



Common Drug Review

Clinical Review Report

July 2015

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| Drug | Macitentan (Opsumit) (10 mg film-coated tablet) |
| Indication | <p>Macitentan (Opsumit) is indicated for long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce morbidity in patients of WHO Functional Class II or III whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease.</p> <p>Macitentan is effective when used as monotherapy or in combination with PDE-5 inhibitors.</p> |
| Listing request | List in the same manner as Tracleer (bosentan) |
| Manufacturer | Actelion Pharmaceuticals Canada Inc. |

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in respiratory who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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TABLE OF CONTENTS

| | |
|---|------|
| ABBREVIATIONS | iii |
| EXECUTIVE SUMMARY | iv |
| 1. INTRODUCTION..... | 1 |
| 1.1 Disease prevalence and incidence..... | 1 |
| 1.2 Standards of therapy | 2 |
| 1.3 Drug | 3 |
| 2. OBJECTIVES AND METHODS | 7 |
| 2.1 Objectives | 7 |
| 2.2 Methods | 7 |
| 3. RESULTS | 9 |
| 3.1 Findings from the literature | 9 |
| 3.2 Included study | 11 |
| 3.3 Patient Disposition | 17 |
| 3.4 Exposure to study treatments | 18 |
| 3.5 Critical appraisal | 18 |
| 3.6 Efficacy..... | 19 |
| 3.7 Subgroup Analyses | 24 |
| 3.8 Harms..... | 28 |
| 4. DISCUSSION | 31 |
| 4.1 Summary of available evidence..... | 31 |
| 4.2 Interpretation of results | 31 |
| 4.3 Other considerations | 34 |
| 5. CONCLUSIONS..... | 35 |
| APPENDIX 1: PATIENT INPUT SUMMARY..... | 36 |
| APPENDIX 2: LITERATURE SEARCH STRATEGY | 39 |
| APPENDIX 3: VALIDITY OF OUTCOME MEASURES | 41 |
| APPENDIX 4: EXCLUDED STUDIES | 44 |
| APPENDIX 5: DETAILED OUTCOME DATA | 45 |
| REFERENCES..... | 51 |
| Tables | |
| Table 1: Summary of Results..... | viii |
| Table 2: World Health Organization Functional Classification of Pulmonary Hypertension | 1 |
| Table 3: 2013 (Nice) Pulmonary Arterial Hypertension Categories..... | 2 |
| Table 4: Key Characteristics of Pulmonary Arterial Hypertension Drugs Available in Canada | 4 |
| Table 5: Inclusion Criteria for the Review | 7 |
| Table 6: Details of Included Study..... | 10 |

| | |
|--|----|
| Table 7: Summary of Demographic and Baseline Characteristics, All Randomized | 13 |
| Table 8: Patient Disposition | 18 |
| Table 9: Key Efficacy Outcomes | 22 |
| Table 10: Change in World Health Organization Functional Class from Baseline to Month Six..... | 24 |
| Table 11: Harms | 29 |
| Table 12: Summary of Relevant Secondary Outcomes Used in SERAPHIN | 43 |
| Table 13: Subgroup Analysis of WHO FC (Baseline to Month Six) in Patients Without PAH Concomitant Therapy at Baseline (Naive) | 45 |
| Table 14: Subgroup Analysis of WHO FC (Baseline to Month Six) in Patients with PAH Concomitant Therapy at Baseline (Add-on)..... | 45 |
| Table 15: Subgroup Analysis of WHO FC (Baseline to Month Six) of Patients in North America | 46 |
| Table 16: Subgroup Analysis of WHO FC (Baseline to Month Six) in Patients of Western Europe and Israel..... | 46 |
| Table 17: Subgroup Analysis of WHO FC (Baseline to Month Six) of Patients in Eastern Europe and Turkey | 46 |
| Table 18: Subgroup Analysis of WHO FC (Baseline to Month Six) of Patients in Asia | 47 |
| Table 19: Subgroup Analysis of WHO FC (Baseline to Month Six) of Patients in Latin America..... | 47 |
| Table 20: Demographics and Baseline Characteristics of Patients in North America | 47 |
| Table 21: Demographics and Baseline Characteristics of Patients in Western Europe and Israel | 49 |

Figures

| | |
|--|----|
| Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies | 9 |
| Figure 2: Seraphin Study Design | 12 |
| Figure 3: Kaplan–Meier Curves of the First Confirmed Morbidity or Mortality Event Up to EOT + 7 Days, All-Randomized Set..... | 20 |
| Figure 4: Subgroup Analysis of the Time to Clinical Worsening (Hazard Ratio and 95% Confidence Intervals), Macitentan 10 mg Versus Placebo, All-Randomized Set..... | 25 |
| Figure 5: Kaplan–Meier Curves of the Time to First Morbidity or Mortality Event for Patients Without (A) or With (B) Concomitant PAH Therapy at Baseline, All-Randomized Set..... | 26 |
| Figure 6: Primary End Point (Hazard Ratio and 95% Confidence Intervals) by Baseline Disease and Demographic Characteristics — Robustness Analyses (Macitentan 10 mg Versus Placebo), All-Randomized Set | 26 |
| Figure 7: Kaplan–Meier Curves of the Time to First Morbidity or Mortality Event by WHO FC I or II (A) or III or IV at Baseline, All-Randomized Set | 27 |
| Figure 8: Subgroup Analysis of Six-Minute Walk Distance at Month Six (Hazard Ratio and 95% Confidence Intervals), Macitentan 10 mg Versus Placebo, All-Randomized Set..... | 28 |
| Figure 9: Subgroup Analysis of Six-Minute Walk Distance At Month Six (Hazard Ratio And 95% Confidence intervals) by Baseline Disease and Demographic Characteristics, Macitentan 10 mg Versus Placebo, All-Randomized Set..... | 28 |

ABBREVIATIONS

| | |
|-----------------|---|
| 6MWD | six-minute walk distance |
| 6MWT | six-minute walk test |
| AE | adverse event |
| ANCOVA | analyses of covariance |
| CI | confidence interval |
| COPD | chronic obstructive pulmonary disease |
| CPET | cardiopulmonary exercise testing |
| CYP3A | cytochrome P450, family 3, subfamily A |
| ERA | endothelin receptor antagonist |
| FC | functional class |
| FPAH | familial pulmonary arterial hypertension |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| IPAH | idiopathic pulmonary arterial hypertension |
| IVR | interactive voice response |
| IWR | interactive Web response |
| MCID | minimal clinically important difference |
| MCS | mental component summary |
| mPAP | mean pulmonary arterial pressure |
| mRAP | mean right atrial pressure |
| NYHA | New York Heart Association |
| PAH | pulmonary arterial hypertension |
| PCS | physical component summary |
| PCWP | pulmonary capillary wedge pressure |
| PD | pharmacodynamic |
| PDE-5 | phosphodiesterase type 5 |
| PH | pulmonary hypertension |
| PHA | Pulmonary Hypertension Association (of Canada) |
| PK | pharmacokinetic |
| PVR | pulmonary vascular resistance |
| SAE | serious adverse event |
| SC | subcutaneous |
| SD | standard deviation |
| SERAPHIN | Study With an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome |
| SF-36 | Short-Form Health Survey 36-Item questionnaire) |
| sGC | soluble guanylate cyclase |
| SSC | Scleroderma Society of Canada |
| WHO | World Health Organization |

EXECUTIVE SUMMARY

Introduction

Pulmonary arterial hypertension (PAH; also classified as Group 1 pulmonary hypertension [PH]) is a rare, debilitating, progressive, and life-threatening disease of the pulmonary vasculature, characterized by vascular proliferation and remodelling of small pulmonary arteries.¹ PAH is defined by an increase in mean pulmonary arterial pressure (mPAP) \geq 25 mm Hg and a pulmonary wedge pressure of \leq 15 mm Hg.² If left untreated, it can lead to right heart failure and premature death.¹

Prior to the availability of PAH drug therapies, the median survival time was 2.8 years, with survival rates of 68%, 48%, and 34% at one, three, and five years following diagnosis, respectively.^{3,4} The survival of patients with PAH has improved since the introduction of advanced PAH therapy, with current average survival in adults reaching from five to seven years following diagnosis.⁵⁻⁷ Recent survival data for patients with idiopathic PAH (IPAH) or familial PAH (FPAH), which are the two largest subgroups of PAH, from an American registry estimate the one-, three-, five-, and seven-year survival rates to be 85%, 68%, 57%, and 49%, respectively.⁸

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

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

Macitentan is an orally active, non-peptide, potent dual ERA (ET_A and ET_B). In Canada, macitentan is indicated for the long-term treatment of PAH (WHO Group I) to reduce morbidity in patients whose WHO Functional Class (FC) is II or III, whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease. Macitentan is available as 10 mg film-coated tablets and is to be taken orally at a dose of 10 mg once daily, with or without food.

The objective of this review was to evaluate the beneficial and harmful effects of macitentan (Opsumit) as monotherapy or in combination with other drugs for the treatment of PAH patients (WHO Group 1) of WHO FC II or III.

Results and interpretation

Included studies

The evidence for this review was derived from one phase 3 study — Study With an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) — which was a randomized, double-blind, placebo-controlled, event-driven trial in patients with symptomatic PAH. The objective of the trial was to demonstrate that macitentan reduces the risk of morbidity and mortality. A total of 742 patients with WHO FC II or III were randomized in a 1:1:1 ratio to macitentan oral 3 mg once daily, macitentan oral 10 mg once daily, and placebo groups. The mean duration of study treatment was 96.2 weeks. Of note, the only dose approved by Health Canada for the treatment of PAH is 10 mg daily, and as such, data for the 3 mg once-daily dose are not reported in this review.

Demographics and baseline characteristics were generally balanced between groups. The majority of patients in the SERAPHIN trial population were female (77%), Caucasian (55%), aged between 18 and

64 years (83%), and had IPAH (55%), with heart failure symptoms rated as WHO FC II (52%) and III (46%). About 12% of patients in each group were recruited from North American centres. With respect to PAH therapy at baseline, the SERAPHIN population consisted of 36% treatment-naïve patients and 64% patients who were being treated with a PDE-5 inhibitor (61.4%) or non-injectable prostanoids (5.4%).

The primary efficacy outcome in SERAPHIN was the time to first morbidity or mortality event, which was defined as the time from the initiation of treatment to the first event defined as all-cause death, atrial septostomy lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH. The events of the primary end point were reviewed and adjudicated by members of the Clinical Event Committee (CEC) in a blinded fashion.

The secondary outcomes — e.g., six-minute walk distance (6MWD) and proportion of patients with improvement in WHO FC — were assessed from baseline to month six. Death-related end points (death or hospitalization due to PAH) were analyzed up to seven days after end of treatment. Other outcomes, including Borg Dyspnea Index, pulmonary hemodynamics, and quality of life, were evaluated in an exploratory fashion. Safety data included common adverse events (AEs), serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and death occurring up to 28 days after end of treatment.

SERAPHIN was the first longer-term (more than three years), double-blind, randomized clinical trial having a large sample size (N = 742) and using a clinically meaningful primary outcome (i.e., time to clinical worsening). Many other studies on drugs to treat PAH were much smaller in sample size (N = 22 to 443), were conducted over a shorter duration (eight to 16 weeks), and used improvement in 6MWD (a surrogate outcome with uncertain clinical relevance in PAH) as the primary outcome. Key limitations, however, include the large and somewhat differential proportion of patients who discontinued the study (22.0% placebo, 16.9% macitentan). Most discontinuations (17.6% placebo, 14.0% macitentan) were due to death and likely censored according to the time-to-event primary outcome. However, the differential loss to follow-up (2.8% versus 0.8%) is a potential source of bias, although the overall proportions are small and may not have affected the findings of the study. The high proportion of discontinuations may also affect the validity of the results for the secondary outcomes, such as change from baseline to month six in WHO FC and 6MWD, for which missing data were imputed using the last observation carried forward. SERAPHIN included patients aged 12 years and older; however, those aged 12 years to 17 years or 65 years or older comprised a small proportion of the study population (< 3% and < 14%, respectively). Hence, the clinical effects in these age groups have yet to be fully determined.

Efficacy

Macitentan 10 mg had a statistically significantly longer time to first morbidity or mortality event versus placebo during the entire treatment period up to 36 months. The hazard ratio compared with placebo was 0.547 (97.5% confidence interval [CI], 0.39 to 0.76; $P < 0.0001$). This difference was mainly driven by lower rates of worsening of PAH (24.4% versus 37.3%) and prostanoid initiation (0.4% versus 2.4%) for macitentan versus placebo, but not due to a reduction in death rate (6.6% versus 6.8%).

Changes in 6MWD, WHO FC, and death-related end points (death or hospitalization due to PAH) were secondary efficacy outcomes. A statistically significant increase in 6MWD from baseline to month six was observed for macitentan 10 mg compared with placebo (the between-group difference in mean change [standard deviation] was 22.0 m [92.6]; $P = 0.0078$). The clinical relevance of this finding is uncertain because this value is lower than the reported minimal clinically important difference (MCID) for 6MWD in PAH, which is approximately 33.0 m (range 25.1 m to 38.6 m). Unlike baseline 6MWD and absolute distance walked in six minutes, change from baseline in 6MWD may not correlate with clinically

important outcomes such as mortality and morbidity. The majority of patients in both groups remained unchanged in WHO FC from baseline to month six (70.7% for macitentan and 65.9% for placebo). Statistically significantly more patients improved in WHO FC (22.3% versus 12.9%, $P = 0.007$) and fewer worsened in WHO FC (7.0% versus 21.6%; $P < 0.0001$) in the macitentan 10 mg group compared with the placebo group. The proportion of patients who died or were hospitalized due to PAH was also statistically significantly lower with macitentan compared with placebo ($P < 0.0001$). However, there were no statistically significant differences between macitentan and placebo in the rate of death due to PAH or death due to all causes.

Macitentan 10 mg statistically significantly improved both the physical and mental component summaries (PCS and MCS) of the Short-Form 36 questionnaire (SF-36) used to assess quality of life from baseline to month six versus placebo in the SERAPHIN study. The between-group differences (97.5% CI) for PCS and MCS were 3.0 (1.3 to 4.7) and 3.4 (0.9 to 5.9), respectively. These differences on the component scores may be clinically meaningful based on the general MCID for the SF-36 ranging from 2.5 to 5 points; however, the MCID for the SF-36 among patients with PAH is uncertain. Macitentan 10 mg was also associated with numerical improvement in pulmonary hemodynamics; these were analyzed in a subset of the SERAPHIN trial population who participated in the pharmacokinetic (PK) and pharmacodynamic (PD) sub-study (67 patients in placebo and 57 patients in macitentan 10 mg).

In subgroup analyses, there were no major differences in clinical effect with respect to gender, race, PAH etiology, PAH therapy at baseline, or disease severity (i.e., baseline WHO FC). The clinical effect of macitentan was observed in patients of different age groups (i.e., < 18 years, 18 to 64 years, and ≥ 65 years); a statistically significant difference between macitentan and placebo was, however, not reached for patients younger than 18 years or those older than 64 years, due to the small sample size of these subpopulations. Macitentan 10 mg did not show superior efficacy versus placebo in patients recruited from North American centres (Canada and US) as judged either by time to clinical worsening (hazard ratio 1.068, 95% confidence interval, 0.287 to 3.982), [REDACTED]. The small study sample size of North American participants may partially explain this observation, but other factors may also be involved. Hence, these findings require further investigation.

Harms

The overall incidence of AEs (94.6% versus 96.4%), SAEs (45.0% versus 55.0%), and WDAEs (10.7% versus 12.4%) was lower in the macitentan 10 mg group compared with the placebo group. This was mainly due to the lower incidence of PAH (21.9% versus 34.9%) and right ventricular failure (13.2% versus 22.5%) in the macitentan group. However, compared with placebo, the use of macitentan 10 mg was associated with a higher frequency of a number of specific AEs: anemia (13.2% versus 3.2%), headache (13.6% versus 8.8%), upper respiratory tract infection (15.3% versus 13.3%), urinary tract infection (8.7% versus 5.6%), bronchitis (11.6% versus 5.6%), influenza (5.8% versus 1.6%), and thrombocytopenia (5.0% versus 2.8%). Serious anemia was also more frequent in the macitentan 10 mg group compared with the placebo group (2.5% versus 0.4%); these were measured by a marked and clinically relevant decrease in hemoglobin (i.e., values < 11 g/dL and a decrease of 15% from baseline), which occurred more frequently with macitentan 10 mg than with placebo (13.9% versus 3.8%). Lastly, the percentage of patients with liver disorders and abnormal liver function (8.7% versus 14.5%) or impaired renal function (both groups 0.5%) in SERAPHIN was lower than or similar to that for placebo.

Other considerations

Serious birth defects and anemia are listed as warnings and precautions in the product monograph.

Pharmacoeconomic summary

The manufacturer submitted a cost minimization analysis comparing macitentan with brand-name bosentan (Tracleer). No direct or indirect evidence comparing macitentan with bosentan or other drugs indicated for the treatment of PAH was provided; consequently, the comparative effectiveness of macitentan is uncertain. Macitentan has similar drug acquisition costs to Tracleer, but is \$30,441 more costly than generic bosentan per patient annually. Using the estimated current proportion of brand-name (83%) versus generic (17%) bosentan use for PAH in Canada suggests that macitentan is \$5,166 more costly per patient annually. This incremental cost will increase if the proportion of patients receiving generic bosentan is greater.

At the submitted price of \$128.33 per tablet (\$128.33 per day), macitentan is also more expensive than ambrisentan (\$122.52 per day), generic and brand-name sildenafil (\$18.76 to \$33.36 per day, based on the recommended dose of 20 mg three times daily),, and tadalafil (\$26.72 per day).

