Common Drug Review
Clinical Review Report

July 2015

Drug	riociguat (Adempas)
Indication	Management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4) or persistent or recurrent CTEPH after surgical treatment in adult patients ≥ 18 years of age with WHO functional class II or III pulmonary hypertension
Listing request	As per indication
Manufacturer	Bayer HealthCare

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ABBREVIATIONS

6MWD	six-minute walk distance
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
CDEC	Canadian Drug Expert Committee
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CrI	credible interval
CTEPH	chronic thromboembolic pulmonary hypertension
CUA	cost-utility analysis
eGFR	estimated glomerular filtration rate
ERA	endothelin receptor antagonist
EQ VAS	EuroQol visual analogue scale
EQ-5D	EuroQol 5-dimensions questionnaire
FC	functional class
GI	gastrointestinal
HRQoL	health-related quality of life
ICUR	incremental cost-utility ratio
ITC	indirect treatment comparison
ITT	intention-to-treat
IVRS	interactive voice response system
LOCF	last observation carried forward
LPH	Living With Pulmonary Hypertension questionnaire
LS	least squares
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
MCID	minimum clinically important difference
MTC	mixed treatment comparison
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PAH	pulmonary arterial hypertension
PAP_{mean}	mean pulmonary artery pressure
PDE-5	phosphodiesterase-5
PEA	pulmonary endarterectomy
PH	pulmonary hypertension

PVR	pulmonary vascular resistance
QoL	quality of life
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RIO	riociguat
SBP	systolic blood pressure
WDAE	withdrawal due to adverse event
WHO	World Health Organization

EXECUTIVE SUMMARY

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease subtype of pulmonary hypertension.[1] It is a progressive disease characterized by the presence of non-resolving or recurrent thrombi distributed within the pulmonary arteries. This can obstruct or occlude the luminal space, eventually leading to increased pulmonary vascular resistance (PVR), pulmonary hypertension, and right-sided heart failure.[1-3] Although the exact etiology of CTEPH remains poorly understood, it may arise following an initial episode of acute pulmonary embolism (PE); however, up to 60% of CTEPH patients have not had any antecedent episode of acute PE.[3] The epidemiology of CTEPH is likewise not well established. Some surveillance data estimate CTEPH to occur in 0.1% to 0.5% of patients surviving an initial episode of acute PE;[4] however, the true incidence of CTEPH is likely to be higher, owing to an unknown number of undetected cases either presenting occultly or latently in the setting of acute PE or through non-venous thromboembolism etiologies.[3]

The current gold standard treatment intervention in CTEPH is surgery, specifically, pulmonary endarterectomy (PEA), which has the potential to be curative;[5] however, there is no universally accepted criteria for operability.[6] For patients who are not eligible for surgical intervention (up to 50%[3]) or who refuse it, there are several classes of medical therapies indicated for pulmonary arterial hypertension (PAH) that have been used off-label as monotherapy in CTEPH patients. These include endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE-5) inhibitors, and prostanoids (including prostacyclins and prostacyclin analogues).[3]

Riociguat is a first-in-class drug of the soluble guanylate cyclase stimulator class of drugs, which works by producing vasorelaxation independent of the endogenous vasodilatory effects of nitrous oxide.[7] It is also the first drug to be marketed in Canada for the treatment of CTEPH. Riociguat is initiated at a dose of 1.0 mg orally three times a day and adjusted by 0.5 mg increments every two weeks (according to systemic systolic blood pressure readings) to a maximum dose of 2.5 mg three times a day. Riociguat has a Health Canada indication for the management of inoperable CTEPH (World Health Organization [WHO] Group 4), or persistent or recurrent CTEPH after surgical treatment in adults aged ≥ 18 years with WHO functional class II or III pulmonary hypertension.[8] Reimbursement is being sought by the manufacturer in accordance with this indication.

