physical functioning</td><td>Placebo</td><td>2.31 ± 7.65</td><td>--</td></tr>
<tr><td>5 mg Ambrisentan</td><td>3.68 ± 7.14</td><td>0.543</td></tr>
<tr><td>10 mg Ambrisentan</td><td>4.52 ± 7.16</td><td>0.111</td></tr>
</table>
*Data from FDA Clinical Review
</td></tr>
<tr><td colspan="3">Conclusions: There were no statistically significant differences between placebo and ambrisentan for physical functioning and the rest of the SF-36 scales.</td></tr>
<tr><td>ARIES-2 (2008)[18]

Placebo
Ambrisentan 5 mg</td><td>SF-36 Health Survey</td><td>
<table>
<tr><th>SF-36 scale</th><th>Treatment</th><th>Change from baseline, mean (SD)*</th><th>P value</th></tr>
<tr><td rowspan="2">Physical functioning</td><td>Placebo</td><td>–0.20 ± 7.14</td><td>--</td></tr>
<tr><td>5 mg Ambrisentan</td><td>2.96 ± 6.81</td><td>0.040</td></tr>
</table>
*Data from FDA Clinical Review
</td></tr>
<tr><td colspan="3">Conclusions: There were improvements with ambrisentan for physical functioning and several other SF-36 scales, including Role–Physical, Vitality, Role–Emotional, and General Health.</td></tr>
<tr><td>Badesch et al. (2000)[19]</td><td>NR</td><td>NR</td></tr>
<tr><td rowspan="2">Barst et al. (1996)[20]

Conventional therapy
Epoprostenol</td><td>Chronic Heart Failure Questionnaire</td><td>
<table>
<tr><th>Scale</th><th>Treatment</th><th>Change from baseline, median</th><th>Hodges-Lehmann estimate (95% CI)[a]</th></tr>
<tr><td rowspan="2">Dyspnea</td><td>Conventional</td><td>0.0</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>8.0</td><td>7.0 (4.0 to 10.0)</td></tr>
<tr><td rowspan="2">Fatigue</td><td>Conventional</td><td>0.0</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>5.0</td><td>5.0 (3.0 to 7.0)</td></tr>
<tr><td rowspan="2">Emotional function</td><td>Conventional</td><td>–1.0</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>6.0</td><td>7.0 (3.0 to 10.0)</td></tr>
<tr><td rowspan="2">Mastery[b]</td><td>Conventional</td><td>–0.5</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>3.0</td><td>2.5 (1.0 to 4.0)</td></tr>
</table>
[a]positive values indicate improvement
[b]patient's feeling of control over his or her disease
</td></tr>
<tr><td>Nottingham Health Profile</td><td>
<table>
<tr><th>Scale</th><th>Treatment</th><th>Change from baseline, median</th><th>Hodges-Lehmann estimate (95% CI)[c]</th></tr>
<tr><td rowspan="2">Emotional reaction</td><td>Conventional</td><td>0.0</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>–10.0</td><td>–14.7 (–24.5 to –4.9)</td></tr>
<tr><td rowspan="2">Energy</td><td>Conventional</td><td>0.0</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>–36.8</td><td>–36.8 (–60.8 to 0.0)</td></tr>
<tr><td rowspan="2">Pain</td><td>Conventional</td><td>0.0</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>0.0</td><td>0.0 (–5.8 to 0.0)</td></tr>
<tr><td rowspan="2">Physical mobility</td><td>Conventional</td><td>–6.4</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>–11.2</td><td>–9.2 (–19.9 to 2.0)</td></tr>
<tr><td rowspan="2">Sleep</td><td>Conventional</td><td>0.0</td><td>--</td></tr>
<tr><td>Epoprostenol</td><td>–16.1</td><td>–21.7 (–34.3 to –9.1)</td></tr>
<tr><td>Social isolation</td><td>Conventional</td><td>0.0</td><td>--</td></tr>
</table>
</td></tr>
</table>

Study	Instrument used	Findings
		Epoprostenol | 0.0 | 0.0 (–20.1 to 0.0) [c] negative values indicate improvement
	Dyspnea-Fatigue Rating	Treatment | Change from baseline, median | Hodges-Lehmann estimate (95% CI)[d] Conventional | 0.0 | -- Epoprostenol | 1.0 | 2.0 (1.0 to 3.0) [d] positive values indicate improvement
Conclusions: There were statistically significant improvements with epoprostenol in four parts of the Chronic Heart Failure Questionnaire, in two of six parts of the Nottingham Health Profile, and in the Dyspnea-Fatigue Rating ($P < 0.01$).		
BREATHE-1 (2002)[21]	NR	NR
BREATHE-5 (2006)[22]	NR	NR
Channick et al. (2001)[23]	NR	NR
EARLY (2008)[32] Placebo Bosentan	SF-36 Health Survey	Scale | Treatment effect of bosentan relative to placebo: Effect size (95% CI) | *P* value Physical functioning | 3.1 (–2.5 to 8.7) | 0.2563 Role–physical | 7.7 (–1.3 to 16.7) | 0.1285 Pain index | 1.6 (–7.3 to 10.5) | 0.9281 General health perceptions | 5.5 (0.2 to 10.8) | 0.0674 Vitality | 4.0 (–2.2 to 10.2) | 0.1822 Social functioning | 1.4 (–7.3 to 10.2) | 0.6883 Mental health | 4.3 (–1.9 to 10.5) | 0.1577 Role–emotional | –0.4 (–9.1 to 8.3) | 0.9383
Conclusions: There were no statistically significant differences between bosentan and placebo for 8 components of SF-36.		
Galiè et al. (2005)[24] Ambrisentan 5 mg Ambrisentan 10 mg	Subject Global Assessment	• The mean Subject Global Assessment score for all ambrisentan dose groups (1 mg, 2.5 mg, 5 mg, 10 mg) combined improved by +11.3 ± 2.4 mm at week 12 compared with baseline ($P < 0.0001$). • There were no differences among dose groups.
Conclusions: There were improvements with ambrisentan in quality of life judging from Subject Global Assessment compared with baseline.		
McLaughlin et al. (2003)[25]	NR	NR
PATENT-1 (2013)[33] Placebo Riociguat 1.5 mg Riociguat 2.5 mg	EQ-5D	Treatment | Change from baseline, mean (SD) | *P* value Placebo | –0.03 ± 0.30 | -- 1.5 mg Riociguat | 0.08± 0.3 | 0.09 2.5 mg Riociguat | 0.03 ± 0.24 | 0.07
	LPH Questionnaire	Treatment | Change from baseline, mean (SD) | *P* value Placebo | 0.4 ±18 | -- 1.5 mg Riociguat | –10 ± 21 | < 0.0001 2.5 mg Riociguat | –6 ± 18 | 0.002
Conclusions: There were no statistically significant differences between Riociguat and placebo in EQ-5D score. However, on the LPH scores, there were significant improvements with Riociguat.		
PHIRST (2009)[34] Placebo Tadalafil 40 mg	SF-36 Health Survey	Tadalafil 40 mg had statistically significant improvements in 6 of the 8 domains of the SF-36 health survey ($P < 0.01$).
	EQ-5D	Tadalafil 40 mg displayed improvements in all sections of the EQ-5D questionnaire ($P < 0.02$)
Conclusions: Tadalafil 40 mg improved HRQoL from baseline to week 16 of treatment.		

<table>
<tr><th>Study</th><th>Instrument used</th><th>Findings</th></tr>
<tr><td>Rubenfire et al. (2007)[26]</td><td>NR</td><td>NR</td></tr>
<tr><td>Rubin et al. (1990)[27]</td><td>NR</td><td>NR</td></tr>
<tr><td>SERAPHIN (2013)[35]

Placebo
Macitentan 3 mg
Macitentan 10 mg</td><td>SF-36</td><td>Macitentan of both doses showed improvements in all domains of SF-36 compared with placebo (data reported in graphical form in the FDA Clinical Review).

Risk (hazard ratio) of deterioration of HRQoL scores (as measured bt time to first occurrence of a ≥ 5 point decrease)
<table><tr><th>Macitentan</th><th>PCS</th><th>MCS</th></tr><tr><td>3 mg</td><td>0.70 (0.54, 0.92)</td><td>0.81 (0.63, 1.03)</td></tr><tr><td>10 mg</td><td>0.65 (0.50, 0.85)</td><td>0.79 (0.61, 1.01)</td></tr></table>Metha et al. (2013)[89]</td></tr>
<tr><td colspan="3">Conclusions: Macitentan showed improvements in quality of life compared with placebo</td></tr>
<tr><td>Simonneau et al. (2002)[28]

Placebo
Treprostinil</td><td>Minnesota Living with Heart Failure Questionnaire (global, physical, and emotional)</td><td><table><tr><th>Scale</th><th>Treatment</th><th>Change from baseline, mean (SD)*</th><th>P value</th></tr><tr><td>Global</td><td>Placebo</td><td>–1.9 ± 1.4</td><td>--</td></tr><tr><td></td><td>Treprostinil</td><td>–6.6 ± 1.6</td><td>0.17</td></tr><tr><td>Physical</td><td>Placebo</td><td>–1.9 ± 1.4</td><td>--</td></tr><tr><td></td><td>Treprostinil</td><td>–4.5 ± 0.7</td><td>0.0064</td></tr><tr><td>Emotional</td><td>Placebo</td><td>–0.3 ± 0.5</td><td>--</td></tr><tr><td></td><td>Treprostinil</td><td>–1.3 ± 0.5</td><td>NR</td></tr></table></td></tr>
<tr><td colspan="3">Conclusions: Treprostinil showed significant improvement only in physical dimension score at week 12.</td></tr>
<tr><td>STRIDE-2 (2006)[29]</td><td>NR</td><td>NR</td></tr>
<tr><td>SUPER (2005)[30]

Placebo
Sildenafil 20 mg</td><td>SF-36 Health Survey</td><td><table><tr><th>Scale</th><th>Treatment</th><th>Change from baseline, mean (SD)*</th><th>P value</th></tr><tr><td>Physical functioning</td><td>Placebo</td><td>4.48</td><td>--</td></tr><tr><td></td><td>Sildenafil pooled</td><td>13.71</td><td>< 0.001</td></tr><tr><td>General health</td><td>Placebo</td><td>0.31</td><td>--</td></tr><tr><td></td><td>Sildenafil pooled</td><td>7.98</td><td>< 0.001</td></tr><tr><td>Vitality</td><td>Placebo</td><td>5.5</td><td>--</td></tr><tr><td></td><td>Sildenafil pooled</td><td>11.69</td><td>< 0.05</td></tr></table></td></tr>
<tr><td></td><td>EQ-5D</td><td>Sildenafil had statistically significant improvements in the current health state and utility index scores on the EQ-5D at week 12 (both P < 0.01).</td></tr>
<tr><td colspan="3">Conclusions: Sildenafil showed statistically significant improvements in the physical functioning, general health, and vitality scores of SF-36. Improvements were also observed in the current health status and utility index scores of the EQ-5D. There was no evidence of a dose-related response.</td></tr>
<tr><td>TRUST (2010)[31]</td><td>NR</td><td>NR</td></tr>
</table>

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; HRQoL = health-related quality of life; LPH = Living with Pulmonary Hypertension; MCS = mental component score; NR = not reported; PCS = physical component score; SD = standard deviation; SF-36 = Short-Form (36-Item) Health Survey.