Conclusions

From a single adequately designed randomized controlled trial (SERAPHIN), macitentan reduces the risk of morbidity and mortality compared with placebo in patients with symptomatic PAH of WHO FC II and III over a median treatment duration of more than two years. Although death from any cause was a component of the primary end point, the difference in the time to first morbidity or mortality event between macitentan and placebo groups is driven mainly by less frequent worsening of PAH in patients using macitentan, not by less death. Macitentan reduces the number of in-patient hospital days and improves WHO FC, 6MWD, Borg Dyspnea Index, pulmonary hemodynamics, and health-related quality of life compared with placebo. Among subpopulations, there appear to be no major differences in clinical effect regarding gender, race, PAH etiology, PAH therapy at baseline, or disease severity. The clinical efficacy of macitentan was not demonstrated in the SERAPHIN trial for patients from North America; clinical effect was, however, shown for all other geographical regions.

In the SERAPHIN trial, the use of macitentan was more commonly associated with anemia, headache, and infection. There is no evidence as yet that macitentan negatively affects liver or renal function. Use of macitentan is not associated with gains in long-term survival of patients with PAH. Compared with placebo, macitentan is associated with lower risks of serious SAEs related to worsening of PAH and right ventricular heart failure. However, its use is associated with more risk of developing severe anemia. Rates of withdrawals due to AEs were slightly higher in the placebo group.

A number of information gaps remain. Safety data from the SERAPHIN open-label extension trial were not available at the time this review was completed. There is also no direct or indirect evidence comparing macitentan with other ERAs, such as bosentan, with which clinicians have years of experience.

TABLE 1: SUMMARY OF RESULTS

| Death or Hospitalization (Up to EOT + 7 days) | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
|--|----------------------|-------------------------------|
| Death due to PAH or hospitalization due to PAH, n (%) | 84 (33.6) | 50 (20.7) |
| HR (97.5% CI) | 0.50 (0.34 to 0.75) | |
| P value ^a | < 0.0001 | |
| Death due to PAH, n (%) | 14 (5.6) | 7 (2.9) |
| HR (97.5% CI) | 0.44 (0.16 to 1.25) | |
| P value ^a | 0.0699 | |
| Death (all causes), n (%) | 19 (7.6) | 14 (5.8) |
| HR (97.5% CI) | 0.64 (0.29 to 1.42) | |
| P value ^a | 0.2037 | |
| Patients with at least one hospitalization (for PAH), n (%) | 82 (32.8) | 49 (20.2) |
| RR (95% CI) ^b | 0.62 (0.45 to 0.84) | |
| P value | 0.002 | |
| HRQoL (Baseline To Month 6) Using SF-36 Questionnaire | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
| | | |
| | | |
| | | |
| Difference in mean change, mean (97.5% CI) | | |
| PCS | 3.0 (1.3 to 4.7) | |
| MCS | 3.4 (0.9 to 5.9) | |
| Time To First Morbidity Or Mortality Event (Up To EOT + 7 Days) | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
| Total patients with at least one confirmed event, n (%) | 116 (46.4) | 76 (31.4) |
| HR (97.5% CI) | 0.55 (0.39 to 0.76) | |
| NNT (95% CI) | 6 (4 to 10) | |
| P value ^a | < 0.0001 | |
| First confirmed event, n (%) | | |
| Worsening of PAH | 93 (37.2) | 59 (24.4) |
| Death from any cause | 17 (6.8) | 16 (6.6) |
| IV/SC prostanoids initiation | 6 (2.4) | 1 (0.4) |
| Lung transplantation | 0 | 0 |
| Who FC (Baseline to Month Six) | Placebo (N = 249) | Macitentan 10 mg (N = 242) |
| Patients with WHO FC improved, n/N (%) | 32/249 (12.9) | 54/242 (22.3) |
| RR (95% CI) ^b | 1.74 (1.16 to 2.59) | |
| NNT (95% CI) ^c | 11 (5 to 49) | |
| P value | 0.007 | |
| Patients with WHO FC unchanged, n/N (%) | 164/249 (65.9) | 171/242 (70.7) |
| RR (95% CI) ^b | 1.07 (0.95 to 1.21) | |
| NNT (95% CI) ^c | 22 (8 to 31) | |
| P value | 0.25 | |
| Patients with WHO FC worsened, n/N (%) | 53/245 (21.6) | 17/242 (7.0) |
| RR (95% CI) ^b | 0.32 (0.19 to 0.54) | |
| NNT (95% CI) ^c | 7 (6 to 11) | |
| P value | < 0.0001 | |
| Change (number of FC ^d), n (%) | | |
| -2 | 2 (0.8) | 0 |
| -1 | 30 (12.0) | 54 (22.3) |

CDR CLINICAL REVIEW REPORT FOR OPSUMIT

| Who FC (Baseline to Month Six) | Placebo (N = 249) | Macitentan 10 mg (N = 242) |
|--|----------------------|-------------------------------|
| 0 | 164 (65.9) | 171 (70.7) |
| 1 | 46 (18.5) | 16 (6.6) |
| 2 | 7 (2.8) | 1 (0.4) |
| 6MWD (Baseline To Month Six) | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
| Change from baseline (m), mean (SD) | -9.4 (100.6) | 12.5 (83.5) |
| Difference in mean change, mean (SD) | 22.0 (92.58) | |
| 97.5% CI of mean | (3.2 to 40.8) | |
| P value ^e | 0.0078 | |
| Borg Dyspnea Index (Baseline To Month Six); Borg Scale 0 To 10 | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
| Change from baseline (m), mean (SD) | 0.4 (2.10) | -0.1 (2.02) |
| Difference in mean change, mean (SD) | -0.5 (2.06) | |
| 97.5% CI of mean | (-1.0 to -0.1) | |
| Hemodynamics (Baseline To Month Six); All-Randomized Set, Patients Participating In The PK/PD Sub-Study | Placebo (N = 67) | Macitentan 10 mg (N = 57) |
| PVR, change from baseline (dyn × sec/cm ⁵), mean (SD) | 504 (919) | -25 (688) |
| Mean per cent change over placebo (97.5% CI) | 61.8 (49.9 to 76.5) | |
| mRAP, change from baseline (mm Hg), mean (SD) | 7.4 (18.68) | 7.8 (27.62) |
| Difference in mean change, mean (97.5% CI) | 0.4 (-9.1 to 9.9) | |
| mPAP, change from baseline (mm Hg), mean (SD) | 6.6 (14.37) | 3.9 (28.39) |
| Difference in mean change, mean (97.5% CI) | -2.7 (-11.7 to 6.3) | |
| Cardiac index, change from baseline (L/min/m ²), mean (SD) | -0.48 (0.701) | 0.13 (0.887) |
| Difference in mean change, mean (97.5% CI) | 0.61 (0.28 to 0.93) | |
| AEs (End Of Treatment + 28 Days) | Placebo (N = 249) | Macitentan 10 mg (N = 242) |
| Total patients with at least one AE, n (%) | 240 (96.4) | 229 (94.6) |
| Total patients with at least one SAE, n (%) | 137 (55.0) | 109 (45.0) |
| Total patients who withdrew with at least one AE, n (%) | 31 (12.4) | 26 (10.7) |
| Notable Harms | | |
| Anemia | 8 (3.2) | 32 (13.2) |
| Headache | 22 (8.8) | 33 (13.6) |
| Upper respiratory tract infection | 33 (13.3) | 37 (15.3) |
| Urinary tract infection | 14 (5.6) | 21 (8.7) |
| Bronchitis | 14 (5.6) | 28 (11.6) |
| Influenza | 4 (1.6) | 14 (5.8) |
| Thrombocytopenia | 7 (2.8) | 12 (5.0) |
| Death (EOT + 28 Days) | Placebo (N = 249) | Macitentan 10 mg (N = 242) |
| Patients with at least one cause, n (%) | 21 (8.4) | 16 (6.6) |

AE = adverse event; CI = confidence interval; EOT = end of treatment; FC = functional class; HRQoL = health-related quality of life; HR = hazard ratio; IV = intravenous; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; MCS = mental component summary; NNT = number needed to treat; NS = not significant difference; PAH = pulmonary arterial hypertension; PCS = physical component summary; PK/PD = pharmacokinetic/pharmacodynamic; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; SAE = serious adverse event; SC = subcutaneous; SD = standard deviation; SF-36 = Short-Form 36-item questionnaire; WHO = World Health Organization.

^a Log-rank.

^b Calculated by CADTH using RevMan 4.2.

^c Calculated using Visual Rx version 3.

^d A negative (-) sign indicates improvement in FC.

^e Wilcoxon rank-sum.

Source: SERAPHIN Clinical Study Report.⁹

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 the remodelling of small pulmonary arteries.¹ If left untreated, it can lead to right heart failure and premature death.¹ PAH is defined by an increase in mean pulmonary arterial pressure (mPAP) \geq 25 mm Hg and a pulmonary wedge pressure of \leq 15 mm Hg.²

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

Source: European Society of Cardiology/European Respiratory Society Guidelines.¹⁰

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 2013.¹¹ The four main categories of Group 1 include idiopathic PAH (IPAH), heritable or familial PAH (FPAH), drug- and toxin-induced PAH, and PAH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, or schistosomiasis (Table 3).

TABLE 3: 2013 (NICE) PULMONARY ARTERIAL HYPERTENSION CATEGORIES

| | |
|--------|---|
| 1 | PAH |
| 1.1 | Idiopathic |
| 1.2 | Heritable |
| 1.2.1. | BMPR2 |
| 1.2.2. | ALK1, ENG, CAV1, KCNK3, SMAD9 |
| 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 |
| 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; KCNK3 = potassium channel super family K member-3; PAH = pulmonary arterial hypertension; SMAD9 = mothers against decapentaplegic homolog 9.

Although PAH affects males and females of all ethnicities and ages,¹² the disease is more common among women and among people between 20 and 40 years of age.¹³ In adults, the prevalence of PAH is approximately 12 to 50 cases per million people.¹⁴⁻¹⁶ The incidence and prevalence of PAH in Canada have not been published. However, based on data from the US, UK, Ireland, France, Spain, and Switzerland, the estimated annual incidence of diagnosed PAH ranges from 0.9 to 7.6 cases per million persons, and the prevalence is between 6.6 and 26 cases per million persons.¹⁷ With a Canadian population of 35,158,304 in 2013,¹⁸ the estimated incidence and prevalence of PAH in Canada would be 32 to 267 new cases and 232 to 914 cases, respectively.

In the early 1980s, when advanced PAH drug therapies were not available, the median survival time for patients with primary PH was 2.8 years, with survival rates of 68%, 48% and 34% at one, three, and five years following diagnosis, respectively.^{3,4} However, since the introduction of advanced PAH drug therapies, the average survival after diagnosis in adults is estimated at five to seven years.⁵⁻⁷ The REVEAL registry (March 2006 to December 2009) for patients in the US with IPAH or FPAH (N = 2,635) has estimated that the one-, three-, five-, and seven-year survival rates were 85%, 68%, 57%, and 49%, respectively.⁸

1.2 Standards of therapy

Treatment of PAH is generally categorized as primary or advanced therapy. Primary therapy refers to treatment directed at the underlying causes of the disease, and includes the use of diuretics, oxygen, anticoagulants, and digoxin. Advanced therapy is targeted at the disease itself. As primary therapies are generally not effective in PAH, advanced therapy is often needed.

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

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

1.3 Drug

Macitentan is an orally active, non-peptide, potent dual ERA (ET_A and ET_B). In vitro, macitentan selectively inhibits the binding of endothelin-1 (ET-1) to ET_A and ET_B receptors. By inhibiting the effects of elevated ET-1 levels, ERAs reduce vasoconstriction, smooth muscle cell proliferation, and pulmonary vessel fibrosis. Macitentan is available as 10 mg film-coated tablets, and is to be taken orally at a dose of 10 mg once daily, with or without food.

In Canada, macitentan is indicated for the long-term treatment of PAH (WHO Group I) to reduce morbidity in patients of WHO FC II or III whose PAH is either idiopathic, heritable, or associated with connective tissue disease or congenital heart disease.

| |
|---|
| Indication Under Review |
| OPSUMIT (macitentan) is indicated for long-term treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce morbidity in patients of WHO Functional Class II or III whose PAH is either idiopathic or heritable, or associated with connective tissue disease or congenital heart disease. OPSUMIT is effective when used as monotherapy or in combination with PDE-5 inhibitors. |
| Listing Criteria Requested by Sponsor |
| List in the same manner as Tracleer (bosentan). |

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

| | Macitentan ¹⁹ | Ambrisentan ²⁰ | Bosentan ²¹ | Riociguat ²² | Sildenafil ²³ | Tadalafil ²⁴ | Epoprostenol ²⁵ | Treprostinil ²⁶ |
|---|---|---|---|---|--|---|---|---|
| Drug class | ERA | | | sGC Stimulator | PDE-5I | | Prostanoid | |
| Mechanism of action | Decreases mean pulmonary arterial pressure without affecting systemic blood pressure, decreased pulmonary arterial hypertrophy, and right ventricular remodelling | Selective inhibition of the receptor that inhibits C-mediated vasoconstriction | Decreases pulmonary and systemic vascular resistance, resulting in increased cardiac output without increased heart rate | Dual mode of action acting in synergy with endogenous nitric oxide and also directly stimulating sGC independently of nitric oxide availability | Selective inhibition of PDE-5, thereby increasing cGMP, leading to selective vasodilation of the pulmonary vascular bed and systemic circulation | Selective inhibition of PDE-5, 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 | Idiopathic or heritable PAH of WHO FC II or III, or PAH associated with connective tissue disease or congenital heart disease | Idiopathic (“primary”) PAH (IPAH) and PAH associated with connective tissue disease in patients with WHO FC II or III symptoms who have not responded to conventional therapy | WHO FC III or IV primary PH, or PH secondary to scleroderma or congenital heart disease or HIV in patients who did not respond adequately to conventional therapy | PAH (WHO Group 1), as monotherapy or in combination with ERAs, in adult patients (≥ 18 years of age) with WHO FC II or III | Oral: Primary PH or PH secondary to connective tissue disease in patients with WHO FC II or III who did not respond adequately to conventional therapy Intravenous: patients who are temporarily unable to take oral medication | Idiopathic primary PAH or PAH associated with connective tissue disease, congenital heart disease, or anorexigen use in patients with WHO FC II or III who have not responded to conventional therapy | Primary PH and secondary PH due to scleroderma spectrum of disease in NYHA Class III and IV patients who did not respond adequately to conventional therapy | PAH in NYHA Class III and IV patients who did not respond adequately to conventional therapy |
| Route of administration | Oral | Oral | Oral | Oral | Oral or intravenous | Oral | Continuous chronic intravenous infusion via central venous catheter | Subcutaneous or intravenous (long-term) |

CDR CLINICAL REVIEW REPORT FOR OPSUMIT

| | Macitentan ¹⁹ | Ambrisentan ²⁰ | Bosentan ²¹ | Riociguat ²² | Sildenafil ²³ | Tadalafil ²⁴ | Epoprostenol ²⁵ | Treprostinil ²⁶ |
|--|---|---|---|---|---|--|---|---|
| Recommended dose | 10 mg once daily | <u>Initial:</u> 5 mg/day <u>Increase:</u> 10 mg/day may be necessary for patients with connective tissue disease | <u>Initial:</u> 62.5 mg twice daily for 4 weeks <u>Increase:</u> 125 mg twice daily | 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg three times daily | <u>Oral:</u> 20 mg three times daily <u>Intravenous:</u> 10 mg three times daily; administered as an intravenous bolus injection | 40 mg once daily <u>Patients with mild renal insufficiency:</u> 20 mg once daily, increased to 40 mg once daily based on tolerability <u>Patients with mild or moderate hepatic impairment:</u> 20 mg once daily | <u>Initial:</u> 2 ng/kg/min <u>Incremental increase:</u> 1 to 2 ng/kg/min, between at least 15-minute intervals | <u>Initial:</u> 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 |
| Contra-indications (according to product monograph) | Patients who are hypersensitive to drug Patients who are pregnant or may become pregnant | Patients with idiopathic pulmonary fibrosis Patients with known hypersensitivity to the drug or any of the ingredients in the formulation Patients who are pregnant or may become pregnant Patients with clinically significant anemia | Patients who are hypersensitive to drug or any excipient in the formulation Patients who are pregnant Patients with moderate or severe liver impairment Concomitant use of cyclosporine A or glyburide | PDE-5Is (sildenafil, tadalafil, vardenafil) Nitrates Nitric oxide donors, such as amyl nitrate Patients who are pregnant, nursing, or hypersensitive to drug or any ingredient in the formulation or component | Patients on nitrate drug therapy or utilizing short-acting nitrate-containing medications Patients who are hypersensitive to drug or any ingredient in the formulation or component of the container | Patients with severe renal insufficiency Patients with severe hepatic impairment | Patients with congestive heart failure due to severe left ventricular systolic dysfunction Patients with known or suspected hypersensitivity to the drug or any of its excipients Patients who develop pulmonary edema during dose initiation | Patients with known hypersensitivity to the drug, any of its excipients, or to structurally related compounds |
| Warnings and precautions (according to product monograph) | Potential for hepatic enzyme elevations; therefore, not to be used in patients with | Potential development of decreases in hemoglobin and hematocrit Potential for | Reversible increases in liver enzymes; potential for hepatic cirrhosis; liver | Risk of hypotension, particularly in patients with concomitant or underlying conditions, such as | Not recommended for patients with pulmonary veno-occlusive disease Patients with | Patients should not be administered nitrates (including nitroglycerin) within 48 hours of last dose of | Abrupt withdrawal should be avoided. Not to be used in | Abrupt withdrawal should be avoided Administration must be performed in |

CDR CLINICAL REVIEW REPORT FOR OPSUMIT

| | Macitentan ¹⁹ | Ambrisentan ²⁰ | Bosentan ²¹ | Riociguat ²² | Sildenafil ²³ | Tadalafil ²⁴ | Epoprostenol ²⁵ | Treprostinil ²⁶ |
|--|---|--|--|---|--|---|--|---|
| | <p>moderate to severe hepatic impairment</p> <p>Potential for development of decrease in hemoglobin; not recommended for use in patients with severe anemia</p> <p>Patients with moderate or severe renal impairment could experience hypotension and anemia.</p> | <p>hepatic enzyme elevations; therefore, not to be used in patients with severe hepatic impairment, and used with caution in patients with moderate hepatic impairment</p> <p>Peripheral edema, with the possibility of pulmonary veno-occlusive disease</p> | <p>failure</p> <p>Potential for worsening of chronic heart failure, possibly due to fluid retention</p> <p>Potential for decreases in hemoglobin</p> | <p>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</p> <p>Risk of additive or synergistic effects on systemic blood pressure when concomitantly used with PDE-5 inhibitors, nitrates or nitric oxide donors</p> <p>Risk of bleeding, particularly in patients taking anticoagulants</p> | <p>abnormal discs or previously diagnosed with NAION, due to potential development of NAION</p> <p>Concomitant administration of ritonavir</p> <p>Caution is advised when co-administered with alpha-blockers, as both are vasodilators with blood pressure lowering effects</p> | <p>tadalafil</p> <p>Potential to significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease</p> <p>Patients with abnormal discs or previously diagnosed with NAION, due to potential development of NAION</p> | <p>patients having pulmonary edema during dose initiation</p> <p>Administration must be performed in hospital with adequate personnel and equipment for physiologic monitoring and emergency care</p> <p>Increased risk for hemorrhagic complications in patients with other risk factors for bleeding</p> | <p>hospital with adequate personnel and equipment for physiologic monitoring and emergency care.</p> <p>Dosage should be adjusted at the first sign of recurrence or worsening of symptoms attributable to PAH or the occurrence of intolerable AEs</p> |

AE = adverse event; cGMP = cyclic guanosine monophosphate; ERA = endothelin receptor antagonist; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; NAION = non-arteritic anterior ischemic optic neuropathy; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; PH = pulmonary hypertension; SGC = soluble guanylate cyclase; WHO = World Health Organization.