The objective of this systematic review was to evaluate the beneficial and harmful effects of riociguat for the treatment of patients with WHO functional class II or III CTEPH who are deemed inoperable or have persistent or recurrent CTEPH after surgical treatment.

Results and Interpretation

Included Studies

The evidence for this review was drawn from one phase III (CHEST-1) double-blind, randomized (2:1), placebo-controlled trial comprising 262 patients with WHO functional class II or III CTEPH, which was either inoperable or characterized by post-operative residual pulmonary hypertension (PH). Patients were randomly assigned riociguat (1.0 mg initially) orally three times a day or matching placebo for 16 weeks. During the first eight weeks, an individual dose titration protocol was used to target a final dose of 2.5 mg three times a day or the maximally tolerated dose; the remaining eight weeks comprised a dose-maintenance phase. The primary efficacy outcome in CHEST-1 was the change in the six-minute walk distance (6MWD) baseline after 16 weeks. The trial has been criticized by the FDA for its single active treatment arm and the forced titration protocol used, which was considered aggressive and

potentially placing patients at risk for symptomatic hypotension. At 16 weeks in duration, the trial is limited to providing short-term efficacy data from surrogate end points. Most (> 90%) of the patients studied were from outside North America; however, results were still considered generalizable to Canadian practice by the clinical expert consulted by the CADTH Common Drug Review (CDR) because of the large proportion (> 40%) of Western European patients represented in the trial and the similar approach to PH management known to exist between Canada and Western Europe.

Efficacy

A statistically significant increase in 6MWD from baseline to 16 weeks was observed favouring riociguat versus placebo in CHEST-1 (adjusted least-squares [LS] mean difference: 45.7 m; 95% confidence interval [CI], 24.7 m to 66.6 m). The FDA's recalculated median difference of 39 m (95% CI, 25 m to 54 m) was performed after statistical testing revealed that the data on which the original estimate was based were not normally distributed. Since the minimal clinically important difference (MCID) for the 6MWD has been reported as being 33 m, it would appear the treatment difference was clinically meaningful in either case. Pre-specified subgroup analyses on the primary outcome were largely consistent with the primary analysis.

Although survival and hospitalizations were identified in the systematic review protocol as key efficacy outcomes, the trial was not powered to study these, and data were only analyzed as components of the composite secondary outcome of clinical worsening; overall event numbers were too few to draw any conclusions. Change in WHO functional class (FC) was a secondary efficacy outcome in the trial, which exhibited a statistically significant pattern of improvement (from baseline to the end of the double-blind period) of one or two categories favouring riociguat treatment (P = 0.0026). However, WHO FC was unchanged for the majority of patients in both groups (riociguat: 62%, placebo: 78%). Hemodynamic markers, specifically PVR (adjusted LS mean difference: –246.4 dyn*s*cm^{-5}; 95% CI, –303.3 dyn*s*cm^{-5} to –189.5 dyn*s*cm^{-5}) and mean pulmonary artery pressure (adjusted LS mean difference: –5.0 mm Hg; 95% CI, –6.8 mm Hg to –3.2 mm Hg), improved under riociguat treatment.

To reduce the risk of finding a treatment difference when one does not exist (i.e., Type I error) as a result of multiple statistical comparisons, the manufacturer planned a hierarchical step-down testing procedure for the formal testing of treatment differences between riociguat and placebo on a series of seven pre-specified secondary efficacy outcomes (i.e., PVR, NT-proBNP, WHO FC, time to clinical worsening, Borg Dyspnea Scale, EQ-5D, and Living With Pulmonary Hypertension [LPH] Questionnaire). This sequential testing was to proceed only if a statistically significant treatment difference favouring riociguat was initially detected in the primary efficacy outcome (i.e., 6MWD). Statistical testing stopped when time to clinical worsening was found to be not statistically significant between the treatment groups. As a result of this multiple testing adjustment strategy, only the results for 6MWD, PVR, NT-proBNP, and WHO FC were reported as statistically significant, in contrast to none of the patient-reported outcomes (i.e., Borg CR10 Scale, EQ-5D and LPH questionnaires), despite observed improvements on each of the patient-reported outcomes.

