Common Drug Review
Clinical Review Report

December 2015

Drug	Riociguat (Adempas)
Indication	Treatment of pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1), as monotherapy or in combination with endothelin receptor antagonists in adult patients (≥ 18 years of age) with Functional Class II or III pulmonary hypertension.
Listing request	Treatment of pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists in adult patients (≥ 18 years of age) with Functional Class II or III pulmonary hypertension *who are unable to achieve disease control with another PAH therapy*
Dosage form(s)	0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets for oral administration
NOC date	March 2014
Manufacturer	Bayer HealthCare Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

6MWD	six-minute walk distance
AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
CDEC	CADTH Canadian Drug Expert Committee
CTEPH	chronic thromboembolic pulmonary hypertension
COPD	chronic obstructive pulmonary disease
EQ-5D	EuroQol 5-Dimensions Questionnaire
ERA	endothelin receptor antagonist
ITC	indirect treatment comparison
ITT	intention-to-treat
LOCF	last observation carried forward
LPH	Living with Pulmonary Hypertension questionnaire
MCID	minimal clinically important difference
MD	mean difference
mPAP	mean pulmonary arterial pressure
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PA	prostacyclin agonist
PAH	pulmonary arterial hypertension
PDE5	phosphodiesterase type 5
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RCT	randomized controlled trial
SAE	serious adverse event
SBP	systolic blood pressure
WHO	World Health Organization
VAS	visual analogue scale

EXECUTIVE SUMMARY

Introduction

Pulmonary arterial hypertension (PAH) is an uncommon, debilitating, progressive, and life-threatening disease of the pulmonary vasculature, characterized by vascular proliferation and remodelling of small pulmonary arteries.[1] It can lead to right-sided heart failure and premature death.[1] PAH is defined by an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg.[1] The four main categories of PAH (classified as Group 1 pulmonary hypertension) include idiopathic PAH, heritable or familial PAH, drug- and toxin-induced PAH, and PAH associated with other conditions such as connective tissue disease, human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease, or schistosomiasis.[2] The symptoms of PAH include breathlessness, fatigue, weakness, chest pain, light-headedness/fainting, and edema/ascites. PAH has a significant impact on the lives of patients and caregivers. Patients with PAH have a day-to-day life that is difficult and exhausting, and they progressively lose the ability to care for themselves. While therapy may delay progression, reduce the severity of symptoms, and make certain tasks easier, there is still no cure for PAH.

Health Canada has approved eight advanced treatment options covering four different classes of drugs for PAH, Group 1:

- prostanoids (epoprostenol, treprostinil)
- endothelin receptor antagonists (ERAs) (bosentan, ambrisentan, macitentan)
- phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil)
- soluble guanylate cyclase (sGC) stimulator (riociguat).

In 2014, CADTH conducted a Therapeutic Review to assess the comparative efficacy and safety and to determine the cost-effectiveness of pharmacologic treatments for adults with PAH.[3] Based on the Therapeutic Review and patient group input, the CADTH Canadian Drug Expert Committee (CDEC) recommended the following:

- sildenafil or tadalafil be the preferred initial therapy for adult patients with functional class II and III PAH
- add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug.[4]

The objective of this systematic review is to evaluate the beneficial and harmful effects of riociguat 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets for the treatment of PAH in adults (World Health Organization [WHO] functional class II or III).

Riociguat is a first-in-class drug of the soluble guanylate cyclase stimulator class of drugs, which works by producing vasorelaxation independent of the endogenous vasodilatory effects of nitrous oxide.[5] Riociguat is initiated at a dose of 1.0 mg orally three times daily and adjusted by 0.5 mg increments every two weeks according to systolic systemic blood pressure readings, to a maximum dose of 2.5 mg three times daily.[6]

Indication under review
Treatment of pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists in adult patients (≥ 18 years of age) with functional class II or III pulmonary hypertension.
Listing criteria requested by sponsor
Treatment of pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists in adult patients (≥18 years of age) with functional class II or III pulmonary hypertension *who are unable to achieve disease control with another PAH therapy*

PAH = pulmonary arterial hypertension; WHO = World Health Organization.

Results and interpretation

Included studies

One randomized, double-blind study met the inclusion criteria (PATENT-1) (N = 443). The safety and efficacy of 12 weeks of riociguat (titrated up to a maximum of 2.5 mg three times daily) was compared with placebo in adults with symptomatic PAH. The study also included an exploratory lower-dose riociguat group (titrated up to a maximum 1.5 mg three times daily). Randomization was stratified by the patients' prior treatment history. Of those enrolled, half were treatment-naive, and half were receiving ERA or prostanoid therapy that was continued during the study period. The primary outcome was the change from baseline in six-minute walk distance (6MWD) at 12 weeks, and secondary outcomes included time to clinical worsening, and the change from baseline in WHO functional class, pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, Borg CR10 dyspnea scale, EuroQol 5-Dimensions Questionnaire (EQ-5D), and Living with Pulmonary Hypertension (LPH) questionnaire. The key limitations were the short duration of the trial and lack of data for the requested listing.

Efficacy

A total of six deaths occurred during the study: three in the placebo group (PAH, anxiety, respiratory failure with circulatory collapse), two in the riociguat 2.5 mg group (sepsis, hemoptysis), and one in the riociguat 1.5 mg group (right ventricular failure/PAH).

The data from the PATENT-1 trial (total study population) suggested that riociguat up to 2.5 mg three times daily for 12 weeks provides a clinically and statistically significant increase in 6MWD from baseline compared with placebo (mean difference [MD] between groups 36 m; 95% confidence interval [CI], 20 to 52). The trial duration was insufficient to assess survival; however, riociguat showed statistically significant differences in the time to clinical worsening (log-rank $P = 0.005$), a composite outcome that included morbidity and mortality events that are important to patients, compared with placebo.

Statistically significant differences were detected between riociguat 2.5 mg and placebo in the change in WHO functional class. In addition, statistically significant differences were detected between riociguat 2.5 mg and placebo for the change in PVR and NT-proBNP levels, which the clinical expert consulted for this review considered clinically important. No statistical or clinically important differences were detected between treatments in health-related quality of life based on the EQ-5D or LPH. Moreover, the differences between riociguat 2.5 mg and placebo for dyspnea symptoms were statistically significant, but the clinical importance of the differences was unclear.

The results for the exploratory riociguat 1.5 mg group were similar in magnitude and direction as the riociguat 2.5 mg group. Subgroup data suggested that the treatment effect of riociguat 2.5 mg versus placebo was similar for treatment-naive patients (i.e., monotherapy) and when administered as add-on therapy to stable ERA or prostanoid regimens across outcomes. However, statistical comparisons were conducted only on subgroup comparisons for the primary outcome. Similar findings were noted for functional class I/II and III/IV subgroups.

Indirect evidence from the manufacturer-provided indirect treatment comparison (ITC) found [redacted] The findings of the ITC were generally consistent with the Therapeutic Review conducted by CADTH.[3] No conclusions could be drawn for changes in functional class due to methodologic limitations of the analysis. The combination therapy analysis may be limited by clinical heterogeneity between trials. For some outcomes, data were sparse (EQ-5D) or the credible intervals were wide (namely clinical worsening events and PVR), suggesting there is uncertainty in the findings.

The available data were limited by the short duration of PATENT-1 (12 weeks). Although the open-label extension study suggests that treatment effects are maintained with longer-term treatment (median treatment duration 91 weeks), these results should be viewed with caution, given the possible selection bias, lack of control group, and unblinded assessment. The PATENT-1 study was powered for the change in 6MWD, which is a surrogate outcome that has demonstrated moderate to poor correlation with key clinical outcomes in PAH.[7-9]

For both PATENT-1 and the manufacturer-provided ITC, there were no data on the efficacy and safety of riociguat for the listing requested by the manufacturer: patients who are unable to achieve disease control with another PAH drug. The subgroup data from PATENT-1 suggest that riociguat provides benefits to patients when administered as add-on therapy to stable ERA or prostanoid treatment; however, data in patients unable to achieve disease control targets with other PAH drugs are lacking.

Harms

In the 12-week PATENT-1 study, serious adverse events were reported in 11% and 18% of patients in the riociguat groups and 18% of patients in the placebo group. More patients stopped treatment due to adverse events in the placebo group (7%) than in the riociguat groups (2% and 3%).

Of the notable harms, the incidence of anemia and hypotension was numerically higher in the riociguat 2.5 mg group than the placebo and riociguat 1.5 mg groups, whereas the incidence of syncope was higher in the placebo group than the riociguat groups. Both the Health Canada and FDA reviews noted potential risks with regards to the dose-related increase in hypotension observed with the riociguat 2.5 mg dose.[10,11] The incidence of any bleeding event was similar across treatments in PATENT-1; however, serious bleeding events occurred more frequently in the riociguat groups than the placebo group. Although anemia was reported more frequently by patients receiving riociguat than placebo, the

use of anti-anemia medications was similar between treatment groups.[10,11] Of the other notable harms identified in the review protocol, peripheral edema was also higher in the riociguat groups than in the placebo group. The most common adverse events in the riociguat groups were headache, dizziness, and gastrointestinal events.

Patients who completed PATENT-1 were eligible to enroll in the open-label extension study, PATENT-2.[12] A total of 396 patients enrolled (98% of eligible patients) and of these, 82% were still receiving treatment at the March 2013 cut-off of this ongoing clinical trial. Patients received riociguat up to a maximum of 2.5 mg three times daily. In PATENT-2, 52% of patients experienced a serious adverse event and 21% had a clinical worsening event (median treatment duration 91 weeks).[12] A total of 27 deaths were reported over the 718 person-years of exposure.[12] No new safety signals were identified.

No data on the comparative safety of riociguat versus other PAH therapies were available from the manufacturer-provided ITC, and no head-to-head studies were identified. Additional data are needed to determine the long-term safety of riociguat.

Potential place in therapy[1]

The clinical expert involved in the review noted that while riociguat is a first-line therapy option for treatment-naive patients, an important limitation versus other oral drugs is the long dose titration period. Hence, likely the most benefit for this drug will be seen as a combination therapy strategy, as add-on to ERA or prostacyclin background. The clinical expert described the combination therapy data from PATENT-1 as compelling, although one cannot conclude that these were patients failing to meet treatment goals, as the inclusion criteria of the study did not specify that criterion.

Given the CDEC recommendation suggesting sildenafil or tadalafil use as first-line therapy for patients with PAH functional class II or III, the role of this drug may be considered in the following scenarios:

1. As add-on to current ERA therapy in patients who are not meeting treatment goals and require additional therapy (CDEC could not make a recommendation regarding the choice of a second-line therapy when considering combination therapy).
2. As add-on to current prostacyclin therapy in patients who are not meeting treatment goals and require additional therapy.
3. For patients who are unable to tolerate PDE5 inhibitors as monotherapy due to an adverse event and needing to make a switch to another therapeutic class.

There is the possibility of using riociguat as initial therapy in patients who have a contraindication to PDE5 inhibitor use, although because of the overlap in contraindications between PDE5 inhibitors and riociguat (e.g., concomitant use of nitrates), there is potential that riociguat would be contraindicated as well.

The clinical expert noted that the strategy of switching from a PDE5 inhibitor to riociguat in patients who are not meeting treatment goals as possible; however, there is limited evidence of efficacy for this strategy. The switch strategy (i.e., switching to riociguat in patients with insufficient treatment response to PDE5 inhibitors) is currently being studied in the RESPITE study.[13]

[1] Based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review reviewers for the purpose of this review.

Conclusions

Riociguat was associated with statistically significant improvement in the time to clinical worsening (a composite of morbidity and mortality) versus placebo, based on a single, double-blind, 12-week randomized controlled trial (RCT) in adults with symptomatic PAH who were either treatment-naive or who were receiving therapy with ERAs or prostanoids. More patients on riociguat maintained a favourable functional class, and riociguat was associated with clinically and statistically significant increases in 6MWD. The improvement in 6MWD with riociguat treatment was augmented by clinically relevant improvements in hemodynamic parameters.

Indirect evidence suggests the efficacy of riociguat (alone or in combination with ERAs) may be similar to other PAH treatments.

Serious adverse events were frequent for both riociguat and placebo and included a total of six deaths: three in the placebo group and three in the riociguat groups. Withdrawals due to adverse events were less frequent in the riociguat groups than in the placebo group. Adverse events of anemia and hypotension occurred more frequently in the riociguat 2.5 mg group than the placebo and riociguat 1.5 mg groups, whereas the incidence of syncope was higher in the placebo group than the riociguat groups. More serious bleeding events occurred among patients receiving treatment with riociguat than with placebo. The most common adverse events in the riociguat groups were headache, dizziness, and gastrointestinal events. No data on the comparative safety of riociguat versus other PAH therapies were available. Although no new safety signals were identified in the open-label extension study (PATENT-2), additional data are needed to determine the long-term safety of riociguat.

There were no data from the RCT or ITC on the efficacy and safety of riociguat for the listing requested by the manufacturer: patients who are unable to achieve disease control with another PAH drug.

TABLE 1: SUMMARY OF RESULTS

Outcome	PATENT-1[a]		
	Placebo	**Riociguat 2.5 mg**	**Riociguat 1.5 mg**
Time to Clinical Worsening	**N = 126**	**N = 254**	**N = 63**
Any event, n (%)	8 (6)	3 (1)	2 (3)
P value versus placebo[b]	--	0.029	0.33[c]
Change in WHO Functional Class, n (%)	**N = 125**	**N = 254**	**N = 63**
–2	0	[redacted](< 1)	0
–1	[redacted](14)	[redacted](21)	[redacted] (24)
0	89 (71)	192 (76)	43 (68)
+1	[redacted] (12)	[redacted] (3)	[redacted] (6)
+2	[redacted](2)	[redacted] (< 1)	[redacted] (2)
+3	0	v (< 1)	0
P value versus placebo	--	0.003	0.07[c]
EQ-5D Utility Score	**N = 124**	**N = 253**	**N = 62**
Baseline, mean (SD)	0.68 (0.24)	0.68 (0.24)	[redacted]
Change from baseline to week 12, mean (SD)	–0.03 (0.30)	0.03 (0.24)	0.08 (0.31)
Least squares MD (95% CI) versus placebo	--	0.06 (0.01 to 0.11)	NR

Outcome	PATENT-1[a]		
	Placebo	**Riociguat 2.5 mg**	**Riociguat 1.5 mg**
P value		0.07[a]	NS
6MWD	**N = 126**	**N = 254**	**N = 63**
Baseline, mean (SD)	368 (75)	361 (68)	363 (67)
Change from baseline to week 12, mean (SD)	–6 (86)	30 (66)	31 (79)
Least squares MD (95% CI) versus placebo	--	36 (20 to 52)	37 (12 to 63)[c]
P value versus placebo	--	*P* < 0.0001	*P* < 0.0001[c]
Withdrawals	**N = 126**	**N = 254**	**N = 63**
n (%)	15 (12)	17 (7)	6 (10)
Adverse Event Leading to Discontinuation of Study Drug			
n (%)	9 (7)	8 (3)	1 (2)
Serious Adverse Events			
Patients with ≥ 1 serious adverse event, n (%)	23 (18)	29 (11)	11 (18)
Deaths, n (%)	3 (2)	2 (1)	1 (2)
Notable Harms, n (%)			
Anemia	3 (2)	21 (8)	1 (2)
Bleeding events[d]	12 (10)	28 (11)	7 (11)
Syncope, presyncope, or loss of consciousness	7 (6)	8 (3)	2 (3)
Peripheral edema	14 (11)	44 (17)	14 (22)
Hypotension (pooled MedDRA terms)	3 (2)	25 (10)	2 (3)

6MWD = six-minute walk distance; CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; ERA = endothelin receptor antagonist; MD = mean difference; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; PH = pulmonary hypertension; SD = standard deviation; WHO = World Health Organization.

[a] Data presented are for the overall study population, of which half were treatment-naive (i.e., on monotherapy) and half continued on ERA of prostanoid treatments they were receiving prior to the study.

[b] The time to clinical worsening was analyzed using the stratified log-rank test, with Kaplan–Meier estimates of the proportion of patients with the event. Clinical worsening events included death, heart or lung transplantation, atrial septostomy, 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 functional class due to deterioration of PH.

[c] Post-hoc data reported by the FDA.

[d] Bleeding events were identified retrospectively based on a standardized MedDRA query for "hemorrhages" and related terms (excluding laboratory terms).

Source: Ghofrani 2013,[14] Clinical Study Report,[15] FDA Medical Review.[11]

1. INTRODUCTION

1.1 Disease prevalence and incidence

Pulmonary arterial hypertension (PAH) is an uncommon, debilitating, progressive, and life-threatening disease of the pulmonary vasculature, characterized by vascular proliferation and remodelling of small pulmonary arteries.[1] If left untreated, it can lead to right-sided heart failure and premature death.[1] PAH is defined by an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg.[1]

The symptoms of PAH include breathlessness, fatigue, weakness, chest pain, light-headedness/fainting, and edema/ascites. Severity of disease is based on symptoms and assessed using the New York Heart Association (NYHA) or World Health Organization (WHO) functional classification of heart failure symptoms, ranging from functional class I to IV, with functional class IV being the most severe (Table 2).