APPENDIX 14: COMBINATION THERAPY IN PULMONARY ARTERIAL HYPERTENSION — STUDIES NOT INCLUDED IN THERAPEUTIC REVIEW

Table 230: Characteristics of Combination Therapy Studies

First Author, Publication Year, Country, Sponsor	Study Design, Length of follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparators	Clinical Outcomes
Systematic reviews					
Fox et al., 2011[93] Canada Sponsor: Public funding	SR/MA of 6 DB placebo-controlled RCTs (PHIRST-1b, TRIUMPH-1, PACES, STEP, COMBI, BREATHE-2)	Total 729 PAH patients Mean age: 51 years Class II to IV IPAH APAH Patients were naive or had been on stable doses of first PAH therapy	Add-on therapy: Tadalafil, treprostinil, sildenafil, iloprost, bosentan	Baseline therapy: Bosentan, sildenafil, epoprostenol	• 6MWD • NYHA FC • Mortality • Hospitalization • Need for escalation therapy • Premature discontinuation • Clinical worsening
RCTs					
Humbert et al., 2004[137] BREATHE-2 USA, France, Italy, Netherlands Sponsor: Actelion	DB RCT; 16 weeks	33 PAH patients started epoprostenol 2 days before randomization Mean age: 46 years Class III (76%); Class IV (24%) Idiopathic (82%) Associated (18%)	Bosentan 125 mg twice daily (n = 22) + epoprostenol	Placebo (n = 11) + epoprostenol	• TPR • Cardiac index • PVR • mPAP • mRAP • 6MWD • Dyspnea-Fatigue Rating • NYHA FC • Safety
Observational studies					
Bergot et al., 2014[94] France Sponsor: Actelion	Retrospective study (French PH registry from 2006 to 2010) First assessment: median 4 months Follow-up: median 24 months	Newly diagnosed adult PAH patients (N = 78) Mean age: 48 years Class III/IV (92%) Idiopathic (76%) Heritable (17%) Anorexigen (7)	First-line therapy (n=43): Epoprostenol (n=17) Combination (epoprostenol + ERA and/or PDI-5 I) (n = 26) Add-on therapy (n = 35) 94% received ERA and/or PDE-5 I prior to epoprostenol		• NYHA FC • 6MWD • Hemodynamics • Survival
Sitbon et al., 2014[95]	Retrospective study (French	Newly diagnosed adult PAH	Triple therapy: Epoprostenol i.v.		• NYHA FC • 6MWD

Table 230: Characteristics of Combination Therapy Studies					
First Author, Publication Year, Country, Sponsor	**Study Design, Length of follow-up**	**Patient Characteristics, Sample Size (n)**	**Intervention**	**Comparators**	**Clinical Outcomes**
France Sponsor: NR	PAH registry from 2007 to 2012) First assessment: 4 months Follow-up: 1 year after enrolment of last patient	patients (N = 19) Mean age: 39 years Class III (42%) Class IV (58%) Idiopathic (47%) Heritable (53%)	Bosentan 125 mg twice daily Sildenafil 20 mg thrice daily		• Hemodynamics • Survival • AEs
Kemp et al., 2012[96] France Sponsor: NR	Retrospective study (French PAH Reference Centre from 2001 to 2008) First assessment: 4 months Long-term follow-up: range 7 to 81 months	Newly diagnosed adult PAH patients (N = 69) Mean age: 43 years Class III (72%) Class IV (28%) Idiopathic (65%) Heritable (16%) Anorexigen (19%)	Upfront Epoprostenol /Bosentan 125 mg twice daily (n = 23)	Epoprostenol (n = 46)	• NYHA FC • 6MWD • Hemodynamics • Survival • AEs
Keogh et al., 2011[97] Australia Sponsor: Drugs provided by manufacturers	Prospective uncontrolled study (data collection from six centres) Follow-up: 0, 1, 6, 12, 18 months after start of monotherapy	PAH patients who failed monotherapy (N = 112) Mean age: 51 years Class II (9%) Class III (67%) Class IV (24%)	Combination therapy (bosentan, sildenafil, ambrisentan, sitaxsentan, iloprost) First drug: bosentan > sildenafil > ambrisentan = sitaxsentan Second drug: Sildenafil > iloprost > bosentan > ambrisentan		• Survival • 6MWD • WHO FC • Safety
D'Alto et al., 2010[98] Italy Sponsor: NR	Open-label single- group prospective study (single centre) Follow-up: 6 months	PAH patients deteriorated on bosentan (N = 32) Mean age: 37 years Congenital heart disease-related PAH (100%)	Sildenafil 20 mg thrice daily add-on to bosentan 125 mg twice daily		• 6MWD • WHO FC • Hemodynamics • Safety
Jacobs et al., 2009[99] The Netherlands	Retrospective study Follow-up: 4 months, end of study	PAH patients who failed on oral therapy (bosentan and/or sildenafil) (N=16)	Prostanoids added to bosentan (n=6)	Prostanoids added to bosentan/sildenafil (n=10)	• 6MWD • NYHA FC • Cardiac MRI parameters • Safety

Table 230: Characteristics of Combination Therapy Studies					
First Author, Publication Year, Country, Sponsor	**Study Design, Length of follow-up**	**Patient Characteristics, Sample Size (n)**	**Intervention**	**Comparators**	**Clinical Outcomes**
Sponsor: Industries	(18 months)	Mean age: 37 years IPAH (100%) Class III (100%)			
Benza et al., 2008[100] USA Sponsor: Actelion	Retrospective study (data from Pulmonary Vascular Disease Clinic)	PAH patients (N = 38) Mean age: 49 years IPAH (42%) APAH (58%) Class II (5%) Class III (76%) Class IV (18%)	Treprostinil (n = 19) Last follow-up: 714 days	Treprostinil and bosentan combination (n = 19) (Bosentan was added to 19 patients who stayed unchanged at FC III) Last follow-up: 1,256 days	• Hemodynamics • 6MWD • NYHA FC • Borg dyspnea index • Safety
Ruiz et al., 2006[101] Spain Sponsor: NR	Retrospective study (from 2001 to 2004) Follow-up: 1, 2 years	Severe PAH patients who deteriorated on long-term treatment with prostanoids (N = 20) Mean age: 42 years Class II (10%) Class III (80%) Class IV (10%)	Addition of sildenafil (dose unspecified) as recue therapy to long-term treatment with prostanoids		• NYHA FC • 6MWD • Safety

6MWD = six-minute walk distance; AEs = adverse events; APAH = associated pulmonary arterial hypertension; BP = blood pressure; DB = double-blind; ERA = endothelin receptor antagonists; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; i.v. = intravenous; MA = meta-analysis; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; MRI = magnetic resonance imaging; NR = not reported; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDI-5 I = phosphodiesterase type-5 inhibitors; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; SR = systematic review; TPR = total pulmonary resistance; WHO = World Health Organization.

Table 231: Summary of Findings of Combination Therapy

First Author, Publication Year, Country	Main Findings
Systematic reviews	
Fox et al., 2011[93] Canada Sponsor: Public funding	**Combination therapy versus monotherapy**

Parameters	No. RCTs (No. patients)	Heterogeneity (I^2)	Effect size (95% CI)
6MWD	4 (450)	0%	WMD = 25.2 m (13.1 to 37.2)
FC improvement	3 (183)	77%	RR = 1.32 (0.38 to 4.50)
FC worsening	3 (194)	0%	RR = 0.78 (0.32 to 1.89)
Death	4 (624)	48%	RR = 0.42 (0.08 to 2.25)
Hospital admission	4 (594)	21%	RR = 0.72 (0.36 to 1.44)

Table 231: Summary of Findings of Combination Therapy

First Author, Publication Year, Country	Main Findings

Need for escalation therapy	3 (421)	0%	RR = 0.36 (0.09 to 1.39)
Study discontinuation	5 (642)	0%	RR = 0.89 (0.53 to 1.48)
Clinical worsening	4 (656)	38%	RR = 0.42 (0.17 to 1.04)

Authors' Conclusions: "*This meta-analysis suggests that in PAH, combination therapy does not offer an advantage over monotherapy apart from modestly increasing exercise capacity*" p.1177

Limitations: Pooled data from studies comparing different combination of PAH therapy; between-study heterogeneity in patient baseline characteristics; small sample size in 4 out of 6 RCTs; between-study heterogeneity in "escalation of PAH therapy; publication bias in the combination therapy literature.

RCTs

Humbert et al., 2004[137]

BREATHE-2

USA, France, Italy, Netherlands

Sponsor: Actelion

Efficacy

Variables	Placebo/epoprostenol	Bosentan/epoprostenol	*P* value
	% change from baseline (mean ± SE)		
TPR (dyn.s^{-1}cm^{5})	–22.6 ± 6.2	–36.3 ± 4.3	0.08
Cardiac index (L.min^{-1}m^{2})	37.9 ± 13.3	48.7 ± 11.0	0.6
PVR (dyn.s^{-1}cm^{5})	–25.7 ± 7.2	–35.2 ± 5.4	0.3
mPAP (mm Hg)	–2.2 ± 3.6	–9.0 ± 6.0	0.3
mRAP (mm Hg)	0.3 ± 1.3	–1.9 ± 1.4	0.7
	Placebo/epoprostenol	Bosentan/epoprostenol	
6MWD — median (m)	68	74	
Dyspnea-fatigue	Improved by 1.0 unit	No change	
FC improved	5/11 (45%)	13/22 (59%)	NS

Safety
Epoprostenol (jaw pain, diarrhea, flushing, headache)
Bosentan (edema)
Serious adverse events (no difference between groups)

Authors' Conclusions: "*This study showed a trend but no statistical significance toward hemodynamics or clinical improvement due to the combination of bosentan and epoprostenol therapy in patients with pulmonary arterial hypertension*" p 353

Limitations: small sample size, not power.