⁹ Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a review of the beneficial and harmful effects of macitentan as monotherapy or in combination with PDE-5 inhibitors for the treatment of PAH patients (WHO Group 1) with WHO FC II or III.

2.2 Methods

Studies selected for inclusion in the review included the pivotal studies supporting the Health Canada indication provided in the manufacturer's submission to the CADTH Common Drug Review (CDR), as well as those meeting the selection criteria presented in Table 5.

TABLE 5: INCLUSION CRITERIA FOR THE REVIEW

| | |
|---------------------------|--|
| Patient Population | PAH patients (WHO, Group 1) aged 12 years or older Subgroup: <ul style="list-style-type: none"> • Age • Baseline WHO FC • Baseline 6MWD • Gender • PAH etiology subtype • Background PAH therapy |
| Intervention | Macitentan (Opsumit) tablets, 10 mg daily |
| Comparators | <ul style="list-style-type: none"> • Active comparators (epoprostenol, treprostinil, ambrisentan, bosentan, sildenafil, tadalafil, riociguat) • Placebo or no treatment |
| Outcomes | <p>Key efficacy outcomes:</p> <ul style="list-style-type: none"> • Death (all-cause, PAH-related) • Health-related quality of life • Hospitalization • Clinical worsening^a <p>Other efficacy outcomes:</p> <ul style="list-style-type: none"> • WHO FC (improved, unchanged, worsened) • 6MWD • Borg Dyspnea Index • Hemodynamic parameters: PVR, mPAP, cardiac index <p>Harms outcomes:</p> <p>SAEs, WDAEs, AEs, and AEs of special interest (liver toxicity, edema, anemia, hypotension)</p> |
| Study Design | Published and unpublished DB RCTs |

6MWD = six-minute walk distance; AE = adverse events; DB = double-blind; FC = functional class; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events; WHO = World Health Organization.

^a The definition of clinical worsening may vary among included studies.

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 concepts were Opsumit (macitentan).

No methodological filters were applied to limit the 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 June 10, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on October 15, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (<http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters>): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), 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 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.

3. RESULTS

3.1 Findings from the literature

One study was identified from the literature for inclusion in this review (Figure 1). The study is summarized in Table 6 and described in Section 3.2.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

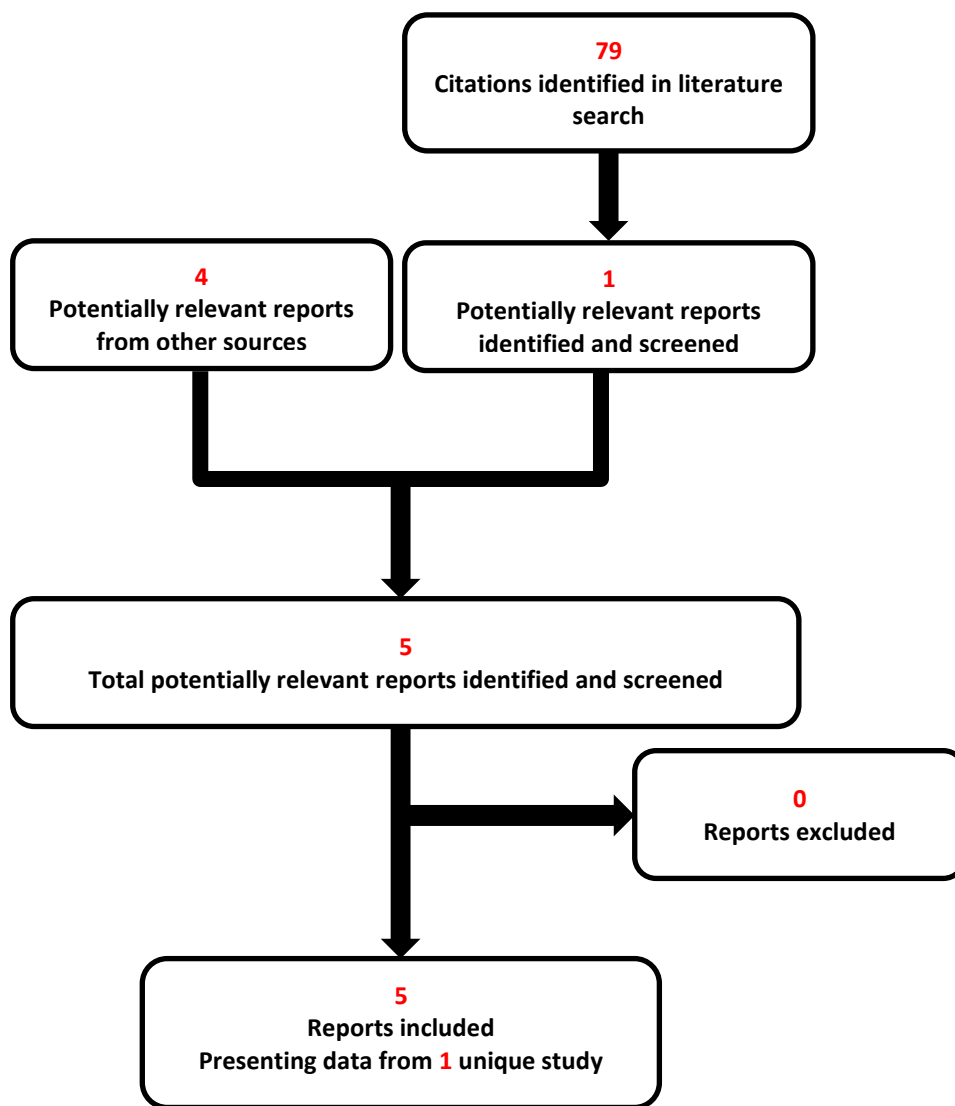


TABLE 6: DETAILS OF INCLUDED STUDY

| | | Seraphin |
|-----------------------|---------------------------|--|
| DESIGNS & POPULATIONS | Study Design | Phase 3, multi-centre (151 centres), multi-country (39 countries), double-blind, randomized, placebo-controlled trial. |
| | Locations | Europe, Russia, Asia, South Africa, South America, US, Canada |
| | Randomized (N) | 742 |
| | Inclusion Criteria | Age ≥ 12 years; PAH (idiopathic, familial, or associated with connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, or drug use or toxin exposure); WHO FC II to IV; 6MWD ≥ 50m; treatment-naive patients or treatment-experienced patients who were on stable background treatment (at least 3 months before randomization) with oral PDE-5 inhibitors, oral or inhaled prostanoids, calcium channel blockers, or L-arginine |
| | Exclusion Criteria | Treatment with intravenous or subcutaneous prostanoids |
| DRUGS | Intervention | Macitentan 3 mg and 10 mg orally once daily (Note: Health Canada approved only the 10 mg dose once daily for the treatment of PAH, and as such, the 3 mg dosage arm was excluded from this review.) |
| | Comparator(s) | Matching placebo orally once daily |
| DURATION | Phase | |
| | Screening | Up to 28 days |
| | Double-blind | From randomization to end of treatment: up to 36 months |
| | Follow-up | 7 days post end of treatment |
| OUTCOMES | Primary End Point | <p><u>Time to first morbidity or mortality event</u>: Time from the initiation of treatment to the first event, defined as:</p> <ul style="list-style-type: none"> • All-cause death • Atrial septostomy • Lung transplantation • Initiation of treatment with intravenous or subcutaneous prostanoids • Worsening of PAH, defined as the occurrence of all three of the following events: <ul style="list-style-type: none"> ○ A decrease in the 6MWD of ≥ 15% from baseline, confirmed by 2 tests on different days ○ Worsening of PAH symptoms, which must have included either an increase in WHO FC by ≥ 1 class or no change in patients who were in WHO FC IV at baseline, or the appearance or worsening of signs of right heart failure that did not respond to oral diuretic therapy ○ The need for additional PAH treatment. |
| | Other End Points | <ul style="list-style-type: none"> • Change from baseline to month 6 in the 6MWD • Time to death due to PAH or hospitalization for PAH up to end of treatment • Time to death from all-cause up to end of treatment and up to end of study • Proportion of patients with improvement in WHO FC from baseline to month 6 • Change in Borg Dyspnea Index from baseline to month 6 • Change in hemodynamic variables (PVR, mPAP, cardiac index) from baseline to month 6 • Change from baseline in HRQoL assessed by the SF-36 questionnaire from baseline to month 6. |

| | | Seraphin |
|--------------|---------------------|------------------------------------|
| NOTES | Publications | Pulido et al. (2013) ²⁷ |

6MWD = six-minute walk distance; FC = functional class; HRQoL = health-related quality of life; mPAP = mean pulmonary arterial pressure; PDE-5 = phosphodiesterase type 5; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; SF-36 = Short-Form 36-Item questionnaire; WHO = World Health Organization. Source: SERAPHIN Clinical Study Report;⁹ FDA clinical report;²⁸ Health Canada report.²⁹

3.2 Included study

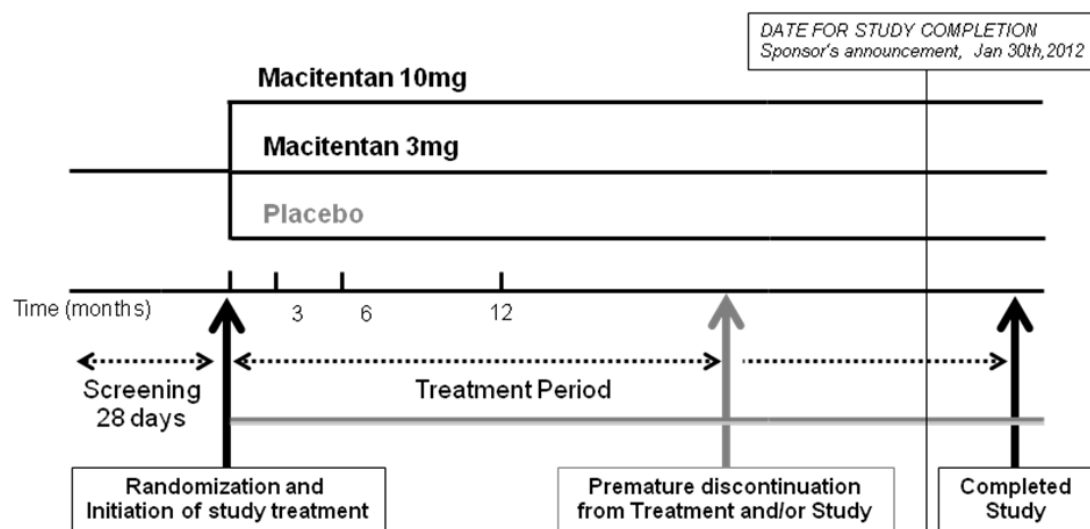
3.2.1 Description of study

The Study With an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) was a multi-centre (158 centres), multinational (39 countries), double-blind, randomized, placebo-controlled, parallel-group, event-driven, phase 3 study that compared treatment with 3 mg and 10 mg doses of macitentan versus placebo in patients with symptomatic PAH. In North America, 83 patients were recruited from 38 centres including Canada (5 centres) and the US (33 centres). The duration of the study was anticipated to be a maximum of 4.5 years from the first enrolled patient until the last observed morbidity or mortality event. The SERAPHIN study design is shown in Figure 2. There was a screening period of up to 28 days followed by a treatment period from randomization to end-of-treatment visit. The end of study occurred when the target of 285 total events of morbidity or mortality was achieved. The primary objective of the trial was to investigate whether the long-term treatment of macitentan reduces the risk of morbidity and mortality among patients with symptomatic PAH. A total of 742 patients were randomized (1:1:1) into three treatment groups: placebo (N = 250), macitentan 3 mg (N = 250), and macitentan 10 mg (N = 242). Randomization was stratified by study centre.

The trial had a Clinical Event Committee (CEC) composed of three PAH experts who were responsible for reviewing all morbidity and mortality events in a blinded fashion and adjudicating these events for the main analysis of the primary end point. Ongoing background therapy at stable doses at baseline was allowed to continue during the treatment period. Dose selection was based on the maximum blockage of the endothelin receptors at the 10 mg dose and the pharmacological effect for blood pressure reduction, which was near plateau at the 10 mg dose.

In this report, only the macitentan 10 mg dose was included and described in the following sections because it is the sole dose approved by Health Canada.

FIGURE 2: SERAPHIN STUDY DESIGN



Source: SERAPHIN Clinical Source Report.⁹

3.2.2 Populations

a) Inclusion and exclusion criteria

SERAPHIN enrolled patients of WHO FC II to IV with IPAH, FPAH, PAH associated with connective tissue disease, PAH associated with simple congenital systemic-to-pulmonary shunts at least one year post-surgical repair, or PAH associated with either HIV infection or drug and toxin use. Eligible patients were men or women ≥ 12 years of age with a baseline six-minute walk distance (6MWD) ≥ 50 m; mean pulmonary arterial pressure (mPAP) > 25 mm Hg; pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure ≤ 15 mm Hg; or pulmonary vascular resistance (PVR) at rest ≥ 320 dyn \times sec/cm⁵. Patients were excluded if receiving ERAs (bosentan or ambrisentan), intravenous or subcutaneous prostanoids, specific immunosuppressants, cytochrome P 450 (CYP) 3A inducers, or any investigational drug other than the study drug.

b) Baseline characteristics

Baseline characteristics were generally balanced between groups (except for sex and age) (Table 7). Patients were predominantly female (77% overall; 73.9% placebo and 80.2% macitentan) and Caucasian (55%), with a mean age of 46 years and a mean time from diagnosis of 32 months. The majority of patients were aged between 18 and 64 years (83.4%); a higher proportion of patients in the placebo group (17.3%) versus the macitentan group (11.2%) were aged ≥ 65 years. IPAH was the most common etiology (55.0%), followed by PAH associated with connective tissue disease (30.5%) and PAH associated with congenital shunts (8.4%). FPAH and PAH associated with HIV infection, drug use, or toxin exposure ranged from 1.4% to 3.0%. The study population was predominantly WHO FC II (52%) and FC III (46%). Overall at baseline, patients had a mean 6MWD of 360 m, mPAP of 54 mm Hg, mean PVR of 1,026 dyn \times sec/cm⁵, and cardiac index of 2.4 L/min/m². The SERAPHIN study had a mixed population, comprising 64% of patients who had been treated with PDE-5 inhibitors (61.4%) and prostanoids (5.4%), and 36% of patients who were naive to PAH therapy. Sildenafil was the most common PAH therapy at baseline (58%).