TABLE 2: WORLD HEALTH ORGANIZATION FUNCTIONAL CLASSIFICATION OF PULMONARY HYPERTENSION

Class	Description
I	No limitations of physical activity
II	Slight limitation of physical activity, but no symptoms at rest
III	Marked limitation of physical activity, but no symptoms at rest
IV	Inability to perform any physical activity without discomfort; symptoms may be present at rest; signs of right failure present

Source: European Society of Cardiology/European Respiratory Society Guidelines.[1]

PAH is classified as Group 1 of the pulmonary hypertension (PH) classification, which was recently revised and updated in the fifth World Symposium on Pulmonary Hypertension, held in Nice (France), in 2013.[2] The four main categories of Group 1 include idiopathic PAH, heritable or familial PAH, drug- and toxin-induced PAH, and PAH associated with other conditions such as connective tissue disease, human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease, or schistosomiasis (Table 3).

TABLE 3: 2013 (NICE) PULMONARY ARTERIAL HYPERTENSION CATEGORIES

Categories
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

Categories
1''. Persistent pulmonary hypertension of the newborn

ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; KCNK3 = potassium channel super family K member-3; Smad 9 = mothers against decapentaplegic 9.
Source: Simonneau 2013.[2]

There are no published data on the incidence or prevalence of PAH in Canada; however, data from US and European registries provide some information.[16-19] The incidence of PAH ranges from 2.3 to 7.6 cases per million based on data from the US, France, Spain, and Scotland.[16-19] Data on the prevalence of PAH varies from 12.4 (US), 15 to 16 (France, Spain), and 26 to 52 cases per million (Scotland).[16-19] Based on these figures, and 2014 Canadian population data, the manufacturer estimated there are 434 to 1,820 prevalent cases of PAH, with 81 to 266 new cases developing each year.[5]

1.2 Standards of therapy

Treatment of PAH is generally categorized as supportive therapy or advanced therapy. Supportive therapy includes use of diuretics, oxygen, anticoagulants, and digoxin. Advanced therapy is targeted at the disease itself. As supportive therapies are generally not effective in PAH, advanced therapy is almost always needed.

Health Canada has approved eight advanced treatment options covering four different classes of drugs for PAH, WHO Group 1 (Table 4):

- prostanoids (epoprostenol, treprostinil)
- endothelin receptor antagonists (ERAs) (bosentan, ambrisentan, macitentan)
- phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil)
- soluble guanylate cyclase (sGC) stimulator (riociguat).

In 2014, CADTH conducted a Therapeutic Review to assess the comparative efficacy and safety and to determine the cost-effectiveness of pharmacologic treatments for adults with PAH.[3] Results from the systematic review and network meta-analysis suggest that there were no significant differences in clinical worsening and functional class worsening between drugs used to treat PAH as monotherapy. For functional class improvement and six-minute walk distance (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 PDE5 inhibitor or prostanoids background therapy and addition of riociguat or tadalafil on ERA background therapy produce improvement in clinical worsening, functional class improvement, functional class worsening, and/or 6MWD versus monotherapy with background therapy. 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 health-related quality of life (HRQoL) compared with placebo. Adverse events were treatment-specific.[3]

Based on the Therapeutic Review and patient group input, the CADTH Canadian Drug Expert Committee (CDEC) recommended the following:

- sildenafil or tadalafil be the preferred initial therapy for adult patients with functional class II and III PAH
- add-on therapy should be used in adult PAH patients who are unable to achieve disease control with a single drug.[4]

CDEC could not make a specific recommendation pertaining to subgroups of patients (based on disease severity or other disease characteristics) who may benefit more from specific drugs or combinations of drugs based on the evidence reviewed.[4]

PAH has a significant impact on the lives of patients and caregivers. Patients with PAH have a day-to-day life that is difficult and exhausting, and they progressively lose the ability to care for themselves. While therapy may delay progression, reduce the severity of symptoms, and make certain tasks easier, there is still no cure for PAH.

1.3 Drug

Riociguat is a first-in-class drug of the soluble guanylate cyclase stimulator class of drugs, which works by producing vasorelaxation independent of the endogenous vasodilatory effects of nitrous oxide.[5] Riociguat is initiated at a dose of 1.0 mg orally three times daily and adjusted by 0.5 mg increments every two weeks according to systolic systemic blood pressure readings, to a maximum dose of 2.5 mg three times daily.[6]

CDEC reviewed riociguat in 2014 and recommended that it be listed for the management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4) or persistent or recurrent CTEPH after surgical treatment in adult patients (≥ 18 years of age) with WHO functional class II or III PH, if the following conditions were met:

- riociguat should be prescribed by a clinician with experience in the diagnosis and treatment of CTEPH
- a substantial reduction in price.

The riociguat indication under review in this report is the treatment of PAH (WHO Group1), in adults with functional class II or III PH.

Indication under review
Treatment of pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists in adult patients (≥ 18 years of age) with functional class II or III pulmonary hypertension.
Listing criteria requested by sponsor
Treatment of pulmonary arterial hypertension (PAH, WHO Group 1), as monotherapy or in combination with endothelin receptor antagonists in adult patients (≥ 18 years of age) with functional class II or III pulmonary hypertension *who are unable to achieve disease control with another PAH therapy*

PAH = pulmonary arterial hypertension; WHO = World Health Organization.

TABLE 4: KEY CHARACTERISTICS OF PULMONARY ARTERIAL HYPERTENSION DRUGS AVAILABLE IN CANADA

	Riociguat[6]	Macitentan[20]	Ambrisentan[21]	Bosentan[22]	Sildenafil[23]	Tadalafil[24]	Epoprostenol[25]	Treprostinil[26]
Drug class	sGC stimulator	ERA			PDE5 inhibitor		Prostanoid	
Mechanism of action	Dual mode of action acting in synergy with endogenous nitric oxide and also directly stimulating sGC independently of nitric oxide availability.	Decreases mean pulmonary arterial pressure without affecting systemic blood pressure, decreased pulmonary arterial hypertrophy, and right ventricular remodelling.	Selective inhibition of the endothelin type A receptor that inhibits C-mediated vasoconstriction.	Decreases pulmonary and systemic vascular resistance, resulting in increased cardiac output without increased heart rate.	Selective inhibition of PDE5, thereby increasing cGMP, leading to selective vasodilation of the pulmonary vascular bed and systemic circulation.	Selective inhibition of PDE5, thereby increasing cGMP, leading to selective vasodilation of the pulmonary vascular bed.	Direct vasodilation of pulmonary and systemic arterial beds. Inhibition of platelet aggregation.	Direct vasodilation of pulmonary and systemic arterial beds. Inhibition of platelet aggregation.
Approved indications[a]	PAH (WHO Group 1), as monotherapy or in combination with ERAs, in adult patients (≥ 18 years of age) with WHO functional class II or III.	Idiopathic or heritable PAH of WHO functional class II or III, or PAH associated with connective tissue disease or congenital heart disease.	Idiopathic ('primary') PAH and PAH associated with connective tissue disease in patients with WHO functional class II or III symptoms.	WHO functional class 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 functional class II or III who did not respond adequately to conventional therapy. Intravenous: Patients who are temporarily unable to take oral medication.	Idiopathic primary PAH or PAH associated with connective tissue disease, congenital heart disease, or anorexigen use in patients with WHO functional class II or III who have not responded to conventional therapy.	The long-term intravenous treatment of idiopathic or heritable PAH or PAH associated with CTDs in patients with WHO functional class III to IV symptoms who did not respond adequately to conventional therapy.	PAH in NYHA Class III and IV patients who did not respond adequately to conventional therapy.

	Riociguat[6]	Macitentan[20]	Ambrisentan[21]	Bosentan[22]	Sildenafil[23]	Tadalafil[24]	Epoprostenol[25]	Treprostinil[26]
Route of administration	Oral	Oral	Oral	Oral	Oral or intravenous	Oral	Continuous chronic intravenous infusion via central venous catheter	Subcutaneous or intravenous (long-term)
Recommended dose	0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg three times daily	10 mg once daily	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: 10 mg 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 tolerability Patients with mild or moderate hepatic impairment: 20 mg once daily	Initial: 2 ng/kg/min Incremental increase: 1 to 2 ng/kg/min, between at least 15 minute intervals	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 and symptoms and side effects
Contraindications (according to product monograph)	PDE5 inhibitors (sildenafil, tadalafil, vardenafil) Nitrates Nitric oxide donors, such as amyl nitrate Patients who are	Patients who are hypersensitive to drug. Patients who are pregnant or may become pregnant.	Patients with idiopathic pulmonary fibrosis. Patients who are pregnant, breastfeeding, or may become pregnant. Patients with	Patients who are hypersensitive to drug or any excipient in the formulation. Patients who are pregnant. Patients with moderate or	Patients on nitrate drug therapy or utilizing short-acting nitrate-containing medications. Patients with previous episode of NAION.	Patients with previous episode of NAION. Patients on nitrate drug therapy.	Patients with congestive heart failure due to severe left ventricular systolic dysfunction. Patients who develop pulmonary edema during dose initiation.	Patients with known hypersensitivity to the drug, any of its excipients, or to structurally related compounds.

	Riociguat[6]	Macitentan[20]	Ambrisentan[21]	Bosentan[22]	Sildenafil[23]	Tadalafil[24]	Epoprostenol[25]	Treprostinil[26]
	pregnant, or during nursing		severe hepatic impairment or liver enzymes > 3x ULN.	severe liver impairment. Concomitant use of cyclosporine A or glyburide.	In combination with the most potent of the CYP3A4 inhibitors.			
Warnings and precautions (according to product monograph)	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 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	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 moderate or severe renal impairment could experience hypotension and anemia.	Patients with clinically significant anemia. 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. Peripheral edema may develop. Acute pulmonary edema with the possibility of pulmonary venoocclusive disease.	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 venoocclusive disease. Patients with abnormal discs or previously diagnosed with NAION, due to potential development of NAION. Patients with pulmonary hypertension secondary to sickle cell anemia. The use of sildenafil with bosentan is not recommended in patients with PAH	Potential to significantly worsen the cardiovascular status of patients with pulmonary venoocclusive disease. Patients with abnormal discs or previously diagnosed with NAION, due to potential development of NAION. Patients with severe renal or hepatic insufficiency.	Abrupt withdrawal should be avoided. Not be used in patients having pulmonary edema during dose initiation. Acute dose initiation must be performed in hospital with adequate personnel and equipment for physiologic monitoring and emergency care. Increased risk for hemorrhagic complications in patients with other risk factors for bleeding.	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 attributable to PAH or the occurrence of intolerable adverse events.

	Riociguat[6]	Macitentan[20]	Ambrisentan[21]	Bosentan[22]	Sildenafil[23]	Tadalafil[24]	Epoprostenol[25]	Treprostinil[26]
	systemic blood pressure when concomitantly used with PDE5 inhibitors, nitrates, or nitric oxide donors. Risk of bleeding, particularly in patients taking anticoagulants. May worsen cardiovascular status of patients with pulmonary venoocclusive disease.				associated with CTD. Caution is advised when co-administered with alpha-blockers, as both are vasodilators with blood pressure–lowering effects.			

cGMP = cyclic guanosine monophosphate; CTD = connective tissue disease; ERA = endothelin receptor antagonist; NAION = non-arteritic anterior ischemic optic neuropathy; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase; ULN = upper limit of normal; WHO = World Health Organization.

[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of riociguat 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets for the treatment of PAH in adults (WHO functional class II or III).

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 5.

TABLE 5: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults (≥ 18 years of age) with PAH (WHO Group I) in WHO functional class II or III pulmonary hypertension **Subpopulations:** • Patients unable to achieve disease control with another PAH therapy • Functional class • Patients receiving mono or combination PAH therapy
Intervention	Riociguat as monotherapy or in combination with endothelin receptor antagonists, at Health Canada approved doses
Comparators	Medical intervention/pharmacotherapy: • endothelin receptor antagonists (e.g., bosentan, macitentan, ambrisentan) • phosphodiesterase type 5 inhibitors (e.g., sildenafil, tadalafil) • prostanoids (i.e., prostacyclins, prostacyclin analogues such as epoprostenol, treprostinil)

Outcomes	**Key efficacy outcomes:**
	• Survival
	• Hospitalization
	• Clinical worsening
	• Change in WHO functional class
	• HRQoL
	
	Other efficacy outcomes:
	• 6MWD
	• Cardiopulmonary exercise testing (i.e., peak VO_2)
	• Change in pulmonary hypertension symptoms
	• Change in:
	  ○ PVR
	  ○ mPAP
	  ○ Cardiac index
	  ○ BNP/ NT-proBNP
	• Use of supplemental oxygen
	
	Harms outcomes:
	• Adverse events
	• Serious adverse events
	• WDAEs
	• Adverse events of interest: anemia, bleeding events, hypotension, orthostatic hypotension, presyncope, syncope, peripheral edema, acute renal failure, gastrointestinal adverse events

Study Design	Published and unpublished phase 3 RCTs

6MWD = six-minute walk distance; BNP = brain natriuretic peptide; HRQoL = health-related quality of life; mPAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; peak VO_2 = maximal oxygen consumption; WDAE = withdrawal due to adverse event; WHO = World Health Organization.

The literature search was performed by an information specialist using a peer-reviewed search strategy. 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; 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 concept was Adempas (riociguat).

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 23, 2015. Regular alerts were established to update the search until the CDEC meeting on November 18, 2015. 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 CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and Internet search. 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 contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 6; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

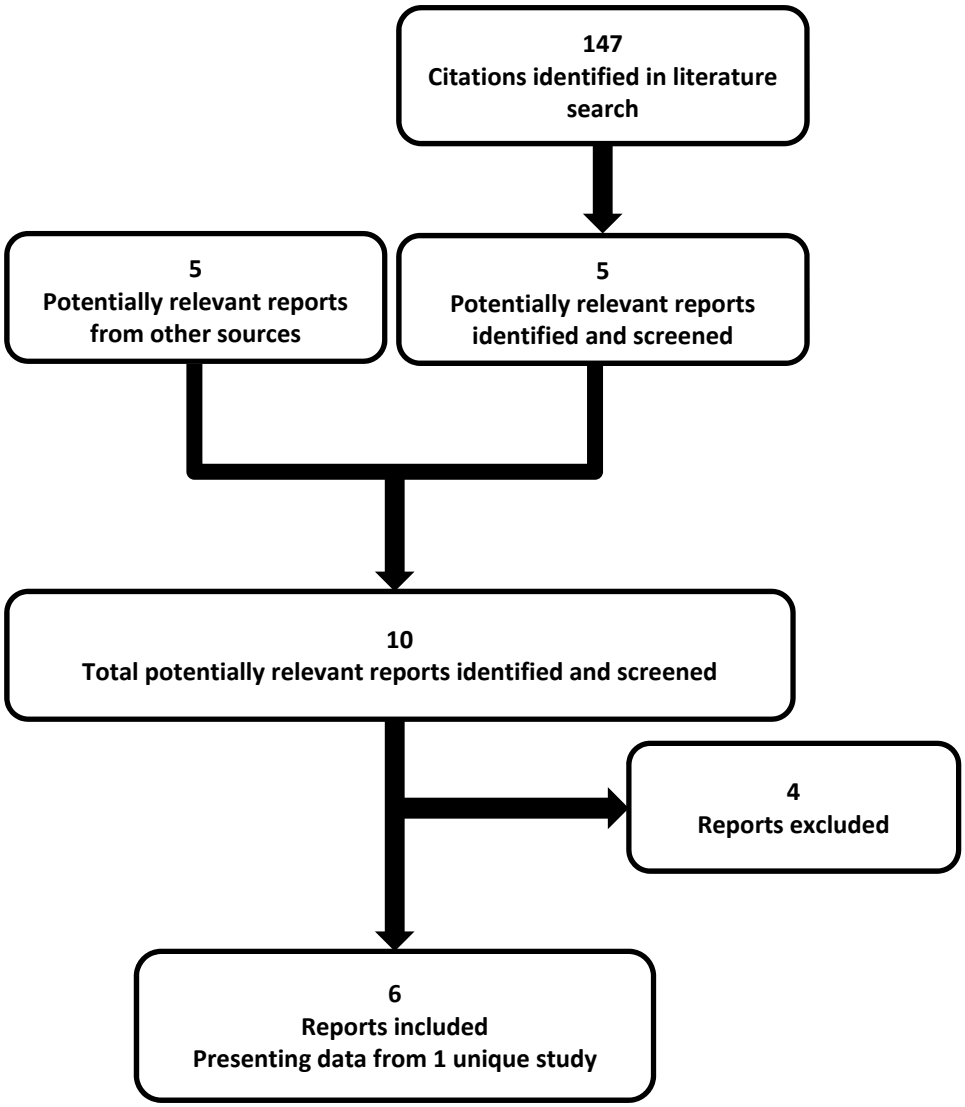

TABLE 6: DETAILS OF INCLUDED STUDIES

		PATENT-1
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	North America, South America, Europe, Asia
	Randomized (N)	443
	Inclusion Criteria	Patients 18 to 80 years of age with symptomatic PAH (idiopathic, familial, or associated with connective tissue disease, congenital heart disease, portal hypertension with liver cirrhosis, or anorexigen or amphetamine use), and: • pulmonary vascular resistance greater than 300 dyn·s·cm^{-5} • mean pulmonary arterial pressure of at least 25 mm Hg • 6-minute walk distance of 150 m to 450 m. Patients who were treatment-naive or those on stable regimens of ERAs or prostanoids (excluding IV prostanoids) were eligible for inclusion.
	Exclusion Criteria	• Other forms of Group 1 PAH (e.g., PAH associated with HIV) • Patients receiving PDE5 inhibitors, IV prostanoids, or nitrates • Moderate to severe obstructive lung disease (FEV_1 < 60% predicted) or severe restrictive lung disease (total lung capacity < 70%), oxygen saturation < 88% despite supplemental oxygen • SBP < 95 mm Hg • Left-sided heart failure with ejection fraction < 40% • Severe coronary artery disease or symptomatic atherosclerotic disease, atrial fibrillation, hypertrophic obstructive cardiomyopathy • Medical disorder with anticipated life expectancy below 2 years (e.g., active cancer) • Severe renal insufficiency • Unable to perform 6MWD test • Patients with a relative difference of more than 15% between the eligibility and baseline 6MWD test
DRUGS	**Intervention**	• Riociguat up to 2.5 mg three time daily, orally • Riociguat up to 1.5 mg three times daily, orally
	Comparator(s)	Placebo
DURATION	**Phase**	3
	Dose titration	8 weeks
	Maintenance	4 weeks
	Follow-up	4 weeks
OUTCOMES	**Primary End Point**	Change from baseline to week 12 in 6MWD
	Other End Points	Change from baseline to week 12 in: • PVR • NT-proBNP levels • WHO functional class • Modified Borg dyspnea score/Borg CR10 scale • EQ-5D • LPD questionnaire Time to clinical worsening Harms

		PATENT-1
NOTES	**Publications**	Ghofrani 2013[14]

6MWD = six-minute walk distance; DB = double-blind; EQ-5D = EuroQol 5-Dimensions Questionnaire; ERA = endothelin receptor antagonists; FEV_1 = forced expiratory volume in one second; IV = intravenous; LPD = Living with Pulmonary Hypertension; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; PDE5 = phosphodiesterase type 5; RCT = randomized controlled trial; SBP = systolic blood pressure; WHO = World Health Organization.
Note: Four additional reports were included (CADTH Common Drug Review Submission,[5] FDA Medical and Statistical reports,[11,27] Health Canada Reviewer report.[10]
Source: Ghofrani 2013,[14] Clinical Study Report.[15]

3.2 Included studies

3.2.1 Description of studies

One pivotal, double-blind, 12-week RCT met the inclusion criteria and has been summarized in this report (PATENT-1) (Table 6). This trial was designed to evaluate the superiority of riociguat (up to 2.5 mg three times daily) versus placebo in patients with symptomatic PAH. It also included an exploratory lower dosage group with riociguat up to 1.5 mg three times daily.