Harms

The overall frequency of adverse events appeared slightly higher with riociguat (RIO) (91.9%) compared with placebo (PB) (86.4%). Compared with placebo, riociguat treatment was most commonly associated with headache (RIO: 24.9% versus PB: 13.6%) and dizziness (RIO: 22.5% versus PB: 12.5%); followed by dyspepsia (RIO: 17.9% versus PB: 8.0%); peripheral edema (RIO: 15.6% versus PB: 20.5%); nasopharyngitis (RIO: 15.0% versus PB: 9.1%); nausea (RIO: 11.0% versus PB: 8.0%); diarrhea (RIO: 9.8% versus PB: 4.5%); vomiting (RIO: 9.8% versus PB: 3.4%); and hypotension (RIO: 9.2% versus PB: 3.4%). Serious adverse events were common (RIO: 19.7% versus PB: 15.9%) and most often classified as cardiac disorders (RIO: 5.8% versus PB: 6.8%) or respiratory, thoracic, and mediastinal disorders (RIO: 6.4% versus PB: 2.3%). Withdrawals due to adverse events (WDAEs) occurred in 2.9% of patients in the riociguat group and 2.3% in the placebo group. Death was studied as an efficacy outcome within the composite end point of clinical worsening. Two (1.2%) deaths were reported in the riociguat group compared with 3 (3.4%) in the placebo group.

Following the completion of CHEST-1, patients were enrolled in an open-label extension trial called CHEST-2. Patients who received riociguat during CHEST-1 were continued on the same dose they received on their last day of follow-up in CHEST-1, while patients who had received placebo during CHEST-1 were initiated on riociguat using the same, eight-week dose titration protocol used in CHEST-1. At the time of the March 2013 safety update, 237 (90.8%) participants were enrolled in CHEST-2. Of these, 155 (89.6%) were from the former riociguat treatment group, and 82 (93.2%) were from the placebo group. The findings were consistent with those observed in CHEST-1 and no new safety signals were identified from this limited snapshot of observational data.

Pharmacoeconomic Summary

Riociguat (Adempas) is being reviewed for the treatment of inoperable CTEPH, or persistent or recurrent CTEPH after surgical treatment in adult patients (≥ 18 years of age) with WHO FC II or III PH. Riociguat is administered based on an individual dose titration of between 0.5 to 2.5 mg taken three times a day. The manufacturer submitted a price of $42.75 per tablet (0.5 mg, 1 mg, 1.5 mg, 2 mg, or 2.5 mg), or a daily cost of $128.25.

Summary of Economic Analysis

The manufacturer conducted a cost-utility analysis (CUA) from the Canadian public payer perspective, over a 20-year time horizon, comparing riociguat with placebo, and riociguat with generic and brand-name bosentan (Tracleer). The 16-week Markov model cycle included the following health states: WHO FC II, WHO FC III, WHO FC IV, and death. The clinical data from CHEST-1 and CHEST-2 trials were used to establish: the characteristics of patients entering the economic model; transition probabilities between FC for placebo (CHEST-1) and riociguat (CHEST-2) for the first model cycle (16 weeks); the frequency of adverse events; and utility measurement. An indirect treatment comparison (ITC) of riociguat and bosentan was performed using the CHEST-1 and BENEFiT trial. Within each Markov cycle, patients can remain in the same health state, improve by one FC, worsen by one FC, or die. After the first cycle, FC transitions were derived from the extrapolation of survival curves derived from statistical fitting of the trial data. Only liver toxicity and hypotension were included in the model as adverse events. Mortality data by FC were from a European chart review commissioned by the manufacturer.