Observational studies

Bergot et al., 2014[94]

France

Sponsor: Actelion

First assessment after epoprostenol initiation (median 4 months):
First-line therapy (monotherapy (n = 17) and combination therapy (n = 26))
- FC improved: 79%
- 6MWD: + 146 m (*P* < 0.0001)
- Cardiac index: +1.2 L.min^{-1}.m^{-2} (*P* < 0.0001)
- PVR: –700 dyn.s.cm^{-5} (*P* < 0.001)
- mPAP: –10.3 mm Hg (*P* = 0.0002)
- RAP: –3.6 mm Hg (*P* = 0.0004)

Add-on therapy (n = 35)
- FC improved: 44%
- 6MWD: + 41 m (*P* = 0.03)
- Cardiac index: +0.5 L.min^{-1}.m^{-2} (*P* = 0.006)
- PVR: –299 dyn.s.cm^{-5} (p < 0.001)
- mPAP: –2.3 mm Hg (NS)
- RAP: –0.2 mm Hg (NS)

Follow-up (median 24 months)
First-line therapy (monotherapy (n = 17) and combination therapy (n = 26))

Table 231: Summary of Findings of Combination Therapy	
First Author, Publication Year, Country	**Main Findings**
	• 30/43 (70%) on triple therapy • 9/43 (21%) on double therapy • 4/43 (9%) on monotherapy • Survival: 90%, 85%, 81% for 1, 2, 3 years, respectively • Survival for combination only: 92%, 88% for 1, 3 years, respectively Add-on therapy (n = 35) • 28/35 (80%) on triple therapy • 7/37 (20%) on double therapy • Survival: 76%, 58%, 53% for 1, 2, 3 years respectively (difference between naive (first-line) and add-on may be due to difference in patient characteristics at initiation)
Authors' Conclusions: "*First-line therapy with epoprostenol, especially when combined with oral PAH treatment, was associated with a substantial improvement in clinical and hemodynamic status and favourable survival estimates in patients with severe IHA-PAH*" p.561 **Limitations:** Lack of control group. Prone to selection bias since only patients who survived underwent follow-up assessment and not all patients had the same treatment background prior to epoprostenol initiation. Results on survival were not adjusted for potential differences in demographic, functional and hemodynamic differences.	
Sitbon et al., 2014[95] France Sponsor: not reported	Month 4 visit • FC improved: 17/19 (89%) • 18 patients had hemodynamic improvement ($P < 0.01$) • Significant increase in 6MWD ($P < 0.01$) Final follow-up visit (median 39 months) • FC improved: 18/19 (95%) • 18 patients had hemodynamic improvement ($P < 0.01$) • Significant increase in 6MWD ($P < 0.01$) • Survival: 100%, 100%, 100% at 1, 2, 3 years • Expected survival calculated from French equation: 75%, 60%, 49% at 1, 2, 3 years Safety: • One patient underwent heart-lung transplantation at month 3 • Two patients discontinued bosentan due liver enzyme elevation after 11.5 and 31.5 months • Epoprostenol (jaw pain, headache, diarrhea, flushing)
Authors' Conclusions: "*This pilot study provides preliminary evidence of the long-term benefits of upfront triple combination therapy in patients with severe PAH*" p.1691 **Limitations:** Lack of control group; cannot be directly compared with monotherapy or dual therapy. Prone to selection bias since only patients who survived underwent follow-up assessment, and not all patients had the same treatment background prior to treatment initiation. Results on survival were not adjusted for potential differences in demographic, functional, and hemodynamic differences. Small sample size.	
Kemp et al., 2012[96] France Sponsor: NR	Combination therapy (upfront Epoprostenol / Bosentan) • Survival: 100%, 94%, 94%, 74% at 1, 2, 3, 4 years • Transplant-free survival: 96%, 85%, 77%, 60% at 1, 2, 3, 4 years Comparison of combination therapy with epoprostenol monotherapy (3-4 months) • No significant difference in NYHA FC improvement, 6MWD or hemodynamics, except PVR • No significant difference in survival
Authors' Conclusions: "*Initial combination therapy with epoprostenol and bosentan in patients with severe PAH is associated with improvements in important outcomes such as functional class, exercise capacity, and hemodynamics*" p.150 **Limitations:** Retrospective and non-controlled design. Small sample size. Risk of selection bias.	
Keogh et al., 2011[97]	Monotherapy (from start to censor data 2009) • Mean time on treatment: 18.7 months

Table 231: Summary of Findings of Combination Therapy	
First Author, Publication Year, Country	**Main Findings**
Australia Sponsor: Drugs provided by manufacturers	• Survival: 98%, 88%, 77%, 69%, 57% at 1, 2, 3, 4, 5 years • 6MWD improved and then dropped back to baseline due to deterioration • Mean FC improved from 3.1 to 2.5, then deteriorated to 3.1 Dual therapy • Mean time on treatment: 7.9 months • Survival: 88%, 71%, 61% at 1, 2, 3 years • Steady improvement of 6MWD up to month 12 • Mean FC improved from 3.1 to 2.2 by 12 months
Authors' Conclusions: "*Dual non-parenteral therapy appears safe and effective and should be considered for PAH patients who are deteriorating on monotherapy to improve long-term outcomes*" p.235 **Limitations:** Prone to selection bias due to using of historical control group. No placebo control group.	
D'Alto et al., 2010[98] Italy Sponsor: NR	After 6 months of combination therapy • WHO FC improved from 2.9 to 2.1 (P = 0.042) • 6MWD improved from 293 m to 360 m (difference 67 m, P = 0.005) • Borg dyspnea index improved from 4.4 to 2.9 (P = 0.036) • Hemodynamics also improved (significant for PVR)
Authors' Conclusions: "*Addition of sildenafil in adults with CHD-related PAH and Eisenmenger syndrome after oral bosentan therapy failure is safe and well tolerated at 6-month follow-up, resulting in a significant improvement in clinical status, effort SpO_2, exercise tolerance and hemodynamics*" p.378 **Limitations:** Prone to selection bias due to open-label uncontrolled approach. Small sample size.	
Jacobs et al., 2009[99] The Netherlands Sponsor: Industries	After 4-6 months • NYHA improved after addition of prostanoids (P = 0.002) • 6MWD improved 64 m (P < 0.001) • No significant difference between epoprostenol and treprostinil in 6MWD • Improved cardiac MRI parameters End of observation (18 months) • 6MWD improved 73 m (P < 0.001) • 1 dead (in the bosentan-prostanoid group) Bosentan versus Bosentan-Sildenafil • 6MWD improved at 4 months was 86 m for bosentan and 41 m for bosentan-sildenafil (NS)
Authors' Conclusions: "*addition of subcutaneous of intravenous prostanoids can be efficacious in PAH deteriorating on oral therapy*" p.280 **Limitations:** small sample size, lack of control group.	
Benza et al., 2008[100] USA Sponsor: Actelion	All patients treprostinil therapy (n = 38) • 6MWD improved 35 m (P = 0.022) • Borg dyspnea index improved –0.9 (P = 0.023) • Hemodynamics improved for PAP, RAP, cardiac output, but not PVR • Improved in NYHA FC Bosentan added to treprostinil (n = 19) • 6MWD improved 41 m (P = 0.071) • Borg dyspnea index improved -0.4 (NS) • Hemodynamics improved for PAP, RAP, but not PVR, cardiac output • Improved in NYHA FC
Authors' Conclusions: "*Long-term treatment with subcutaneous treprostinil-based therapy improved functional parameters and hemodynamics in patients with moderate-to-severe PAH. IN patients requiring combination therapy,*	

Table 231: Summary of Findings of Combination Therapy	
First Author, Publication Year, Country	**Main Findings**
the addition of oral bosentan to treprostinil-based therapy was safe, well tolerated, and associated with further improvement" p.139 **Limitations:** Retrospective nature, lack of control group, small sample size, open-label, risk of selection bias.	
Ruiz et al., 2006[101] Spain Sponsor: NR	Sildenafil added to Prostanoids as rescue therapy • FC improved from 3.0 to 2.1 at 1 year ($P < 0.001$) and to 2.2 at 2 years ($P = 0.005$) • 6MWD improved 79 m at 1 year ($P = 0.02$) and 105 m at 2 years • Echocardiographic parameters improved at 1 and 2 years
Authors' Conclusions: "*Adjunct sildenafil to long-term prostacyclin therapy in patients with severe PAH provided sustained clinical stabilization and an improved clinical situation, exercise capacity and echocardiographic parameters of right ventricular function. The benefit effects were strong and lasted > 24 months*" p.1353 **Limitations:** Small sample size from single institution, lack of control group, open-label, retrospective nature.	

6MWD = six-minute walk distance; AEs = adverse events; BP = blood pressure; CI = confidence interval; ERA = Endothelin receptor antagonists; FC = functional class; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; MRI = magnetic resonance imaging; NR = not reported; NS = not significant; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PDI-5 I = phosphodiesterase type-5 inhibitors; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RCT = randomized controlled trial; RR = relative risk; SE = standard error; TPR = total pulmonary resistance; WMD = weighted mean difference.

APPENDIX 15: REVIEW OF PREVIOUS PHARMACOECONOMIC ANALYSES

A systematic review of the literature examining the cost-effectiveness of medical treatments for pulmonary arterial hypertension was conducted. The literature review was used to inform the current economic analysis including the provision of information regarding resource use, costs, transition probabilities and utilities. The literature review also sought to compare the results of existing studies to enable contextualization of the current analysis.

Literature Searches
The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and Embase. A parallel search was run in the Health Economic Evaluations Database (HEED). The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search terms were the brand and generic names of therapies used in the treatment of PAH, various nomenclature for PAH, and appropriate economic terms.

Selection Criteria
The following selection criteria were considered in identifying relevant economic studies:

a) Population, Intervention, and Comparators
The selection criteria for the population, interventions, and comparators were the same as within the clinical review. The population included adult patients (≥ 18 years of age) diagnosed with primary arterial hypertension functional class II, III and IV. Interventions included macitentan, riociguat, epoprostenol, treprostinil, bosentan, ambrisentan, sildenafil, tadalafil and placebo or conventional medical treatment.

b) Outcome
Studies that reported incremental cost, incremental effectiveness (e.g., quality-adjusted life-years gained, life-years saved), and/or incremental cost-effectiveness ratios (ICER) were included.

c) Study Design
Studies that were cost-effectiveness analyses (CEA), cost-utility analyses (CUA), cost-minimization analyses (CMA), and/or cost-benefit analyses (CBA) were included.

Selection Method
Two reviewers independently screened the titles and abstracts of all the citations that were retrieved during the literature search based on the selection criteria. Disagreements were discussed and resolved. The full text of the selected studies was then obtained. The reviewers independently reviewed the full text articles to select studies that met the inclusion criteria. Disagreements were resolved through consensus. The review did not include studies published only in abstract form.

Data Extraction Strategy
One reviewer extracted information using the data extraction sheet. A second reviewer ensured the accuracy of the data extraction. Disagreements were resolved through consensus.

Strategy for Validity Assessment
The selected studies were critically appraised based on the Drummond et al. checklist. (Drummond 1997) Caution was exercised when using studies that rated low on the checklist. Although the checklist is useful in assessing the quality of the reporting of the studies, it does not necessarily reflect the accuracy of the model results because of the potential for either inappropriate assumptions or input parameters; therefore, further critical appraisal of the methods was also conducted.

Data Analysis Methods
A qualitative approach was taken to summarize and review the included studies. Areas of focus included the population, perspective, sponsorship, type of analysis, model assumptions regarding model structure and input data, and reported results of the base case and sensitivity analyses. A summary of the limitations of the current literature is also provided.

Study Characteristics
a) Population
One study included PAH patients with NYHA/WHO functional class II, III,[138] two included only those with class III[82,139] and six studies included those with class III and IV[1,70,81,140-142] Only one study conducted analysis by different functional classes.[1]

One study included only those who had either failed or were not eligible for bosentan treatment.[141] Only one study conducted subgroup analysis based on etiology of pulmonary arterial hypertension, considering idiopathic PAH and PAH resulting from connective tissue disease separately.[139] Two studies included only patients with idiopathic PAH. [141,142]

Perspectives and Discount Rates
All of the studies were conducted from the healthcare system perspective, with the study by Einarson also incorporating an analysis from a societal perspective. Discount rates for costs and effectiveness were generally set at 3% except for the analyses by Stevenson and Chen which used 3.5% and Wlodarczyk which used 5%.[1,139,142] The two studies that were one year in duration did not discount costs or QALYs.[81,140]

Study Sponsorship
All studies cite either pharmaceutical industry funding or conflicts of interest, except for the cost-utility analysis by Highland from a US perspective and the health technology assessment conducted by NICE.[1,81]

b) Types of Analysis
Six studies conducted CEAs[81,82,142] and/or CUAs;[1,81,82,139,140] whereas, three were CMA.[70,138,141] The outcomes within the CUAs were cost per QALYs gained and the outcomes in the CEA were cost per LYs gained.

c) Model Assumptions
Four of the nine models adopted a three-year time horizon,[70,82,138,141] two adopted a one-year time horizon[81,140]with the remaining three adopting a lifetime horizon.[1,139,142] The rationale, stated by the authors, for adopting a one-year time horizon was the lack of evidence supporting longer-term efficacy and the long-term impact of treatment on survival.