The computer-generated randomization sequence (block size of 7) was created by the sponsor with separate blocks for treatment-naive patients and those receiving PAH therapies. Patients were allocated to treatments using an interactive voice response system. Matched placebo, including sham titration for placebo and riociguat 1.5 mg groups, was used to maintain blinding.

3.2.2 Populations

a) Inclusion and exclusion criteria

PATENT-1 enrolled adults with symptomatic PAH of one of the following subclasses: idiopathic, familial, or associated with connective tissue disease, congenital heart disease, portal hypertension with liver cirrhosis, or anorexigen or amphetamine use. Those enrolled were either PAH treatment-naive or receiving a stable regimen of ERAs or prostanoids (excluding intravenous prostanoids). Patients receiving PDE5 inhibitors were excluded.

b) Baseline characteristics

The majority of patients enrolled in PATENT-1 were female (78% to 80%), with an average age per treatment group of 49 to 51 years. Idiopathic PAH was the most common subgroup of patients (59% to 67%), followed by PAH associated with connective tissue disease (20% to 28%). Half the patients were on PAH therapy prior to enrollment: ERA (43% to 44%); prostanoid (5% to 7%).

Most patients were WHO functional class III (46% to 62%) or class II (30% to 48%). There were fewer patients with functional class II and more with class III in the riociguat groups than the placebo group. In general, the other characteristics were balanced between treatment groups.

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS IN PATENT-1 STUDY

Characteristic	Placebo N = 126	Riociguat 2.5 mg N = 254	Riociguat 1.5 mg N = 63
Female, N (%)	98 (78)	203 (80)	49 (78)
Age — years, mean (SD)	51 (17)	51 (17)	49 (16)
PAH classification, N (%)			
Idiopathic	84 (67)	149 (59)	39 (62)
Familial	1 (1)	7 (3)	1 (2)
Associated with connective tissue disease	25 (20)	71 (28)	15 (24)
Associated with congenital heart disease	12 (10)	15 (6)	8 (13)
Associated with portopulmonary hypertension	2 (2)	11 (4)	0
Associated with anorexigen or amphetamine use	2 (2)	1 (< 1)	0
WHO functional class, N (%)			
I	4 (3)	5 (2)	5 (8)
II	60 (48)	108 (43)	19 (30)
III	58 (46)	140 (55)	39 (62)
IV	3 (2)	1 (< 1)	0
6MWD — m, mean (SD)	368 (75)	361 (68)	363 (67)
6MWD category, n (%)			
< 320 m	27 (21)	67 (26)	14 (22)
< 380 m	53 (42)	139 (55)	30 (48)
PVR (dyn·s·cm^{-5}), mean (SD)	834 (477), n = 107	791 (453), n = 232	848 (548), n = 58
mPAP (mm Hg), mean (SD)	49 (15), n = 109	47 (15), n = 235	52 (16), n = 58
Receipt of additional PAH treatments			
None	66 (52)	123 (48)	32 (51)
ERA	54 (43)	113 (44)	27 (43)
Prostanoid	6 (5)[a]	18 (7)[a]	4 (6)

6MWD = six-minute walk distance; ERA = endothelin receptor antagonists; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; SD = standard deviation; WHO = World Health Organization.

[a] Two patients in the 2.5 mg riociguat group and one patient in the placebo group were receiving an ERA and prostanoid. These patients have been included in the ERA subgroup.

Source: Ghofrani 2013, [14] Clinical Study Report.[15]

3.2.3 Interventions

Patients were randomized in a 2:4:1 ratio to placebo, oral riociguat titrated up to a maximum of 2.5 mg three times daily, or oral riociguat up to a maximum of 1.5 mg three times daily. Randomization was stratified by prior PAH treatment (treatment-naive versus those receiving ERAs or prostacyclin analogues). The 1.5 mg riociguat dose was considered exploratory and was not included as part of the efficacy analysis.

Riociguat was initiated at 1 mg three times daily and the dose was adjusted every two weeks according to the patient's systolic blood pressure (SBP) or signs of hypotension. Dose titration was as follows:

- If trough SBP ≥ 95 mm Hg, increase dose by 0.5 mg three times daily.
- If trough SBP = 90 to 94 mm Hg, maintain same dose.

- If trough SBP < 90 mm Hg without symptoms of hypotension, reduce dose by 0.5 mg three times daily.
- If trough SBP < 90 mm Hg with symptoms of hypotension (e.g., dizziness, presyncope), stop treatment; restart after 24 hours with dose reduced 0.5 mg three times daily.
- For patients experiencing medication adverse effects, a decision to alter the titration schedule and to maintain or reduce the dosage was allowed.

The dosage range was 0.5 mg to 2.5 mg three times daily for patients in the riociguat 2.5 mg dose group, and 0.5 mg to 1.5 mg three times daily for patients in the riociguat 1.5 mg dosage group. The dose was adjusted over the first eight weeks and then maintained for another four weeks. Patients in the 1.5 mg dose group and placebo group received sham adjustment of doses to maintain blinding. All dosage decisions (increase, maintain, or decrease dose) were entered in the interactive voice response system and the correct blinded medication bottles were then dispensed for use over the next two weeks.

Concomitant administration of anticoagulant drugs, oxygen, diuretics, digitalis, or calcium channel blockers was allowed. In addition, patients receiving ERAs or prostacyclin analogues (oral, subcutaneous, or inhaled) were enrolled in the trial. Patients receiving PDE5 inhibitors or intravenous prostacyclin analogues were excluded.

Among those enrolled, 55% to 57% were using oral anticoagulants, [redacted] were using diuretics, 20% to 27% were using calcium channel blockers, and 14% to 17% were using digitalis during the study.

3.2.4 Outcomes

The primary end point in PATENT-1 was the change from baseline in 6MWD after 12 weeks. Secondary outcomes included change from baseline to week 12 in: pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP), WHO functional class, Borg CR10 scale or modified Borg Dyspnea Scale, EuroQol 5-Dimensions Questionnaire (EQ-5D) and Living with Pulmonary Hypertension (LPH) questionnaire. Time to clinical worsening was also evaluated based on events (Table 8) recorded by the investigator. Patients who fulfilled any of the events defined as clinical worsening were withdrawn from the study. The exploratory outcomes of interest to this review included mPAP, cardiac index, and use of supplemental oxygen. Patients were assessed at weeks 2, 4, 6, 8, and 12, with a final follow-up visit 30 days after the last dose of study drug.

TABLE 8: TIME TO CLINICAL WORSENING: COMPONENTS OF COMPOSITE END POINT

Efficacy Outcome
Death (all-cause mortality)
Heart/lung transplantation
Atrial septostomy
Hospitalization due to persistent worsening of PH[a,b]
Start of new PH-specific treatment, or modification of pre-existing prostacyclin analogue treatment due to worsening PH: *Includes endothelin receptor antagonists, prostacyclin analogues, PDE5 inhibitors*
Persistent decrease of more than 15% from baseline or more than 30% compared with the last study-related measurement in 6MWD due to worsening PH[b,c]
Persistent worsening of functional class due to deterioration of PH[b,c] *Patients who deteriorate from class II or III to class IV*

6MWD = six-minute walking distance; PDE5 = phosphodiesterase type 5; PH = pulmonary hypertension.
[a] Transient deteriorations of clinical status requiring hospitalization (e.g., treatment with short time intravenous diuretics, positive inotropic drugs, or non-invasive ventilation) and allowing patients discharge within 48 hours were not considered persistent with respect to the event of special interest definition.
[b] In case of clinical deterioration, the investigator was to carefully assess if the deterioration of the patient's condition (e.g., worsening functional class) was related to the underlying PH or could be explained by an alternative cause (e.g., transient infection, musculoskeletal disease, surgical or medical intervention [other than PH-related], exacerbation of a concomitant lung disease, medication non-compliance). Only persistent clinical deteriorations caused by the underlying PH were considered events of special interest.
[c] The persistence of the decrease in 6MWD or change in functional class had to be confirmed by a second measurement performed after 14 days. In case that the period between first occurrence of the event and visit 6/termination visit is less than 14 days, the decrease needs to be confirmed at visit 6/termination visit.
Source: Clinical Study Report.[15]

The 6MWD test was performed according to the American Thoracic Society guideline, and measured the distance a patient could walk on a flat surface in six minutes. Following the 6MWD test, patients were asked to rank their difficulty breathing using the modified Borg Dyspnea Scale, or, after a protocol amendment, using the Borg CR10 scale. Patients who were enrolled prior to protocol amendment continued to use the modified Borg Dyspnea Scale throughout PATENT-1. Patients ranked dyspnea on a categorical scale from 0 (no dyspnea) to 10 (maximal dyspnea) on both instruments, although patients could rate dyspnea as higher than 10 on the Borg CR10 instrument.

Functional class was determined according to WHO classification (Table 2). Although the WHO functional class system is used widely in clinical practice and as an outcome in clinical trials, clinician assessment of functional class may vary widely in PAH, especially when classifying patients as functional class II or III.[28]

HRQoL was assessed using the generic EQ-5D instrument. It consists of five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that were converted to a utility score (range –0.594 to 1.0). It also includes a visual analogue scale (range 0 [worst health state] to 100 [best health state]).

The LPH questionnaire is a PAH-specific HRQoL instrument that consists of 21 items. The total score ranges from 0 to 105, with higher numbers showing more severe impact of pulmonary hypertension on quality of life.

The minimal clinically important difference (MCID) for time to clinical worsening and hemodynamic parameters are currently unknown. For change from baseline in 6MWD, the estimated MCID value is 33.0 m (range: 25.1 m to 38.6 m) (APPENDIX 5).[29] The MCID for the Borg dyspnea score has been estimated to be approximately 1 point among patients with chronic obstructive pulmonary disease (COPD) and heart failure.[30,31] No published reports on the MCID for the Borg index in PAH were identified, although an abstract for a recent analysis using both distribution- and anchor-based methods suggested a MCID for the Borg index of < 1 point in patients with PAH.[32] The MCID for the EQ-5D utility score in PAH is unknown; however, in general use, the MCID ranges from 0.033 to 0.074.[33] The MCID for the LPH has been estimated to be 7 points for the change in the total score and 3 points for the change in the physical and emotional subscale scores (APPENDIX 5).

Adverse events were defined as any untoward medical occurrence in a patient administered a drug, but that did not necessarily have a causal relationship with the treatment. Any adverse events that started or worsened from the time of the first dose of study drug until two days after the last dose were included. Serious adverse events were defined as any event that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, was a congenital anomaly or birth defect, or was an important medical event because it might have jeopardized the patient or required intervention to prevent another serious condition.

3.2.5 Statistical analysis

The study was designed to test the superiority of riociguat 2.5 mg versus placebo for the primary outcome of the change from baseline in 6MWD to week 12. With 250 patients enrolled in the riociguat 2.5 mg group and 125 patients in the placebo group, the study had 90% power to detect a 25 m mean difference in 6MWD at a two-sided significance level. The riociguat 1.5 mg group was exploratory and its results were presented descriptively.

The primary outcome was analyzed using an analysis of covariance (ANCOVA) model with baseline 6MWD as a covariate, and treatment group, stratification group (treatment-naive or add-on therapy), and region (North America, South America, Europe, China and Asia/Pacific) as main effects. The residuals from the ANCOVA were tested for normality using the Shapiro-Wilk test, and if significant, then the non-parametric stratified Wilcoxon test was performed (stratified by region and prior treatment). A hierarchical testing procedure was used to adjust for multiplicity (i.e., type I error associated with multiple pairwise statistical comparisons). The pre-specified sequence for formal testing of treatment differences between riociguat and placebo on a series of seven secondary efficacy outcomes could proceed only if a statistically significant treatment difference favouring riociguat was initially detected on the primary efficacy outcome (i.e., 6MWD) at the two-sided 5% level. The order of subsequent statistical testing for secondary outcomes was:

- PVR
- NT-proBNP
- WHO functional class
- time to clinical worsening
- Borg CR10 scale (or modified Borg Dyspnea Scale)
- EQ-5D
- LPH questionnaire.

If, at any point during the execution of this sequential testing, a non-statistically significant difference was encountered for one of the secondary outcomes, the testing would cease and any remaining secondary outcomes in the sequence would simply be deemed non-statistically significant.

Secondary outcomes measured on a semi-continuous scale (change from baseline to week 12 in PVR, NT-proBNP, EQ-5D, and LPH) were measured using the same methods as 6MWD. The functional class change score (e.g., number of patients who were unchanged, improved, or deteriorated by one or more functional class, range –3 to +4) and the change in Borg CR10/modified Borg dyspnea scores were analyzed using a stratified Wilcoxon test (stratified by region and prior treatment). The time to clinical worsening was analyzed using the stratified log-rank test, with Kaplan–Meier estimates of the proportion of patients with the event.

Final visit data were imputed for those with missing outcome values. For any patient without a terminal visit who withdrew due to a clinical worsening event or who died, the worst possible value was assumed (i.e., 0 m on 6MWD test, 10 on modified Borg Dyspnea Scale or Borg CR10, functional class IV for patients who withdrew due to worsening or class V for patients who died, worst score for EQ-5D or LPH). For patients with missing data for reasons other than clinical worsening or death, the last observation carried forward method was used (LOCF). LOCF was used for all patients with missing PVR or NT-proBNP levels. Since effect estimates using the LOCF method may be biased if data are not missing completely at random, sensitivity analyses were conducted for the primary outcome to evaluate the impact of missing data. [redacted]

Pre-specified subgroup analyses were conducted based on prior treatment history, cause of PAH, functional class at baseline, baseline 6MWD (< 320 m or ≥ 320 m; < 380 m or ≥ 380 m), sex, age (< 65 years), race, and region. Subgroup data were reported descriptively, with no statistical testing performed except for 6MWD, the primary outcome.

a) Analysis populations

The study used a modified intention-to-treat (ITT) population for the efficacy and safety outcomes, which included all randomized patients who received at least one dose of study drug. The per-protocol analysis included all patients in the modified ITT analysis who had no major protocol violations, a valid 6MWD test at baseline and at week 12 or the termination visit (for those who withdrew). For patients who withdrew due to death or clinical worsening, the post-baseline 6MWD test distance was the imputed worst value (i.e., 0 m).

3.3 Patient disposition

Of the 586 patients screened for inclusion in the PATENT-1 trial, 445 (76%) were randomized and 443 received at least one dose of study drug. Of those enrolled, 12%, 7%, and 10% in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg groups, respectively, did not complete treatment. Adverse events were the most common reason for discontinuation in the placebo (6%) and riociguat 2.5 mg (3%) groups, whereas protocol violations (3%) and withdrawal of consent (3%) were the most common reasons in the riociguat 1.5 mg group.

TABLE 9: PATIENT DISPOSITION

	PATENT-1		
	Placebo	**Riociguat 2.5 mg**	**Riociguat 1.5 mg**
Screened, N	586		
Randomized, N (%)	443 (76)[a]		
	126	254	63
Discontinued, N (%)	15 (12)	17 (7)	6 (10)
Adverse event	7 (6)	8 (3)	1 (2)
Died	2 (2)[b]	0[b]	1 (2)
Lack of efficacy	1 (1)	0	0
Protocol violation	2 (2)	1 (< 1)	2 (3)
Withdrew consent	3 (2)	6 (2)	2 (3)
Lost to follow-up	0	1 (< 1)	0
Non-adherent	0	1 (< 1)	0
Modified ITT, N	126	254	63
PP, N	106	218	55
Safety, N	126	254	63

ITT = intention-to-treat; PP = per-protocol.
[a] 141 patients were excluded due to: adverse event, n = 4 (1%); were not eligible, n = 129 (22%); withdrew consent, n = 8 (1%). An additional 2 (0.4%) patients (placebo and riociguat 1.5 mg groups) underwent randomization in error and were excluded from the modified ITT analysis.
[b] An additional three patients who withdrew from the study died during the 30-day follow-up period: one patient in the placebo group and two patients in the riociguat 2.5 mg group.
Source: Ghofrani 2013,[14] Clinical Study Report.[15]

3.4 Exposure to study treatments

The mean and median duration of treatment were similar in all three treatment groups in the PATENT-1 study (mean number of days: [redacted]) (Table 10).