Utilities associated with FC status were collected from the CHEST-1 study. Drug costs for riociguat were provided by the manufacturer, while costs for Tracleer and generic bosentan were obtained from the Quebec formulary. Treatment-specific one-off initiation costs were based on discussions with clinical experts. Supportive care use (such as supplemental oxygen, warfarin, and diuretics) was based on the European chart review, with the unit cost derived from Canadian sources. Similarly, ongoing health care resource utilization associated with CTEPH (hospitalizations, specialists visits, and examination and diagnostic testing) were also based on the European chart review, with the unit costs estimated from Canadian sources.

Results of Manufacturer's Analysis

Using the health-payer perspective, the manufacturer reports an incremental cost per quality-adjusted life-year (QALY) of $173,524 for riociguat compared with placebo. The incremental cost per QALY for riociguat compared with generic bosentan is $187,347. Riociguat dominates Tracleer.

Interpretations and Key Limitations

- It is not established that long-term differences in FC will occur. If the treatment effect is not durable or attenuates, the cost-effectiveness ratio will be greater.
- In the model, mortality is assumed to increase by worsening FC (which, according to the clinical expert, is a reasonable assumption), but mortality is also impacted by treatment strategy, regardless of FC health state (informed by the ITC). This might lead to double counting of the potential mortality benefit of riociguat.
- The odds ratios (ORs) for transition to FC health states in patients treated with bosentan were estimated from the BENEFiT study (bosentan arm only) using a calibration approach. Of note, the ITC submitted by the manufacturer reported non-statistically significant increase in the odds of being in a better FC at study end point when treated with riociguat compared with bosentan (OR 1.15, 95%, CrI 0.51 to 2.61). The true relative efficacy of riociguat and bosentan is not clear.

Results of CADTH Common Drug Review Analysis

Riociguat Versus Placebo

- When the time horizon was shortened to five years, the incremental QALYs associated with riociguat compared with placebo decreased from 0.887 to 0.275, and the cost per QALY increased to $434,311 for riociguat versus placebo. This highlighted that a majority of the incremental benefit accrued in the model is well beyond the time frame of current RCTs.
- Incremental cost-utility ratio (ICUR) increases to $350,519 per QALY in the CDR analyses when mortality risk by FC class only is considered.

Riociguat Versus Generic Bosentan

- When the time horizon was shortened to five years, the incremental QALYs decreased from 0.416 to 0.137 for riociguat compared with generic bosentan, and the cost per QALY increased to $492,361.
- Riociguat is dominated by generic bosentan (more costly and less effective) in the CDR analyses when mortality risk by FC class only is considered; however, true differences in mortality between riociguat and bosentan are unknown.

Riociguat Versus Tracleer

- Riociguat dominated Tracleer in all time horizons tested.
- Riociguat is less costly but less effective than Tracleer when mortality risk by FC class only is considered.

In the CDR reanalysis, eliminating the possible double counting of mortality benefit, the ICUR increases to $350,519 per QALY for riociguat versus placebo, and riociguat results in lower QALYs than bosentan (riociguat is dominated by generic bosentan; riociguat is less costly, but less effective than Tracleer). There is significant uncertainty in the ICUR given the lack of head-to-head trials of riociguat versus bosentan, the approach to modelling relative efficacy, and the lack of data on long-term outcomes. Several scenarios result in greater ICURs than the base case presented by the manufacturer.

If drug costs of riociguat versus bosentan only are examined, riociguat has similar costs in jurisdictions where all patients are receiving Tracleer, but the incremental costs of riociguat versus bosentan rise as this proportion falls.