A number of studies did not consider treatment discontinuations or switches in therapy upon a deterioration in a patient's functional class.[81,140-142] In the studies by NICE and Roman, patients deteriorating to FC IV were assumed to switch to epoprostenol therapy.[1,82] In the two studies

that compared various prostaglandins, patients were assumed to remain on their respective treatment in Einarson, even if they deteriorated to FC IV; whereas, in Roman a percentage of those receiving iloprost or treprostinil were switched to epoprostenol upon deteriorating to functional class IV. In the CMA by Dranitsaris comparing oral therapies for PAH, patients who discontinued therapy were moved to a second line oral therapy. Assumptions regarding the choice of second line therapy differed based on the first-line therapy and may have influenced the results of the analysis.[138]

d) Mortality

Differing assumptions regarding the effects of PAH treatments on mortality have been made within the published literature.

The studies by Einarson and Narine assumed equal survival for epoprostenol and treprostinil; whereas, Roman compared epoprostenol, iloprost, and treprostinil and based the differential survival estimates for the treatments on a meta-analysis. Unfortunately, the details of this estimation are unavailable due to the fact that the referenced online appendix is missing. The meta-analysis referenced within the publication compared the mortality rates with all PAH therapies as a group versus supportive care and each class of PAH therapy as a whole versus supportive care. It does not appear to address the equivalency of the effects of each prostaglandin on mortality which is the assumption incorporated within the Roman study.

In the two studies that compared bosentan with supportive care, one study assumed equivalent survival with bosentan and supportive care, with bosentan delaying disease progression;[139] whereas the other based the differential survival on long-term open-label follow-up with bosentan and a survival estimate derived from a risk equation for supportive care.[142]

In the one study that included just oral therapies by Dranitsaris, survival was assumed to be equivalent for all treatments.[138]

In the three studies that included both oral and prostaglandin therapies the assumptions regarding mortality were unclear in one study,[140] the second used the relative changes from baseline in 6MWD for the therapies to estimate differences in survival[81] and the third used long-term follow-up from open-label studies for both therapies and supportive care groupsfor each comparison.[1]

e) Efficacy

The conduct of a CMA implies equivalent efficacy of the treatments being studied. In the two CMAs that compared the cost-effectiveness of epoprostenol with treprostinil, this assumption was based on the survival data from an open-label follow-up study with treprostinil compared with published survival data for epoprostenol.[70,141] No formal statistical methods were employed. In the CMA comparing the cost-effectiveness of oral therapies, equal efficacy was justified based on a meta-regression analysis of the placebo corrected average 6MWD with data derived from two to four randomized controlled trials for each drug, as well as a comparison of the relative risk versus placebo for improvement in NYHA classification.[138]

In all other studies the comparative efficacy of treatments was required for input to the economic models. The lack of head-to-head clinical trials meant that in all cases efficacy estimates were derived from separate clinical trials for each therapy, generally trials in which the treatment was compared with placebo or supportive care.

In three of the studies the relative change from baseline versus placebo in 6MWD was mislabelled as a relative risk.[81,82,140] These relative changes from baseline were then applied to changes in NYHA functional class for each of the therapies being studied with bosentan as the reference case. The method of these calculations is unclear as the online appendix providing this information is missing. In all three of these models, the 3 month transition probabilities were assumed to remain constant for the duration of the models; however, the additional assumption that functional class I and II were absorbing states was incorporated within the model developed by Roman.

Two studies compared bosentan plus conventional therapy with conventional therapy alone and derived efficacy estimates from 12 to 16 week randomized controlled trials and open-label long-term follow-up.[139,142] In the first study efficacy was assessed based on the time to clinical deterioration, which was defined as the addition of another agent or death.[139] In the second study therapy was discontinued in those who did not experience a clinical response after 6 months of treatment based on an assessment of right heart catheterization, echocardiography and the 6MWT.[142] Long-term efficacy of bosentan in the study by Stevenson was estimated by extrapolating data from a long-term follow-up database for bosentan which provided follow-up information up to 3 years.[139] A parametric survival analysis was then conducted to extrapolate this data further to allow estimation of time to clinical deterioration. Within the Wlodarczyk study long-term efficacy was based on the same long-term follow-up database for bosentan.[142] Response to bosentan treatment was assumed to be maintained over the 15 years of the study in those who continued to respond to treatment at each 6-month follow-up, except in two cases. Firstly, 5% of patients were assumed to discontinue bosentan treatment each year and in patients who died, it was assumed that they discontinued bosentan treatment 12 months prior to death.

In the final study, the pooling of the placebo results from multiple trials was deemed inappropriate due to differences in the baseline characteristics of the trial populations between the studies.[1] Consequently, each treatment was compared individually against the placebo group of the trial or trials from which the efficacy was derived. For the analyses of epoprostenol and of sildenafil a single RCT was used; whereas, for the analyses of bosentan and of sitaxsentan, pooled analyses of two RCTs were used. Efficacy of treatments was assessed as the odds ratio for improvement, or deterioration in NYHA functional class versus supportive care alone. With respect to long-term efficacy assumptions, for all treatments apart from epoprostenol, the improvement relative to supportive care based on controlled trials was applied during the first 12 week cycle of the model. Subsequently, patients did not further improve their functional class; however, the relative rate of deterioration for the treatment versus supportive care was applied in subsequent cycles for the duration of the model. This resulted in those receiving treatment deteriorating at a slower rate than those on supportive care. Patients in functional class IV received epoprostenol and could therefore improve from FC IV to FCIII at a rate greater than supportive care in all cycles of the model. As the improvement and deterioration in functional class was generally reported within the clinical trials for the overall population, the assumption that these numbers applied to patients in each functional class was required.

One study conducted an exploratory analysis of combination therapy, examining the cost-effectiveness of adding iloprost to patients already receiving bosentan; however, the transition probabilities for the combination of iloprost and bosentan could not be extracted from the clinical trial and therefore only the benefit and cost of additional iloprost was considered within this analysis.[140]

Although the primary efficacy measure within the clinical trials was generally the 6MWD, the association between improvements and deteriorations in this measurement and a patient's quality of life and utility has not been established; therefore, in all cases where effectiveness was measured as the number of QALYs gained, each NYHA/WHO functional class was associated with a utility value based on information from the literature to allow the calculation of the increased number of QALYs associated with treatment (further details are provided under the section entitled Utilities).

f) Resource Use and Costs

All studies considered appropriate resources within the analyses with sources including published clinical trials, treatment guidelines and expert clinical opinion. They generally included the costs of medication, initiation of therapy (including hospitalizations), medical supplies, medication consultations, serious adverse events (such as sepsis and line infections), liver function tests for endothelin receptor antagonists and in some cases diagnostic procedures. In the three studies which considered palliative or supportive care the costs of warfarin, furosemide, digoxin and oxygen were also included.[1,139,142] The sources for cost data were appropriate and included administrative databases, PAH specialist centres, drug manufacturers, national formularies and hospital databases.

g) Utilities

In those studies which considered the cost utility of interventions, the majority used utility values derived from a study by Keogh et al. Within this study the SF-36 was administered to patients with pulmonary arterial hypertension who were treated with bosentan. Generally, an average utility value was calculated based on functional class which could then be applied for all treatments. The only exception to this was the Highland study in which utility values were based on the results of the EuroQol completed by clinical experts.[81]

Results from Included Studies

The types of interventions considered within the included economic analyses can be summarized as four types of comparisons:

- comparisons versus supportive care or palliative care
- comparisons of prostaglandins and oral therapies
- comparisons of only oral agents
- comparisons of only prostaglandin agents.

The economic studies are summarized by the type of comparisons that were made.

Comparisons Versus Supportive Care/Palliative Care

There are three studies which compared the cost-effectiveness of therapies for pulmonary arterial hypertension with supportive care / palliative care.[1,139,142] One included both prostaglandins and oral agents whereas the other two analyses only included bosentan as a comparator.

In the HTA commissioned by NICE in 2009, separate analyses were conducted for functional class III and functional class IV.[1] Only the cost-effectiveness of epoprostenol was considered for FC IV as it was the only therapy indicated for this severity of disease and the analysis was limited to only approved indications for therapies. Additionally, each treatment was compared individually with supportive care due to the lack of comparability of the trial populations from one therapy to another. In FC III, sildenafil dominated supportive care (SC). In FC III, the ICER for sitaxsentan versus SC was £25,000/QALY. For bosentan versus SC the ICER was £27,000/QALY, for iloprost versus SC it was £101,000/QALY and for epoprostenol versus SC it

was £277,000/QALY. For those with PAH FC IV the ICER for epoprostenol versus SC was £343,000/QALY. At the usual threshold for assessing cost-effectiveness implemented by NICE of £20,000 to £30,000 per QALY, the oral therapies sildenafil, sitaxsentan and bosentan would be considered cost-effective relative to SC. Three parameters were tested within deterministic sensitivity analyses: time horizon, alternative epoprostenol prices and alternative utility values. For all therapies but epoprostenol, reducing the time horizon resulted in the treatments being more cost-effective, primarily due to less time being spent in class IV where patients were assumed to receive therapy with epoprostenol. On the other hand, reducing the price of epoprostenol resulted in the oral therapies being less cost-effective producing ICERs greater than £30,000 for both sitaxsentan and bosentan versus supportive care. Sildenafil no longer dominated supportive care with a reduced price of epoprostenol resulting in an ICER of £3,700/QALY versus supportive care. Alternate utility values did not significantly affect the results.

The two studies which compared bosentan versus palliative or supportive care found differing results.

This first study was a cost-utility analysis from a UK perspective which found that bosentan dominated palliative care in both idiopathic PAH and PAH due to connective tissue disease.[139]

The second analysis was a cost-effectiveness study from an Australian perspective which estimated the ICER for bosentan versus conventional therapy at AUS$55,927 per life-year gained.[142] This analysis was designed to simulate an agreed upon reimbursement strategy and therefore many of the results may have been influenced by the stopping rules. In deterministic sensitivity analyses results were sensitive to assumptions regarding mortality rates and the continuation rules.

Comparisons Including Prostaglandins and Oral Therapies

There are two studies which have directly compared the cost-effectiveness of prostaglandins and oral therapies. [81,140]

The first study which compared both oral treatments and prostaglandins in FC III and IV found that sildenafil dominated all other treatments including bosentan, sitaxsentan, ambrisentan, epoprostenol, inhaled iloprost and treprostinil.[140] The oral therapies bosentan, sitaxsentan and ambrisentan also dominated both epoprostenol and inhaled iloprost and when compared with treprostinil, the resulting ICERs were between US$73,000 and US$76,000 per QALY gained. The ICERs for epoprostenol and inhaled iloprost versus treprostinil were over US$1,000,000 per QALY. Caution should be exercised in interpreting the results of this study as the relative changes from baseline in 6MWD for treatments versus placebo were used to calculate relative changes in functional class as compared with bosentan, the validity of which has not been established.