In the riociguat 2.5 mg group, 75% of patients received the maximum dose, 15% were on 2 mg three times daily, and 10% were on ≤ 1.5 mg three times daily (Table 10). All but [redacted] received riociguat 1.5 mg three times daily (95%) in the lower-dose group. During the study period, the dose was decreased in 31 patients (12%) in the riociguat 2.5 mg group, two patients (3%) in the riociguat 1.5 mg group, and in 11 (9%) patients in the placebo group.

TABLE 10: EXTENT OF EXPOSURE

Outcome	PATENT-1		
	Placebo	**Riociguat 2.5 mg**	**Riociguat 1.5 mg**
TREATMENT DURATION, DAYS	**N = 126**	**N = 254**	**N = 63**
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
TOTAL DOSE IN MG,	**N = 126**	**N = 254**	**N = 63**
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
PROPORTION OF PATIENTS AT EACH RIOCIGUAT DOSE AT WEEK 12, N (%)		**N = 236**	**N = 57**
2.5 mg three times daily	NA	[redacted] (75)	[redacted]

Outcome	PATENT-1		
	Placebo	**Riociguat 2.5 mg**	**Riociguat 1.5 mg**
2.0 mg		[redacted] (15)	[redacted]
1.5 mg		[redacted] (6)	[redacted]
1.0 mg		[redacted] (3)	[redacted]
0.5 mg		[redacted] (2)	[redacted]

NA = not applicable; SD = standard deviation.

[redacted]

Source: Clinical Study Report.[15]

3.5 Critical appraisal

3.5.1 Internal validity

In the PATENT-1 study, patients were randomized using accepted methods and adequate allocation concealment. The computer-generated randomization sequence (block size of seven) was created by the sponsor with separate blocks for treatment-naive patients and patients receiving PAH therapies. Patients were allocated to treatments using an interactive voice response system. Matched placebo, including sham titration for placebo and riociguat 1.5 mg groups, was used to maintain blinding.

Baseline characteristics were generally balanced between groups, although there were more patients with functional class III and who had PAH associated with connective tissue disease in the riociguat groups than the placebo group. These differences suggest there were more patients with a worse prognosis in the riociguat groups; however, the imbalances were generally small and the clinical expert consulted in this review stated that if any bias was present, it would be in favour of the placebo group. Overall, 9% of patients withdrew from the study, with more patients in the placebo group (12%) dropping out compared with the riociguat groups (7% and 10%).

PATENT-1 was powered to detect differences between the riociguat 2.5 mg dosage group and placebo for the primary outcome of 6MWD. Although the trial included another riociguat dosage group (up to 1.5 mg three times daily), it was not powered for comparisons with the placebo or riociguat 2.5 mg groups. The study was also not powered to detect differences between the treatment-naive and pre-treated subgroups of patients and was not designed to test the efficacy of riociguat as add-on therapy versus monotherapy.

The study used a modified ITT population that included those patients who were randomized and received at least one dose of study medication. The analyses of continuous outcomes were performed using an ANCOVA model, adjusted for stratification variables. A hierarchical testing procedure was used for secondary outcomes to control for multiplicity. Multiple analyses were conducted using different imputation methods for missing data. Of note, more patients in the placebo group dropped out, thus with the worst-case imputation method used for the primary analysis, would lower the change values more in the placebo than in the riociguat 2.5 mg group, potentially biasing the results in favour of riociguat. Other imputation methods tested all showed statistically significant differences between riociguat 2.5 mg and placebo; however, in some scenarios, the point estimates dropped below the MCID for 6MWD.

Although functional class is considered an important clinical outcome, clinicians' assessment of functional class may vary in PAH, especially when classifying patients as functional class II or III (which

were the vast majority of patients in PATENT-1).[28] Of note, the occurrence of clinical worsening events was determined by the investigators and there was no independent adjudication of the events.

3.5.2 External validity

The clinical expert consulted for this review considered that patients enrolled in PATENT-1 were largely representative of patients with PAH observed in clinical practice. The majority of PAH patients enrolled were female with idiopathic PAH or PAH associated with connective tissue disease. As there were few patients with functional class I or IV, the generalizability of the findings to these patients is limited. Of note, the trial did not provide any information on the efficacy and safety of riociguat in the subpopulation requested for listing; that is, patients who are unable to achieve disease control with another PAH therapy. Although the study enrolled patients on ERA or prostanoid therapy at baseline, these were likely stable, prevalent cases that would be able to tolerate placebo if randomized to that group. Thus the PATENT-1 trial provides information on riociguat as add-on therapy to stable ERA or prostanoids regimens, but not for patients who are deteriorating clinically or are unable to meet disease control targets with existing PAH therapies.

The clinical expert indicated that in practice, the target dose for riociguat is 2.5 mg three times daily and most patients are able to tolerate 2 mg to 2.5 mg dosages, thus the riociguat 1.5 mg dosage group may be considered less relevant to the Canadian context.

The duration of the trial was limited to 12 weeks, thus it cannot provide data on longer-term safety and efficacy of this new drug class. Although the trial did include data on some key outcomes to patients (clinical worsening, quality of life), it was powered for change in 6MWD, a surrogate outcome. In PAH patents, baseline and the absolute 6MWD during treatment has been shown to correlate with long-term outcomes such as morbidity and mortality; however, the change in 6MWD has demonstrated moderate to poor correlation with key clinical outcomes in PAH.[7-9]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 5). See APPENDIX 4 for detailed efficacy data.

No data were available on cardiopulmonary exercise tests, which was an outcome of interest as specified in the protocol.

Unless otherwise specified, the data presented are for the overall study population, of which half were treatment-naive (i.e., on monotherapy) and half continued on ERA or prostanoid treatments they were receiving prior to the start of the study.

3.6.1 Survival

Deaths were accrued in the safety data set and were not evaluated as an efficacy assessment in PATENT-1.

A total of six deaths occurred during the study: three in the placebo group (PAH, anxiety, respiratory failure with circulatory collapse), two in the riociguat 2.5 mg group (sepsis, hemoptysis), and one in the riociguat 1.5 mg group (right ventricular failure/PAH) (Table 13).

3.6.2 Hospitalization

Hospitalizations due to PH were reported as part of the composite clinical worsening outcome. No statistical analysis was conducted on hospitalizations. One patient (< 1%) in the riociguat 2.5 mg group and none in the riociguat 1.5 group were hospitalized due to PAH during the 12-week trial, compared with four patients (3%) in the placebo group (Table 11).

3.6.3 Clinical worsening events

Clinical worsening events were reported for 8 (6%), 3 (1%), and 2 (3%) of patients in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg treatment groups, respectively (Table 11). The time to clinical worsening was statistically significantly different favouring riociguat 2.5 mg versus placebo. Data from the FDA reported no statistically significant differences for the riociguat 1.5 mg group versus the placebo group. In the placebo group, start of a new PAH therapy (five events), hospitalization (four), and death (three) were the most frequent events reported. In the riociguat groups, no event was reported in more than two patients.

Clinical worsening events for subgroups based on treatment history and functional class at baseline are summarized in Appendix 4, Table 14.

3.6.4 Functional class

More patients who received riociguat showed an improvement in their functional class at the end of study compared with baseline (placebo: 14%; riociguat 2.5 mg: 21%; riociguat 1.5 mg: 24%) (Table 11). In the placebo, riociguat 2.5 mg, and 1.5 mg groups, 71%, 76%, and 68%, respectively, showed no change in functional class, and 14%, 4%, and 8% had their functional class worsen by one to three classes. The differences between riociguat 2.5 mg and placebo were statistically significant. Similar results were noted within subgroups based on treatment history and functional class at baseline (Appendix 4, Table 15): no statistical testing was performed.

TABLE 11: KEY EFFICACY OUTCOMES

Outcome	PATENT-1		
	Placebo	**Riociguat 2.5 mg**	**Riociguat 1.5 mg**
Time to Clinical Worsening	**N = 126**	**N = 254**	**N = 63**
Any event, N (%)	8 (6)	3 (1)	2 (3)
Hospitalization due to PH	4 (3)	1 (< 1)	0
Start of a new PH therapy	5 (4)	1 (< 1)	1 (2)
Decrease in 6MWD due to PH	2 (2)	1 (< 1)	1 (2)
Persistent worsening of functional class due to PH	1 (1)	0	0
Death	3 (2)	2 (1)	1 (2)
P value (stratified log-rank test) versus placebo	--	0.005	0.39[a]
P value (Mantel-Haenszel) versus placebo	--	0.029	0.33 [a]
Change in WHO Functional Class, n (%)	**N = 125**	**N = 254**	**N = 63**
–2	0	[redacted] (< 1)	0
–1	[redacted] (14)	[redacted] (21)	[redacted] (24)
0	89 (71)	192 (76)	43 (68)
+1	[redacted] (12)	[redacted] (3)	[redacted] (6)
+2	[redacted] (2)	[redacted] (< 1)	[redacted] (2)
+3	0	[redacted] (< 1)	0
P value versus placebo	--	0.003	0.067 [a]

6MWD = six-minute walk distance; PH = pulmonary hypertension.
[a] Based on post-hoc data reported by FDA.
Source: Ghofrani 2013, [14] Clinical Study Report,[15] FDA Medical Review.[11]

3.6.5 EuroQol 5-Dimensions Questionnaire

The EQ-5D utility scores were similar between groups at baseline, ranging from [redacted]. The mean change from baseline to week 12 values were –0.03, 0.03, and 0.08, in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg groups, respectively (Appendix 4, Table 16). The mean difference (MD) was 0.06 (95% CI, 0.01 to 0.11) for riociguat 2.5 mg versus placebo and was not statistically significant based on the non-parametric stratified Wilcoxon test (*P* = 0.07).

The EQ-5D visual analogue scale (VAS) was analyzed as an exploratory outcome. [redacted] were detected between riociguat 2.5 mg and placebo (MD [redacted]) (Appendix 4, Table 16).

Subgroup data by treatment history and functional class showed similar changes in EQ-5D utility scores after 12 weeks of therapy (Appendix 4, Table 17). No statistical testing was performed on subgroup data.

3.6.6 Six-minute walk distance

The change in 6MWD was the primary outcome for PATENT-1. The mean distance walked at baseline ranged from 361 m to 368 m across the treatment groups (Table 12). After 12 weeks, the mean distance walked decreased 6 m in the placebo group and increased 30 m and 31 m in the riociguat 2.5 and riociguat 1.5 mg groups, respectively. The differences between riociguat 2.5 mg and placebo were statistically significant (MD 36 m; 95% CI, 20 to 52) and clinically significant based on the MCID reported in the literature (33 m, range 25.1 m to 38.6 m) (APPENDIX 5). The FDA medical review reported similar

findings for the comparison of riociguat 1.5 mg versus placebo (MD 37 m; 95% CI, 12 to 63; $P < 0.0001$).[11]

The results for the change from baseline in 6MWD in the per-protocol analysis and sensitivity analyses examining different missing data imputation scenarios were generally similar to the primary, modified ITT analysis. However, the treatment differences between riociguat 2.5 mg and placebo dropped below the MCID of 33 m in some of the conservative multiple imputation analyses that imposed a penalty after dropout for patients in the riociguat group (MD range: 26 m to 35 m). In all analyses, the 95% CI did not cross zero, indicating the differences were statistically significant.

Subgroup analyses based on prior treatment history showed similar results as the overall study findings (Appendix 4, Table 18). The MD for riociguat 2.5 mg versus placebo was 38 m (95% CI, 14 to 62) in treatment-naive patients, and 36 m (95% CI, 15 to 56) in the add-on therapy subgroup (interaction term $P = 0.80$). The differences between riociguat 2.5 mg and placebo were not statistically significant in the subgroup of patients with WHO functional class I or II at baseline. Patients with functional class III or IV showed a statistically and clinically significant difference between riociguat 2.5 mg and placebo (MD 60 m; 95% CI, 36 to 83) (*P* value for interaction term not reported).

TABLE 12: PRIMARY EFFICACY OUTCOME

Outcome	PATENT-1		
	Placebo	**Riociguat 2.5 mg**	**Riociguat 1.5 mg**
6MWD	**N = 126**	**N = 254**	**N = 63**
Baseline, mean (SD)	368 (75)	361 (68)	363 (67)
Change from baseline to week 12, mean (SD)	–6 (86)	30 (66)	31 (79)
Least squares MD (95% CI) versus placebo	--	36 (20 to 52)	37 (12 to 63)
P value versus placebo (ANCOVA)	--	< 0.0001[a]	0.0042
P value versus placebo (stratified Wilcoxon test)		< 0.0001[a]	< 0.0001

6MWD = six-minute walk distance; ANCOVA = analysis of covariance; CI = confidence interval; MD = mean difference; SD = standard deviation.
[a] Wilcoxon test was used to determine statistical significance because the Shapiro-Wilk test for normality of the ANCOVA residuals was statistically significant.
Source: Ghofrani 2013, [14] Clinical Study Review,[15] FDA Medical Review.[11]

3.6.7 Borg Dyspnea Scale

The mean Borg CR10 dyspnea scores ranged from 3.4 to 3.9 at baseline, with mean change from baseline values of 0.1, –0.4, and –0.3 reported in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg groups, respectively (Appendix 4, Table 16). The treatment differences between riociguat 2.5 mg and placebo were statistically significant ($P = 0.002$, data not reported).

The subgroup analyses by treatment history and functional class showed similar results (Appendix 4, Table 20).

3.6.8 Living with Pulmonary Hypertension questionnaire

The LPH questionnaire scores were similar between groups at baseline (range 42 to 43) (Appendix 4, Table 16). In the placebo, riociguat 2.5 mg, and 1.5 mg groups, the mean change from baseline to week 12 values were 0.4, –6, and –10, respectively. The MD for riociguat 2.5 mg versus placebo was reported

as not statistically significant, as testing was stopped due to a non-significant finding in a prior outcome in the statistical hierarchy (MD –6; 95% CI, –10 to –3).

The subgroup analyses by treatment history and functional class showed similar results (Appendix 4, Table 19).

3.6.9 Pulmonary vascular resistance

At baseline, the mean PVR ranged from 791 to 848 dyn·s·cm^{-5} (Appendix 4, Table 16). After 12 weeks, the mean PVR decreased by 9, 223, and 168 dyn·s·cm^{-5} in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg groups, respectively. The least squares MD between riociguat 2.5 mg and placebo was statistically significant (MD –226; 95% CI, –281 to –170; $P < 0.0001$).

3.6.10 N-terminal pro-brain natriuretic peptide

In PATENT-1, the mean NT-proBNP levels at baseline were 1,228, 1,027, and 1,190 pg/mL in the placebo, riociguat 2.5, and riociguat 1.5 mg groups, respectively (Appendix 4, Table 16). After 12 weeks of treatment, the mean NT-proBNP level increased 232 pg/mL in the placebo group, and decreased 198 and 472 pg/mL in the riociguat 2.5 mg and riociguat 1.5 mg groups, respectively. The differences between riociguat 2.5 mg and placebo were statistically significant (MD –432; 95% CI, –782 to –82, $P < 0.001$).

3.6.11 Exploratory hemodynamic parameters

mPAP decreased –0.5, –3.9, and –4.5 mm Hg after 12 weeks, from baseline values of 48.9, 47.1, and 52.1 mm Hg, in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg groups, respectively. The MD was –3.8; 95% CI, –5.6 to –2.1, for riociguat 2.5 mg versus placebo (Appendix 4, Table 21).

The cardiac index ranged from 2.5 L/min/m^2 to 2.7 L/min/m^2 at baseline in the PATENT-1 study (Appendix 4, Table 21). The mean cardiac index decreased (–0.02 L/min/m^2) in the placebo group, and increased in the riociguat 2.5 mg and riociguat 1.5 mg groups (0.5 and 0.3 L/min/m^2, respectively). The MD for riociguat 2.5 mg and placebo groups was 0.6; 95% CI, 0.4 to 0.7. These outcomes were outside the statistical hierarchy, thus no statistical inferences have been reported in this summary.

3.6.12 Use of supplemental oxygen

The proportion of patients using oxygen at the start of the trial was 18%, 19%, and 25%, in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg groups, respectively. A similar proportion of patients started oxygen during the 12-week trial (5%, 4%, and 8%) (Appendix 4, Table 21). These data were reported descriptively and no statistical testing was conducted.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). *See* Appendix 4 *for detailed harms data.*

3.7.1 Adverse events

The most frequently reported system organ class events in all three treatment groups were gastrointestinal disorders (37% to 60%), general disorders and administration site conditions (37% to 41%), infections and infestations (31% to 35%), nervous system disorders (35% to 54%), and respiratory, thoracic and mediastinal disorders (27% to 34%).

MedDRA system organ classes with a frequency ≥ 5% higher in the riociguat 2.5 mg group than the placebo group included gastrointestinal disorders (55% versus 37%), nervous system disorders (42% versus 35%), blood and lymphatic system disorders (11% versus 5%), and cardiac disorders (18% versus 13%). Respiratory, thoracic, and mediastinal disorders were reported less frequently in the riociguat 2.5 mg group than the placebo group (28% versus 34%). The frequency of adverse events according to system order class was similar in the riociguat 1.5 mg group and the riociguat 2.5 mg group.