Conclusions

In a single adequately designed randomized controlled trial, riociguat was shown to improve the primary efficacy outcome of change from baseline in 6MWD (compared with placebo) in patients with WHO FC II or III CTEPH who were either not eligible for surgery or who had persistent or residual PH symptoms post-operatively. The improvement in 6MWD with riociguat treatment is augmented by the accompanying improvements noted in hemodynamic parameters and in WHO FC. Although survival and hospitalization were identified as key outcomes in the systematic review protocol, they were studied only as components of the secondary composite outcome of clinical worsening, which was not powerful enough to detect statistically significant differences between treatments. Riociguat treatment was more commonly associated with headache, dizziness, dyspepsia, nasopharyngitis, diarrhea, vomiting, and hypotension versus placebo. Serious adverse events were frequent in both groups and most often classified as “cardiac” or “respiratory, thoracic, and mediastinal” disorders. WDAEs were infrequent and similar between groups. Five deaths occurred during the trial: two in the riociguat group and three in the placebo group. No additional safety signals were identified from the data in the open-label extension trial (CHEST-2). How well riociguat compares with other drugs used in CTEPH is uncertain, as the data from the ITC submitted by the manufacturer are limited; comparisons of tolerability are further hampered by the omission of relevant safety outcomes (i.e., hypotension) from the analysis.

TABLE 1: SUMMARY OF KEY RESULTS

Outcome	CHEST-1	
Primary: 6MWD	**Riociguat N = 173**	**Placebo N = 88**
Change From Baseline to Week 16 (metres)		
Adjusted[a] LS mean of change	**42.8**	–2.9
Mean difference (95% CI)	45.7 (24.7, 66.6)	
P value[b]	< 0.0001	
FDA Recalculation[9]		
Median difference (95% CI)	39 (25, 54)	
Clinical Worsening		
Number of patients with clinical worsening, n (%):	**4 (2.3)**	5 (5.7)
Hospitalization due to PH, n (%)	**0**	1 (1.1)
Start of new PH treatment, n (%)	**2 (1.2)**	1 (1.1)
Decrease in 6MWD due to PH, n (%)	**1 (0.6)**	2 (2.3)
Persistent worsening of functional class due to PH, n (%)	**0**	1 (1.1)
Death, n (%)	**2 (1.2)**	3 (3.4)
P value[b]	0.1724	
P value (Mantel–Haenszel[c])	0.2180	
WHO Functional Class		
Change From Baseline to Last Visit (Number of Classes)		
–2	4 (2.3)	0
–1	53 (30.6)	13 (14.9)
0	107 (61.8)	68 (78.2)
1	7 (4.0)	3 (3.4)
2	1 (0.6)	3 (3.4)
3	1 (0.6)	0
P value (stratified Wilcoxon test)	0.0026	
HRQoL[d]		
LPH Total Score		
N (%)	**170 (98.3)**	86 (97.7)
Adjusted[a] LS mean of change	**–8.2**	–2.5
Mean difference (95% CI)	–5.8 (–10.5, –1.1)	
P value[b]	0.1220	
EQ-5D Utility Score		
N (%)	**172 (99.4)**	87 (98.9)
Adjusted[a] LS mean of change	**0.08**	–0.06
Mean difference (95% CI)	0.1 (0.1, 0.2)	
P value[b]	< 0.0001	

Outcome	CHEST-1	
Primary: 6MWD	**Riociguat N = 173**	**Placebo N = 88**
AEs		
n (%)	**159 (91.9)**	76 (86.4)
SAEs		
n (%)	**34 (19.7)**	14 (15.9)
WDAEs		
n (%)	**5 (2.9)**	2 (2.3)
Notable Harms		
Peripheral edema	**27 (15.6)**	18 (20.5)
Hypotension and syncope events:	**24 (13.9)**	7 (8.0)
Blood pressure decreased	**3 (1.7)**	1 (1.1)
Presyncope	**2 (1.2)**	0
Syncope	**4 (2.3)**	3 (3.4)
Hypotension	**16 (9.2)**	3 (3.4)
Orthostatic hypotension	**1 (0.6)**	0
Bleeding events[e]	**23 (13.3)**	10 (11.4)
Anemia	**6 (3.5)**	1 (1.1)
Gastritis	**6 (3.5)**	0
Acute renal failure	**1 (0.6)**	0