In the US study by Highland which compared bosentan versus epoprostenol and treprostinil in patients with FC class III and IV PAH, bosentan dominated both epoprostenol and treprostinil, resulting in greater QALYs at lower cost.[81] Treprostinil was more expensive than epoprostenol with a gain of only 0.01 QALYs per 100 patients. Caution should also be exercised in interpreting the results of this study as similar to in the study by Garin, the relative changes in 6MWD for treatments versus placebo were used to adjust the changes in functional class with epoprostenol and treprostinil versus bosentan.

Comparisons of Only Oral Agents

In a cost-minimization analysis examining oral agents for PAH from a Canadian perspective sildenafil was found to be the least costly with a three-year cost of $48,351, followed by ambrisentan at $148,443, sitaxsentan at $158,444 and finally bosentan at $164,745.[138] Some of the differences in costs between the therapies may be due to differing assumptions regarding second line therapy. Those who discontinued ambrisentan were switched to sildenafil, a less costly therapy; whereas, those discontinuing sitaxsentan or bosentan were moved to ambrisentan, a more costly therapy. Those discontinuing sildenafil were moved to bosentan, also a more costly therapy.

Comparison of Only Prostaglandins

There were three studies that examined the comparative cost-effectiveness of the prostaglandins.[70,82,141]

In the CMA including patients with NYHA FC III and IV PAH by Einarson, from a Canadian perspective, the total healthcare system costs over 3 years were lower for treprostinil at $8,867,003 compared with epoprostenol at $11,477,645.[70] The results, however, are sensitive to the assumed comparative dose ratio for epoprostenol versus treprostinil.

A second CMA analysis conducted from a US perspective over the same time period of 3 years also found treprostinil to be less costly at US$294,193 as compared with epoprostenol at US$331,625.[141] Adverse events for treprostinil were not incorporated within the analysis.

Caution should be exercised in interpreting the results of these two studies as the evidence for equivalent efficacy of treprostinil and epoprostenol is weak, based on open-label follow-up from studies conducted separately for each of the therapies.

In 2012 Roman et al completed a cost-effectiveness / cost-utility analysis from the perspective of the Spanish healthcare system comparing three prostaglandins, intravenous epoprostenol, inhaled iloprost and subcutaneous treprostinil.[82] A cohort of patients with pulmonary arterial hypertension NYHA class III was entered into a Markov model which simulated disease progression over a period of 3 years. Iloprost was the least costly strategy at €132,840 over 3 years as compared with treprostinil at €359,869 and epoprostenol at €429,775. Epoprostenol resulted in the greatest number of life-years and QALYs gained (2.73 life-years and 1.78 QALYs) followed by iloprost (2.69 LYs and 1.74 QALYs) and treprostinil (2.69 LYs and 1.73 QALYs). As a result, iloprost dominated therapy with treprostinil as it led to greater life-years and QALYs at a lower cost. Relative to iloprost, epoprostenol resulted in an incremental cost per life-year gained of €8,825,982 and an incremental cost per QALY gained of €6,847,284. In probabilistic sensitivity analyses using Monte Carlo simulation techniques, iloprost was dominant over treprostinil in 45% of simulations and had an ICUR of below €30,000/QALY in a further 39 % of simulations. Epoprostenol dominated iloprost in 15% of simulations but was not cost-effective in 83% of simulations.

There are a number of limitations of this study which should be considered when interpreting these results. As mentioned previously, the method of deriving transition probabilities for function class changes based on the application of the relative change from baseline in 6MWD has not been validated. Additionally, some of the assumptions incorporated within this analysis may have biased the results against epoprostenol and treprostinil. Firstly, a proportion of patients whose PAH deteriorated to class IV were assumed to be transitioned to epoprostenol if they had been receiving either iloprost or treprostinil previously. The percentage transitioned was higher with treprostinil with 75% being transitioned to epoprostenol versus only 70% being

transitioned to epoprostenol from iloprost. The justification for this is not provided within the paper. Given the high cost of epoprostenol this assumption would serve to increase the costs associated with the treprostinil strategy. Additionally, only the costs of adverse events for epoprostenol were incorporated within the model. Finally, one of the assumptions within the model was that NYHA functional class I and II were absorbing states, meaning that once patients entered these states it was assumed that their disease would stabilize and never deteriorate. This inaccurately represents the natural history of the disease given that even if patients improve on therapy, they are likely to worsen over the course of 3 years.

Limitations of Selected Studies

There are a number of limitations of the published literature each of which is discussed briefly below.

The most significant concern is with respect to the validity of the use of a relative mean change from baseline in 6MWD versus placebo to estimate the relative improvement and deterioration in functional class. This relative mean change from baseline was used as a relative risk to estimate transition probabilities for disease progression within the modelling exercises in four studies.[81,82,138,140] The validity of such a relationship has not been established and calls into question the estimates of the effectiveness of treatments within these analyses.

As there is a dearth of studies comparing the treatments for PAH directly, establishing the relative efficacy of treatments is challenging. Three of the nine studies were cost-minimization studies which reported only a cost comparison of treatments with the assumption of equivalent efficacy.[70,138,141] The assumption of equivalence in efficacy between treatments was not established through head-to-head clinical trials and in only one case was an indirect comparison conducted.[138]

There is a variety of approaches taken within the studies with respect to estimating the effect of treatment on mortality. As there are little long-term data regarding the impact of treatments on mortality, in general, any modelling exercise will require assumptions regarding mortality. These assumptions may significantly affect the results of cost-effectiveness analyses within this area as the medications used down the line as the disease progresses may significantly impact the costs within the treatment and supportive care groups. In comparing all treatments for PAH, the study by Chen is the only paper which provided detailed justification regarding assumptions of treatment effect on mortality which may be helpful in information future models.[1] They assumed the reduced risk of mortality with treatment was a result of the reduced risk of transition from FC III to FC IV.

Additional limitations include the absence of studies examining the cost-effectiveness of combination therapies and the fact that only a small selection of studies have included all therapies for PAH in addition to supportive care. Moreover, none of the cost-effectiveness studies were conducted from a Canadian perspective. The only two studies conducted from a Canadian perspective were CMA, which did not include both prostaglandins and oral agents in a single analysis. The newer agents, riociguat and macitentan were not included in any previously published study.

In assessing the results of the reviewed studies one should keep in mind that the majority of studies were of poor to moderate quality in which the estimates of treatment efficacy were derived using erroneous methodology. Based on the available published literature the following may be surmised:

- In general, the evidence supports the cost-effectiveness of the oral agents as compared with supportive / palliative care in pulmonary arterial hypertension class III
- Treatment with prostaglandin agents was generally not found to be cost-effective
- When comparing agents, sildenafil was generally found to be the least costly agent, whereas epoprostenol was generally the most costly. The comparative efficacy of the treatments has not been well established due to the lack of head-to-head clinical trials and the fact that the comparability of the populations studied with each of the agents has not been established. It is therefore not possible to provide conclusions regarding the relative cost-effectiveness of the oral agents or of the prostaglandins based on currently available literature.

Quality Assessment

The quality of the reporting of the selected studies was evaluated based on the Drummond et al quality checklist with the results. In most publications a clear question was posed, suitable resources and costs were incorporated and costs and consequences were discounted appropriately. Although most studies adequately described the comparators under study, only three studies included a supportive or palliative care group as a comparator.[1,139,142] Some studies used appropriate references to establish efficacy estimates including randomized controlled trials, literature reviews and/or observational data.[1,139,142] In four of the studies the relative change from baseline in six-minute walk distance was incorrectly applied as a relative risk and used to adjust the changes in functional class with the treatments under study.[81,82,138,140] The validity of this approach is questionable. Additionally, there were three CMA which sought to establish equivalent efficacy of the treatments under study. In two of the CMAs which compared prostaglandins the approach to establishing equivalent efficacy was questionable and not based on a head-to-head clinical trial.[70,141] In the third CMA[138] the equivalent efficacy of treatments, although not based on head-to-head studies, was established based on a more rigorous process; however, the same misapplication of a relative change from baseline in 6MWD was applied to the changes in functional class as has been discussed above. In most studies the costs and consequences appear to be measured accurately and valued credibly. The only exception was with respect to the Highland study in which the adverse events of therapy do not appear to have been considered within the analysis and the utility values were arbitrarily adjusted downward for prostaglandins due to the inconvenience of their administration requirements.[81] In most cases the results were reported as an incremental analysis of costs and consequences except in the case of the three CMA. All studies conducted some form of sensitivity analysis, either deterministic or probabilistic or both; however, in some cases the results were reported in limited detail. Finally, most studies contextualized their results with respect to previously published literature, but few discussed issues of generalizability, distribution and implementation apart from those studies by Chen and Wlodarczyk.[1,142]

Quality Assessment of Economic Studies										
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**
Chen Y-F et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dranitsaria G et al. 2009	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	NC
Einarson TR et al. 2005	Yes	No	NC	Yes	Yes	NC	Yes	No	Yes	No
Garin MC et al. 2009	Yes	No	No	Yes	Yes	Yes	Yes	Yes	NC	Yes
Highland KB et al. 2003	Yes	No	No	No	No	No	Yes	Yes	NC	Yes
Narine L et al 2005	Yes	No	NC	Yes	Yes	No	Yes	No	Yes	No
Roman A et al. 2012	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stevenson MD et al. 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NC	Yes
Wlodarczyk JH et al. 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

N = no; NA = not applicable; NC = not clear; Y = yes.

Description of questions: 4
Q1: Was a well-defined question posed in answerable form?
Q2: Was a comprehensive description of the competing alternatives given?
Q3: Was the effectiveness of the programmes or services established?
Q4: Were all the important and relevant costs and consequences for each alternative identified?
Q5: Were costs and consequences measured accurately in appropriate physical units?
Q6: Were costs and consequences valued credibly?
Q7: Were costs and consequences adjusted for differential timing?
Q8: Was an incremental analysis of costs and consequences of alternatives performed?
Q9: Was allowance made for uncertainty in the estimates of costs and consequences?
Q10: Did the presentation and discussion of study results include all issues of concern to users?