3.7.2 Serious adverse events

Serious adverse events were reported in 18%, 11%, and 18% of patients in the placebo, riociguat 2.5 mg and riociguat 1.5 mg groups, respectively. The most common serious adverse event was syncope, which was reported in five (4%) placebo patients, three (1.2%) riociguat 2.5 mg patients, and no riociguat 1.5 mg patients. Right ventricular failure was reported most frequently in the riociguat 1.5 mg group (three patients, 5%) compared with two (1%) patients in the riociguat 2.5 mg group, and one (1%) patient in the placebo group.

3.7.3 Withdrawals due to adverse events

More patients in the placebo group (8%) stopped therapy due to adverse events than patients in the riociguat 2.5 mg or riociguat 1.5 mg groups (3% and 2%, respectively).

3.7.4 Notable harms

Anemia was reported more frequently in the riociguat 2.5 mg group (8%) than in the other groups (2%). Bleeding events were identified through a retrospective search of “hemorrhage” related MedDRA terms. The incidence of bleeding was similar between groups (10% to 11%), with epistaxis and hemoptysis reported most frequently (Table 13). Serious treatment-emergent bleeding events were reported in four patients (2%) in the riociguat 2.5 mg group, two (3%) patients in the riociguat 1.5 mg group, and no patients who received placebo. Of note, 55% to 57% of patients were on oral anticoagulants during the PATENT-1 trial.

Treatment-emergent adverse events of syncope and hypotension were analyzed as adverse events of special interest and included a pooled analysis of MedDRA terms for syncope and hypotension. Syncope-related events were reported in 6%, 3%, and 3% of patients in the placebo, riociguat 2.5 mg, and riociguat 1.5 mg groups, respectively. Hypotension-related events were reported more frequently among patients in the riociguat 2.5 mg group (10%) than in the riociguat 1.5 mg (3%) or placebo groups (2%).

Peripheral edema was also reported more frequently in the riociguat 2.5 mg and riociguat 1.5 mg groups (17% and 22%, respectively) than placebo (11%). Acute renal failure was reported in one patient in the riociguat 2.5 mg group.

TABLE 13: HARMS IN PATENT-1 STUDY

	PATENT-1		
Adverse Events	**Placebo N = 126**	**Riociguat 2.5 mg N = 254**	**Riociguat 1.5 mg N = 63**
Patients with ≥ 1 Adverse event, n (%)	108 (86)	227 (89)	58 (92)
Most common adverse events[a]			
Headache	25 (20)	69 (27)	20 (32)
Dyspepsia	10 (8)	48 (19)	8 (13)
Nausea	16 (13)	40 (16)	10 (16)
Dizziness	15 (12)	40 (16)	15 (24)
Diarrhea	13 (10)	35 (14)	6 (10)
Vomiting	11 (9)	26 (10)	7 (11)
Nasopharyngitis	14 (11)	26 (10)	6 (10)
Hypotension	3 (2)	25 (10)	2 (3)
Dyspnea	14 (11)	16 (6)	4 (6)
Cough	13 (10)	12 (5)	3 (5)
Pyrexia	4 (3)	8 (3)	6 (10)
Serious Adverse Events			
Patients with ≥ 1 serious adverse event, n (%)	23 (18)	29 (11)	11 (18)
Most common serious adverse events[b]			
Right ventricular failure	1 (1)	2 (1)	3 (5)
Chest pain	1 (1)	2 (1)	0
Pneumonia	0	2 (1)	1 (2)
Syncope	5 (4)	3 (1)	0
Acute renal failure	0	2 (1)	0
Hemoptysis	0	2 (1)	0
PAH	2 (2)	1 (< 1)	1 (2)
WDAE			
Adverse event leading to discontinuation of study drug, n (%)	9 (7)[c]	8 (3)	1 (2)
Most common reasons[d]			
Cardiac disorders	1 (1)	2 (1)	1 (2)
Respiratory, thoracic and mediastinal disorders	5 (4)	1 (< 1)	0
Deaths			
Number of deaths, n (%)	3 (2)	2 (1)	1 (2)
Notable harms, n (%)			
Anemia,	3 (2)	21 (8)	1 (2)
Bleeding events[e]	12 (10)	28 (11)	7 (11)
Epistaxis	1 (1)	11 (4)	1 (2)
Hemoptysis	2 (2)	6 (2)	0
Syncope, presyncope or loss of consciousness (pooled MedDRA terms)	7 (6)	8 (3)	2 (3)
Presyncope	1 (1)	5 (2)	2 (3)
Syncope	5 (4)	3 (1)	0
Peripheral edema	14 (11)	44 (17)	14 (22)

	PATENT-1		
Adverse Events	**Placebo N = 126**	**Riociguat 2.5 mg N = 254**	**Riociguat 1.5 mg N = 63**
Hypotension (pooled MedDRA terms)[f]	3 (2)	25 (10)	2 (3)
Blood pressure decreased (pooled MedDRA terms)	1 (1)	1 (< 1)	1 (2)
Acute renal failure	0	2 (1)	0

PAH = pulmonary arterial hypertension; WDAE = withdrawals due to adverse event.
[a] Frequency ≥ 10% in any treatment group.
[b] Serious adverse events reported in more than one patient in any treatment group.
[c] The placebo data included two patients who developed treatment-emergent adverse events (malignant melanoma, pneumothorax) during the PATENT-1 trial but were able to complete PATENT-1. These patients subsequently died (either during PATENT-2 or prior to enrolling in PATENT-2) but were listed as a withdrawal due to an adverse event, even though withdrawal of patients occurred during PATENT-2.
[d] Adverse events by MedDRA system organ class that lead to discontinuation of study drug in more than one patient in any treatment group.
[e] Bleeding events were identified retrospectively based on a standardized MedDRA query for "hemorrhages" and related terms (excluding laboratory terms).
[f] Included the following MedDRA terms: blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure orthostatic decreased, blood pressure systolic decreased, blood pressure systolic inspiratory decreased, hypotension, orthostatic hypotension, diastolic hypotension.
Source: Ghofrani 2013, [14] Clinical Study Report.[15]

4. DISCUSSION

4.1 Summary of available evidence

One randomized, double-blind study met the inclusion criteria (PATENT-1). The safety and efficacy of 12 weeks of riociguat (titrated up to a maximum of 2.5 mg three times daily) was compared with placebo in adults with symptomatic PAH. The study also included an exploratory lower riociguat dosage group (titrated up to 1.5 mg three times daily). Randomization was stratified by the patients' prior treatment history (treatment-naive or those receiving ERA or prostanoid therapy). The primary outcome was the change from baseline in 6MWD, and secondary outcomes included time to clinical worsening and the change from baseline in WHO functional status, PVR, NT-proBNP levels, Borg CR10 dyspnea scale, EQ-5D score, and LPH questionnaire score. The key limitations were the short duration of the trial (12 weeks) and lack of data for the requested listing: in adult patients with PAH who are unable to achieve disease control with another PAH therapy.

4.2 Interpretation of results

4.2.1 Efficacy

Patient group input (see APPENDIX 1) revealed that patients with PAH hope that riociguat would alleviate symptoms and improve energy levels, thus allowing for a better quality of life.

The data from the PATENT-1 trial suggest that riociguat up to 2.5 mg three times daily for 12 weeks provides a clinically and statistically significant increase in 6MWD compared with placebo (MD 36 m; 95% CI, 20 to 52). Although the 6MWD test is used in clinical practice and is widely accepted by regulatory agencies, the change in 6MWD is a surrogate outcome and has demonstrated moderate to poor correlation with key clinical outcomes in PAH.[7-9] The trial duration was insufficient to assess impacts on survival; there were a total of six deaths (riociguat: 1% to 2%, placebo: 2%). However riociguat, versus placebo, showed statistically significantly longer time to clinical worsening, a composite outcome that included morbidity and mortality events that are important to patients. Fewer patients in the riociguat groups were hospitalized due to PAH than in the placebo group, although the data were sparse and should be interpreted with caution.

Statistically significant differences were detected between the riociguat 2.5 mg and placebo groups in the change in functional class. In addition, statistically significant differences were detected between riociguat 2.5 mg and placebo for the change in PVR and NT-proBNP levels, which the clinical expert consulted for this review considered clinically important. No statistical or clinically important differences were detected between treatments in quality of life based on EQ-5D or LPH questionnaire. Moreover, the differences between riociguat 2.5 mg and placebo for dyspnea symptoms were statistically significant, but the clinical relevance is uncertain.

At the end of treatment, the riociguat 1.5 mg group showed similar results compared with the riociguat 2.5 mg group; however, this dosage was exploratory and no statistical testing was performed as part of the study plan. Post-hoc data from the FDA reported statistically significant differences for riociguat 1.5 mg versus placebo for the change in 6MWD, PVR, and NT-proBNP, but not for clinical worsening events, dyspnea, or HRQoL. Of note, this group was small (n = 63) and was underpowered to detect differences between groups. The FDA reviewer stated that use of the higher riociguat dose may not be warranted, considering that the treatment response appeared similar for the 1.5 mg and 2.5 mg dosage groups, and the higher dose was associated with an increased incidence of hypotension.[11] The clinical

expert consulted for this review considered the 1.5 mg dosage low, as most patients in Canadian clinical practice would receive 2 mg to 2.5 mg three times daily.

Subgroup data suggest that the treatment effect of riociguat 2.5 mg was similar for treatment-naive patients (i.e., monotherapy) and when administered as add-on therapy to stable ERA or prostanoid regimens. Similar trends were noted for functional class I/II and III/IV subgroups. Although these subgroups were pre-specified and randomization was stratified by prior treatment history, these subgroup data were reported descriptively with no statistical testing performed except for 6MWD, the primary outcome.

The open-label extension study reported that the treatment effects of riociguat were maintained with longer-term treatment (median 91 weeks); however, these data should be viewed with caution given the possible selection bias, lack of control group, and unblinded assessment (APPENDIX 6).

As there were no direct head-to-head studies comparing riociguat with other PAH therapies, the manufacturer submitted an ITC. [redacted]

The findings of the manufacturer-provided ITC were generally consistent with CADTH's Therapeutic Review[3] and suggest riociguat has similar efficacy to other PAH treatments in patients with functional class II or III PAH. Key limitations included possible clinical heterogeneity between trials for the combination therapy analyses, sparse data (e.g., EQ-5D), or wide credible intervals (particularly for clinical worsening events and PVR), suggesting there is uncertainty in the findings. The evidence available was limited to short-term clinical trials (12 to 16 weeks) and it is unclear if the findings can be extrapolated to longer-term use. The comparative safety of treatments for PAH was not assessed.

There were no data on the efficacy and safety of riociguat for the listing requested by the manufacturer: patients who are unable to achieve disease control with another PAH drug. The subgroup data from PATENT-1 suggest that riociguat provides benefits to patients when administered as add-on therapy to stable ERA or prostanoid treatment; however, data in patients unable to achieve disease control targets with other PAH drugs is lacking. These data are lacking for other PAH therapies as well, and this evidence gap was noted in CADTH Therapeutic Review.[3,4] CDEC recommended PDE5 inhibitors as initial therapy for patients with functional class II or III PAH based on clinical cost-effectiveness data from the Therapeutic Review.[3,4] Considering that riociguat requires several weeks to titrate up to the maximal dose, and the PDE5 inhibitors are contraindicated for patients on riociguat (thus cannot be administered

concurrently during the titration phase), it is unclear how to manage a switch between these drugs. There is an open-label, single-group study underway (RESPITE[13]) that will evaluate the efficacy and safety of riociguat in patients who showed an insufficient response to PDE5 inhibitors. Once completed, the RESPITE trial may provide some data to help determine the role of riociguat as second-line therapy.

4.2.2 Harms

The adverse events reported in PATENT-1 were similar to those observed in the riociguat clinical trial in patients with CTEPH. In the 12-week PATENT-1 study, serious adverse events were reported in 11% and 18% of patients in the riociguat 2.5 mg and 1.5 mg groups, respectively, and in 18% of patients in placebo. More patients stopped treatment due to adverse events in the placebo group (7%) than in the riociguat groups (3% and 2% for the riociguat 2.5 mg and 1.5 mg groups, respectively).

Of the notable harms, the number of patients experiencing bleeding was similar across treatments in PATENT-1 (riociguat 2.5 mg and riociguat 1.5 mg: 11%, placebo: 9.5%); however, there were more serious bleeding events in the riociguat than placebo groups (riociguat 2.5 mg: 4 (1.6%); riociguat 1.5 mg: 2 (3.2%); placebo: 0), including one case of hemoptysis that was fatal. The incidence of anemia and hypotension was numerically higher in the riociguat 2.5 mg group than the placebo and riociguat 1.5 mg groups, whereas the incidence of syncope was higher in the placebo than riociguat groups. Both the Health Canada and FDA reviews noted potential risks with regards to the dose-related increase in hypotension observed for the riociguat 2.5 mg dose,[10,11] and the Canadian product monograph includes warnings with regards to hypotension and bleeding with riociguat.[6] The monograph states that bleeding risk should be carefully assessed prior to initiating riociguat and monitored periodically, particularly in patients taking anticoagulants, as the risk of serious and fatal bleeding may be further increased for those receiving riociguat.[6] Although anemia was reported more frequently by patients receiving riociguat than placebo in both PATENT-1 and the CHEST-1 study (CTEPH population),[34] the use of anti-anemia medications was similar between treatment groups.[11] The FDA stated that it is unclear the degree to which anemia is a consequence of occult bleeding in some patients versus direct hematopoietic toxicity.[11] The Health Canada reviewer's report noted that all six patients who experienced a hemorrhagic and anemia event were in the riociguat 2.5 mg group.[10] Of the other notable harms identified in the protocol, peripheral edema was also higher in the riociguat groups than in the placebo group. The most common adverse events in the riociguat groups were headache, dizziness, and gastrointestinal events.

Patients who completed PATENT-1 were eligible to 30nrol in the open-label extension study, PATENT-2 (APPENDIX 6).[12] A total of 396 patients enrolled (98% of eligible patients) and of these, 82% were still receiving treatment at the March 2013 cut-off date for this ongoing clinical trial. Patients received riociguat up to a maximum of 2.5 mg three times daily. In PATENT-2, 52% of patients experienced a serious adverse event and 21% had a clinical worsening event (median treatment duration 91 weeks).[12] A total of 27 deaths were reported over the 718 person-years of exposure.[12] No new safety signals were identified.

No data on the comparative safety of riociguat and other PAH therapies were available from the manufacturer-provided ITC, and no head-to-head studies were identified. Additional data are needed to determine the long-term safety of riociguat.

4.3 Potential place in therapy[2]

PAH remains a serious disease with significant morbidity and mortality despite optimal and aggressive therapy. There is no cure for this disease and the burden of illness is substantial. As a result, new therapies, especially oral therapies, are needed to help to improve the quantity and quality of life for these patients. Riociguat is a first-in-class new PAH medication, with evidence from the PATENT-1 study of improving functional capacity and delaying clinical worsening, albeit in the context of a relatively short duration randomized controlled trial (RCT). Importantly, this effect was seen in both treatment-naive patients and patients on background therapy (either ERA or prostacyclin). Hence, this drug represents an alternative PAH treatment as monotherapy, and it demonstrates additional efficacy when used in combination as add-on therapy.

The clinical expert involved in the review noted that while riociguat is a first-line therapy option for treatment-naive patients, an important limitation versus other oral drugs is the long dose titration period; many PAH experts would likely not want to wait two to three months to reach the highest tolerated dose, especially in patients who are less stable when initiating therapy. Hence, likely the most benefit for this drug will be seen as a combination therapy strategy, as an add-on to ERA or prostacyclin background. The clinical expert described the combination therapy data from PATENT-1 as compelling, although one cannot conclude that these were patients failing to meet treatment goals, as the inclusion criteria of the study did not specify that criterion.

Given the CDEC recommendation suggesting sildenafil or tadalafil use as first line for patients with PAH functional class II or III, the role of this drug may be considered in the following scenarios:

1. As an add-on to current ERA therapy in patients who are not meeting treatment goals and require additional therapy (CDEC could not make a recommendation regarding the choice of a second-line therapy when considering combination therapy).
2. As an add-on to current prostacyclin therapy in patients who are not meeting treatment goals and require additional therapy.
3. For patients who are unable to tolerate PDE5 inhibitors as monotherapy due to an adverse event and needing to switch to another therapeutic class.

There is the possibility of using riociguat as initial therapy in patients who have a contraindication to PDE5 inhibitor use, although because of the overlap in contraindications between PDE5 inhibitors and riociguat (e.g., concomitant use of nitrates), there is potential that riociguat would be contraindicated as well.

The clinical expert noted that the strategy of switching from a PDE5 inhibitor to riociguat in patients who are not meeting treatment goals as possible; however, there is limited evidence of efficacy for this strategy. The switch strategy (i.e., switching to riociguat in patients with insufficient treatment response to PDE5 inhibitors) is currently being studied in the RESPITE study.[13]

[2] This information is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

5. CONCLUSIONS

Riociguat was associated with statistically significant improvement in the time to clinical worsening (a composite of morbidity and mortality) versus placebo, based on a single, double-blind, 12-week randomized controlled trial (RCT) in adults with symptomatic PAH who were either treatment-naive or who were receiving therapy with ERAs or prostanoids. More patients on riociguat maintained a favourable functional class, and riociguat was associated with clinically and statistically significant increases in 6MWD. The improvement in 6MWD with riociguat treatment was augmented by clinically relevant improvements in hemodynamic parameters.

Indirect evidence suggests the efficacy of riociguat (alone or in combination with ERAs) may be similar to other PAH treatments.