AE = adverse event; CI = confidence interval; HRQoL = health-related quality of life; EQ-5D = EuroQol 5-dimensions questionnaire; LPH = Living With Pulmonary Hypertension questionnaire; LS = least squares; PH = pulmonary hypertension; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a]Adjustments for baseline value, treatment group, and region.
[b]Wilcoxon log-rank test, stratified by region, and performed if test of normality was statistically significant.
[c]Sensitivity test for the difference in incidences stratified by region.
[d]Change from baseline to week 16.
[e]Bleeding events included hemorrhage, but not laboratory adverse events.
Source: CHEST-1 Clinical Study Report.[7]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease subtype of pulmonary hypertension (PH).[1] It is a progressive disease characterized by the presence of non-resolving or recurrent thrombi distributed within the pulmonary arteries. This can obstruct or occlude the luminal space, eventually leading to increased pulmonary vascular resistance (PVR), PH, and right-sided heart failure.[1-3] Although the exact etiology of CTEPH remains poorly understood, CTEPH may arise following an initial episode of acute pulmonary embolism (PE) and the ensuing pulmonary vascular remodelling; however, it has been reported that up to 60% of CTEPH patients have not had any antecedent episode of acute PE.[3] Likewise, the epidemiology of CTEPH is not well established. Some surveillance data estimate that CTEPH occurs in 0.1% to 0.5% of patients surviving an initial episode of acute PE (PE is estimated to occur in 0.5 to 0.6 million people in the United States);[4] however, another report suggests the cumulative incidence of CTEPH could be 1% to 4%.[3] Nonetheless, the true incidence of CTEPH is likely to be higher, owing to an unknown number of undetected cases presenting either occultly or latently in the setting of acute PE or through non-venous thromboembolism etiologies.[3] The World Health Organization (WHO) functional classification of PH (Table 2) is used to monitor disease severity and is a predictor of survival.[1]

TABLE 2: WORLD HEALTH ORGANIZATION FUNCTIONAL CLASSIFICATION OF PULMONARY HYPERTENSION

Class	Description
I	No limitation 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-sided heart failure present

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

1.2 Standards of Therapy

The current gold standard treatment intervention in CTEPH is surgery, specifically, pulmonary endarterectomy (PEA);[5] however, there is no universally accepted criteria for operability.[6] In contrast to medical therapy or transplantation, PEA can potentially be curative in surgically eligible patients with proximal lesions.[5] In patients who undergo PEA, it has been reported that 80% will experience a reduction in PVR and 90% will be alive at five years.[6] When PEA is performed by an experienced surgeon, 30-day perioperative mortality has been reported to be between 4% and 10%, with persistent PH being the most frequent cause of early perioperative death.[3]

For patients not eligible for (up to 50%[3]), or refusing, surgical intervention, there are several classes of medical therapies indicated in pulmonary arterial hypertension (PAH) that have been used off-label as monotherapy in CTEPH patients. These include endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE-5) inhibitors, and prostanoids (including prostacyclins and prostacyclin analogues)[3] (Table 3). In addition to PAH-specific medications, long-term anticoagulation with warfarin is indicated to reduce the risk of thrombosis, and supplemental oxygen to relieve hypoxemia at rest.[1,3]

Clinical practice guidelines for the medical management of CTEPH are limited in terms of the guidance provided, reflecting the paucity of available evidence for treating this subtype of PH.[1,3]

1.3 Drug

Riociguat is a first-in-class drug of the soluble guanylate cyclase stimulator class of drugs that works by producing vasorelaxation independent of the endogenous vasodilatory effects of nitrous oxide.[7] It is also the first drug to be marketed in Canada for the treatment of CTEPH. Riociguat is initiated at a dose of 1.0 mg orally three times a day and adjusted by 0.5 mg increments every two weeks (according to systemic systolic blood pressure readings) to a maximum dose of 2.5 mg three times a day. Riociguat has a Health Canada indication for the management of inoperable CTEPH (WHO Group 4) or persistent or recurrent CTEPH after surgical treatment in adults aged ≥ 18 years with WHO functional class (FC) II or III PH.[8] Reimbursement is being sought by the manufacturer in accordance with this indication.