#	Literature Search
1	Hypertension, Pulmonary/
2	pah.mp.
3	pulmonary hypertension.mp.
4	pulmonary arterial hypertension.mp.
5	pulmonary artery hypertension.mp.
6	or/1-5
7	(epoprostenol or flolan or prostacyclin).mp.
8	(iloprost or ventavis).mp.
9	(treprostinil or remodulin).mp.
10	(bosentan or tracleer).mp.
11	(sitaxsentan or sitaxsentan or thelin).mp.
12	(ambrisentan or volibris).mp.
13	(sildenafil or revatio).mp.
14	(tadalafil or adcirca).mp.
15	(macitentan or opsumit).mp.
16	(riociguat or adempas).mp.
17	or/7-16
18	6 and 17
19	Economics/
20	exp "costs and cost analysis"/
21	Cost of Illness/
22	exp health care costs/
23	economic value of life.mp.
24	exp economics medical/

#	Literature Search
25	exp economics hospital/
26	Economics, Pharmaceutical/
27	exp "fees and charges"/
28	(econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
29	(expenditure$ not energy).tw.
30	(value adj1 money).tw.
31	budget$.tw.
32	or/19-31
33	18 and 32
34	18 and 32
35	limit 34 to yr="2007 -Current"
36	Quality of Life/
37	life style/
38	health status/
39	health status indicators/
40	value of life/
41	quality adjusted life.mp.
42	or/36-41
43	6 and 42
44	6 and 42
45	limit 44 to yr="2007 -Current"

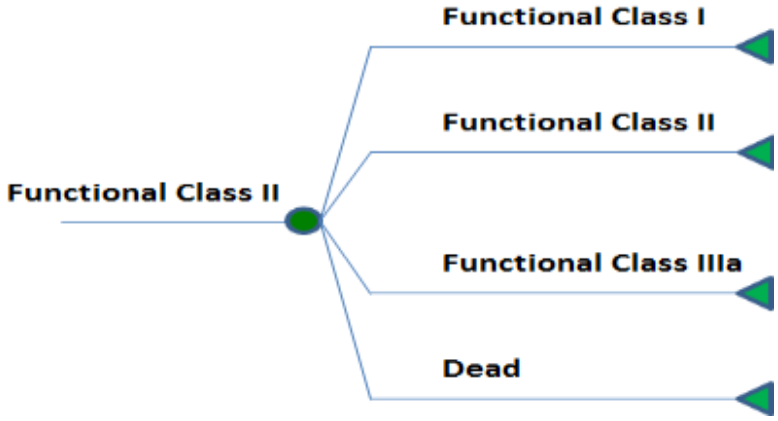
References for Cost-Effectiveness Analyses

Reference	Description
NICE HTA Chen Y-F, Jowett S, Barton P et al. Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxsentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation. Health Technology Assessment 2009; 13 (49)[1]	
Stevenson MD, Macdonald FC, Langley J et al. The cost-effectiveness of bosentan in the United Kingdom for patients with pulmonary arterial hypertension of WHO functional class III. Value in Health 2009;8:1100-1105.[139]	UK cost-utility analysis
Roman A, Barbera JA, Escribano P et al. Cost effectiveness of prostacyclins in pulmonary arterial hypertension. Appl Health Econ Health Policy 2012;10(3):175-180.[82]	Spanish cost-utility analysis
Highland KB, Strange C, Mazur J et al. Treatment of pulmonary arterial hypertension. Chest 2003;124(6):2087-2092.[81]	US cost-utility analysis
Garin MC, Clark L, Chumney ECG et al. Cost-utility of treatments for pulmonary arterial hypertension. Clin Drug Investig 2009;29(10):635-646.[140]	US cost-utility analysis
Einarson TR, Granton JT, Vicente C et al. Cost-effectiveness of treprostinil versus epoprostenol in patients with pulmonary arterial hypertension: A Canadian analysis. Can Respir J 2005;12(8):419-425.[70]	Canadian cost-minimization analysis
Wlodarczyk JH, Cleland LG, Keogh AM et al. Public funding of bosentan for the treatment of pulmonary artery hypertension in Australia. Pharmacoeconomics 2006;24(9):903-915.[142]	Australian cost-effectiveness analysis (cost per life-year saved)
Narine L, Hague LK, Walker JH et al. Cost-minimization analysis of treprostinil vs. epoprostenol as an alternate to oral therapy non-responders for the treatment of pulmonary arterial hypertension. Current Medical Research and Opinion 2005;21(12):2007-2016.[141]	US cost-minimization analysis
Dranitsaris G and Mehta S. Oral therapies for the treatment of pulmonary arterial hypertension. A population-based cost-minimization analysis. Appl Health Econ Policy 2009;7(1):43-59.[138]	Canadian cost-minimization analysis

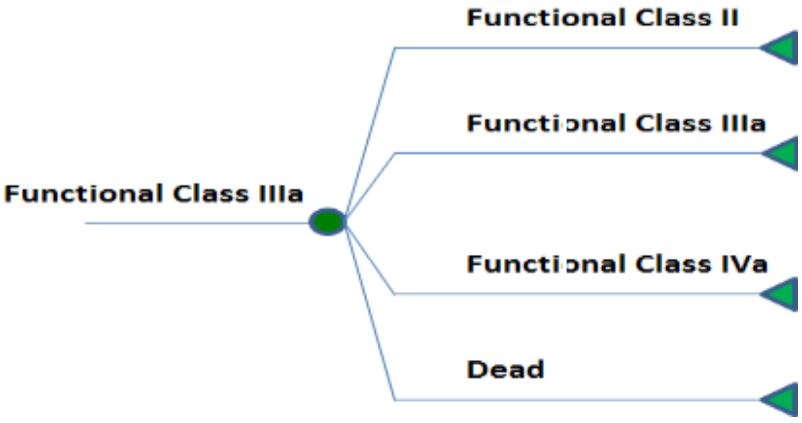
APPENDIX 16: SCHEMATIC OF MARKOV MODEL

Diagram of Decision Tree for the First Cycle of the Model for Cohorts Starting in Functional Class II, Functional Class III, and Functional Class IV

Possible Transitions for First Cycle from Functional Class II



Possible Transitions for First Cycle From Functional Class IIIa



Possible Transitions for First Cycle From Functional Class IVa

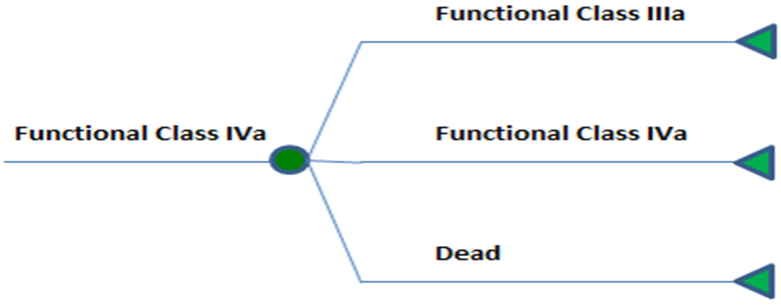
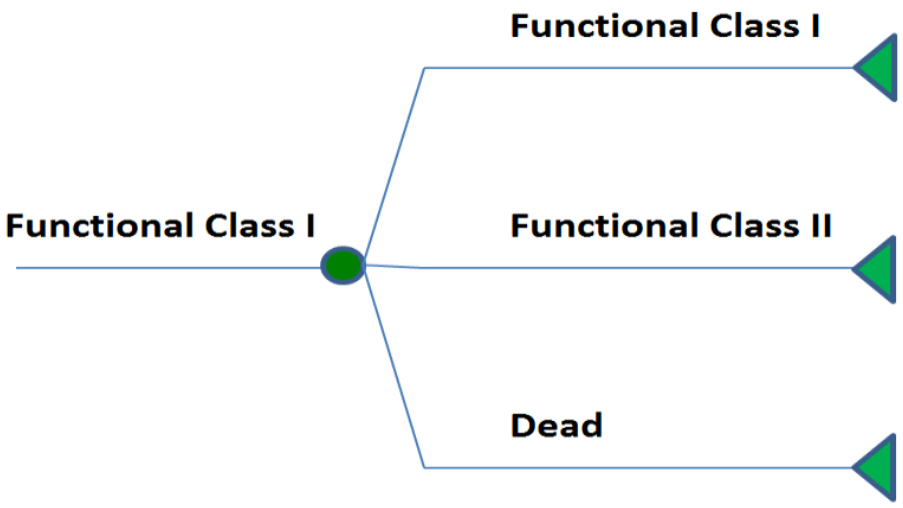
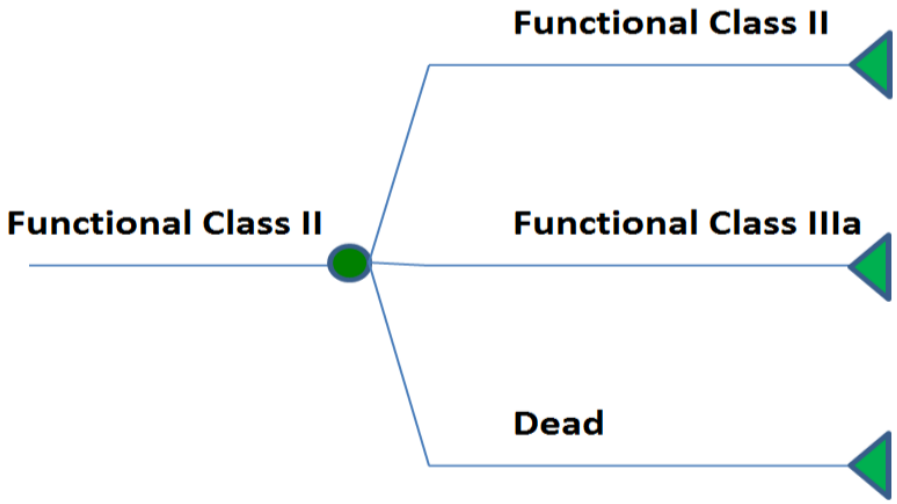


Diagram of Decision Tree for Subsequent Cycles of the Model

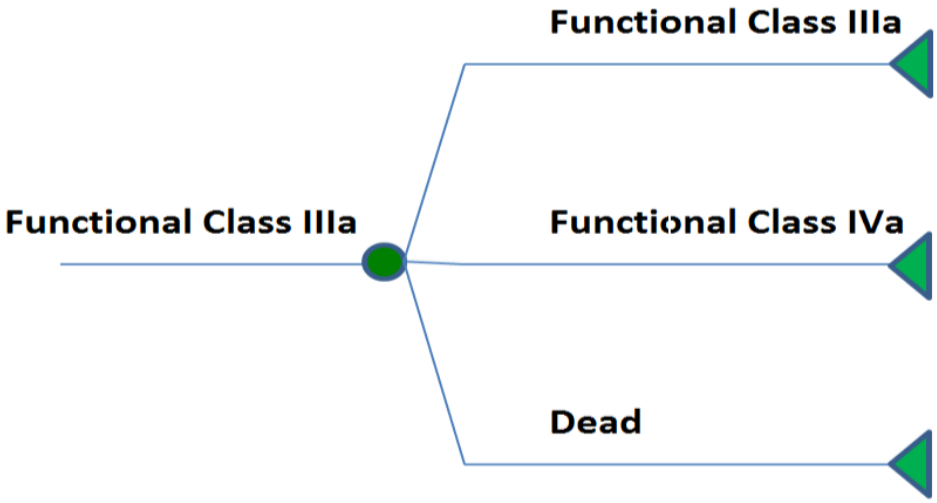
Possible Transitions from Functional Class I after First Cycle



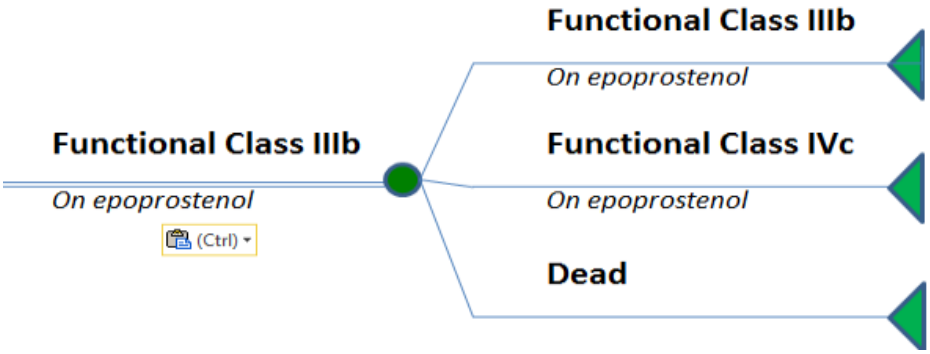
Possible Transitions From Functional Class II After First Cycle