Serious adverse events were frequent for both riociguat and placebo and included a total of six deaths: three in the placebo group and three in the riociguat groups. Withdrawals due to adverse events were less frequent in the riociguat groups than in the placebo group. Adverse events of anemia and hypotension occurred more frequently in the riociguat 2.5 mg group than the placebo and riociguat 1.5 mg groups, whereas the incidence of syncope was higher in the placebo group than the riociguat groups. More serious bleeding events occurred among patients receiving treatment with riociguat than with placebo. The most common adverse events in the riociguat groups were headache, dizziness, and gastrointestinal events. No data on the comparative safety of riociguat versus other PAH therapies were available. Although no new safety signals were identified in the open-label extension study (PATENT-2), additional data are needed to determine the long-term safety of riociguat.

There were no data from the RCT or ITC on the efficacy and safety of riociguat for the listing requested by the manufacturer: patients who are unable to achieve disease control with another PAH drug.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief description of patient group supplying input

Input was received from one patient group.

The Pulmonary Hypertension Association of Canada (PHA Canada) is a charitable organization aiming to provide education and support to patients with pulmonary hypertension (PH) and their caregivers. In addition, they strive to end isolation, create a connected PH community, and increase awareness of this disease. PHA Canada receives funding from its Standing Corporate Committee Members, which consists of pharmaceutical companies (including Bayer). Funding is provided through membership dues and unrestricted grants.

No conflicts of interest were declared regarding this submission; however, of note, the Chair of the Board of Directors reviewed and approved this submission. He has received financial support from various pharmaceutical companies, including Bayer, including consulting and speaking fees, research grant support, and investigator fees.

2. Condition-related information

Information for this submission was obtained through patient and caregiver interviews, a survey of patients receiving Adempas, the Burden of Illness Survey from fall 2003 (in which 118 respondents were patients and 61 were caregivers), and through the six-year history of working within the PH community.

PH has a significant impact on the quality of life of both the patient and the caregiver. In addition to the shock of this ultimately life-changing diagnosis, patients must deal with numerous symptoms and challenges associated with having PH. The main symptoms that patients experience, and would ultimately like to control, include difficulty breathing following little to no physical exertion, peripheral edema, dizziness, and syncope. In addition to the aforementioned symptoms, patients also experience fatigue, chest pain, low energy, headaches, and sleep disturbances. Everyday life and daily activities can be severely limited, even in patients experiencing mild symptoms associated with their PH. Patients are noted to have trouble climbing stairs, walking short distances, having telephone conversations, carrying objects (particularly groceries and children), performing regular daily household chores (e.g., vacuuming, preparing meals, making beds), and taking care of themselves (e.g., bathing, dressing). Patients and their families are limited in their ability to plan ahead due to the daily fluctuation in symptoms and are often precluded from daily or social activities, thus introducing significant isolation. In addition, intimacy can also be affected due to the physical limitations and psychosocial challenges associated with PH.

Psychological symptoms also plague the PH patient. Depression, anxiety, and feelings of both helplessness and hopelessness often accompany patients with a PH diagnosis, as they are faced with the loss of the ability to fulfill their roles as caregivers to their families, they often have to cut back on or cease their careers, and women have to give up their dreams of becoming pregnant (as pregnancy is strictly contraindicated in patients with PH). There is also a stigma associated with PH as, outwardly, patients appear healthy and thus the public and even family members sometimes struggle to understand the diagnosis. This further compounds the patient's isolation and depression. The fact that this rare disease has no known cure and PH patients are faced with a high risk of death in a shorter time period adds to an increase in negative psychological symptoms.

Caregivers are also negatively affected by the PH diagnosis of their loved ones. In addition to becoming the main support for patients in terms of attending doctors' appointments and managing the dosing regimen and side effects of the medications, they may also become the primary financial provider, take on the bulk of household work, and also become the main or sole provider for any children. In many instances, caregivers are forced to alter their employment arrangements in order to care for the PH patient and can spend up to 50% of their time caring for their loved one. With this increase in responsibility, caregivers often experience isolation, negative psychological symptoms, and burnout. Family relationships and particularly marriages often fall victim to the strains on the caregiver and the patient. As one respondent put it, "If PH patients are suffering from an invisible disability, then their caregivers are even more invisible victims."

3. Current therapy-related information

Several PH therapies have been approved in Canada, including (oral drugs) Revatio, Adcirca, Volibris, Tracleer, Adempas, and Opsumit, along with injectable treatments that include Flolan, Remodulin, and Thermostable Caripul. While some patients experience benefits with monotherapy, the vast majority are on combinations of therapies (especially those with moderate to severe PH). In addition to PH-specific therapies, many patients reported taking concomitant diuretics, blood thinners, and antiemetics.

Experience with the aforementioned therapies was generally described as positive, with patients experiencing reductions in the severity of their PH symptoms and increases in their ability to carry out light physical activity. Though the effectiveness of therapy varies depending on age, gender, type of PH, severity of PH, and underlying medical conditions, most patients described the effectiveness of their current therapies as "fair." There were some patients who experienced drastic improvements, with less shortness of breath; however, there were also those who remained quite ill even with therapy.

Many patients disclosed their hardships regarding access to required PH therapies, initial approvals for combination therapy, and the cost burden associated with the medications. In addition, adverse events associated with PH therapies were bothersome and included nausea (the most common), gastrointestinal discomfort and pain, diarrhea, fatigue, insomnia, bruising, weight gain, headaches, and skin flushing or redness.

4. Expectations about the drug under review

The primary unmet need faced by patients with PH is a cure for the disease. In addition, issues that continually plague the individual already on PH therapies include difficulty breathing and dizziness. Among patients with no experience with the disease, there is the expectation that Adempas would offer an additional option when current therapies stopped being effective or for those with contraindications to other treatments. There is also the hope that the new drug would alleviate symptoms and improve energy levels, thus allowing for a better quality of life.

Patients with PH are willing to tolerate some adverse events as long as the benefits outweighs the risks and they are able to live a life more closely resembling that which they had prior to developing PH. Specific adverse events deemed tolerable were headaches, nausea, and nasal pharyngitis, as long as their condition stabilized.

In a survey of patients who had experience with Adempas, patients reported an almost immediate decrease in shortness of breath once treatment had begun. In addition, they experienced improved exercise tolerance, decreases in fainting spells, easier breathing in cold air (which was previously prohibitive), an increase in their ability to move around with greater ease, improvements to their quality

of life, and the ability to resume normal activities with family and friends. Adempas was said to be easy to take and there was hope that it would continue to improve patients' hemodynamics and quality of life. Adverse events experienced by those taking Adempas included dizziness upon standing after taking a dose (that subsided over time), while others indicated that there were no additional adverse events to those of their concomitant medications.

APPENDIX 2: LITERATURE SEARCH STRATEGY

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:	July 23, 2015
Alerts:	Biweekly (twice monthly) search updates until November 18, 2015.
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were 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
MeSH	Medical Subject Heading
exp	Explode 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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
.kw	Keyword heading
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

MULTI-DATABASE STRATEGY

#	Searches
1	(625115-55-1 or C542595 or RU3FE2Y4XI).rn,nm.
2	(riociguat* or Adempas* or BAY 63-2521 or BAY63-2521 or BAY 632521).ti,ot,ab,hw,sh,rn,nm,kw.
3	or/1-2
4	3 use pmez
5	*riociguat/
6	(riociguat* or Adempas* or BAY 63-2521 or BAY63-2521 or BAY 632521).ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	8 not conference abstract.pt.

MULTI-DATABASE STRATEGY	
#	**Searches**
10	4 or 9
11	exp animals/
12	exp animal experimentation/ or exp animal experiment/
13	exp models animal/
14	nonhuman/
15	exp vertebrate/ or exp vertebrates/
16	animal.po.
17	or/11-16
18	exp humans/
19	exp human experimentation/ or exp human experiment/
20	human.po.
21	or/18-20
22	17 not 21
23	10 not 22
24	remove duplicates from 23

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

Dates for Search:	July 2015
Keywords:	Adempas (riociguat), pulmonary arterial hypertension
Limits:	No date or language limits used

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
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Rosenkranz S, Ghofrani HA, Beghetti M, Ivy D, Frey R, Fritsch A, et al. Riociguat for pulmonary arterial hypertension associated with congenital heart disease. Heart [Internet]. 2015 Jul 1 [cited 2015 Jul 28]. Available from: http://heart.bmj.com/content/early/2015/07/01/heartjnl-2015-307832.full.pdf+html	Wrong population
Galie N, Muller K, Scalise AV, Grunig E. PATENT PLUS: a blinded, randomised and extension study of riociguat plus sildenafil in pulmonary arterial hypertension. Eur Respir J. 2015 May;45(5):1314-22.	Wrong intervention
Rubin LJ, Galie N, Grimminger F, Grunig E, Humbert M, Jing ZC, et al. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). Eur Respir J. 2015 May;45(5):1303-13.	Wrong study design
Langleben D, Galie N, He J, Huang Y, Humbert M, Keogh A, et al. Use of clinically relevant responder threshold criteria to evaluate the response to treatment in the phase III PATENT-1 study. J Heart Lung Transplant. 2015 Mar;34(3):338-47.	Outcomes not of interest

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 14: SUBGROUP ANALYSES FOR CLINICAL WORSENING EVENTS

Subgroup	PATENT-1		
NUMBER OF PATIENTS WITH CLINICAL WORSENING, N/N (%)	Placebo Total N = 126	Riociguat 2.5 mg Total N = 254	Riociguat 1.5 mg Total N = 63
TREATMENT-NAIVE	[redacted]	[redacted]	[redacted]
PRE-TREATED	[redacted]	[redacted]	[redacted]
FUNCTIONAL CLASS I OR II	[redacted]	[redacted]	[redacted]
FUNCTIONAL CLASS III OR IV	[redacted]	[redacted]	[redacted]

Source: Clinical Study Report.[15]

TABLE 15: SUBGROUP ANALYSES FOR CHANGE IN WORLD HEALTH ORGANIZATION FUNCTIONAL CLASS

Subgroup	PATENT-1		
CHANGE IN WHO FUNCTIONAL CLASS (BASELINE TO LAST VISIT), N (%)	Placebo Total N = 126	Riociguat 2.5 mg Total N = 254	Riociguat 1.5 mg Total N = 63
TREATMENT-NAIVE	N = 66	N = 123	N = 32
–2	[redacted]	[redacted]	[redacted]
–1	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
+1	[redacted]	[redacted]	[redacted]
+2	[redacted]	[redacted]	[redacted]
+3	[redacted]	[redacted]	[redacted]
PRE-TREATED	N = 59	N = 131	N = 31
–2	[redacted]	[redacted]	[redacted]
–1	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
+1	[redacted]	[redacted]	[redacted]
+2	[redacted]	[redacted]	[redacted]
+3	[redacted]	[redacted]	[redacted]
FUNCTIONAL CLASS I OR II	N = 64	N = 113	N = 24
–1	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
+1	[redacted]	[redacted]	[redacted]
+2	[redacted]	[redacted]	[redacted]
+3	[redacted]	[redacted]	[redacted]
FUNCTIONAL CLASS III OR IV	N = 61	N = 141	N = 39
–2	[redacted]	[redacted]	[redacted]
–1	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]
+1	[redacted]	[redacted]	[redacted]
+2	[redacted]	[redacted]	[redacted]

WHO = World Health Organization.
Source: Clinical Study Report.[15]

TABLE 16: SECONDARY EFFICACY OUTCOMES

	PATENT-1		
Outcome	**Placebo N = 126**	**Riociguat 2.5 mg N = 254**	**Riociguat 1.5 mg[a] N = 63**
EQ-5D utility score	**N = 124**	**N = 253**	**N = 62**
Baseline, mean (SD)	0.68 (0.24)	0.68 (0.24)	[redacted]
Change from baseline to week 12, mean (SD)	–0.03 (0.30)	0.03 (0.24)	0.08 (0.31)
Least squares MD (95% CI) versus placebo	--	0.06 (0.01 to 0.11)	NR
P value		0.07[a]	NS
EQ-5D VAS score	**N = 123**	**N = 250**	**N = 62**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12, mean (SD)	–1.4 [redacted]	3.6 [redacted]	6.1 [redacted]
Least squares MD (95% CI) versus placebo	--	[redacted]	[redacted]
P value		[redacted]	[redacted]
LPH score	**N = 122**	**N = 247**	**N = 62**
Baseline, mean (SD)	42 (23)	42 (22)	43 (23)
Change from baseline to week 12, mean (SD)	0.4 (18.2)	–6 (18)	–10 (21)
Least squares MD (95% CI) versus placebo	--	–6 (–10 to –3)	NR
P value		NS[c]	NS
Borg CR10 score	**N = 126**	**N = 254**	**N = 63**
Baseline, mean (SD)	3.9 (2.5)	3.9 (2.2)	[redacted]
Change from baseline to week 12, mean (SD)	0.1 (2.1)	–0.4 (1.7)	–0.3 (1.5)
Least squares MD (95% CI) versus placebo	--	NR	NR
P value		0.002	NS
PVR (dyn·s·cm^{-5})	**N = 107**	**N = 232**	**N = 58**
Baseline, mean (SD)	834 (477)	791 (453)	848 (548)
Change from baseline to week 12, mean (SD)	–9 (317)	–223 (260)	–168 (320)
Least squares MD (95% CI) versus placebo	--	–226 (–281 to –170)	NR
P value		< 0.0001	< 0.0001
NT-proBNP (pg/ml)	**N = 106**	**N = 228**	**N = 54**
Baseline, mean (SD)	1,228 (1,775)	1,027 (1,799)	1,190 (1,405)
Change from baseline to week 12, mean (SD)	232 (1,011)	–198 (1,721)	–472 (913)
Least squares MD (95% CI) versus placebo	--	–432 (–782 to –82)	NR
P value		< 0.001	< 0.0001

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; LPH = Living with Pulmonary Hypertension questionnaire; MD = mean difference; NR = not reported; NS = not statistically significant; NT-proBNP = N-terminal pro-brain natriuretic peptide; PVR = pulmonary vascular resistance; SD = standard deviation; VAS = visual analogue scale.

[a] Statistical testing based on post-hoc data from the FDA Medical Review.

[b] Based on the stratified Wilcoxon test.

[c] Not statistically significant due to failure to achieve statistical significance in a prior outcome in the hierarchical testing procedure.

Source: Ghofrani 2013, [14] Clinical Study Report,[15] FDA Medical Review.[11]

TABLE 17: SUBGROUP ANALYSES FOR EQ-5D UTILITY SCORE

Subgroup	PATENT-1		
EQ-5D Utility Score	**Placebo Total N = 126**	**Riociguat 2.5 mg Total N = 254**	**Riociguat 1.5 mg Total N = 63**
Treatment-naive	**N = 64**	**N = 123**	**N = 32**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Pre-Treated	**N = 60**	**N = 130**	**N = 30**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Functional class I or II	**N = 63**	**N = 113**	**N = 24**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Functional class III or IV	**N = 60**	**N = 140**	**N = 38**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]

EQ-5D = EuroQol 5-Dimensions Questionnaire; SD = standard deviation.
Source: Clinical Study Report.[15]

TABLE 18: SUBGROUP ANALYSES FOR SIX-MINUTE WALK DISTANCE TEST

Subgroup	PATENT-1		
6MWD, m	**Placebo Total N = 126**	**Riociguat 2.5 mg Total N = 254**	**Riociguat 1.5 mg Total N = 63**
Treatment-naive	**N = 66**	**N = 123**	**N = 32**
Baseline, mean (SD)	360 (80)	370 (66)	347 (72)
Change from baseline to week 12, mean (SD)	–6 (88)	32 (74)	49 (47)
Least squares MD (95% CI) versus placebo		38 (14 to 62)	55 (22 to 89)
Pre-treated	**N = 60**	**N = 131**	**N = 31**
Baseline, mean (SD)	376 (68)	353 (69)	380 (57)
Change from baseline to week 12, mean (SD)	–5 (83)	27 (58)	12 (100)
Least squares MD (95% CI) versus placebo		36 (15 to 56)	17 (–22 to 56)
Treatment group by prior treatment interaction term *P* value		[redacted]	[redacted]
Functional class I or II	**N = 64**	**N = 113**	**N = 24**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12, mean (SD)	18 (63)	[redacted]	[redacted]
Least squares MD (95% CI) versus placebo		12 (–8 to 32)	17 (–12 to 45)
Functional class III or IV	**N = 61**	**N = 141**	**N = 39**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12, mean (SD)	–30 (99)	[redacted]	[redacted]
Least squares MD (95% CI) versus placebo		60 (36 to 83)	59 (19 to 99)
Treatment group by functional class interaction term *P* value		[redacted]	[redacted]

6MWD = six-minute walk distance; CI = confidence interval; m = metres; MD = mean difference; SD = standard deviation.
Source: Clinical Study Report,[15] FDA Medical Review.[11]

TABLE 19: SUBGROUP ANALYSES FOR LIVING WITH PULMONARY HYPERTENSION QUESTIONNAIRE TOTAL SCORE

Subgroup	PATENT-1		
LPH Total Score	**Placebo Total N = 126**	**Riociguat 2.5 mg Total N = 254**	**Riociguat 1.5 mg Total N = 63**
Treatment-naive	**N = 65**	**N = 120**	**N = 32**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Pre-Treated	**N = 57**	**N = 127**	**N = 30**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Functional class I or II	**N = 62**	**N = 110**	**N = 24**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Functional class III or IV	**N = 59**	**N = 137**	**N = 38**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]

LPH = Living with Pulmonary Hypertension questionnaire; SD = standard deviation.
Source: Clinical Study Report.[15]

TABLE 20: SUBGROUP ANALYSES FOR BORG CR10 SCORE

Subgroup	PATENT-1		
Borg CR10 Scale	**Placebo Total N = 126**	**Riociguat 2.5 mg Total N = 254**	**Riociguat 1.5 mg Total N = 63**
Treatment-naive	**N = 66**	**N = 123**	**N = 32**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Pre-Treated	**N = 60**	**N = 131**	**N = 31**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Functional class I or II	**N = 64**	**N = 113**	**N = 24**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]
Functional class III or IV	**N = 61**	**N = 141**	**N = 39**
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to last visit, mean (SD)	[redacted]	[redacted]	[redacted]

SD = standard deviation.
Source: Clinical Study Report.[15]

TABLE 21: EXPLORATORY OUTCOMES

	PATENT-1		
	Placebo N = 126	**Riociguat 2.5 mg N = 254**	**Riociguat 1.5 mg N = 63**
mPAP (mm Hg)	**N = 109**	**N = 235**	[redacted]
Baseline, mean (SD)	48.9 (15.2)	47.1 (14.8)	[redacted]
Change from baseline to week 12, mean (SD)	–0.5 (9.4)	–3.9 (7.8)	[redacted]
Least squares MD (95% CI) versus placebo		–3.8 (–5.6 to –2.1)	[redacted]
P value		NS[a]	NS[b]
Cardiac Index (L/min/m^2)	**N = 108**	**N = 233**	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Change from baseline to week 12, mean (SD)	–0.02 (0.6)	0.54 (0.6)	[redacted]
Least squares MD (95% CI) versus placebo		0.56 (0.44 to 0.69)	[redacted]
P value		NS[a]	NR
Supplemental Oxygen Therapy	**N = 126**	**N = 254**	**N = 63**
Prior therapy, n (%)	22 (18)	47 (19)	16 (25)
Concomitant therapy, n (%)	24 (19)	50 (20)	18 (29)
New concomitant therapy, n (%)	6 (5)	9 (4)	5 (8)

CI = confidence interval; MD = mean difference; mPAP = mean pulmonary artery pressure; NR = not reported; NS = not statistically significant; SD = standard deviation.