Indication Under Review
Management of inoperable CTEPH (WHO Group 4) or persistent or recurrent CTEPH after surgical treatment in adult patients ≥ 18 years of age with WHO functional class II or III pulmonary hypertension.
Listing Criteria Requested by Sponsor
As per indication.

TABLE 3: KEY CHARACTERISTICS OF ENDOTHELIN RECEPTOR ANTAGONISTS, PDE-5 INHIBITORS, AND PROSTANOIDS

	Riociguat	Endothelin Receptor Antagonists (Bosentan, Ambrisentan)	PDE-5 Inhibitors (Sildenafil, Tadalfil)	Prostanoids (i.e., Prostacyclins-Epoprostenol, Prostacyclin Analogues-Treprostinil)
Mechanism of Action	Produces vasorelaxation independent of the endogenous vasodilatory effects of nitrous oxide[7]	*Bosentan*: dual (ET_A, ET_B) endothelin receptor antagonist; decreases PVR and SVR[10] *Ambrisentan*: selective (ET_A) endothelin receptor antagonist; inhibits vasoconstriction and cell proliferation[10]	Vasodilation via selective inhibition of cGMP specific phosphodiesterase type-5 (PDE-5) in smooth muscle of the pulmonary vasculature[10]	Direct vasodilation of pulmonary and systemic arterial vascular beds; inhibition of platelet aggregation[10]
Health Canada Indication	Management of inoperable CTEPH (WHO Group 4) or persistent or recurrent CTEPH after surgical treatment in adult patients ≥ 18 years of age with WHO functional class II or III PH[8]	Not indicated in CTEPH	Not indicated in CTEPH	Not indicated in CTEPH
Route of Administration	Oral	Oral	Oral	Intravenous, subcutaneous (treprostinil only)[1]
Recommended Dose	Initially, 1 mg three times a day for 2 weeks, then increasing by 0.5 mg every 2 weeks to a maximum of 2.5 mg three times a day[8]	*Bosentan*: Initially, 62.5 mg twice daily for 4 weeks then 125 mg twice daily[10] *Ambrisentan*: Initially, 5 mg once daily; dose may be increased to 10 mg once daily[10]	*Sildenafil*: 20 mg three times a day[10] *Tadalafil*: 40 mg once daily[10]	*Epoprostenol*: Initially, 2 ng/kg/min then increased until dose-limiting adverse effects or until a tolerance limit is achieved[10] *Treprostinil*: Initially, 1.25 ng/kg/min; if not tolerated, reduce infusion rate to 0.625 ng/kg/min[11]

	Riociguat	Endothelin Receptor Antagonists (Bosentan, Ambrisentan)	PDE-5 Inhibitors (Sildenafil, Tadalfil)	Prostanoids (i.e., Prostacyclins-Epoprostenol, Prostacyclin Analogues-Treprostinil)
Serious Side Effects/Safety Issues	Risk of hypotension in susceptible patients; excess risk of bleeding (above inherent risk in PH); not recommended in PVOD, severe hepatic or renal impairment, combination with strong multi-pathway CYP or P-gp/BCRP inhibitors. Contraindicated with drugs that increase cGMP: nitrates, PDE-5 inhibitors, NO donors.[12]	*Bosentan*: May experience reversible, dose-related increase in LFTs; rare reports of liver cirrhosis or failure, dose-related reductions in Hgb; caution in severe chronic HF and hypotension (SBP < 85 mm Hg). Contraindicated in moderate or severe liver impairment, or with concomitant CyA or glyburide.[10] *Ambrisentan*: May experience: elevations in LFTs or drug-related reduction in Hgb, Hct; cases of autoimmune hepatitis or liver injury, dose-dependent peripheral edema have been reported. Contraindicated in idiopathic pulmonary fibrosis, with or without PH.[10]	Not recommended in patients with PVOD; caution in underlying CVD; a sudden loss of vision in one or both eyes may indicate NAION. Contraindicated with concomitant nitrates.[10]	*Epoprostenol*: Abrupt withdrawal or sudden large reductions in dose may trigger rebound PH; risk of hemorrhage due to potent platelet inhibition; bradycardia, severe hypotension (including fatalities), elevations in blood glucose may occur. Contraindcated in CHF due to severe LV systolic dysfunction and in patients who develop pulmonary edema following dose initiation.[10] *Treprostinil*: Abrupt withdrawal or sudden large reductions in dose may trigger rebound PH; escalate dose cautiously in setting of hepatic dysfunction.[11]