TABLE 7: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS, ALL RANDOMIZED

| Characteristics | Placebo (N = 250) | Macitentan 10 Mg (N = 242) | All Patients (N = 742) ^A |
|---|----------------------|-------------------------------|--|
| Female sex, n (%) | 184 (73.9) | 194 (80.2) | 565 (76.5) |
| Age (years), mean (SD) | 46.7 (17.0) | 45.5 (15.0) | 45.6 (16.1) |
| Age, n (%) | | | |
| < 18 | 7 (2.8) | 6 (2.5) | 20 (2.7) |
| 18 to 64 | 199 (79.9) | 209 (86.4) | 616 (83.4) |
| ≥ 65 | 43 (17.3) | 27 (11.2) | 103 (13.9) |
| Race, n (%) | | | |
| Caucasian | 131 (52.6) | 135 (55.8) | 403 (54.5) |
| Black | 8 (3.2) | 6 (2.5) | 19 (2.6) |
| Asian | 71 (28.5) | 65 (26.9) | 205 (27.7) |
| Hispanic | 37 (14.9) | 35 (14.5) | 109 (14.7) |
| Other | 2 (0.8) | 1 (0.4) | 3 (0.4) |
| BMI (kg/m ²), mean (SD) | 25.2 (5.1) | 25.6 (6.1) | 25.5 (5.9) |
| SBP (mm Hg), mean (SD) | 115.7 (13.5) | 116.3 (14.1) | 115.8 (13.7) |
| DBP (mm Hg), mean (SD) | 74.1 (9.6) | 74.4 (9.2) | 74.1 (9.8) |
| PAH diagnosis (years), mean (SD) | 2.6 (3.7) | 2.6 (3.6) | 2.7 (4.0) |
| PAH etiology, n (%) | | | |
| Idiopathic | 126 (51.0) | 134 (55.6) | 404 (55.0) |
| Familial | 3 (1.2) | 2 (0.8) | 13 (1.8) |
| Collagen vascular disease | 81 (32.8) | 73 (30.3) | 224 (30.5) |
| Congenital shunts | 26 (10.5) | 21 (8.7) | 62 (8.4) |
| HIV infection | 3 (1.2) | 6 (2.5) | 10 (1.4) |
| Drugs and toxins | 8 (3.2) | 5 (2.1) | 22 (3.0) |
| 6MWD (m), mean (SD) | 352.4 (110.6) | 362.6 (93.2) | 359.6 (100.2) |
| Borg Dyspnea Index, mean (SD) | 3.5 (2.1) | 3.5 (2.3) | 3.5 (2.2) |
| NT-proBNP (fmol/mL), mean (SD) | ██████████ | ██████████ | ██████████ |
| WHO FC, n (%) | | | |
| I | 0 | 1 (0.4) | 1 (0.1) |
| II | 129 (51.8) | 120 (49.6) | 387 (52.4) |
| III | 116 (46.6) | 116 (47.9) | 337 (45.6) |
| IV | 4 (1.6) | 5 (2.1) | 14 (1.9) |
| Hemodynamics | | | |
| mRAP (mm Hg), mean (SD) | 8.8 (5.6) | 9.2 (6.0) | 9.1 (5.6) |
| mPAP (mm Hg), mean (SD) | 53.1 (18.1) | 53.5 (17.6) | 53.9 (17.5) |
| PCWP (mm Hg), mean (SD) | 9.5 (3.4) | 9.5 (3.4) | 9.6 (3.4) |
| CI (L/min/m ²), mean (SD) | 2.4 (0.8) | 2.4 (0.8) | 2.4 (0.8) |
| PVR (dyn × sec/cm ⁵), mean (SD) | 996 (784.3) | 1,040 (672.5) | 1,026 (696.7) |
| Background PAH therapy, n (%) | | | |
| Yes | 154 (61.8) | 154 (63.6) | 471 (63.7) |
| No | 95 (38.2) | 88 (36.4) | 268 (36.3) |

| Characteristics | Placebo (N = 250) | Macitentan 10 Mg (N = 242) | All Patients (N = 742) ^A |
|-------------------------------|----------------------|-------------------------------|--|
| Background PAH therapy, n (%) | | | |
| PDE-5 inhibitors | 150 (60.2) | 150 (62.0) | 454 (61.4) |
| Oral or inhaled prostanoids | 7 (2.8) | 16 (6.6) | 41 (5.5) |
| Concomitant medication, n (%) | | | |
| Anticoagulants | | | |
| Antithrombotic agents | | | |
| Diuretics | | | |
| Calcium channel blockers | | | |
| HRQoL (SF-36), mean (SD) | | | |
| Physical functioning | | | |
| Role — physical | | | |
| Pain index | | | |
| General health perceptions | | | |
| Vitality | | | |
| Social functioning | | | |
| Role — emotional | | | |
| Mental health index | | | |
| Physical component summary | | | |
| Mental component summary | | | |

6MWD = six-minute walk distance; BMI = body mass index; CI = cardiac index; DBP = diastolic blood pressure; FC = functional class; HRQoL = health-related quality of life; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; NT-proBNP = N-terminal pro b-type natriuretic peptide; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; SBP = systolic blood pressure; SD = standard deviation; SF-36 = Short-Form Health Survey 36-Item questionnaire.

^aTotal patients in placebo, macitentan 3 mg, and macitentan 10 mg groups.

Source: SERAPHIN Clinical Study Report.⁹

3.2.3 Interventions

Following a 28-day screening period, patients were randomized to macitentan 3 mg, macitentan 10 mg, or matched placebo in a 1:1:1 ratio in a double-blind fashion. Patients received macitentan or placebo tablets in addition to their usual PAH treatment, including PDE-5 inhibitors, oral or inhaled prostanoids, anticoagulants, diuretics, calcium channel blockers, or L-arginine. Most patients did not use supplemental oxygen (> 95%). Patients had to be on a stable dose of PDE-5 inhibitors and oral or inhaled prostanoids for at least three months before randomization, with doses remaining unchanged during the study. Prohibited concomitant medications included ERAs (bosentan, ambrisentan), intravenous or subcutaneous prostanoids, specific immunosuppressants, and CYP3A (cytochrome P450, family 3, subfamily A) inducers.

3.2.4 Outcomes

The primary efficacy outcome in SERAPHIN was the time from start of study treatment to the first morbidity or mortality event up to end of treatment plus seven days, which was a composite end point defined in Table 6. The definition of *time to first morbidity or mortality event* is consistent with that recommended by McLaughlin et al.³⁰ and used in other studies examining the efficacy of PAH treatments³¹⁻³⁸ to define the composite outcome of clinical worsening. The secondary efficacy outcomes were change in 6MWD from baseline to month six, proportion of patients with improvement in WHO FC

from baseline to month six, and death. Quality of life (assessed using the SF-36 questionnaire), PAH symptoms including Borg Dyspnea Index, and hemodynamic parameters were evaluated in an exploratory fashion. APPENDIX 3 presents a detailed description of those outcomes as well as information on the validity and minimal clinically important differences (MCIDs). The MCIDs for clinical worsening and hemodynamic parameters are currently unknown. The MCID for the Borg Dyspnea Index has been estimated to be approximately 1 point among patients with chronic obstructive pulmonary disease (COPD) and heart failure.^{39,40} 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 an MCID for the Borg Index of < 1 point in patients with PAH.⁴¹ For change from baseline in 6MWD, the estimated MCID value is 33.0 m (range: 25.1 to 38.6 m).⁴² For SF-36, the MCID value is generally accepted to be a change of 5 to 10 points in each dimension or 2.5 to 5 points in each component summary.^{43,44}

Exploratory efficacy outcomes included:

- Change in 6MWD from baseline to all assessed time points
- Achievement and/or maintenance of a 6MWD \geq 380 m at all assessed time points
- Change in Borg Dyspnea Index from baseline to all assessed time points
- Change in WHO FC from baseline to all assessed time points
- Change in N-terminal pro-B type natriuretic peptide from baseline to month six
- Change in health-related quality of life (HRQoL) assessed by SF-36 questionnaire
- Time to death due to PAH up to end of study
- Time to death due to PAH up to end of treatment
- Hemodynamic end points.

Safety data included common adverse events (AEs), serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), and death occurring up to 28 days after end of treatment.

3.2.5 Statistical analysis

SERAPHIN was designed to test the superiority of macitentan (3 mg and 10 mg) to placebo for the risk of first occurrence of morbidity or mortality event (primary end point) up to seven days after end of treatment. A total of 285 events were needed to detect a hazard ratio (HR) for macitentan versus placebo of 0.55 (a risk reduction of 45%) for at least one dose over an estimated maximum duration of 4.1 years, with 90% power.

The primary end point (time to first morbidity or mortality event) was analyzed using the Kaplan–Meier method and the null hypothesis was tested by means of the log-rank test. No adjustment for covariates was performed for the primary analysis. Given the time-to-event analysis, patients without a primary end point event (confirmed by the CEC) were right censored at the earliest date between the date of study drug discontinuation plus seven days and the end-of-study date. No imputation method was used for the primary efficacy end point in the case of missing data, due to its time-to-event definition.

The secondary end points were analyzed hierarchically to control for type 1 error for each dose group versus placebo in the following sequence:

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| Positive Study Global Alpha = 0.05 (Two-Sided) | Conclusive Study Global Alpha = 0.01 (Two-Sided) |
|---|---|
| Primary end point $P < 0.025$ | Primary end point $P < 0.005$ |
| ↓ | ↓ |
| Change from baseline in 6MWD at month 6 (Wilcoxon rank-sum test) $P < 0.025$ | Change from baseline in 6MWD at month 6 (Wilcoxon rank-sum test) $P < 0.005$ |
| ↓ | ↓ |
| Proportion of patients with improving WHO FC (Fisher's exact test) $P < 0.025$ | Proportion of patients with improving WHO FC (Fisher's exact test) $P < 0.005$ |
| ↓ | ↓ |
| Time to death or hospitalization due to PAH up to 7 days after end of treatment (log-rank) $P < 0.025$ | Time to death or hospitalization due to PAH up to 7 days after end of treatment (log-rank) $P < 0.005$ |
| ↓ | ↓ |
| Time to death of all causes up to 7 days after end of treatment or end of study (log-rank) $P < 0.025$ | Time to death of all causes up to 7 days after end of treatment or end of study (log-rank) $P < 0.005$ |
| ↓ | ↓ |
| Time to death of all causes up to end of study (log-rank) $P < 0.025$ | Time to death of all causes up to end of study (log-rank) $P < 0.005$ |

6MWD = six-minute walk distance; FC = functional class; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

According to the SERAPHIN statistical analysis plan, each comparison of macitentan versus placebo was tested at a nominal type-I error level of 0.005 (two-sided) using Bonferroni's approach, to compensate for multiplicity of testing and to keep the study-wise type-I error to the required two-sided 0.01 level in the presence of multiple tests. As indicated in the previous table, statistical significance could be claimed if:

- the pre-defined nominal significance level ($P < \alpha/2$ two-sided) has been reached for the primary end point for the same dose group
- the pre-defined nominal significance level ($P < \alpha/2$ two-sided) has been reached for all the previous end points in the sequence for the same dose group, where $\alpha = 0.005$ two-sided for a conclusive study and $\alpha = 0.025$ two-sided for a positive study.

Analysis of exploratory efficacy outcomes was performed using analyses of covariance (ANCOVA) with adjustment for the 6MWD at baseline and were used to determine the overall treatment effect, by PAH background therapy, and by WHO FC at baseline.

Hemodynamics and SF-36 data were reported for both absolute and changes from baseline to month six. Treatment effect estimates were accompanied by two-sided 97.5% confidence intervals (CIs).

Subgroup analyses, classifying patients according to important baseline characteristics, were performed for both primary and secondary end points using interaction tests for heterogeneity. The Cox model was included. The pre-specified subgroups included PAH therapy at baseline, with or without concomitant PAH therapy; sex (male versus female); race (Caucasian, Asian, and others); PAH etiology at baseline (idiopathic, familial, HIV infection, drugs, and toxins versus connective tissue disease versus congenital shunts); geographic regions (North America; Western Europe and Israel; Eastern Europe and Turkey; Asia; and Latin America). The subgroup specified after unblinding was WHO FC at baseline (I/II versus II/IV).

The main analyses for the primary and secondary end points were performed using the intention-to-treat approach. No imputation method was used for the primary efficacy end point due to its definition. For secondary and exploratory outcomes, the last observation carried forward (the last available post-baseline value obtained up to last day of the month six window) was used to impute missing value. For patients without post-baseline value, missing data were imputed by carrying the baseline value forward.

Four main analysis sets were defined: an all-randomized set (all randomized patients, whether they received the study drug or not); an all-treated set (all randomized patients who received the study drug at least once); a per-protocol set (all patients from the all-treated set who did not deviate from the protocol; i.e., without major protocol violations); and a pharmacokinetic/pharmacodynamic (PK/PD) set (all patients from the all-treated set who participated in the PK/PD sub-study). Of 742 patients in the all-randomized set, 590 (79.5%) completed the study. One patient in the placebo group did not receive treatment and was therefore excluded from the all-treated set (741 patients).

a) Analysis Populations

The efficacy end points were analyzed in the all-randomized set (N = 742), which included all randomized patients whether they received the study drug or not. The hemodynamic variables were analyzed in the all-randomized set who participated in the PK/PD sub-study (N = 187). The safety outcomes were analyzed in the all-treated set (N = 741).

3.3 Patient Disposition

Table 8 presents a summary of the reasons for premature discontinuation from the study. A higher proportion of patients in the placebo group (22.0%) discontinued the study than that in the macitentan 10 mg group (16.9%). Death was the main reason for study discontinuation (17.6% in the placebo group versus 14.0% in the macitentan 10 mg group). One patient in the placebo group received no medication after randomization and was excluded from the all-treated set (safety data set). This patient was retained for the efficacy analysis, but not for the safety analysis.

TABLE 8: PATIENT DISPOSITION

| | Seraphin | |
|---------------------------------------|------------|------------------|
| | Placebo | Macitentan 10 mg |
| Screened, N | 955 | |
| Randomized, N (%) | 250 (26.2) | 242 (25.3) |
| Discontinued from study, N (%) | 55 (22.0) | 41 (16.9) |
| Death | 44 (17.6) | 34 (14.0) |
| Withdrawal of subject's consent | 4 (1.6) | 4 (1.7) |
| Lost to follow-up | 7 (2.8) | 2 (0.8) |
| Administrative reason | 0 | 1 (0.4) |
| ITT, N (%) | 250 (100) | 242 (100) |
| Safety, N (%) | 249 (99.6) | 242 (100) |

ITT = intention-to-treat.

Source: SERAPHIN Clinical Study Report.⁹

3.4 Exposure to study treatments

The median duration of exposure in the macitentan 10 mg group (118.4 weeks) was longer than the exposure in the placebo group (101.3 weeks). The maximum treatment duration was 188.0 weeks in the macitentan 10 mg groups and 184.9 weeks in the placebo group. However, only one patient in the placebo group and two in the macitentan 10 mg group remained on treatment at 42 months.

3.5 Critical appraisal

3.5.1 Internal validity

SERAPHIN was performed in a double-blind fashion, where the investigators and patients remained blinded to the study drug allocation until study completion. The study drugs of macitentan and placebo were indistinguishable. Patients were randomized using a centralized randomized system via Interactive Voice Response (IVR) or Interactive Web Response (IWR). In case of emergency, the study drug was systematically unblinded through the IVR/IWR unblinding procedure.

Time to first morbidity or mortality event was chosen as the primary end point, which is relevant for a progressive and fatal disease if it remains untreated. Unlike SERAPHIN, change in 6MWD was used as a primary end point in many other PAH studies. However, some reports have suggested that improvement in 6MWD from baseline did not reflect the benefit in clinical outcomes, such as all-cause death, hospitalization, and initiation of PAH rescue therapy.⁴⁵ SERAPHIN was the first longer-term trial designed to evaluate drug therapy for PAH with a patient-important primary outcome; i.e., clinical worsening.

No imputation method was used for the primary efficacy end point given the time-to-event design; however, the last-observation-carried-forward approach was used to impute missing values of secondary and exploratory outcomes. More patients in the placebo group than in the macitentan group discontinued the study (22.0% versus 16.9%), mostly due to death (17.6% versus 14.0%) and loss to follow-up (2.8% versus 0.8%). These differences may have some impact on the validity of the analysis.

3.5.2 External validity

Patients in the SERAPHIN trial were recruited based on the Venice PH Classification. Although this was the third formal PH classification introduced more than 10 years ago (i.e., in 2003) and the fifth classification was recently released (i.e., Nice 2013), its use in SERAPHIN should not have a major impact

on the external validity of the results, given that the Venice Classification is the one that introduced the terms IPAH, FPAH, and associated PAH. As such, it still has clinical relevance.

The demographic characteristics of the SERAPHIN population were similar to those of the general adult PAH population, according to the clinical expert involved in the review, and balanced between macitentan and placebo groups. Patients were mostly of WHO FC II (52%) and III (46%); only 2% were of FC IV. Those patients were of less advanced disease, but likely to have disease progression if untreated. Patients were predominantly female (77%) with a mean age of 46 years. Adolescents (aged 12 to 17 years) and elderly patients (≥ 65 years) were included in the study, but their numbers were relatively small compared with the number of patients aged 18 to 64 years. Therefore, the true populations of adolescents and elderly patients were not represented in SERAPHIN. Patients were mainly Caucasian (54.5%) and Asian (27.7%), and were mainly recruited at centres in Eastern and Western Europe and Asia. About 12% of patients in each treatment group were recruited from North American centres, including those in Canada and the US. The medical care provided in North America and Western Europe should be similar, according to the manufacturer.

Most patients did not use supplemental oxygen during the baseline walk test (92.8% in the placebo group versus 96.7% in the macitentan 10 mg group), suggesting that patients included in this study might have less severe disease. However, according to the clinical expert involved in the review, hypoxia would not be revealed until very late in the disease, and because patients were mostly WHO FC II and III, it is not unusual that they did not need supplemental oxygen during the walk test.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported, in Section 2.2, Table 5). The results of key efficacy outcomes are presented in Table 9. Baseline values of 6MWD, Borg Dyspnea Index, hemodynamics, and HRQoL are presented in Table 7.

3.6.1 Death

Death was a component of the composite end point of morbidity and mortality (refer to Section 3.6.3). The incidence of death due to PAH was lower in the macitentan 10 mg group (2.9%) compared with the placebo group (5.6%). However, the difference was not statistically significant ($P = 0.0699$). There was no difference in all-cause death between the macitentan and placebo groups (5.8% versus 7.6%; $P = 0.2037$).

3.6.2 Hospitalization

The mean (\pm SD) number per year of all-cause hospitalizations was similar between the placebo group (1.0 ± 1.81) and the macitentan 10 mg group (0.5 ± 2.27).

The mean (\pm SD) number per year of in-patient hospital days for all-cause hospitalizations was lower in the macitentan 10 mg group (5.7 days \pm 19.38) compared with the placebo group (12.2 days \pm 37.57). Similar results were seen for PAH-related hospitalizations.