[a] Outcome was outside the statistical hierarchy and thus is considered not statistically significant.

[b] Statistically significant differences were reported by the FDA based on post-hoc analyses. These outcomes were exploratory and outside the statistical hierarchy.

Source: Ghofrani 2013, [14] Clinical Study Report,[15] FDA Medical Review.[11]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures used in PATENT-1 and report minimal clinically important difference (MCID) estimates where available:

- Six-minute walk distance (6MWD)
- Borg CR10 or modified Borg Dyspnea Scale
- World Health Organization (WHO) functional class
- Clinical worsening
- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- Living with Pulmonary Hypertension (LPH) questionnaire

Findings

Six-minute walk distance

The 6MWD test measures the distance a patient can walk in six minutes. Change in 6MWD is the most widely used test to assess exercise capacity in pulmonary arterial hypertension (PAH) and is used in most PAH trials as a primary outcome.[35-39] 6MWD is also used in clinical practice and is widely accepted by regulatory agencies. The main advantage of 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).[38] 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.[7] However, change in 6MWD is a surrogate outcome and has demonstrated moderate to poor correlation with key clinical outcomes in PAH.[7-9] Performance on 6MWD 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.[40-42] Furthermore, in multi-centre trials, experience and technical skills may vary between sites, and the correlations between 6MWD and CPET might improve over time with increasing experience.[43] There is also evidence of a ceiling effect on 6MWD, whereby the effect of the treatment on the test is diminished due to the inclusion of patients with milder disease (New York Heart Association [NYHA]/WHO functional class II, baseline 6MWD > 450 m) who demonstrate a smaller improvement with treatment given the relatively higher baseline 6MWD value versus patients with more severe PAH.[44] Despite these limitations, improvement in function, as reflected by 6MWD, remains clinically valuable in PAH. Mathai et al., using distributional and anchor-based methods of estimating an MCID, reported a change of 33.0 m (range 25.1 m to 38.6 m) compared with placebo for patients with PAH.[29]

Modified Borg Dyspnea Scale and Borg CR10

The Borg CR10 and the Modified Borg Dyspnea scales are patient self-reported measures of one's difficulty in breathing upon exertion. The instruments provide a standard method for patients to select ratings of dyspnea on a scale based on descriptors that correspond to specific numbers (which are not linearly spaced). The CR10 is a categorical scale with a score from 0 to 10, where 0 represents normal breathing and 10 represents maximum dyspnea.[45] However, patients 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;[45] it uses a scale from 0 to 10, where 0 represents no dyspnea and 10 represents maximal dyspnea. Scores are obtained at the end of the 6MWD test and reflect 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, the modified Borg dyspnea scale 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.[46-48] No published studies have clearly addressed the MCID of the Borg dyspnea scores in PAH. Distribution-based analyses of data from trials in patients with COPD and heart failure suggest the MCID is 1 point.[30,31] A recent study (abstract) indicated that the MCID in patients with PAH may be < 1, with distribution-based estimates ranging from 0.70 to 1.24 points and an anchor-based estimate of 0.36 points.[32] The authors suggested their MCID estimates are smaller than for COPD or heart failure because of differences in the perception of dyspnea between diseases.

World Health Organization functional classification for pulmonary hypertension

The WHO functional class system for pulmonary hypertension (PH) was adapted from the NYHA functional classification system for heart failure.[1] The WHO functional class 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.[28] The intra-class correlation coefficient was low (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.

Clinical worsening

The composite outcome of clinical worsening — combining the events of death, heart or lung transplantation, atrial septostomy, 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 functional class 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.[49] Therefore, it is likely a clinically relevant outcome. However, there are limitations using composite outcomes in PH studies:[49]

- Confounding may occur if a component outcome occurs at a different rate versus others in the composite outcome, especially during a trial of short duration.
- The inclusion of 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 end point in clinical trials of PAH.[50]

EuroQol 5-Dimensions questionnaire

EQ-5D[51,52] is a generic quality of life 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.[51,52] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 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 that best represents their health on that day.

Hence, the EQ-5D produces three types of data for each respondent:

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference-weighted health index score based on the descriptive system.
- 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 Medical Research Council (MRC) Dyspnoea Scale in both primary and specialist care settings within the UK and US and across five EU countries.[53] The MCID for the EQ-5D in general use ranges from 0.033 to 0.074.[33]

Living with Pulmonary Hypertension questionnaire

The LPH questionnaire 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 to 40, eight items) and an emotional dimension score (range 0 to 25, five items) can also be calculated. A higher score on all LPH scores indicates that patients are more affected by their PH.[54] 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 sub-scales (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.

TABLE 22: SUMMARY OF RELEVANT OUTCOMES USED IN PATENT-1

Instrument	Description	Evidence of validity in PAH	MCID	Comments
6MWD[29,36,38,40-43,54-57]	Total distance walked in 6 minutes. Submaximal test to assess exercise capacity. Widely used in studies and clinical	Yes	33.0 m (range: 25.1 m to 38.6 m)	Baseline 6MWD correlated with outcomes in PAH.[7] Absolute 6MWD during treatment is correlated with outcomes in PAH. Change in 6MWD moderately to poorly

Instrument	Description	Evidence of validity in PAH	MCID	Comments
	practice; accepted by regulatory agencies.			correlated with outcomes in PAH.[7-9] Ceiling effect in patients with less severe disease.[58]
Borg dyspnea score[46-48]	Modified Borg Scale: 11-point scale (ranges from 0 [no dyspnea] to 10 [max dyspnea] points). Borg CR10: open scale (ranges from 0 [no dyspnea] to 10 [max dyspnea] points) with ability for patient to assign scores above 10.	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.[46,47]
WHO functional class[28]	PH severity classification system.	No	Unknown	Based on NYHA functional classification system for heart failure.[1]
Clinical Worsening[49,50]	Composite outcome includes various components designed to measure PH morbidity and mortality. May also be reported as time to clinical worsening.	No	Unknown	Recommended as a key outcome for use in PAH studies by 2008 Dana Point and 2013 NICE clinical trial design task forces.[59]
EQ-5D	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: range 0.033 to 0.074[33]	Different utility scores 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.
LPH	PH-specific HRQoL scale derived from the MLHFQ. 6-point Likert scale (21 items) range: 0 (no) to 5 (very much). Total score range: 0 to 105; higher score	Yes	Physical and emotional sub-scales: change of 3 points Total score: change of 7 points	

Instrument	Description	Evidence of validity in PAH	MCID	Comments
	indicates worse HRQoL.			

6MWD = six-minute walk distance; COPD = chronic obstructive pulmonary disease; EQ-5D = EuroQol 5-Dimensions Questionnaire; HRQoL = health-related quality of life; MCID = minimal clinically important difference; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NICE = National Institute for Health and Care Excellence; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; VAS = visual analogue scale; WHO = World Health Organization.

Conclusion

Of the six reviewed outcome measures — 6MWD, modified Borg Dyspnea Scale/CR10, WHO functional class, clinical worsening, EQ-5D, and LPH — used in the PATENT-1 trial, only 6MWD and LPH have been validated in PAH. An MCID of 33.0 m (range: 25.1 m to 38.6 m) has been reported for 6MWD in patients with PAH. The MCID for the change in LPH total score has been reported to be 7 points. Clinical worsening is recommended as a key outcome for use in PAH studies.

APPENDIX 6: SUMMARY OF EXTENSION STUDY

Objective

To summarize the results from the one-year interim analysis of the PATENT-2 trial,[12] which was an open-label extension study including patients with pulmonary arterial hypertension (PAH) who completed the PATENT-1 trial. The following is an ongoing study with these results based on published data from an interim analysis.

Findings

Study design

Patients with PAH who completed the PATENT-1 study were invited to participate in the open-label, single-group PATENT-2 study to assess the long-term safety and efficacy of riociguat. Patients from PATENT-1 were excluded from entering PATENT-2 if they were experiencing riociguat-related serious adverse events (SAEs) or they withdrew from PATENT-1 due to clinical worsening of their pulmonary hypertension.

PATENT-2 was conducted in 97 of the 124 centres involved in the PATENT-1 study, which was an eight-week, double-blind, dose-adjustment phase followed by the open-label portion whereby patients received riociguat doses of up to 2.5 mg three times daily. Permission was allotted to investigators to adjust doses in accordance with the occurrence of adverse events (AEs), systolic blood pressure findings, and progression of patient's PAH.

Assessment

The assessment of the safety and tolerability of riociguat were the primary objectives of the PATENT-2 study and included observations of both AEs and certain laboratory parameters. Efficacy assessments included the following variables:

- Six-minute walk distance (6MWD) test
- N-terminal pro-brain natriuretic peptide (NT-proBNP)
- World Health Organization (WHO) functional class change
- time to clinical worsening
- Borg dyspnea score
- EuroQol 5-Dimensions (EQ-5D) questionnaire
- Living with Pulmonary Hypertension (LPH) questionnaire.

Outcome assessments were performed at PATENT-2 entry and at weeks two, four, six, eight, 12, and every three months thereafter. A follow-up assessment 30 days after any patient discontinued riociguat was also performed. All assessments were analyzed descriptively and were non-comparative. The start of the PATENT-1 study was considered baseline.

Results

Three hundred and ninety-six patients (98%) entered the PATENT-2 study out of the 405 patients who completed the PATENT-1 study. Of these patients, 50% were using additional PAH medications, 43% were using endothelin receptor antagonists (ERAs), 6% were using non-intravenous prostanoids, and 1% were using both ERAs and prostanoids. Seventy-seven per cent, 91%, and 79% of patients from the former placebo, riociguat 1.5 mg, and riociguat 2.5 mg groups, respectively, were receiving a dose of 2.5 mg riociguat three times daily at the end of the eight-week dose-adjustment period. This dosage was

sustained at year one of PATENT-2 study in 86% of patients. In addition, 46% were also using ERAs, 4% were receiving prostanoids, and 4% were using both ERAs and prostanoids at year 1.

Of the 396 patients who started PATENT-2, 81%, 86%, and 81% of patients from the former placebo, riociguat 1.5 mg, and riociguat 2.5 mg groups, respectively, were still receiving treatment at the March 2013 cut-off point of this ongoing study. The median treatment duration was 91 weeks (mean 95 weeks) with a cumulative exposure of 718 person-years. The most common reasons for discontinuation included AEs, death, and lack of efficacy. Detailed patient disposition is provided in Table 23.

TABLE 23: PATIENT DISPOSITION THROUGHOUT THE PATENT-2 STUDY

PATENT-1	Placebo	Riociguat 1.5 mg Max	Riociguat 2.5 mg Max
PATENT-1 randomized and treated, n	443		
Patients completing PATENT-1, n (%)	111 (88)	57 (90)	237 (93)
PATENT-2	**Former Riociguat 2.5 mg Max**	**Former Riociguat 1.5 mg Max**	**Former Placebo**
Patients entering PATENT-2, n (%)	396 (98)		
	109 (98)	56 (98)	231 (97)
Discontinuations, n (%)	21 (19)	8 (14)	43 (19)
AEs	8 (7)	4 (7)	21 (9)
Deaths	6 (6)	3 (5)	10 (4)
Lack of efficacy	1 (1)	1 (2)	2 (1)
Lost to follow-up	-	-	1 (0.4)
Withdrawals	3 (3)	-	6 (3)
Protocol violation	-	-	2 (1)
Non-compliance	3 (3)	-	-
PATENT-2 Follow-up			
Deaths,[a] n (%)	3 (3)	1 (2)	4 (2)
March 2013 Cut-off			
Ongoing, n (%)	88 (81)	48 (86)	188 (81)

AE = adverse event; max = maximum.
[a] Of those who discontinued, these were the patients who died in the follow-up period.
Source: Rubin 2015.[12]

Safety

The majority of patients experienced AEs, with the most common being nasopharyngitis, dizziness, peripheral edema, cough, and gastrointestinal events. Syncope was reported in 7% of all patients, while hypotension was reported in 9%. Hemoptysis/pulmonary hemorrhage was reported as an AE in 6% of patients and as an SAE in 3% of patients throughout the PATENT-2 study. The PATENT-2 AE rate of hemoptysis/pulmonary hemorrhage per 100 patient-years was 6.3 versus 9.9 or 11.1 in the PATENT-1 riociguat or placebo groups, respectively. SAEs were reported in 52% of patients, leading to discontinuations in 6%, 7%, and 8% of the patients from the former placebo, riociguat 1.5 mg, and riociguat 2.5 mg groups, respectively. SAEs were graded as moderate in five patients and severe in another five patients. In addition, the PATENT-2 exposure-adjusted SAE rate of hemoptysis/pulmonary hemorrhage per 100 patient-years was 1.8 versus 4.3 in the PATENT-1 riociguat groups. A total of 27 deaths were reported in the study (7%), three of which were considered drug-related and included

hypoxic-ischemic encephalopathy, hemoptysis/pulmonary hemorrhage and pneumonia, and cardio-respiratory arrest. Detailed harms data are presented in Table 24.

TABLE 24: HARMS IN THE PATENT-2 STUDY

	Former Placebo N = 109	Former Riociguat 1.5 mg Max N = 56	Former Riociguat 2.5 mg Max N = 231
Any AE, n (%)	107 (98)	55 (98)	222 (96)
AEs in ≥ 10% of patients, n (%)			
Nasopharyngitis	27 (25)	13 (23)	55 (24)
Dizziness	28 (26)	12 (21)	53 (23)
Peripheral edema	25 (23)	14 (25)	50 (22)
Cough	20 (18)	6 (11)	52 (23)
Diarrhea	27 (25)	11 (20)	32 (14)
Headache	27 (25)	8 (14)	33 (14)
Nausea	19 (17)	6 (11)	41 (18)
Vomiting	19 (17)	8 (14)	30 (13)
URTI	17 (16)	8 (14)	29 (13)
Dyspnea	12 (11)	11 (20)	28 (12)
Dyspepsia	10 (9)	8 (14)	29 (13)
Chest pain	14 (13)	6 (11)	26 (11)
Epistaxis	12 (11)	10 (18)	22 (10)
Other notable AEs, n (%)			
Hypotension	7 (6)	6 (11)	24 (10)
Syncope	10 (9)	3 (5)	15 (6)
Hemoptysis/pulmonary hemorrhage	7 (6)	2 (4)	16 (7)
Discontinuations due to AEs, n (%)	7 (6)	4 (7)	25 (11)
SAEs, n (%)	60 (55)	30 (54)	114 (49)
Discontinuations due to SAEs, n (%)	7 (6)	4 (7)	18 (8)
Clinical worsening events[a], n (%)	**24 (22)**	**11 (20)**	**49 (21)**
Patients, N	109	56	231
New PH treatment started	17 (16)	9 (16)	34 (15)
Hospitalization due to PH	11 (10)	5 (9)	25 (11)
Death	9 (8)	4 (7)	14 (6)
Decrease in 6MWD due to PH	3 (3)	1 (2)	6 (3)
Worsening of WHO functional class due to PH	1 (1)	0	4 (2)
Transplantation of heart or lung	0	1 (2)	1 (0.4)

6MWD = six-minute walk distance; AE = adverse event; max = maximum; PH = pulmonary hypertension; SAE = serious adverse event; URTI = upper respiratory tract infection; WHO = World Health Organization.
[a] More than one type of event could be experienced by the same patient.
Source: Rubin 2015.[12]

Exploratory efficacy analysis

Following the changeover to riociguat, considerable improvements in the 6MWD test were reported in the PATENT-1 placebo group along with sustained improvements reported at both week 12 and year one in the PATENT-1 riociguat groups. Year one mean changes (± standard deviation [SD]) in the 6MWD test were 53 m (± 70 m), 56 m (± 88 m), and 46 m (± 76 m) in the former riociguat 2.5 mg, riociguat 1.5 mg, and placebo groups, respectively. The absolute mean (± SD) 6MWD at year one in the overall population was 419 m (± 97 m) (n = 327) compared with the baseline value of 367 m (± 67 m) (n = 396). Lower improvements in 6MWD test results were noted upon sensitivity analyses for missing data using various imputation methods; however, the overall interpretation was not affected. At year one of PATENT-2, 36%, 57%, and 7%, of patients were reported to have improved, stabilized, or worsened, respectively, in their WHO functional status. At year one of PATENT-2, 8%, 61%, 28%, and 2% of the total population (n = 339) were observed as WHO functional class I, II, III, and IV, respectively. This was compared with WHO functional class I, II, III, and IV of 3%, 43%, 54%, and 1%, respectively, of the overall population (n = 395) at baseline. Similar to the 6MWD test results, WHO functional class missing data sensitivity analyses reported reduced improvements; albeit, this did not affect the interpretation of the study results.