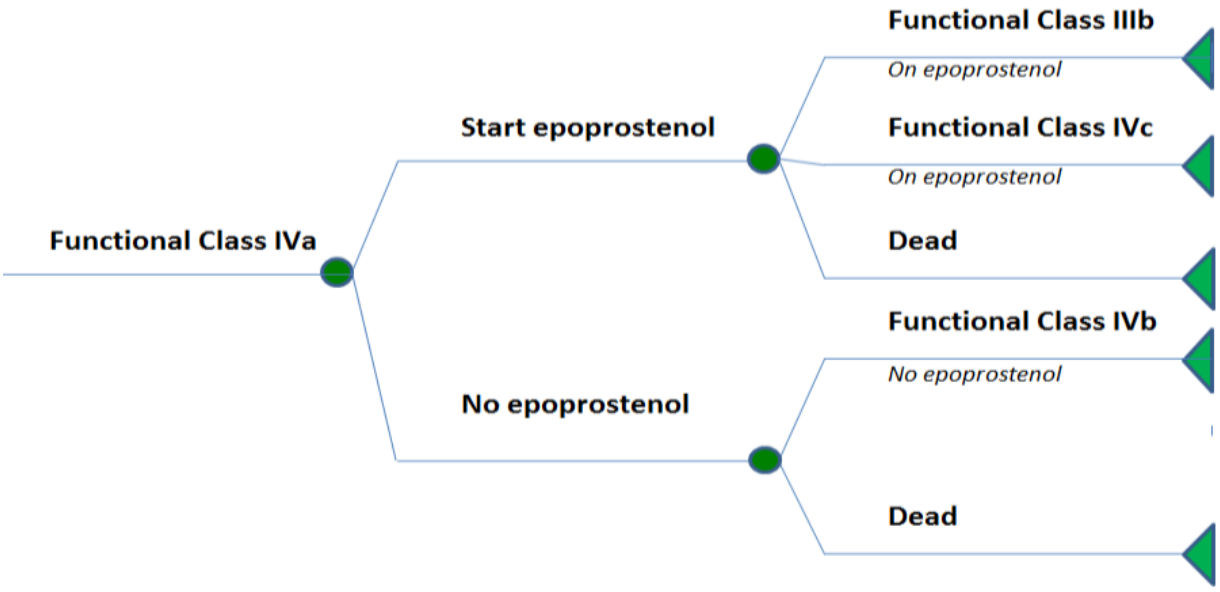
Possible Transitions From Functional Class IIIa After First Cycle



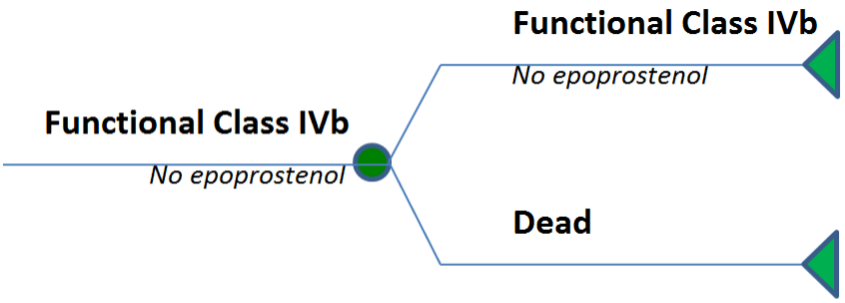
Possible Transitions From Functional Class IIIb After First Cycle



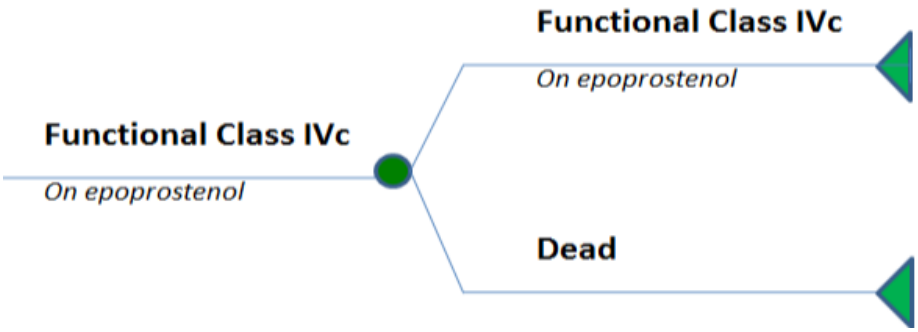
Possible Transitions From Functional Class IVa After First Cycle



Possible Transitions From Functional Class IVb After First Cycle



Possible Transitions From Functional Class IVc After First Cycle



APPENDIX 17: CLINICAL PARAMETERS FOR THE ECONOMIC MODEL

Table 232: Transition Probabilities and Relative Risks for Macitentan		
Transition Probability for Supportive Care		
	FC Improvement	**FC Worsening**
Supportive care ±PDE-5 inhibitor		
First cycles	0.07	0.08
Subsequent cycles	-	0.08
Relative Risks Associated With Treatment Versus Supportive Care		
	FC Improvement (95% CI)	**FC Worsening (95% CI)**
Macitentan +/- PDE-5 inhibitor		
First cycles	1.69	0.20
Subsequent cycles	-	0.20

CI = confidence interval; FC = functional class; PDE-5 = phosphodiesterase type-5.

APPENDIX 18: RESOURCE USE ESTIMATES FOR THE ECONOMIC MODEL

Table 233 : Supportive Care Therapies			
Treatment	**Uptake**	**Dose**	**Cost (per patient per cycle)**
Warfarin	53.4%	5 mg once daily	$4.75
Furosemide	69.3%	100 mg once daily	$6.26
Digoxin	26.4%	0.125 mg once daily	$2.39
Oxygen			
FC II	5%		$58.35
FC III	27%		$315.09
FC IV	71%		$828.57
FC IV (supportive care)	100%		$1,167.00

FC = functional class.

Table 234: Physician and Nurse Contacts for Functional Class II Patients				
Resource	**Mean cost per year (SD)**	**Unit Cost**	**Mean cost per 3 month cycle**	**Reference**
Physician at specialized PAH centre	2.8 (0.8)	$61.25	$42.88	Ontario Schedule of Benefits for Physician Services 2014
Nurse at specialized PAH centre[a]	2.75 (2.8)	$11.93	$8.35	
Physician at non-specialized centre	2.5 (1.1)	$61.25	$36.75	Ontario Schedule of Benefits for Physician Services 2014
Nurse at non-specialized centre[a]	1.0 (1.7)	$11.93	$3.58	
General practitioner	2.6 (1.6)	$38.35	$26.85	Ontario Schedule of Benefits for Physician Services 2014
Emergency physician	0.002	$56.30	$2.03	Ontario Schedule of Benefits for Physician Services 2014

PAH = pulmonary arterial hypertension; SD = standard deviation.
[a] Duration of nurse visit is assumed to be 15 minutes.

Table 235: Hospitalizations and Emergency Room Contacts for Functional Class II Patients				
Resource	**Mean number per year (SD)**	**Mean cost per visit**	**Uptake**	**Mean cost per 3-month cycle**
Hospitalizations	0.8 (0.4)	$13,949.42	18%	$502.18
Emergency room visits	0.002	$94.72	100%	$0.05

SD = standard deviation.

Table 236: Physician and Nurse Contacts for Functional Class III Patients				
Resource	**Mean cost per year (SD)**	**Unit Cost**	**Mean cost per 3-month cycle**	**Reference**
Physician at specialized PAH centre	4.2 (1.1)	$61.25	$67.38	Ontario Schedule of Benefits for Physician Services 2014
Nurse at specialized PAH centre[a]	5.5 (4.4)	$11.93	$16.70	
Physician at non-specialized centre	2.3 (1.1)	$61.25	$36.75	Ontario Schedule of Benefits for Physician Services 2014
Nurse at non-specialized centre[a]	0.8 (1.8)	$11.93	$2.39	
General practitioner	3.8 (1.6)	$38.35	$38.35	Ontario Schedule of Benefits for Physician Services 2014
Emergency physician	0.73 (0.6)	$56.30	$67.56	Ontario Schedule of Benefits for Physician Services 2014

PAH = pulmonary arterial hypertension; SD = standard deviation.
[a] Duration of nurse visit is assumed to be 15 minutes.

Table 237: Hospitalizations and Emergency Room Contacts for Functional Class III Patients				
Resource	**Mean number per year (SD)**	**Mean cost per visit**	**Uptake**	**Mean cost per 3-month cycle**
Hospitalizations	1.4 (0.22)	$13,949.42	38%	$1,855.27
Emergency room visits	0.73	$94.72	100%	$17.29

Table 238: Physician and Nurse Contacts for Functional Class IV Patients				
Resource	**Mean cost per year (SD)**	**Unit cost**	**Mean cost per 3-month cycle**	**Reference**
Physician at specialized PAH centre	7.1 (2.9)	$61.25	$110.25	Ontario Schedule of Benefits for Physician Services 2014
Nurse at specialized PAH centre[a]	8.75 (2.8)	$11.93	$26.25	
Physician at non-specialized centre	1.9 (1.5)	$61.25	$30.63	Ontario Schedule of Benefits for Physician Services 2014
Nurse at non-specialized centre[a]	0.8 (1.1)	$11.93	$2.39	
General practitioner	5.9 (1.2)	$38.35	$57.53	Ontario Schedule of Benefits for Physician Services 2014
Emergency physician	2.6 (1.2	$56.30	$39.41	Ontario Schedule of Benefits for Physician Services 2014

PAH = pulmonary arterial hypertension; SD = standard deviation.
[a] Duration of nurse visit is assumed to be 15 minutes.

Table 239: Hospitalizations and Emergency Room Contacts for Functional Class IV Patients				
Resource	**Mean number per year (SD)**	**Mean cost per visit**	**Uptake**	**Mean cost per 3-month cycle**
Hospitalizations	2.6 (1.2)	$13949.42	70%	$25,387.95
Emergency room visits	2.6	$94.72	100%	$246.27

APPENDIX 19: BREAKDOWN OF COSTS BY COST CATEGORY

Table 240: Costs by Cost Category for Monotherapy in Functional Class II								
	Supportive Care	**Epoprostenol**	**Riociguat**	**Bosentan**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil**	**Tadalafil**
Hospitalizations	$60,412 (38.5%)	$37,036 (7.6%)	$24,646 (6.3%)	$44,353 (11%)	$18,894 (4.9%)	$28,130 (7.4%)	$23,333 (16.3%)	$37,431 (24.7%)
Ambulatory Care/ER	$5,356 (3.4%)	$3,646 (0.7%)	$3,826 (1%)	$4,772 (1.2%)	$3,475 (0.9%)	$4,009 (1.1%)	$3,367 (2.4%)	$4,307 (2.8%)
Drug cost	$52,945 (33.7%)	$297,450 (60.7%)	$354,295 (90.3%)	$330,669 (81.6%)	$351,685 (92.1%)	$333,378 (88%)	$106,098 (74.2%)	$90,843 (60%)
Monitoring costs	$81 (0.1%)	$447 (0.1%)	$12 (0%)	$1,891 (0.5%)	$1,410 (0.4%)	$1,312 (0.3%)	$14 (0%)	$36 (0%)
Equipment costs	$22,092 (14.1%)	$125,234 (25.5%)	$3,188 (0.8%)	$12,864 (3.2%)	$1,115 (0.3%)	$4,705 (1.2%)	$3,786 (2.6%)	$9,814 (6.5%)
Adverse event costs	$3,440 (2.2%)	$19,115 (3.9%)	$496 (0.1%)	$2,003 (0.5%)	$174 (0%)	$732 (0.2%)	$590 (0.4%)	$1,528 (1%)
Supportive care costs	$11,336 (7.2%)	$5,648 (1.2%)	$4,253 (1.1%)	$6,968 (1.7%)	$3,377 (0.9%)	$4,756 (1.3%)	$3,964 (2.8%)	$5,989 (4%)
Therapeutic procedures	$1,337 (0.9%)	$1,624 (0.3%)	$1,706 (0.4%)	$1,469 (0.4%)	$1,799 (0.5%)	$1,658 (0.4%)	$1,833 (1.3%)	$1,582 (1%)
Total	$156,998	$490,200	$392,420	$404,989	$381,930	$378,680	$142,985	$151,529