3.6.3 Time to first morbidity or mortality event

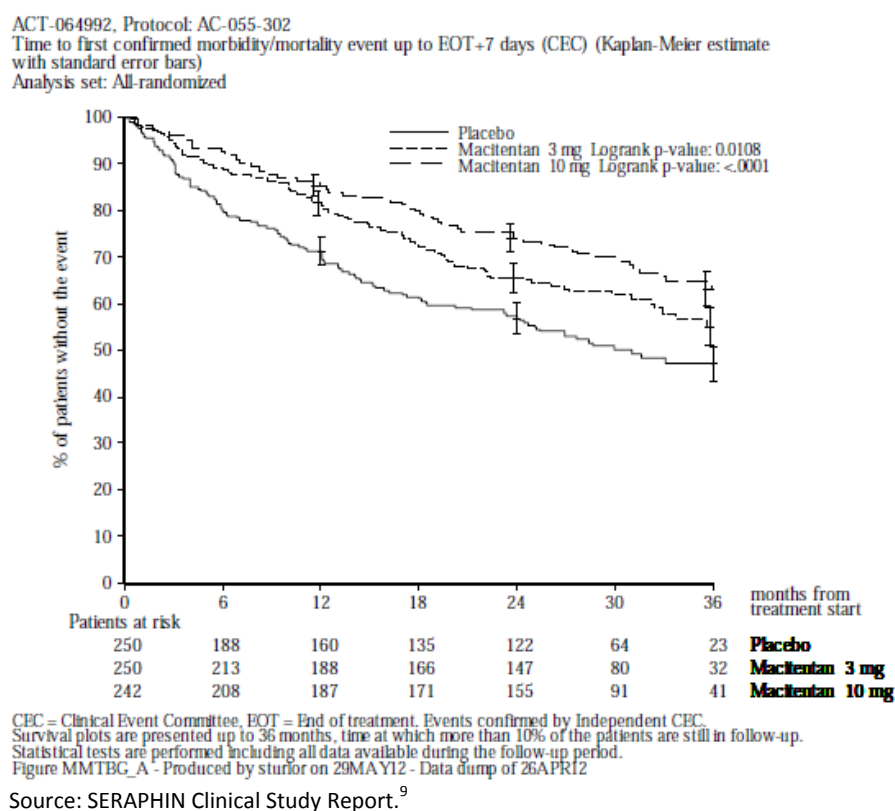
The time to first morbidity or mortality event was the primary end point in SERAPHIN, which was adjudicated by an independent CEC. The CEC-confirmed primary end point event was recorded in 116 patients in the placebo group (46.4%) and 76 patients in the macitentan 10 mg group (31.4%). The absolute risk reduction was 15%, and the number needed to treat was six, with a 95% CI of 4 to 10. The HR for time to clinical worsening in the macitentan 10 mg group versus the placebo group was 0.55

(97.5% CI, 0.39 to 0.76; log-rank $P < 0.0001$). The difference in time to first morbidity or mortality event between macitentan 10 mg and placebo was mainly driven by less frequent worsening of PAH (24.4% versus 37.2%) and the initiation of intravenous or subcutaneous prostanoids (0.4% versus 2.4%) in favour of macitentan, but not by a reduction in the rate of death from any cause.

The Kaplan–Meier curves showed the separation between macitentan and placebo groups at about 12 months, and maintained up to 36 months (

Figure 3). The estimated event-free rates at 12 months were 85.5% for macitentan 10 mg and 71.4%.for placebo.

FIGURE 3: KAPLAN–MEIER CURVES OF THE FIRST CONFIRMED MORBIDITY OR MORTALITY EVENT UP TO EOT + 7 DAYS, ALL-RANDOMIZED SET



3.6.4 Change in World Health Organization functional class

At baseline, most patients were classified at WHO FC II (52%) and III (46%). At month six, most patients had not changed FC, and there was no statistically significant difference in the proportion of patients with unchanged WHO FC between macitentan 10 mg (70.7%) and placebo (65.9%).

For WHO FC improvement, more patients in the macitentan 10 mg group (22.3%) improved compared with placebo (12.9%); $P = 0.007$. There were 54 patients in the macitentan 10 mg group (22.3%) whose WHO FC improved by one FC compared with 30 patients in the placebo group (12.0%) (Table 10). In the macitentan 10 mg group, 7.4% changed from FC II at baseline to FC I; 13.6% changed from FC III at baseline to FC II; and 1.2% changed from FC IV at baseline to FC III. In the placebo group, 2.4% changed

from FC II at baseline to FC I; 9.6% changed from FC III at baseline to FC II; and 0% changed from FC IV at baseline to FC III.

For WHO FC worsening, fewer patients in the macitentan 10 mg group (7.0%) worsened compared with those in the placebo group (21.6%); $P < 0.0001$. There were 16 patients taking macitentan 10 mg (6.6%) whose WHO FC worsened by one FC compared with 46 patients taking placebo (18.5%) (Table 10). In the macitentan 10 mg group, 3.3% changed from FC II at baseline to FC III; 0.4% changed from FC II at baseline to FC IV; and 3.3% changed from FC III at baseline to FC IV. In the placebo group, 6.0% changed from FC II at baseline to FC III; 2.8% changed from FC II at baseline to FC IV; and 12.4% changed from FC III at baseline to FC IV.

3.6.5 Change in six-minute walk distance

At baseline, the mean of 6MWD (SD) for placebo was 352 m (110.6), and for macitentan 10 mg, it was 363 m (93.2). After six months of treatment, the mean change (SD) from baseline in 6MWD for the placebo group was -9.4 m (100.6) compared with $+12.5$ m (83.5) for the macitentan 10 mg group. The placebo-corrected mean change (97.5% CI) was 22.0 m (3.2 to 40.8). This value is, however, lower than the accepted MCID for 6MWD in PAH, which has been estimated as 33.0 m (range: 25.1 m to 38.6 m).⁴²

3.6.6 Change in Borg Dyspnea Index

At baseline, the mean of the Borg Dyspnea Index (SD) for placebo was 3.5 (2.11), and for macitentan 10 mg, it was 3.5 (2.27). At month six, the mean change (SD) from baseline for the placebo group was 0.4 (2.10) compared with -0.1 (2.02) for the macitentan 10 mg group. A decrease in the Borg Dyspnea Index indicates an improvement. The between-group difference in mean change at month six was -0.5 (97.5% CI; -1.0 to -0.1). The treatment effect was maintained up to month 12. The estimated treatment effect over 12 months compared with placebo was -0.38 (95% CI, -0.63 to -0.13 ; $P = 0.0029$) for macitentan 10 mg.

3.6.7 Change in hemodynamic variables

Hemodynamic end points (mean change from baseline to month six) of PVR, mRAP, mPAP, and cardiac index were analyzed in a subset of the SERAPHIN population who participated in the PK/PD sub-study ($N = 187$). Overall, treatment with macitentan 10 mg was associated with improved pulmonary hemodynamics compared with placebo. However, statistically significant differences were not apparent for mRAP and mPAP (Table 9).

3.6.8 Change in health-related quality of life

HRQoL in SERAPHIN was assessed using the SF-36 questionnaire (eight components, scale of 0 to 100). An increase in score indicates an improvement in quality of life. Macitentan 10 mg improved all mean HRQoL scores from baseline to month six compared with placebo. Significant improvement was reached in seven out of eight components of the SF-36 questionnaire ($P < 0.05$, except general health perceptions). The between-group differences in mean change of each domain (except general health perceptions), and physical and mental component summary scores ranged from 2.6 to 3.8, which were close to the MCID of SF-36 (Table 12).

TABLE 9: KEY EFFICACY OUTCOMES

| | Seraphin | |
|--|-----------------------|-------------------------------|
| | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
| Death or Hospitalization (up to EOT + 7 days) | | |
| Death due to PAH or hospitalization due to PAH, n (%) | 84 (33.6) | 50 (20.7) |
| HR (97.5% CI) | 0.50 (0.34 to 0.75) | |
| P value ^a | < 0.0001 | |
| Death due to PAH, n (%) | 14 (5.6) | 7 (2.9) |
| HR (97.5% CI) | 0.44 (0.16 to 1.25) | |
| P value ^a | 0.0699 | |
| Death (all causes), n (%) | 19 (7.6) | 14(5.8) |
| HR (97.5% CI) | 0.64 (0.29 to 1.42) | |
| P value ^a | 0.2037 | |
| Patients with at least one hospitalization, n (%) | 82 (32.8) | 49 (20.2) |
| RR (95% CI) ^b | 0.62 (0.45 to 0.84) | |
| P value | 0.002 | |
| Hospitalization (up to EOT + 28 days) | | |
| Number per year of all-cause hospitalizations, mean (SD) | 1.0 (2.27) | 0.5 (1.81) |
| Median (min, max) | 0.0 (0.0, 24.4) | 0.0 (0.0, 24.4) |
| Number per year of in-patient hospital days for all-cause, mean (SD) | 12.2 (37.57) | 5.7 (19.38) |
| Median (min, max) | 0.0 (0.0, 340.9) | 0.0 (0.0, 182.6) |
| Number per year of PAH-related hospitalizations, mean (SD) | 0.7 (1.65) | 0.3 (1.77) |
| Median (min, max) | 0.0 (0.0, 12.2) | 0.0 (0.0, 24.4) |
| Number per year of in-patient hospital days for PAH, mean (SD) | 8.3 (29.96) | 3.8 (16.73) |
| Median (min, max) | 0.0 (0.0, 325.3) | 0.0 (0.0, 182.6) |
| HRQOL Assessed by SF-36 (Baseline To Month 6); Scale 0 to 100 | | |
| Physical functioning , change from baseline, mean (SD) | -0.1 (8.88) | 2.5 (8.68) |
| Difference in mean change, mean (97.5% CI) | 2.6 (0.8 to 4.4) | |
| Role — physical , change from baseline, mean (SD) | 0.3 (10.21) | 3.1 (10.47) |
| Difference in mean change, mean (97.5% CI) | 2.8 (0.6 to 4.9) | |
| Pain , change from baseline, mean (SD) | -2.2 (11.56) | 1.6 (12.00) |
| Difference in mean change, mean (97.5% CI) | 3.8 (1.4 to 6.2) | |
| General health perceptions , change from baseline, mean (SD) | -0.1 (8.96) | 1.3 (8.45) |
| Difference in mean change, mean (97.5% CI) | 1.3 (-0.4 to 3.1); NS | |
| Vitality , change from baseline, mean (SD) | -1.0 (10.27) | 1.7 (9.92) |
| Difference in mean change, mean (97.5% CI) | 2.7 (0.6 to 4.8) | |
| Social functioning , change from baseline, mean (SD) | -1.3 (11.83) | 1.8 (11.33) |
| Difference in mean change, mean (97.5% CI) | 3.2 (0.8 to 5.5) | |
| Role — emotional , change from baseline, mean (SD) | -1.1 (14.92) | 2.4 (14.29) |
| Difference in mean change, mean (97.5% CI) | 3.5 (0.5 to 6.5) | |
| Mental health index , change from baseline, mean (SD) | -2.4 (13.30) | 1.1 (10.77) |
| Difference in mean change, mean (97.5% CI) | 3.6 (1.1 to 6.0) | |

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| | Seraphin | |
|--|--------------------------|-----------------------------------|
| PCS, change from baseline, mean (SD) | -0.7 (8.68) | 2.3 (7.82) |
| Difference in mean change, mean (97.5% CI) | 3.0 (1.3 to 4.7) | |
| MCS, change from baseline, mean (SD) | -2.1 (12.58) | 1.3 (11.30) |
| Difference in mean change, mean (97.5% CI) | 3.4 (0.9 to 5.9) | |
| Time to First Morbidity or Mortality Event (Up to EOT + 7 Days) | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
| Total patients with at least one confirmed event, n (%) | 116 (46.4) | 76 (31.4) |
| HR (97.5% CI) | 0.55 (0.39 to 0.76) | |
| NNT (95% CI) | 6 (4 to 10) | |
| P value ^a | < 0.0001 | |
| First confirmed event, n (%) | | |
| Worsening of PAH | 93 (37.2) | 59 (24.4) |
| Death from any cause | 17 (6.8) | 16 (6.6) |
| IV/SC prostanoids initiation | 6 (2.4) | 1 (0.4) |
| Lung transplantation | 0 | 0 |
| WHO FC (Baseline to Month 6) | Placebo (N = 249) | Macitentan 10 mg (N = 242) |
| Patients with WHO FC improved, n/N (%) | 32/249 (12.9) | 54/242 (22.3) |
| RR (95% CI) ^b | 1.74 (1.16 to 2.59) | |
| NNT (95% CI) ^d | 11 (6 to 36) | |
| P value | 0.007 | |
| Patients with WHO FC unchanged, n/N (%) | 164/249 (65.9) | 171/242 (70.7) |
| RR (95% CI) ^b | 1.07 (0.95 to 1.21) | |
| NNT (95% CI) ^c | Not calculated | |
| P value | 0.25 | |
| Patients with WHO FC worsened, n/N (%) | 53/245 (21.6) | 17/242 (7.0) |
| RR (95% CI) ^b | 0.32 (0.19 to 0.54) | |
| NNT (95% CI) ^c | 7 (5 to 12) | |
| P value | < 0.0001 | |
| 6MWD (Baseline to Month 6) | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
| Change from baseline (m), mean (SD) | -9.4 (100.6) | 12.5 (83.5) |
| Difference of mean change, mean (SD) | 22.0 (92.58) | |
| 97.5% CI of mean | (3.2 to 40.8) | |
| Difference in median | 15.0 | |
| 97.5% CI of median | (2.0 to 28.0) | |
| P value ^d | 0.0078 | |
| Borg Dyspnea Index (Baseline to Month 6); Borg Scale 0 to 10 | Placebo (N = 250) | Macitentan 10 mg (N = 242) |
| Change from baseline (m), mean (SD) | 0.4 (2.10) | -0.1 (2.02) |
| Difference in mean change, mean (SD) | -0.5 (2.06) | |
| 97.5% CI of mean | (-1.0 to -0.1) | |

| Hemodynamics (Baseline to Month 6); All-Randomized Set, Patients Participating in the PK/PD Sub-study | Seraphin | |
|---|---------------------|---------------------------|
| | Placebo (N = 67) | Macitentan 10 mg (N = 57) |
| PVR, change from baseline (dyn × sec/cm ⁵), mean (SD) | 504 (919) | -25 (688) |
| Mean per cent change over placebo (97.5% CI) | 61.8 (49.9 to 76.5) | |
| mRAP, change from baseline (mm Hg), mean (SD) | 7.4 (18.68) | 7.8 (27.62) |
| Placebo-corrected mean change, mean (97.5% CI) | 0.4 (-9.1 to 9.9) | |
| mPAP, change from baseline (mm Hg), mean (SD) | 6.6 (14.37) | 3.9 (28.39) |
| Placebo-corrected mean change, mean (97.5% CI) | -2.7 (-11.7 to 6.3) | |
| Cardiac index, change from baseline (L/min/m ²), mean (SD) | -0.48 (0.701) | 0.13 (0.887) |
| Placebo-corrected mean change, mean (97.5% CI) | 0.61 (0.28 to 0.93) | |

CI = confidence interval; EOT = end of treatment; FC = functional class; HR = hazard ratio; IV = intravenous; NNT = number needed to treat; NS = not significant difference; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PCS/MCS = physical/mental component summaries; PK/PD = pharmacokinetic/pharmacodynamic; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; SC = subcutaneous; SD = standard deviation; SF-36 = Short-Form 36-Item questionnaire.

^a Log-rank.

^b Calculated by CADTH using RevMan 4.2.

^c Calculated using GraphPad software.

^d Wilcoxon rank-sum.

Source: SERAPHIN Clinical Study Reports.⁹

TABLE 10: CHANGE IN WORLD HEALTH ORGANIZATION FUNCTIONAL CLASS FROM BASELINE TO MONTH SIX

| Change (Number of Classes) ^a | Placebo (N = 249), N (%) | Macitentan 10 Mg (N = 242), N (%) |
|---|--------------------------|-----------------------------------|
| -2 | 2 (0.8) | 0 |
| -1 | 30 (12.0) | 54 (22.3) |
| 0 | 164 (65.9) | 171 (70.7) |
| 1 | 46 (18.5) | 16 (6.6) |
| 2 | 7 (2.8) | 1 (0.4) |

^a A negative (-) sign indicates improvement in functional class.

Source: SERAPHIN Clinical Study Report.⁹

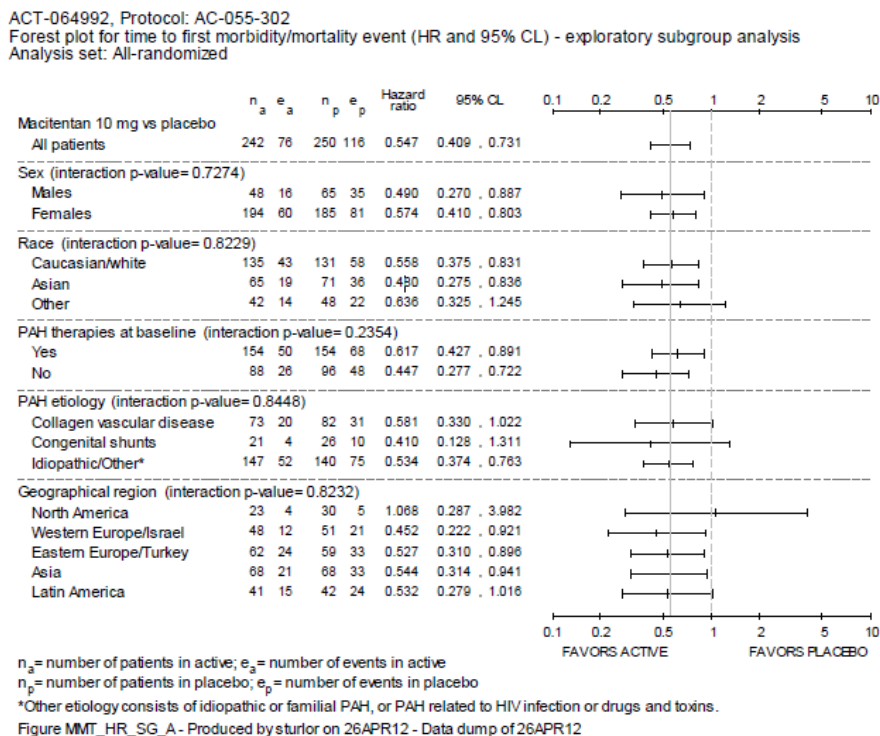
3.7 Subgroup Analyses

3.7.1 Primary End Point (Time to First Morbidity or Mortality Event) Across Subgroups

a) Subpopulations

The efficacy of macitentan 10 mg compared with placebo was demonstrated in all subgroups regardless of sex, race, PAH background therapy, PAH etiology (except congenital shunts), and geographic region (except North America) (Figure 4). Macitentan showed no statistically significant difference from placebo for patients from North America (Canada and US); the HR (95% CI) was 1.068 (0.287, 3.982).