Decreases in the PATENT-1 riociguat NT-proBNP were sustained for up to year one of PATENT-2. PATENT-1 placebo patients who had transitioned to riociguat in PATENT-2 also showed similar decreases in NT-proBNP. Improvements in both EQ-5D and Borg dyspnea scores in those taking riociguat in PATENT-1 were sustained up to year one of PATENT-2. In addition, LPH scores also improved though to week eight of the PATENT-2 study in patients having received either riociguat 2.5 mg or 1.5 mg maximum in the PATENT-1 study, while minimal changes were observed in those patients in the PATENT-1 placebo group. Detailed efficacy results are presented in Table 25.

At least one clinical worsening event was experienced by 21% of the patients during PATENT-2, with an estimated rate of clinical worsening–free survival of 88% (95% confidence interval [CI], 84% to 91%) and an estimated survival rate of 97% (95% CI, 94% to 98%) at one year (with the results assuming that patients who drop out have the same event rates as patients continuing, thus leading to potentially positive bias, especially if the dropout rate was, in fact, higher.) Worst-case sensitivity analyses of the rate of clinical worsening–free survival and rate of survival at one year were 84% (95% CI, 80% to 87%) and 90% (95% CI, 87% to 93%), respectively. These sensitivity analyses assumed that every patient who dropped out had died or experienced a clinical worsening event. Estimated one-year survival rates were also similar between treatment-naive and pre-treated (with ERAs and prostanoids) patients at 97% (95% CI, 93% to 99%). Detailed results regarding clinical worsening events are presented in Table 24.

TABLE 25: EXPLORATORY EFFICACY RESULTS FOR PATIENTS TREATED WITH RIOCIGUAT IN THE PATENT-2 STUDY

	Riociguat/Former Placebo			Riociguat/Former Riociguat 1.5 mg Max			Riociguat/Former Riociguat 2.5 mg Max		
	PATENT-1	PATENT-2		PATENT-1	PATENT-2		PATENT-1	PATENT-2	
	Week 12	Week 12	1 Year	Week 12	Week 12	1 Year	Week 12	Week 12	1 Year
Borg dyspnea score									
[Patients, N] Mean (SD) change from baseline	[108] −0.15 ± 1.88	[102] −0.54 ± 1.90	[84] −0.45 ± 2.06	[55] −0.43 ± 1.19	[54] −0.52 ± 1.64	[49] −0.18 ± 1.58	[228] −0.55 ± 1.52	[218] −0.58 ± 1.84	[192] −0.52 ± 1.98
EQ-5D score									
[Patients, N] Mean (SD) change from baseline	[106] 0.02 ± 0.22	[102] 0.03 ± 0.24	[83] 0.07 ± 0.20	[55] 0.10 ± 0.26	[52] 0.15 ± 0.24	[50] 0.13 ± 0.24	[227] 0.05 ± 0.21	[212] 0.06 ± 0.22	[193] 0.06 ± 0.24
LPH score									
[Patients, N] Mean (SD) change from baseline	[105] −2.7 ± 15.1	[93[a]] −2.1 ± 15.7	-	[55] −11.8 ± 16.1	[54[a]] −14.3 ± 18.9	-	[224] −7.6 ± 16.8	[209[a]] −11.0 ± 18.9	-
NT-proBNP, pg mL^{-1}									
[Patients, N] Mean (SD) change from baseline	[95] 134 (809)	[93] −410 ± 1,023	[80] −294 ± 1,945	[46] –447 (954)	[46] −520 ± 944	[44] −235 ± 1,214	[207] –338 (1,031)	[201] −322 ± 1,206	[177] −291 ± 1,612
6MWD, m									
Baseline absolute values	378	-	-	359	-	-	364	-	-
[Patients, N] Mean absolute values	[108] 390	[103] 433	[85] 426	[55] 406	[54] 414	[50] 417	[228] 400	[218] 417	[192] 417
WHO functional class, %									
Patients, N	**89**	**-**		**51**	**-**		**199**	**-**	
Improved	-	-	26	-	-	31	-	-	36
Stabilized	-	-	66	-	-	67	-	-	57
Worsened	-	-	8	-	-	2	-	-	7
WHO functional class in overall population, %									
	PATENT-1 Baseline			**PATENT-2 1 Year**					
Patients, N	**395**			**339**					
I	3			8					

	Riociguat/Former Placebo			Riociguat/Former Riociguat 1.5 mg Max			Riociguat/Former Riociguat 2.5 mg Max		
	PATENT-1	PATENT-2		PATENT-1	PATENT-2		PATENT-1	PATENT-2	
	Week 12	Week 12	1 Year	Week 12	Week 12	1 Year	Week 12	Week 12	1 Year
II	43				61				
III	54				28				
IV	1				2				

6MWD = six-minute walk distance; EQ-5D = EuroQol 5-Dimensions Questionnaire; LPH = Living with Pulmonary Hypertension questionnaire; m = metres; NT-proBNP = N-terminal pro-brain natriuretic peptide; SD = standard deviation; WHO = World Health Organization.

[a] Week eight data are shown.

Source: Rubin 2015.[12]

Limitations

The main limitation of PATENT-2 remains the fact that it was an open-label, long-term extension study, with no comparator group. In addition, with approximately 50% of patients on concomitant PAH medications, it is difficult to ascertain the absolute safety and efficacy of only riociguat. While informative regarding the safety information, any analysis of efficacy remains exploratory. The potential for an overestimation of the one-year efficacy results is possible due to the fact that the patients who discontinued may not have been doing well on riociguat, leaving only those able to tolerate and, subsequently, do well long-term on riociguat remaining. In addition, AEs may have been underestimated and the safety data could also be biased for the same reasons. Recall bias could also have been a factor due to the decreased frequency of visits in PATENT-2 (every three months) compared with PATENT-1 (every two weeks).

Discussion

It appeared that the safety and tolerability results were similar across the PATENT-1 and PATENT-2 studies, as most patients were continuing riociguat 2.5 mg three times daily at the March 2013 year one cut-off. No new safety signals were observed and the most common AEs were nasopharyngitis, dizziness, peripheral edema, cough, and gastrointestinal events. Notable AEs of interest were syncope, hypotension, and hemoptysis/pulmonary hemorrhage, which occurred in 7%, 9%, and 6% of patients, respectively. Three per cent of patients in PATENT-2 compared with 1% of patients in PATENT-1 experienced hemoptysis/pulmonary hemorrhage as an SAE. The estimated one-year survival rate in PATENT-2 was 97%, with 21% and 10% of patients experiencing incidences of clinical worsening or hospitalization, respectively. There were 27 deaths in total, with three attributed to treatment.

Efficacy results were exploratory in nature. Improvements in both 6MWD test results and WHO functional class were sustained up until year one of the PATENT-2 study; however, the standard deviations were large in most cases. Caution is required when observing the efficacy results of the aforementioned efficacy parameters.

Summary

The safety and tolerability of riociguat 2.5 mg three times daily was similar in both the PATENT-1 study and the PATENT-2 extension study. Most patients experienced AEs (the most common being nasopharyngitis, dizziness, peripheral edema, cough, and gastrointestinal events), with fewer than 10% of all patients experiencing syncope, hypotension, or hemoptysis/pulmonary hemorrhage. The estimated survival rate at one year in PATENT-2 was 97%, with three deaths being attributed to riociguat treatment. The potential for selection bias was a possibility, potentially leading toward bias for patients who responded better to riociguat treatment. While improvements in the 6MWD test and WHO functional class were reported, caution is required for the interpretation of all efficacy variables due to the exploratory nature of the study and the non-comparative analysis.

APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

Given that no direct, head-to-head studies with riociguat were identified in the CADTH Common Drug Review (CDR) systematic review, this section provides a summary and critical appraisal of the indirect evidence available on the comparative efficacy and harms of therapies for pulmonary arterial hypertension (PAH).

Methods

The manufacturer submitted an indirect treatment comparison (ITC) of therapies for PAH.[5] A literature search was undertaken to identify any other relevant published ITCs.

Description of indirect treatment comparisons identified

Two ITCs were identified: the ITC submitted by the manufacturer[5] and the CADTH Therapeutic Review on therapies for PAH.[3] This section focuses on the manufacturer-submitted ITC, and discusses its key differences from the CADTH Therapeutic Review.

Review and appraisal of indirect comparisons

Review of manufacturer's indirect treatment comparison

a) Objectives and rationale

[redacted]

b) Methods

Study eligibility and selection process

[redacted] Table 26.

TABLE 26: INCLUSION CRITERIA FOR SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Population	[redacted]
Interventions	[redacted]
Comparators	[redacted]
Outcomes	[redacted]
Study designs	[redacted]
Exclusion criteria	[redacted]

6MWD = six-minute walk distance; CHD = congenital heart disease; CTD = connective tissue disease; EQ-5D = EuroQol 5-Dimensions Questionnaire; ERA = endothelin receptor antagonist; HRQoL = health-related quality of life; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; NT pro-BNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PA = prostacyclin agonists; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; RTK = receptor tyrosine kinase; sGC = soluble guanylate cyclase; VAS = visual analogue scale; WHO = World Health Organization.

[redacted]

Data extraction

[redacted]

[redacted]

Comparators

[redacted]

[redacted]

TABLE 27: DRUG DOSAGES INCLUDED IN THE INDIRECT TREATMENT COMPARISON[a]

Drug	Doses
[redacted]	

6MWD = six-minute walk distance; ERA = endothelin receptor antagonist; ITC = indirect treatment comparison; IV = intravenous; PA = prostacyclin agonists; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; SC = subcutaneous; sGC = soluble guanylate cyclase.

[redacted]

Outcomes

[redacted]

Quality assessment of included studies

[redacted]

[redacted]

Evidence network

[redacted]

FIGURE 2: GENERAL EVIDENCE NETWORK FOR MONOTHERAPY INDIRECT TREATMENT COMPARISON[A]

Figure redacted at the request of the manufacturer.

ITC = indirect treatment comparison.
[a] Shaded drug names are those that are approved for pulmonary arterial hypertension in Canada.

The network diagrams for the six-minute walk distance (6MWD) and clinical worsening events for the combination therapy analyses are shown in Figure 3 and Figure 4.

[redacted]

FIGURE 3: SIX-MINUTE WALK DISTANCE EVIDENCE NETWORK FOR COMBINATION THERAPY INDIRECT TREATMENT COMPARISON

Figure redacted at the request of the manufacturer.

6MWD = six-minute walk distance; ERA = endothelin receptor antagonist; ITC = indirect treatment comparison; PA = prostacyclin agonists; PDE5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase.

FIGURE 4: CLINICAL WORSENING EVENT EVIDENCE NETWORK FOR COMBINATION THERAPY INDIRECT TREATMENT COMPARISON

Figure redacted at the request of the manufacturer.

ERA = endothelin receptor antagonist; ITC = indirect treatment comparison; PA = prostacyclin agonists; PDE5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase.

[redacted]

c) Indirect comparison methods

[redacted]

d) Results

This summary of results focused on drugs approved for use in Canada only.

Treatment-naive pulmonary arterial hypertension population

[redacted]

[redacted]

[redacted]

Six-minute walk distance

[redacted]

Clinical worsening event

[redacted]

[redacted]

World Health Organization functional class

[redacted]

[redacted]

Borg dyspnea index

[redacted]

[redacted]

[redacted]

Pulmonary vascular resistance

[redacted]

TABLE 28: RESULTS OF MIXED TREATMENT COMPARISON FOR MONOTHERAPY IN TREATMENT-NAIVE PULMONARY ARTERIAL HYPERTENSION POPULATION

Treatment Comparison	6MWD	Clinical Worsening Event	WHO Functional Class I or II[a]	Borg Dyspnea Index	PVR[b]
Intervention versus placebo	**MD (95% CrI)**	**OR (95% CrI)**	**OR (95% CrI)**	**MD (95% CrI)**	**MD (95% CrI)**
[redacted]					
Riociguat 2.5 mg versus comparator					
[redacted]					
Riociguat 1.5 mg versus comparator					
[redacted]					

Treatment Comparison	6MWD	Clinical Worsening Event	WHO Functional Class I or II[a]	Borg Dyspnea Index	PVR[b]
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

6MWD = six-minute walk distance; CrI = credible interval; MD = mean difference; OR = odds ratio; PVR = pulmonary vascular resistance; WHO = World Health Organization.

[redacted]

Source: CADTH Common Drug Review submission.[5]

Mixed pulmonary arterial hypertension population

[redacted]

Six-minute walk distance

[redacted]

Clinical worsening events

[redacted]

Borg dyspnea index

[redacted]

Pulmonary vascular resistance

[redacted]

[redacted]

TABLE 29: RESULTS OF MIXED TREATMENT COMPARISON FOR COMBINATION THERAPY IN MIXED PULMONARY ARTERIAL HYPERTENSION POPULATION

Treatment Comparison	6MWD	Clinical Worsening Event	Borg Dyspnea Index	PVR
Riociguat 2.5 mg versus comparator	**MD (95% CrI)**	**OR (95% CrI)**	**MD (95% CrI)**	**MD (95% CrI)**
[redacted]				
Riociguat 1.5 mg versus comparator				
[redacted]				

6MWD = six-minute walk distance; CrI = credible interval; ERA = endothelin receptor antagonist; MD = mean difference; OR = odds ratio; PA = prostacyclin agonist; PDE5 = phosphodiesterase type 5; PVR = pulmonary vascular resistance.
Source: CADTH Common Drug Review submission.[5]

Health-related quality of life

[redacted]

[redacted]

[redacted]

[redacted]

TABLE 30: RESULTS OF INDIRECT TREATMENT COMPARISON FOR EUROQOL 5-DIMENSIONS QUESTIONNAIRE IN MIXED PULMONARY ARTERIAL HYPERTENSION POPULATION

Treatment Comparison	EQ-5D VAS[a]	EQ-5D Utility Score[a]
Intervention versus Placebo	**MD (95% CrI)**	**MD (95% CrI)**
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Riociguat 2.5 mg ± ERA or PA versus comparator		
[redacted]	[redacted]	[redacted]
Riociguat 1.5 mg ± ERA or PA versus comparator		
[redacted]	[redacted]	[redacted]

CrI = credible interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; ERA = endothelin receptor antagonist; MD = mean difference; PA = prostacyclin agonist; PAH = pulmonary arterial hypertension; VAS = visual analogue scale.
[a] Based on a fixed effects model that included data from two randomized controlled trials with a mixed PAH population (treatment-naive and patients on other treatments for PAH). Values in bold were statistically significant.
Source: CADTH Common Drug Review submission.[5]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Discussion

[redacted]

[redacted]

The manufacturer-submitted ITC had a similar scope and somewhat similar methodology to the Therapeutic Review conducted by CADTH. Table 31 provides a summary of key differences between the two reports [redacted] In CADTH's review, functional class was analyzed as the change from baseline (i.e., improved, declined), [redacted] Another key difference was in the conduct of the combination therapy analysis. [redacted] whereas the CADTH review restricted the analysis to trials of patients on combination therapy.

The results of the manufacturer-provided ITC were generally similar to CADTH's Therapeutic Review. [redacted]

TABLE 31: KEY DIFFERENCES BETWEEN THE MANUFACTURER-SUPPLIED INDIRECT TREATMENT COMPARISON AND CADTH'S THERAPEUTIC REVIEW

	Manufacturer ITC[5]	CADTH Therapeutic Review[3]
Population	[redacted]	Monotherapy: Primary analysis included the overall study populations (for some studies this was a mixed PAH population); secondary analyses in treatment-naive patients only. Combination therapy: Included patients on therapy prior to enrollment Exclusion criteria: • Study duration less than 8 weeks
Interventions	[redacted]	
Outcomes	[redacted]	MTC: Clinical worsening, 6MWD, functional class • Functional class analyzed as the proportion of patients with improvement, no change or worsening • Meta-analysis of adverse event and other efficacy outcomes
Model	[redacted]	Bayesian MTC: Both random and fixed effects models • Dichotomous outcomes reported as relative risk (95% CrI) • Informative priors used for between-studies standard deviation of the effect estimation • Meta-regression and subgroup analyses conducted to explore heterogeneity

6MWD = six-minute walk distance; BDI = Borg dyspnea index; CrI = credible interval; EQ=5D = EuroQol 5 Dimension instrument; FC = functional class; ITC = indirect treatment comparison; MTC = mixed treatment comparison; OR = odds ratio; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; TR = therapeutic review; VAS = visual analogue scale.

Conclusion

[redacted]

These findings were generally consistent with the Therapeutic Review conducted by CADTH. [redacted]

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