Table 241: Costs by Cost Category for Monotherapy in Functional Class III								
	Supportive Care	**Epoprostenol**	**Riociguat**	**Bosentan**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil**	**Tadalafil**
Hospitalizations	$77,060 (37.4%)	$55,577 (12.9%)	$50,971 (13.6%)	$66,950 (16%)	$45,037 (12.9%)	$54,106 (14.5%)	$46,322 (26.8%)	$59,897 (30.2%)
Ambulatory Care/ER	$6,090 (3%)	$5,071 (1.2%)	$5,599 (1.5%)	$5,911 (1.4%)	$5,499 (1.6%)	$5,652 (1.5%)	$5,206 (3%)	$5,649 (2.8%)
Drug cost	$72,047 (35%)	$242,165 (56.3%)	$296,472 (78.9%)	$307,387 (73.3%)	$279,502 (80.3%)	$287,065 (76.8%)	$99,830 (57.7%)	$100,230 (50.5%)
Monitoring costs	$109 (0.1%)	$361 (0.1%)	$40 (0%)	$1,633 (0.4%)	$1,080 (0.3%)	$1,068 (0.3%)	$39 (0%)	$68 (0%)
Equipment costs	$30,115 (14.6%)	$101,657 (23.6%)	$11,076 (2.9%)	$22,699 (5.4%)	$6,549 (1.9%)	$13,461 (3.6%)	$10,780 (6.2%)	$18,851 (9.5%)
Adverse event costs	$4,666 (2.3%)	$15,445 (3.6%)	$1,720 (0.5%)	$3,522 (0.8%)	$1,018 (0.3%)	$2,090 (0.6%)	$1,673 (1%)	$2,925 (1.5%)
Supportive care costs	$14,615 (7.1%)	$8,430 (2%)	$8,520 (2.3%)	$10,294 (2.5%)	$7,878 (2.3%)	$8,859 (2.4%)	$7,671 (4.4%)	$9,377 (4.7%)
Therapeutic procedures	$1,187 (0.6%)	$1,312 (0.3%)	$1,321 (0.4%)	$1,235 (0.3%)	$1,352 (0.4%)	$1,305 (0.3%)	$1,391 (0.8%)	$1,289 (0.7%)
Total	$205,888	$430,017	$375,719	$419,630	$347,915	$373,606	$172,911	$198,287

Table 242: Costs by Cost Category for Monotherapy in Functional Class IV								
	Supportive Care	**Epoprostenol**	**Riociguat**	**Bosentan**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Sildenafil**	**Tadalafil**
Hospitalizations	$93,249 (35.6%)	$79,994 (19.5%)	$89,441 (18.9%)	$92,141 (19.1%)	$88,962 (19.2%)	$89,685 (19.3%)	$79,221 (29.8%)	$86,921 (30.9%)
Ambulatory Care/ER	$6,357 (2.4%)	$6,053 (1.5%)	$6,304 (1.3%)	$6,342 (1.3%)	$6,298 (1.4%)	$6,307 (1.4%)	$6,157 (2.3%)	$6,266 (2.2%)
Drug cost	$96,350 (36.8%)	$209,973 (51.1%)	$320,246 (67.7%)	$323,164 (66.9%)	$309,412 (66.9%)	$310,201 (66.8%)	$133,126 (50.1%)	$133,570 (47.4%)
Monitoring costs	$143 (0.1%)	$311 (0.1%)	$133 (0%)	$1,538 (0.3%)	$1,012 (0.2%)	$1,012 (0.2%)	$105 (0%)	$126 (0%)
Equipment costs	$40,328 (15.4%)	$87,929 (21.4%)	$37,378 (7.9%)	$39,480 (8.2%)	$36,982 (8%)	$37,578 (8.1%)	$29,592 (11.1%)	$35,529 (12.6%)
Adverse event costs	$6,114 (2.3%)	$13,307 (3.2%)	$5,662 (1.2%)	$5,984 (1.2%)	$5,599 (1.2%)	$5,694 (1.2%)	$4,503 (1.7%)	$5,401 (1.9%)
Supportive care costs	$18,106 (6.9%)	$11,931 (2.9%)	$12,998 (2.7%)	$13,280 (2.7%)	$12,948 (2.8%)	$13,023 (2.8%)	$11,925 (4.5%)	$12,731 (4.5%)
Therapeutic procedures	$1,109 (0.4%)	$1,130 (0.3%)	$1,126 (0.2%)	$1,114 (0.2%)	$1,128 (0.2%)	$1,124 (0.2%)	$1,168 (0.4%)	$1,135 (0.4%)
Total	$261,757	$410,629	$473,287	$483,042	$462,341	$464,624	$265,798	$281,680

Table 243: Costs by Cost Category for Add-on Therapies in Functional Class II			
	ERA Plus Placebo	**ERA Plus Riociguat**	**ERA Plus Tadalafil**
Hospitalizations	$61,636 (14.2%)	$35,714 (4.8%)	$46,405 (9.8%)
Ambulatory care/emergency room	$5,330 (1.2%)	$4,133 (0.6%)	$4,755 (1%)
Drug cost	$328,795 (75.7%)	$683,059 (91.9%)	$397,232 (83.6%)
Monitoring costs	$1,766 (0.4%)	$2,072 (0.3%)	$1,900 (0.4%)
Equipment costs	$22,780 (5.2%)	$9,159 (1.2%)	$14,198 (3%)
Adverse event costs	$3,547 (0.8%)	$1,426 (0.2%)	$2,211 (0.5%)
Supportive care costs	$9,131 (2.1%)	$5,723 (0.8%)	$7,194 (1.5%)
Therapeutic procedures	$1,341 (0.3%)	$1,624 (0.2%)	$1,473 (0.3%)
Total	$434,326	$742,909	$475,367

ERA = endothelin receptor antagonist.

Table 244: Costs by Cost Category for Add-on Therapies in Functional Class III			
	ERA Plus Placebo	**ERA Plus Riociguat**	**ERA Plus Tadalafil**
Hospitalizations	$77,101 (17.2%)	$57,676 (8.6%)	$67,342 (14.1%)
Ambulatory care/emergency room	$6,046 (1.3%)	$5,535 (0.8%)	$5849 (1.2%)
Drug cost	$316,661 (70.6%)	$578,337 (85.8%)	$363463 (76.2%)
Monitoring costs	$1,606 (0.4%)	$1,709 (0.3%)	$1644 (0.3%)
Equipment costs	$30,110 (6.7%)	$17,670 (2.6%)	$23302 (4.9%)
Adverse event costs	$4,663 (1%)	$2,741 (0.4%)	$3614 (0.8%)
Supportive care costs	$11,348 (2.5%)	$9,053 (1.3%)	$10262 (2.2%)
Therapeutic procedures	$1,193 (0.3%)	$1,311 (0.2%)	$1243 (0.3%)
Total	$448,729	$674,033	$476,719

ERA = endothelin receptor antagonist.

Table 245: Costs by Cost Category for Add-on Therapies in Functional Class IV			
	ERA Plus Placebo	**ERA Plus Riociguat**	**ERA Plus Tadalafil**
Hospitalizations	$92,310 (19.2%)	$84,772 (12.2%)	$90,495 (17.3%)
Ambulatory Care/emergency room	$6,344 (1.3%)	$6,235 (0.9%)	$6,318 (1.2%)
Drug cost	$321,908 (66.9%)	$549,271 (79.2%)	$368,205 (70.2%)
Monitoring costs	$1,536 (0.3%)	$1,555 (0.2%)	$1,540 (0.3%)
Equipment costs	$39,014 (8.1%)	$33,368 (4.8%)	$37,648 (7.2%)
Adverse event costs	$5,929 (1.2%)	$5,081 (0.7%)	$5,718 (1.1%)
Supportive care costs	$13,297 (2.8%)	$12,506 (1.8%)	$13,107 (2.5%)
Therapeutic procedures	$1,113 (0.2%)	$1,144 (0.2%)	$1,121 (0.2%)
Total	$481,451	$693,932	$524,151

Table 246: Costs by Cost Category for Macitentan Versus Supportive Care in Naive and Experienced Patients in Functional Class II		
	Supportive Care	**Macitentan**
Hospitalizations	$48,676 (29.8%)	$20,927 (4.7%)
Ambulatory Care/emergency room	$4,997 (3.1%)	$3,642 (0.8%)
Drug cost	$80,434 (49.2%)	$411,829 (92.6%)
Monitoring costs	$59 (0%)	$1,020 (0.2%)
Equipment costs	$16,146 (9.9%)	$1,780 (0.4%)
Adverse event costs	$2,514 (1.5%)	$277 (0.1%)
Supportive care costs	$9,117 (5.6%)	$3,706 (0.8%)
Therapeutic procedures	$1,418 (0.9%)	$1,753 (0.4%)
Total	$163,361	$444,935

Table 247: Costs by Cost Category for Macitentan Versus Supportive Care in Naive and Experienced Patients in Functional Class III		
	Supportive Care	**Macitentan**
Hospitalizations	$69,117 (31.7%)	$46,989 (11.6%)
Ambulatory care/emergency room	$5,979 (2.7%)	$5,558 (1.4%)
Drug cost	$98,230 (45.1%)	$332,960 (82.1%)
Monitoring costs	$94 (0%)	$804 (0.2%)
Equipment costs	$26,006 (11.9%)	$8,429 (2.1%)
Adverse event costs	$4,035 (1.9%)	$1,310 (0.3%)
Supportive care costs	$13,115 (6%)	$8,118 (2%)
Therapeutic procedures	$1,220 (0.6%)	$1,337 (0.3%)
Total	$217,796	$405,505

Table 248: Costs by Cost Category for Macitentan Versus Supportive Care in Naive and Experienced Patients in Functional Class IV		
	Supportive Care	**Macitentan**
Hospitalizations	$90,325 (30.6%)	$87,030 (17%)
Ambulatory care/emergency room	$6,312 (2.1%)	$6,267 (1.2%)
Drug cost	$131,806 (44.7%)	$358,479 (70.2%)
Monitoring costs	$147 (0%)	$793 (0.2%)
Equipment costs	$41,310 (14%)	$38,530 (7.5%)
Adverse event costs	$6,261 (2.1%)	$5,838 (1.1%)
Supportive care costs	$17,554 (6%)	$12,743 (2.5%)
Therapeutic procedures	$1,121 (0.4%)	$1,135 (0.2%)
Total	$294,836	$510,813