FIGURE 4: SUBGROUP ANALYSIS OF THE TIME TO CLINICAL WORSENING (HAZARD RATIO AND 95% CONFIDENCE INTERVALS), MACITENTAN 10 MG VERSUS PLACEBO, ALL-RANDOMIZED SET



Source: SERAPHIN Clinical Source Report.⁹

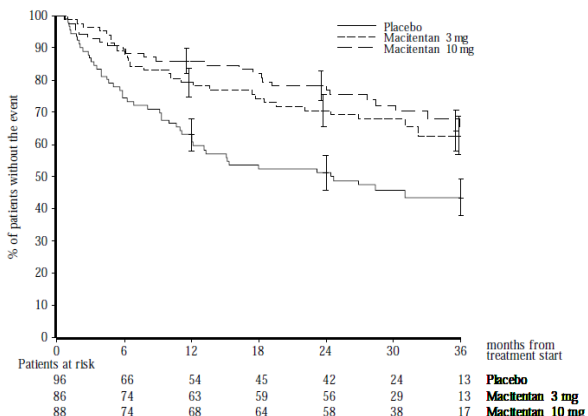
b) Pulmonary arterial hypertension background therapy at baseline

Figure 5 shows the Kaplan–Meier curves of the time to first morbidity or mortality event for patients with or without concomitant PAH therapy at baseline. The effect of macitentan 10 mg was statistically significant for both patients without concomitant PAH therapy at baseline (treatment-naive, HR = 0.447; 95% CI, 0.277 to 0.722) and patients with concomitant PAH therapy at baseline (treatment-experienced, HR = 0.617; 95% CI, 0.427 to 0.891).

FIGURE 5: KAPLAN–MEIER CURVES OF THE TIME TO FIRST MORBIDITY OR MORTALITY EVENT FOR PATIENTS WITHOUT (A) OR WITH (B) CONCOMITANT PAH THERAPY AT BASELINE, ALL-RANDOMIZED SET

A: Without CONCOMITANT PAH THERAPY AT BASELINE

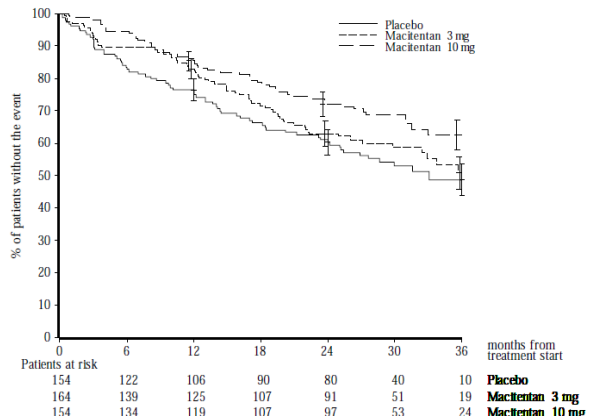
ACT-064992, Protocol: AC-055-302
Time to first confirmed morbidity/mortality event up to EOT+7 days(CEC) by concomitant PAH therapy at baseline (Kaplan-Meier estimate with standard error bars)
Concomitant PAH therapy at baseline: No



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
Figure MMT_PAHBC_A - Produced by sturlor on 20MAY12 - Data dump of 26APR12

B: With CONCOMITANT PAH THERAPY AT BASELINE

ACT-064992, Protocol: AC-055-302
Time to first confirmed morbidity/mortality event up to EOT+7 days(CEC) by concomitant PAH therapy at baseline (Kaplan-Meier estimate with standard error bars)
Concomitant PAH therapy at baseline: Yes



CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.
Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up.
Figure MMT_PAHBC_A - Produced by sturlor on 20MAY12 - Data dump of 26APR12

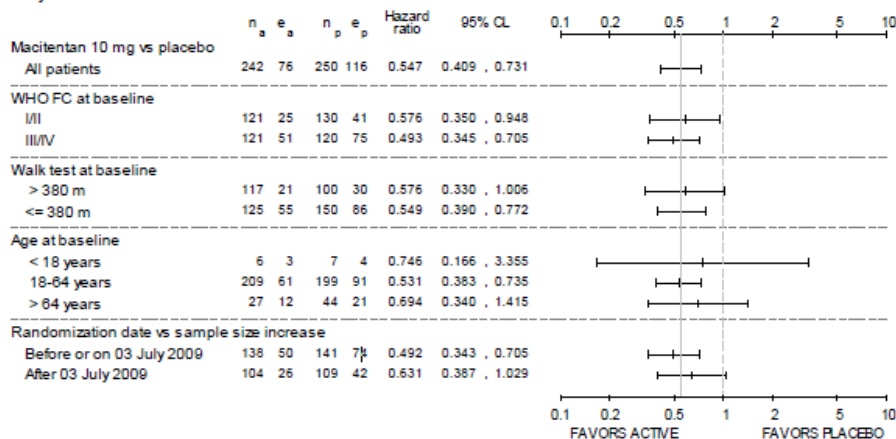
Source: SERAPHIN Clinical Study Report.⁹

c) By baseline disease demographics and characteristics

Figure 6 is a forest plot for the time to first morbidity or mortality event stratified by patients' baseline disease and demographic characteristics. The efficacy of macitentan 10 mg compared with placebo was demonstrated in all subgroups regardless of disease severity (WHO FC and 6MWD at baseline); however, results were inconclusive for adolescents (< 18 years) and for elderly patients (> 64 years).

FIGURE 6: PRIMARY END POINT (HAZARD RATIO AND 95% CONFIDENCE INTERVALS) BY BASELINE DISEASE AND DEMOGRAPHIC CHARACTERISTICS — ROBUSTNESS ANALYSES (MACITENTAN 10 MG VERSUS PLACEBO), ALL-RANDOMIZED SET

ACT-064992, Protocol: AC-055-302
Graphical display for time to first confirmed morbidity/mortality event up to EOT+7 days (CEC)(HR and 95% CL) by baseline disease and demographic characteristics - Robustness of primary endpoint
Analysis set: All-randomized



n_a = number of patients in active; e_a = number of events in active
 n_p = number of patients in placebo; e_p = number of events in placebo

CEC = Clinical Event Committee, EOT = End of treatment. Events confirmed by Independent CEC.

Figure MMT_HR_RG_A - Produced by sturlor on 17MAY12 - Data dump of 26APR12

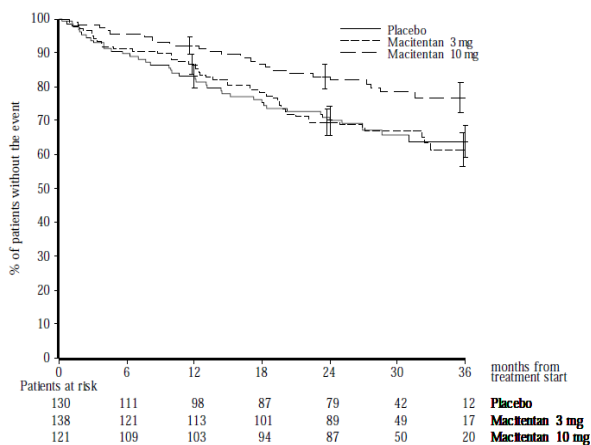
Source: SERAPHIN Clinical Study Report.⁹

Figure 7 shows the Kaplan–Meier curves of the time to first morbidity or mortality event by WHO FC. The effect of macitentan 10 mg was statistically significant for all patients regardless of disease severity at baseline (i.e., WHO FC I or II and WHO FC III or IV) (Figure 6 and Figure 7). There appeared to be a greater separation between the curves of placebo and macitentan 10 mg in sicker patients (i.e., WHO FC III or IV); however, formal statistical tests were not conducted for differences between the subgroups (Figure 7).

FIGURE 7: KAPLAN-MEIER CURVES OF THE TIME TO FIRST MORBIDITY OR MORTALITY EVENT BY WHO FC I OR II (A) OR III OR IV AT BASELINE, ALL-RANDOMIZED SET

A: WHO FC I OR II AT BASELINE

ACT-064992, Protocol: AC-055-302
 Time to first confirmed morbidity/mortality event up to EOT+7 days(CEC) by WHO FC at baseline (Kaplan-Meier estimate with standard error bars)
 WHO class at baseline: I/II

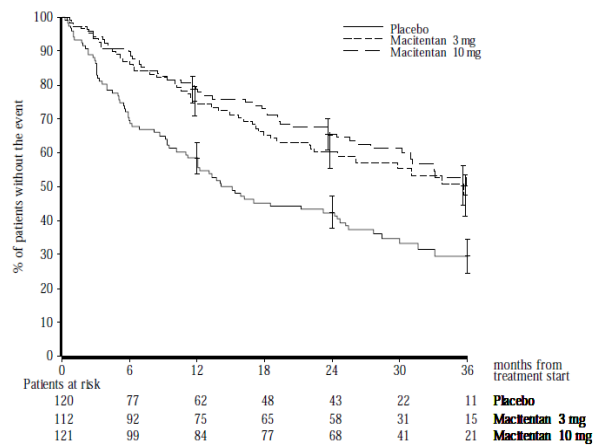


CEC – Clinical Event Committee. EOT – End of treatment. Events confirmed by Independent CEC. Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up. Figure MMT_WHOFC_A - Produced by sturlor on 29MAY12 - Data dump of 26APR12

Source: SERAPHIN Clinical Study Report.⁹

B: WHO FC III OR IV AT BASELINE

ACT-064992, Protocol: AC-055-302
 Time to first confirmed morbidity/mortality event up to EOT+7 days(CEC) by WHO FC at baseline (Kaplan-Meier estimate with standard error bars)
 WHO class at baseline: III/IV



CEC – Clinical Event Committee. EOT – End of treatment. Events confirmed by Independent CEC. Survival plots are presented up to 36 months, time at which more than 10% of the patients are still in follow-up. Figure MMT_WHOFC_B - Produced by sturlor on 29MAY12 - Data dump of 26APR12

3.7.2 Secondary end point (WHO Functional Class) by subgroups

[Redacted]

a) By pulmonary arterial hypertension concomitant therapy at baseline

[Redacted]

b) By geographical region

[Redacted]

3.7.3 Secondary end point (six-minute walk distance) across subgroups

a) Subpopulations



FIGURE 8: SUBGROUP ANALYSIS OF SIX-MINUTE WALK DISTANCE AT MONTH SIX (HAZARD RATIO AND 95% CONFIDENCE INTERVALS), MACITENTAN 10 MG VERSUS PLACEBO, ALL-RANDOMIZED SET

Figure 8 contained confidential data and was deleted at the manufacturer's request.

b) By baseline disease demographics and characteristics



FIGURE 9: SUBGROUP ANALYSIS OF SIX-MINUTE WALK DISTANCE AT MONTH SIX (HAZARD RATIO AND 95% CONFIDENCE INTERVALS) BY BASELINE DISEASE AND DEMOGRAPHIC CHARACTERISTICS, MACITENTAN 10 MG VERSUS PLACEBO, ALL-RANDOMIZED SET

Figure 9 contained confidential data and was deleted at the manufacturer's request.

3.8 Harms

Only those harms identified in the review protocol are reported here.

Table 11 shows an overview of AEs during the treatment period and up to 28 days after treatment discontinuation in the all-treated population.

3.8.1 Adverse events

The proportion of the total number of patients with at least one AE was similar between placebo (96.4%) and macitentan 10 mg (94.6%). However, some common AEs were more frequent in the placebo group, while others were more frequent in the macitentan 10 mg group; there were also situations for which no difference between treatment groups was reported.

The AEs that were more frequent in the placebo group included worsening of PAH (34.9% vs 21.9%); right ventricular failure (22.5% versus 13.2%); fatigue (6.0% versus 3.7%); pain in extremity (6.0% versus 2.9%); back pain (8.4% versus 3.7%); dyspepsia (5.6% versus 2.9%); and liver disorders (14.5% versus 8.7%).

Compared with the placebo group, different types of infection were more frequent in the macitentan 10 mg group, including upper respiratory tract infection (15.3% versus 13.3%), nasopharyngitis (14.0% versus 10.4%), bronchitis (11.6% versus 5.6%), urinary tract infection (8.7% versus 5.6%), pharyngitis (6.2% versus 2.8%), rhinitis (3.3% versus 0.8%), sinusitis (4.5% versus 2.4%), influenza (5.8% versus 1.6%), and viral respiratory tract infection (6.2% versus 3.6%). In addition, macitentan 10 mg was associated with a higher frequency of headache (13.6% versus 8.8%) and anemia (13.2% versus 3.2%). These AEs were correlated with more frequent use of antibiotics and drugs for the treatment of anemia

in the macitentan 10 mg group. During the study (up to 28 days after discontinuation of treatment), the proportion of patients who had started at least one concomitant medication was slightly higher in the macitentan 10 mg group (88.0%) compared with the placebo group (84.8%). A higher proportion of patients in the macitentan 10 mg used acetaminophen (33.4% versus 23.7%), and antibiotics such as amoxicillin (12.0% versus 9.6%) and amoxicillin-clavulanate (12.4% versus 6.4%), compared with the placebo group. In addition, the proportion of patients who started drugs for treatment of anemia (including iron, folic acid, and cyanocobalamin) was 13.6% in the macitentan 10 mg group and 7.2% in the placebo group. Blood substitutes were used in 4.5% of patients in the macitentan 10 mg group, compared with 1.6% of patients in the placebo group. It may therefore be anticipated that there is a greater chance of infection and anemia with the use of macitentan.

The incidence of peripheral edema was similar between placebo and macitentan 10 mg (18% for both), but the rate of hypotension was slightly higher in the macitentan 10 mg group (6.2% versus 4.4%).

3.8.2 Serious adverse events

Among SAEs, worsening of PAH (22.5% versus 13.2%) and right ventricular failure (16.1% versus 9.5%) occurred at a higher frequency in the placebo group, while anemia was more frequent in the macitentan 10 mg group (2.5% versus 0.4%).

3.8.3 Withdrawals due to adverse events

More patients withdrew due to AEs in the placebo group than in the macitentan 10 mg group (12.4% versus 10.7%). This was mainly due to the worsening of PAH (4.0% versus 1.7%) and right ventricular failure (2.4% versus 1.7%).

3.8.4 Mortality

The incidence of death after start of the study to end of treatment plus 28 days was no different between the placebo and the macitentan 10 mg groups (8.4% versus 6.6%). Of note, the death component in the primary end point is time to first event; in PAH, death is, however, generally preceded by a worsening of the disease.

TABLE 11: HARMS

| AEs | Seraphin | |
|---|-------------------|----------------------------|
| | Placebo (N = 249) | Macitentan 10 mg (N = 242) |
| Total number of AEs | 1,365 | 1,446 |
| Total patients with at least one AE, n (%) | 240 (96.4) | 229 (94.6) |
| Most common AEs (≥ 3%) | | |
| PAH | 87 (34.9) | 53 (21.9) |
| Right ventricular failure | 56 (22.5) | 32 (13.2) |
| Fatigue | 15 (6.0) | 9 (3.7) |
| Pain in extremity | 15 (6.0) | 7 (2.9) |
| Back pain | 21 (8.4) | 9 (3.7) |
| Dyspepsia | 14 (5.6) | 7 (2.9) |
| Liver disorders and abnormal liver function | 36 (14.5) | 21 (8.7) |
| Upper respiratory tract infection | 33 (13.3) | 37 (15.3) |
| Nasopharyngitis | 26 (10.4) | 34 (14.0) |
| Bronchitis | 14 (5.6) | 28 (11.6) |

CDR CLINICAL REVIEW REPORT FOR OPSUMIT

| AEs | Seraphin | |
|---|-------------------|----------------------------|
| | Placebo (N = 249) | Macitentan 10 mg (N = 242) |
| Urinary tract infection | 14 (5.6) | 21 (8.7) |
| Pharyngitis | 7 (2.8) | 15 (6.2) |
| Rhinitis | 2 (0.8) | 8 (3.3) |
| Sinusitis | 6 (2.4) | 11 (4.5) |
| Influenza | 4 (1.6) | 14 (5.8) |
| Respiratory tract infection viral | 9 (3.6) | 15 (6.2) |
| Headache | 22 (8.8) | 33 (13.6) |
| Anemia | 8 (3.2) | 32 (13.2) |
| Thrombocytopenia | 7 (2.8) | 12 (5.0) |
| Hypotension | 11 (4.4) | 15 (6.2) |
| Edema peripheral | 45 (18.1) | 44 (18.2) |
| SAEs | | |
| Total number of SAEs | 246 | 189 |
| Total patients with at least one SAE, n (%) | 137 (55.0) | 109 (45.0) |
| PAH | 56 (22.5) | 32 (13.2) |
| Right ventricular failure | 40 (16.1) | 23 (9.5) |
| Pneumonia | 8 (3.2) | 4 (1.7) |
| Anemia | 1 (0.4) | 6 (2.5) |
| WDAEs | | |
| Total number of AEs | 37 | 32 |
| Total patients with at least one AE, n (%) | 31 (12.4) | 26 (10.7) |
| PAH | 10 (4.0) | 4 (1.7) |
| Right ventricular failure | 6 (2.4) | 4 (1.7) |
| Liver disorders and abnormal liver function | 4 (1.6) | 8 (3.3) |
| Headache | 0 | 3 (1.2) |
| Anemia | 0 | 1 (0.4) |
| Deaths | | |
| Patients with at least one cause, n (%) | 21 (8.4) | 16 (6.6) |

AE = adverse event; PAH = pulmonary arterial hypertension; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: SERAPHIN Clinical Study Report.⁹

4. DISCUSSION

4.1 Summary of available evidence

The evidence for this review was derived from SERAPHIN, a phase 3, randomized, double-blind, placebo-controlled, event-driven trial in patients with symptomatic PAH. The objective of the trial was to test the superiority of macitentan in delaying the time to first morbidity or mortality event compared with placebo. A total of 742 patients, mainly WHO FC II or III, were randomized in a 1:1:1 ratio to macitentan 3 mg, macitentan 10 mg, and placebo groups. The mean duration of the study treatment was 96.2 weeks.

4.2 Interpretation of results

4.2.1 Efficacy

The primary efficacy outcome in SERAPHIN was the time from start of study treatment to the first morbidity or mortality up to seven days after end of treatment. The events of the primary end point were reviewed and adjudicated by members of the CEC in a blinded fashion. The CEC-confirmed event rate was lower for macitentan 10 mg (31%) compared with placebo (46%). The treatment difference HR (97.5% CI) was 0.55 (0.39 to 0.76), $P < 0.0001$. The main cause for the difference in the primary end point was less frequent worsening of PAH, the incidence rate of which was higher in the placebo group (37%) compared with the macitentan 10 mg group (24%). There was no difference in the death rate between the two groups (7% each). More patients in the placebo group (2.4%) received intravenous or subcutaneous prostanoids initiation as rescue therapy compared with those in the macitentan 10 mg group (0.4%).

The composite end point time to clinical worsening has also been used in other trials of oral drug therapies for PAH, but only as a secondary or exploratory end point. Those trials were usually of short duration (12 to 16 weeks) and included smaller numbers of patients than SERAPHIN, and therefore they were not powered to detect differences in time to clinical worsening. Studies evaluating the efficacy of epoprostenol and treprostinil did not include clinical worsening as an outcome. CDR requested data from the manufacturer on the time to first morbidity or mortality event at month three and month six of the SERAPHIN trial, but these data were not available. Hence, given differences in study design and duration, it is difficult to make a comparison with macitentan and other oral PAH drugs regarding clinical worsening.

The manufacturer conducted subgroup analyses of the primary end point based on gender, race, PAH therapy at baseline, PAH etiology, geographical region, WHO FC at baseline, 6MWD at baseline, and age. Several limitations of the subgroup analyses include lack of power and lack of stratification. There were few differences in the treatment effect versus placebo with respect to gender and race. For PAH therapy at baseline, the treatment effect of macitentan 10 mg in patients with no PAH background therapy (treatment-naïve) was greater than that of patients taking background therapy (treatment-experienced) (risk reduction 55% versus 38%). Sildenafil was the most common concomitant PAH therapy. Of note, patients on combination therapy had received stable doses of PDE-5 inhibitors or prostanoids (oral or inhaled) for at least three months before randomization. There was no evidence that macitentan demonstrates an effect in patients who had inadequate response or intolerance, or who deteriorated prior to treatment. According to the CDR clinical expert, if patients had no improvement and remained at WHO FC III after six months of treatment, additional treatment would be considered by most clinicians specialized in the care of patients with PAH. This approach remains controversial for patients of WHO FC II. However, it is not uncommon that clinicians may consider intensification of therapy for

patients of both WHO FC II and III after three to six months with no improvement on monotherapy. It is unclear which criteria were used to select patients to receive combination therapy in SERAPHIN.

There were few differences in clinical effect between macitentan and placebo with respect to PAH etiology, although a statistically significant difference was not reached for subgroup patients with congenital shunts due to small sample size. The effect of macitentan 10 mg was larger for sicker patients (WHO FC III or IV or baseline 6MWD \leq 380 m) than for less sick patients (WHO FC I or II or baseline 6MWD $>$ 380 m). A statistically significant difference could not be demonstrated for adolescents ($<$ 18 years) and for elderly patients ($>$ 64 years) due to small sample sizes (3% and 14%, respectively). For geographic regions, it is of concern that macitentan showed no statistically significant difference in clinical effect compared with placebo in the North American centres (five sites in Canada and 33 sites in the US), while a statistically significant difference was reached for all other regions including Western Europe and Israel. It is anticipated that medical care in the latter region is similar to that provided in North America. The manufacturer suggested that the lack of macitentan effect observed in the North American centres was likely due to small sample size. This explanation may be of limited value as the point estimate (HR for primary end point) of macitentan 10 mg compared with placebo in subgroup patients with congenital shunts was 0.41, despite a small sample size (47 patients), while that in subgroup patients from North America was 1.07 with a sample size of 53 patients. Thus, the lack of macitentan effect in North America requires further investigation.

The manufacturer provided additional data on the demographics and baseline characteristics of patients from North America and of those from Western Europe/ Israel (Table 20, Table 21).

[REDACTED]

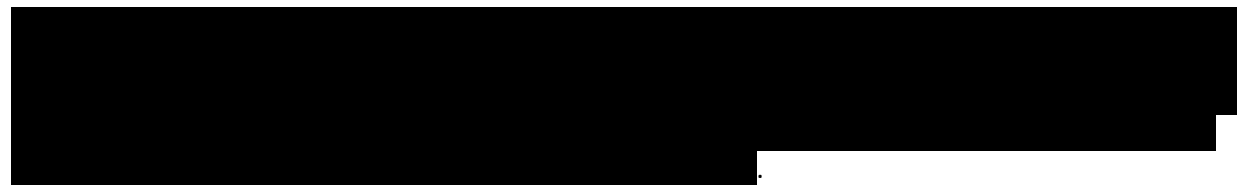
[REDACTED] is consistent with the results of the total SERAPHIN population showing a greater effect of macitentan for patients 18 to 64 years old compared with those $>$ 64 years (Figure 6), and for patients of WHO FC III or IV compared with those of WHO FC I or II (Figure 6 and Figure 7).

Death from any cause was a component of the primary end point. The death component in the primary end point is time to first event and cannot be used to evaluate a survival benefit. In PAH, death is, however, generally preceded by worsening of the disease. Death was also analyzed as a component of the secondary end point as death from PAH or death from all causes. There was no difference between groups in the proportions of patients who died from any cause. However, a lower percentage of patients in the macitentan 10 mg died due to PAH compared with placebo patients (2.9% versus 5.6%). The difference was not statistically significant.

Significantly fewer patients in the macitentan 10 mg group were hospitalized for PAH compared with the placebo group (20% versus 33%; $P = 0.002$). Likewise, the mean number per year of in-patient hospital days for all-cause or for PAH was lower in the macitentan 10 mg group compared with placebo.

The difference in mean change (SD) of 6MWD from baseline to month six was 22.0 m (92.6) in the macitentan 10 mg group. The change was statistically significant. This value appears to be lower than the MCID for 6MWD in PAH, which is 33.0 m (range: 25.1 m to 38.6 m). Also, change from baseline 6MWD may not be correlated with relevant clinical outcomes for assessing the comparative

effectiveness of PAH drugs, although it is acknowledged that it is commonly used in clinical practice to evaluate patients' functional level.



For WHO FC, a higher proportion of patients in the macitentan 10 mg group improved their FC compared with patients in the placebo group (22.3% versus 12.9%). Likewise, fewer patients on macitentan 10 mg had their FC worsen compared with placebo (7.0% versus 21.6%). Data for specific subgroups of patients, especially by PAH background therapy and by geographical region, were not available.

The macitentan 10 mg group showed some improvement in the Borg Dyspnea Index, with a placebo-corrected mean change (SD) of -0.5 (2.06). The difference was statistically significant ($P = 0.0029$).

There were improvements in all pulmonary hemodynamics in patients treated with macitentan 10 mg compared with placebo. The macitentan 10 mg group also improved patients' quality of life as measured by the SF-36 questionnaire.

4.2.2 Harms

The rate of use of concomitant medications during the study was higher in the macitentan 10 mg group compared with the placebo group (88.0% versus 84.8%). Compared with placebo, a higher proportion of patients in the macitentan 10 mg group used acetaminophen (31.4% versus 23.7%); antibiotics such as amoxicillin (12.0% versus 9.6%), amoxicillin-clavulanate (12.4% versus 6.4%), and ciprofloxacin (9.1% versus 4.8%); drugs for the treatment of anemia (13.6% versus 7.2%); and blood substitutes (4.5% versus 1.6%). The use of these concomitant medications reflects the higher incidence of AEs in the macitentan 10 mg group compared with the placebo group, such as headache (13.6% versus 8.8%), influenza (5.8% versus 1.6%), bronchitis (11.6% versus 5.6%), pharyngitis (6.2% versus 2.8%), upper respiratory tract infection (15.3% versus 13.3%), urinary tract infection (8.7% versus 5.6%), and anemia (13.2% versus 3.2%). This raises concerns about whether the use of macitentan is associated with increased risk of headache, infection, and anemia. These AEs are common across classes in PAH medications, and should not discourage the use of macitentan, according to the CDR clinical expert. It is not anticipated that clinicians will change their prescribing habits because of these AEs, but they may change their monitoring practices.

The rate of hypotension was slightly higher in the macitentan 10 mg group (6.2% versus 4.4%), but there was no difference in the rate of peripheral edema between groups (18% in both groups). Of note, the CDR expert indicated that the rate of hypotension in macitentan should not be a concern, because it tends to be more frequent with PDE-5 inhibitors than with ERAs.

The incidence of liver disorders and abnormal liver function was lower in the macitentan 10 mg group compared with the placebo group (8.7% versus 14.5%). The FDA review suggested that this may be related to a lower incidence of right ventricular heart failure with macitentan (13.2% versus 22.5%). This was in contrast with other ERAs such as bosentan, which was associated with increased incidence of hepatotoxicity.⁴⁶

The overall incidence of SAEs was lower in the macitentan 10 mg group compared with the placebo group (45.0% versus 55.0%). This was related to the lower incidence of PAH (13.2% versus 22.5%) and right ventricular failure (9.5% versus 16.1%). However, SAEs of anemia occurred more frequently with macitentan 10 mg than with placebo (2.5% versus 0.4%). By month three, the mean maximum reduction from baseline in hemoglobin was 1.1 g/dL in the macitentan 10 mg group; this value was maintained up to month 18. No apparent decrease in hemoglobin was observed in the placebo group. Compared with placebo, a marked and clinically relevant decrease in hemoglobin level (i.e., values < 11 g/dL and a decrease of 15% from baseline) occurred more frequently in the macitentan 10 mg group (13.9% versus 3.8%).

SAEs of thrombocytopenia occurred at a higher incidence with macitentan 10 mg compared with placebo (5.0% versus 2.8%). That was related to a marked decrease in platelet counts (i.e., values < $100 \times 10^9/L$ and a decrease of 30% from baseline), which was greater in the macitentan 10 mg group (8.3%) compared with the placebo group (3.4%).

The incidence of SAEs with renal impairment was similar for both groups (0.5%).

The proportion of patients who withdrew due to AEs was 11% for macitentan 10 mg and 12% for placebo.

4.3 Other considerations

The product monograph indicates that macitentan should be used with caution in patients older than 75 years due to limited clinical experience.¹⁹ Likewise, the safety and efficacy of macitentan have not yet been established in children and adolescents younger than 18 years.¹⁹

Animal studies showed that macitentan can cause serious birth defects if taken during pregnancy.¹⁹ Therefore, women of child-bearing age must have a pregnancy test before starting macitentan and must have monthly pregnancy tests during the treatment. Women should not take macitentan if they are pregnant.¹⁹

Serious anemia may occur during treatment with macitentan. A blood test is recommended at one month after treatment start and as decided by the physician thereafter.¹⁹

5. CONCLUSIONS

From a single adequately designed randomized controlled trial (SERAPHIN), macitentan reduces the risk of morbidity and mortality compared with placebo in patients with symptomatic PAH of WHO FC II and III over a median treatment duration of more than two years. Although death from any cause was a component of the primary end point, the difference in the time to first morbidity or mortality event between macitentan and placebo groups is driven mainly by less frequent worsening of PAH in patients using macitentan, not by less death. Macitentan reduces the number of in-patient hospital days and improves WHO FC, 6MWD, Borg Dyspnea Index, pulmonary hemodynamics and HRQoL compared with placebo. Among subpopulations, there appear to be no major differences in clinical effect regarding gender, race, PAH etiology, PAH therapy at baseline, or disease severity. However, the clinical efficacy of macitentan was not demonstrated in the SERAPHIN trial for patients from North America; clinical effect was, however, shown for all other geographical regions.

In the SERAPHIN trial, the use of macitentan was more commonly associated with anemia, headache, and infection. There is no evidence as yet that macitentan negatively affects liver or renal function. Use of macitentan is not associated with gain in long-term survival of patients with PAH. Compared with placebo, macitentan is associated with lower risks of SAEs related to worsening of PAH and right ventricular heart failure. However, its use is associated with more risk of developing severe anemia. Rates of withdrawals due to AEs were slightly higher in the placebo group.

A number of information gaps remain. Safety data from the SERAPHIN open-label extension trial were not available at the time this review was completed. There is also no direct or indirect evidence comparing macitentan with other ERAs, such as bosentan, with which clinicians have years of experience.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Patient input was received from the Pulmonary Hypertension Association of Canada (PHA Canada) and the Scleroderma Society of Canada (SSC).

PHA Canada is a charitable organization established by patients, caregivers, parents, and family members, collectively referred to as “Canadians living with PH.” PHA Canada aims to end isolation, provide education, support pulmonary hypertension (PH) patients and their caregivers, and create a united Canadian PH community. It receives funding from its corporate committee members, including Actelion Pharmaceuticals, Bayer Inc., GlaxoSmithKline, McKesson Specialty Pharmacy, Pfizer Canada, Shoppers Drug Mart Specialty Health Network, and Unither Biotech. These members pay yearly membership dues, provide unrestricted grants, and participate in regular meetings about areas of common interest within the PH community. This submission was reviewed and approved by the Chair of the Board of Directors, who has received consulting and speaking fees, research grants, and investigator fees from various pharmaceutical companies.

According to its website, the SSC “serves as an advocate nationally for those affected by the disease and works collaboratively with regional scleroderma organizations and the international scleroderma community to achieve common objectives.” The SSC’s mission is to raise public awareness, support those living with scleroderma, and fund research into treatments for the disease. The SSC received unrestricted funding and/or sponsorship in the last five years from Actelion Pharmaceuticals, Pfizer Canada, Astra Zeneca, GlaxoSmithKline, Bayer Inc., and Shoppers Drug Mart. No conflicts of interest relating to the preparation of this submission were declared.

2. Condition and Current Therapy-Related Information

PHA Canada compiled the information for its submission by requesting it from patients with PH and their caregivers through a combination of interviews and data obtained from a Burden of Illness Survey conducted in 2013, and also through collected stories from patients and caregivers during the organization’s six years of working with the PH community. The SSC compiled the information for its submission through a survey disseminated via its websites, social media, and support groups, and mined the SSC patient registry for relevant health-related quality of life data for scleroderma patients with pulmonary arterial hypertension (PAH).

PH has a significant impact on the lives of patients. Usually unknown to the patient prior to diagnosis, it is a shock and a life-changing experience to learn that one has a rare, usually progressive, and typically terminal illness. PH results in often abrupt life changes for both patients and their caregivers.

For patients with PH, including those with scleroderma who develop PAH, day-to-day life is difficult, exhausting, and challenging. A majority of PH patients experience symptoms ranging in severity from mild to severe or limitation with daily activities. Symptoms include difficulty breathing with any exertion, dizziness with chest constriction or with sudden exertion, fatigue, swelling of the feet and ankles, syncope, and chest pain. Difficulty breathing, shortness of breath, peripheral edema, dizziness, and

syncope are the most important to control. Shortness of breath affects everything patients do during the day: patients have a low tolerance for physical exertion of any kind and are unable to walk more than short distances or up a few stairs, carry heavy objects, lift medium-weight loads (e.g., groceries, children), or complete household chores. Some patients are unable to be fully intimate with their partners, while women with PH must often give up a dream of becoming a parent, since pregnancy is contraindicated in PH. Because patients with PH struggle with even basic tasks such as bathing, dressing, or preparing meals, they lose the ability to care for themselves and their children, and many have to give up their careers in the prime of their lives.

In addition to physical symptoms, patients commonly experience depressed mood, anxiety, and feelings of helplessness and hopelessness as they face a serious illness with a high risk of death within a few years. As PH is most often an invisible disease, patients face social stigma, as exemplified when parking in a handicapped spot and receiving comments about “abusing the system.” A lack of understanding of the disease by others, coupled with patients’ inability to participate in many social activities, contributes to a sense of isolation felt by many patients and caregivers.

Drugs approved by Health Canada, none of which are a cure, include the following oral drugs: sildenafil (Revatio); tadalafil (Adcirca); ambrisentan (Volibris); bosentan (Tracleer); riociguat (Adempas); and macitentan (Opsumit). Infusion therapies include the following: intravenous epoprostenol (Flolan); intravenous and subcutaneous treprostinil (Remodulin); and intravenous thermostable epoprostenol (Caripul). Individual responses to treatment vary greatly, and many patients — especially those with more advanced PAH — often require two or more PAH drugs to gain better control of their symptoms. Most patients rated the effectiveness of their current PAH therapies to control their condition as “fair.” Medication regimens in PAH are further complicated by the need for concomitant diuretics, anticoagulants, and antiemetics. Patients with more advanced PAH may also be receiving treatments for complications from the disease, such as right-sided heart failure. The pre-existing and ongoing damage to the vascular system, along with the fibrosis that characterizes scleroderma, also complicates the treatment of PAH. Treatment effectiveness and survival are reported as being worse for scleroderma patients with PAH than for other subsets of PAH patients. Nausea, gastrointestinal discomfort and pain, diarrhea, fatigue, insomnia, bruising, headaches, skin flushing, redness, and spots on the skin were identified by patients as adverse effects associated with current PAH therapies. Lack of access to combination dual PAH therapy and the associated cost of PAH drugs and adjunctive therapies were identified as specific burdens and stressors.

Caregivers play a significant role in the lives of PH patients. As PH primarily affects women, their husbands and partners take on the brunt of the work around the home as well as financial responsibilities, and become the main providers for any children. Caregivers also attend doctors’ appointments, help with managing adverse effects and medications, provide psychosocial support, and advocate for the patient. As a result of care demands, caregivers often have to make changes to their employment and face emotional and physical burnout with relationships that can fall victim to the strains of a patient–caregiver dynamic. In addition, the effect on children of PH patients is significant. Their parents’ limited ability to interact in family activities is often resented. Children’s fears and concerns over their parent’s situation and prognosis add emotional strain to the patient and caregiver.

3. Related Information About the Drug Being Reviewed

Patients without experience on macitentan hoped that it would offer them an additional option when current therapies either stopped being effective or had to be abandoned due to liver toxicity (e.g., from other endothelin receptor antagonists). Scleroderma patients also expected that macitentan would reduce risk of death and hospitalization due to PAH. Other expectations were that macitentan would improve symptoms and energy for performing daily activities and increase quality of life. Patients also believed that a major benefit of macitentan was its lower risk of liver toxicity, which would obviate the need for monthly bloodwork for liver function monitoring. As long as the new drug was able to deliver on key benefits (i.e., stabilize their PAH, improve their ability to perform daily activities, and reduce their shortness of breath), patients were willing to tolerate certain adverse effects, such as headaches, nausea, and nasopharyngitis.

Patients who had experience with macitentan reported improvements in shortness of breath, energy level, fatigue, functionality, quality of life, and test results. A couple of patients reported less edema. Adverse effects were limited to stuffy nose, occasional headache, and mild flulike symptoms; although annoying, these were not considered intolerable. There were no reports of anemia. One patient reported some trouble manipulating the product packaging. In spite of their hopes for macitentan, patients acknowledge that their disease is progressive and that they will still have to deal with significant limitations in their lives.

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: | June 10, 2014 |
| Alerts: | Weekly search updates until October 15, 2014 |
| 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 |
| fs | Floating subheading |
| 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 |
| # | Truncation symbol for one character |
| ? | Truncation symbol for one or no characters only |
| adj | Requires words are adjacent to each other (in any order) |
| adj# | Adjacency within # number of words (in any order) |
| .ti | Title |
| .ab | Abstract |
| .ot | Original title |
| .hw | Heading word; usually includes subject headings and controlled vocabulary |
| .pt | Publication type |
| .rn | CAS registry number |
| .nm | Name of substance word |
| pmez | Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present |
| oomezd | Ovid database code; Embase 1974 to present, updated daily |

MULTI-DATABASE STRATEGY

| | |
|----|--|
| # | Searches |
| 1 | ("ACT 064992" or ACT-064992 or ACT064992 or Actelion-1 or Macitentan* or Opsumit* or UNII-Z9K9Y9WMVL).ti,ot,ab,sh,hw, rn,nm. |
| 2 | 441798-33-0.rn,nm. |
| 3 | 1 or 2 |
| 4 | 3 use pmez |
| 5 | *macitentan/ |
| 6 | ("ACT 064992" or ACT-064992 or ACT064992 or Actelion-1 or Macitentan* or Opsumit* or UNII-Z9K9Y9WMVL).ti,ab. |
| 7 | 5 or 6 |
| 8 | 7 use oomezd |
| 9 | 4 or 8 |
| 10 | 9 not conference abstract.pt. |
| 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 |

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 of Search: | June 2 - 6, 2014 |
| Keywords: | Opsumit (macitentan), pulmonary 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: VALIDITY OF OUTCOME MEASURES

Validity of outcomes

Aim

To summarize the validity of the following outcome measures used in the Study With an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) and report minimal clinically important difference (MCID) estimates where available:

- Six-minute walk distance (6MWD)
- Borg Dyspnea Index
- World Health Organization (WHO) Functional Class (FC)
- Short-Form Health Survey 36-Item questionnaire (SF-36).

Findings

Six-minute walk distance

The 6MWD measures the distance a patient can walk in six minutes. Change in 6MWD is the most widely used test to assess exercise capacity in pulmonary arterial hypertension (PAH) and is used in most PAH trials as a primary outcome.⁴⁷⁻⁵¹ The 6MWD is also used in clinical practice and is widely accepted by regulatory agencies. The main advantage of the 6MWD is its ease of administration; it is a submaximal exercise test that can be performed by a patient who is unable to tolerate maximal cardiopulmonary exercise testing (CPET).⁴⁷ 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.⁵² However, change in 6MWD is a surrogate outcome and has demonstrated moderate to poor correlation with key clinical outcomes in PAH.^{45,52,53} Performance on the 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.⁵⁴⁻⁵⁶ Furthermore, in multi-centre trials, experience and technical skills may vary among sites, and the correlations between the 6MWD and CPET might improve over time with increasing experience.⁵⁷ There is also evidence of a ceiling effect on the 6MWD, whereby the effect of the treatment on the test is diminished due to the inclusion of patients with milder disease (New York Heart Association [NYHA]/WHO FC 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.⁵⁸ 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 to 38.6 m) compared with placebo for patients with PAH.⁴²

Borg Dyspnea Index

The Borg Dyspnea Index is a patient self-reported measure of one's difficulty in breathing upon exertion. The index provides 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 scale consists of a range in scores from 0 to 10, where 0 represents normal breathing and 10 represents maximal dyspnea.⁵⁹ A patient may also rate his or her difficulty in breathing as 0.5, which represents "very, very slight (just noticeable)" difficulty. The score is obtained during and at the end of the exercise test (e.g., six-minute walk test [6MWT]), and reflects the maximum degree of dyspnea at any time during the walk test. Although it is a subjective assessment scale of the intensity of breathlessness on exertion, it is widely used for quantifying dyspnea in trial patients with chronic obstructive pulmonary disease (COPD) who have undergone an exercise test.^{60,61} No published studies have clearly addressed the MCID of the Borg Dyspnea Index in PAH. Distribution-based analyses of data from trials in patients with COPD and

heart failure suggest the MCID is 1 point.^{39,40} A recent study (abstract) indicated that the MCID in patients with PAH may be < 1, with distribution-based estimates ranging from 0.70 points to 1.24 points and an anchor-based estimate of 0.36 points.⁴¹ The authors suggested their MCID estimates are smaller than for COPD or heart failure because of differences in the perception of dyspnea among diseases.

WHO functional classification for pulmonary hypertension

The WHO FC system for pulmonary hypertension (PH) was adapted from the NYHA FC system for heart failure.¹⁰ The WHO FC system is used widely in clinical practice and as an outcome in clinical trials. One study reported clinicians' assessment of FC varied widely in PAH, especially when classifying patients as FC II or III.⁶² The intra-class correlation coefficient was low (approximately 0.6). In one instance, 53% of clinicians classified a patient as FC II and 47% classified the patient as FC III. Thus, despite wide use of the WHO classification system, inter-rater agreement may be poor.

Short-form health survey 36-item questionnaire

The SF-36 is a 36-item, general health status measure that has been used extensively in clinical trials in many disease areas.⁶³ The SF-36 was designed to understand the burden of chronic disease and the effect of treatments on general health status. It has eight dimensions measuring physical functioning, role functioning (work or other activities) affected by both physical and emotional symptoms, pain, general health, vitality, social functioning, and mental health. These eight subscales may be collapsed into two domain scores reflecting physical and mental components of quality of life. The SF-36 dimensions are scored separately and transformed to a 0 to 100 scale. Each scale is scored positively, which means that higher scores indicate better health-related quality of life (HRQoL) and lower scores indicate worse HRQoL. Among patients with PAH, SF-36 correlates moderately well with the 6MWD, NYHA/WHO FC, and Borg Dyspnea Index score.^{64,65} In general use of SF-36, a change of 5 to 10 points in each dimension or 2.5 to 5 points in each component summary indicates a clinically meaningful improvement.^{43,44}

TABLE 12: SUMMARY OF RELEVANT SECONDARY OUTCOMES USED IN SERAPHIN

| Instrument | Description | Evidence of Validity in PAH | MCID | Comments |
|--|--|-----------------------------|--|---|
| 6MWD ^{42,47,49,54-57,66-69} | Total distance walked in 6 minutes Submaximal test to assess exercise capacity Widely used in studies and clinical practice; accepted by regulatory agencies | Yes | 33.0 m (range: 25.1 to 38.6 m) | <ul style="list-style-type: none"> • Baseline 6MWD correlated with outcomes in PAH⁵² • Absolute 6MWD during treatment is correlated with outcomes in PAH • Change in 6MWD moderately to poorly correlated with outcomes in PAH^{45,52,53} • Ceiling effect in patients with less severe disease⁷⁰ |
| Borg Dyspnea Index ^{60,71,72} | Modified Borg Scale — 11-point scale (ranges 0 [no dyspnea] to 10 [max dyspnea] points) | 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. ^{60,71,72} |
| WHO functional class ⁶² | PH severity classification system | No | Unknown | Based on NYHA functional classification system for heart failure ¹⁰ |
| SF-36 questionnaire | 36-item, general health status instrument consisting of eight health domains; two component summaries: PCS and MCS | No | Unknown for PAH; in general, 5 to 10 points in each dimension or 2.5 to 5 points in each component summary ⁴³ | |

6MWD = six-minute walk distance; COPD = chronic obstructive pulmonary disease; HRQoL = health-related quality of life; MCID = minimal clinically important difference; MCS = mental component summary; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PCS = physical component summary; pts = points; SF-36 = Short-Form Health Survey 36-item questionnaire; WHO = World Health Organization.

Conclusion

Of the four reviewed outcome measures — 6MWD, Borg Dyspnea Index, WHO FC, and the SF-36 — used in the SERAPHIN trial, only the 6MWD has been validated in PAH. A MCID of 33.0 m (range: 25.1 m to 38.6 m) has been reported for the 6MWD in patients with PAH.

APPENDIX 4: EXCLUDED STUDIES

None.

APPENDIX 5: DETAILED OUTCOME DATA

TABLE 13: SUBGROUP ANALYSIS OF WHO FC (BASELINE TO MONTH SIX) IN PATIENTS WITHOUT PAH CONCOMITANT THERAPY AT BASELINE (NAIVE)

| | Placebo (N = 95) | Macitentan 10 MG (N = 88) |
|---|----------------------|------------------------------|
| Patients with WHO FC improved, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC unchanged, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC worsened, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |

CI = confidence interval; FC = functional class; RR = relative risk; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization.

TABLE 14: SUBGROUP ANALYSIS OF WHO FC (BASELINE TO MONTH SIX) IN PATIENTS WITH PAH CONCOMITANT THERAPY AT BASELINE (ADD-ON)

| | Placebo (N = 154) | Macitentan 10 MG (N = 154) |
|---|----------------------|-------------------------------|
| Patients with WHO FC improved, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC unchanged, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC worsened, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |

CI = confidence interval; FC = functional class; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization.

TABLE 15: SUBGROUP ANALYSIS OF WHO FC (BASELINE TO MONTH SIX) OF PATIENTS IN NORTH AMERICA

| | Placebo (N = 30) | Macitentan 10 MG (N = 23) |
|---|----------------------|------------------------------|
| Patients with WHO FC improved, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC unchanged, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC worsened, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |

CI = confidence interval; FC = functional class; RR = relative risk; WHO = World Health Organization.

TABLE 16: SUBGROUP ANALYSIS OF WHO FC (BASELINE TO MONTH SIX) IN PATIENTS OF WESTERN EUROPE AND ISRAEL

| | Placebo (N = 51) | Macitentan 10 MG (N = 48) |
|---|----------------------|------------------------------|
| Patients with WHO FC improved, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC unchanged, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC worsened, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |

CI = confidence interval; FC = functional class; RR = relative risk; WHO = World Health Organization.

TABLE 17: SUBGROUP ANALYSIS OF WHO FC (BASELINE TO MONTH SIX) OF PATIENTS IN EASTERN EUROPE AND TURKEY

| | Placebo (N = 59) | Macitentan 10 MG (N = 62) |
|---|----------------------|------------------------------|
| Patients with WHO FC improved, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC unchanged, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC worsened, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |

CI = confidence interval; FC = functional class; RR = relative risk; WHO = World Health Organization.

TABLE 18: SUBGROUP ANALYSIS OF WHO FC (BASELINE TO MONTH SIX) OF PATIENTS IN ASIA

| | Placebo (N = 68) | Macitentan 10 MG (N = 68) |
|---|----------------------|------------------------------|
| Patients with WHO FC improved, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC unchanged, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC worsened, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |

CI = confidence interval; FC = functional class; RR = relative risk; WHO = World Health Organization.

TABLE 19: SUBGROUP ANALYSIS OF WHO FC (BASELINE TO MONTH SIX) OF PATIENTS IN LATIN AMERICA

| | Placebo (N = 42) | Macitentan 10 MG (N = 41) |
|---|----------------------|------------------------------|
| Patients with WHO FC improved, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC unchanged, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |
| Patients with WHO FC worsened, n/N (%) | ██████ | ██████ |
| RR (95% CI) | ████████████████████ | |
| P value | ████ | |

CI = confidence interval; FC = functional class; RR = relative risk; WHO = World Health Organization.

TABLE 20: DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF PATIENTS IN NORTH AMERICA

| | Placebo (N = 30) | Macitentan 10 MG (N = 23) |
|------------------------|---------------------|------------------------------|
| Female sex, n (%) | ██████ | ██████ |
| Age (years), mean (SD) | ██████ | ██████ |
| Age, n (%) | | |
| < 18 | ██ | ██ |
| 18 to 64 | ██████ | ██████ |
| ≥ 65 | ██████ | ██████ |
| Race, n (%) | | |
| Caucasian | ██████ | ██████ |
| Black | ██████ | ██████ |
| Asian | ██ | ██ |
| Hispanic | ██████ | ██████ |
| Other | ██ | ██ |

CDR CLINICAL REVIEW REPORT FOR OPSUMIT

| | Placebo (N = 30) | Macitentan 10 MG (N = 23) |
|---|---------------------|------------------------------|
| PAH diagnosis (years), mean (SD) | ■ | ■ |
| PAH etiology, n (%) | | |
| Idiopathic | ■ | ■ |
| Familial | ■ | ■ |
| Collagen vascular disease | ■ | ■ |
| Congenital shunts | ■ | ■ |
| HIV infection | ■ | ■ |
| Drugs and toxins | ■ | ■ |
| 6MWD (m), mean (SD) | ■ | ■ |
| Borg Dyspnea Index, mean (SD) | ■ | ■ |
| NT-proBNP (fmol/mL), mean (SD) | ■ | ■ |
| WHO FC, n (%) | | |
| I | ■ | ■ |
| II | ■ | ■ |
| III | ■ | ■ |
| IV | ■ | ■ |
| Hemodynamics | | |
| mRAP (mm Hg), mean (SD) | ■ | ■ |
| mPAP (mm Hg), mean (SD) | ■ | ■ |
| PCWP (mm Hg), mean (SD) | ■ | ■ |
| CI (L/min/m ²), mean (SD) | ■ | ■ |
| PVR (dyn × sec/cm ⁵), mean (SD) | ■ | ■ |
| Background PAH therapy, n (%) | | |
| Yes | ■ | ■ |
| No | ■ | ■ |
| Background PAH therapy, n (%) | | |
| PDE-5 inhibitors | ■ | ■ |
| Oral or inhaled prostanoids | ■ | ■ |
| Concomitant medication, n (%) | | |
| Anticoagulants | ■ | ■ |
| Antithrombotic agents | ■ | ■ |
| Diuretics | ■ | ■ |
| Calcium channel blockers | ■ | ■ |

6MWD = six-minute walk distance; CI = cardiac index; FC = functional class; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; NT-proBNP = N-terminal pro b-type natriuretic peptide; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; SD = standard deviation; WHO = World Health Organization.

TABLE 21: DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF PATIENTS IN WESTERN EUROPE AND ISRAEL

| | Placebo (N = 51) | Macitentan 10 MG (N = 48) |
|---|---------------------|------------------------------|
| Female sex, n (%) | | |
| Age (years), mean (SD) | | |
| Age, n (%) | | |
| < 18 | | |
| 18 to 64 | | |
| ≥ 65 | | |
| Race, n (%) | | |
| Caucasian | | |
| Black | | |
| Asian | | |
| Hispanic | | |
| Other | | |
| PAH diagnosis (years), mean (SD) | | |
| PAH etiology, n (%) | | |
| Idiopathic | | |
| Familial | | |
| Collagen vascular disease | | |
| Congenital shunts | | |
| HIV infection | | |
| Drugs and toxins | | |
| 6MWD (m), mean (SD) | | |
| Borg Dyspnea Index, mean (SD) | | |
| NT-proBNP (fmol/mL), mean (SD) | | |
| WHO FC, n (%) | | |
| I | | |
| II | | |
| III | | |
| IV | | |
| Hemodynamics | | |
| mRAP (mm Hg), mean (SD) | | |
| mPAP (mm Hg), mean (SD) | | |
| PCWP (mm Hg), mean (SD) | | |
| CI (L/min/m ²), mean (SD) | | |
| PVR (dyn × sec/cm ⁵), mean (SD) | | |
| Background PAH therapy, n (%) | | |
| Yes | | |
| No | | |
| Background PAH therapy, n (%) | | |
| PDE-5 inhibitors | | |
| Oral or inhaled prostanoids | | |
| Concomitant medication, n (%) | | |

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| | Placebo (N = 51) | Macitentan 10 MG (N = 48) |
|--------------------------|---------------------|------------------------------|
| Anticoagulants | ■ | ■ |
| Antithrombotic agents | ■ | ■ |
| Diuretics | ■ | ■ |
| Calcium channel blockers | ■ | ■ |

6MWD = six-minute walk distance; CI = cardiac index; FC = functional class; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; NT-proBNP = N-terminal pro b-type natriuretic peptide; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; SD = standard deviation; WHO = World Health Organization.

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