BCRP = breast cancer resistance protein; cGMP = cyclic guanosine monophosphate; CHF = congestive heart failure; CTEPH = chronic thromboembolic pulmonary hypertension; CVD = cardiovascular disease; CyA = cyclosporine A; CYP = cytochrome P450; ET = endothelin receptor; Hct = hematocrit; HF = heart failure; Hgb = hemoglobin; LFT = liver-function test; LV = left ventricular; NAION = non-arteritic anterior ischemic optic neuropathy; NO = nitric oxide; PDE = phosphodiesterase; P-gp = P-glycoprotein; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive vascular disease; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.
Source: e-CPS,[10] European Society of Cardiology/European Respiratory Society Guidelines,[1] Remodulin product monograph.[11]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of riociguat for the treatment of patients with WHO FC II or III CTEPH who are deemed inoperable or have persistent or recurrent CTEPH after surgical treatment.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with CTEPH in WHO functional class II or III who: • are deemed inoperable • have persistent or recurrent CTEPH after surgical treatment. **Subpopulations** • Patient's age • Prior therapy with PH medication • WHO functional class at baseline • 6MWD at baseline • Baseline PVR • Baseline PAP_{mean}
Intervention	Riociguat at Health Canada–approved doses
Comparators	**Medical Intervention/Pharmacotherapy** • Other PH medications: endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostanoids (i.e., prostacyclins, prostacyclin analogues) • Placebo

Outcomes	**Key Efficacy Outcomes**
	• Survival
	• Hospitalization
	• Clinical worsening
	• Change in WHO functional class
	• HRQoL measured by a validated scale
	
	Other Efficacy Outcomes
	• 6MWD
	• Cardiopulmonary exercise testing (i.e., peak VO_2)
	• Change in PH symptoms
	• Change in:
	  ○ PVR
	  ○ PAP_{mean}
	  ○ BNP or NT-proBNP
	• Use of supplemental oxygen

	Harms Outcomes • AEs • SAEs • WDAEs • AEs of interest: anemia, bleeding events, hypotension, orthostatic hypotension, presyncope, syncope, peripheral edema, acute renal failure, gastritis
Study Design	Published and unpublished double-blind RCTs

6MWD = six-minute walk distance; AE = adverse event; BNP = brain natriuretic peptide; CTEPH = chronic thromboembolic hypertension; HRQoL = health-related quality of life; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PAP_{mean} = mean pulmonary artery pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; SAE = serious adverse event; peak VO_2 = maximal oxygen consumption; WDAE = withdrawal due to adverse event; WHO = World Health Organization.

2.3 Supplemental Issues

1. Riociguat open-label extension study (CHEST-2)
2. Validity of outcomes
3. Summary and critical appraisal of the manufacturer submitted network meta-analysis

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 Heading), and keywords. The main search concepts were Adempas and riociguat.

No 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 language. Conference abstracts were excluded from the search results.

The initial search was completed on February 11, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on June 18, 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 (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Advisories & Warnings, Clinical Practice Guidelines, HTA Agency, Health Economics, and Drug Class Reviews. 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** 5; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

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

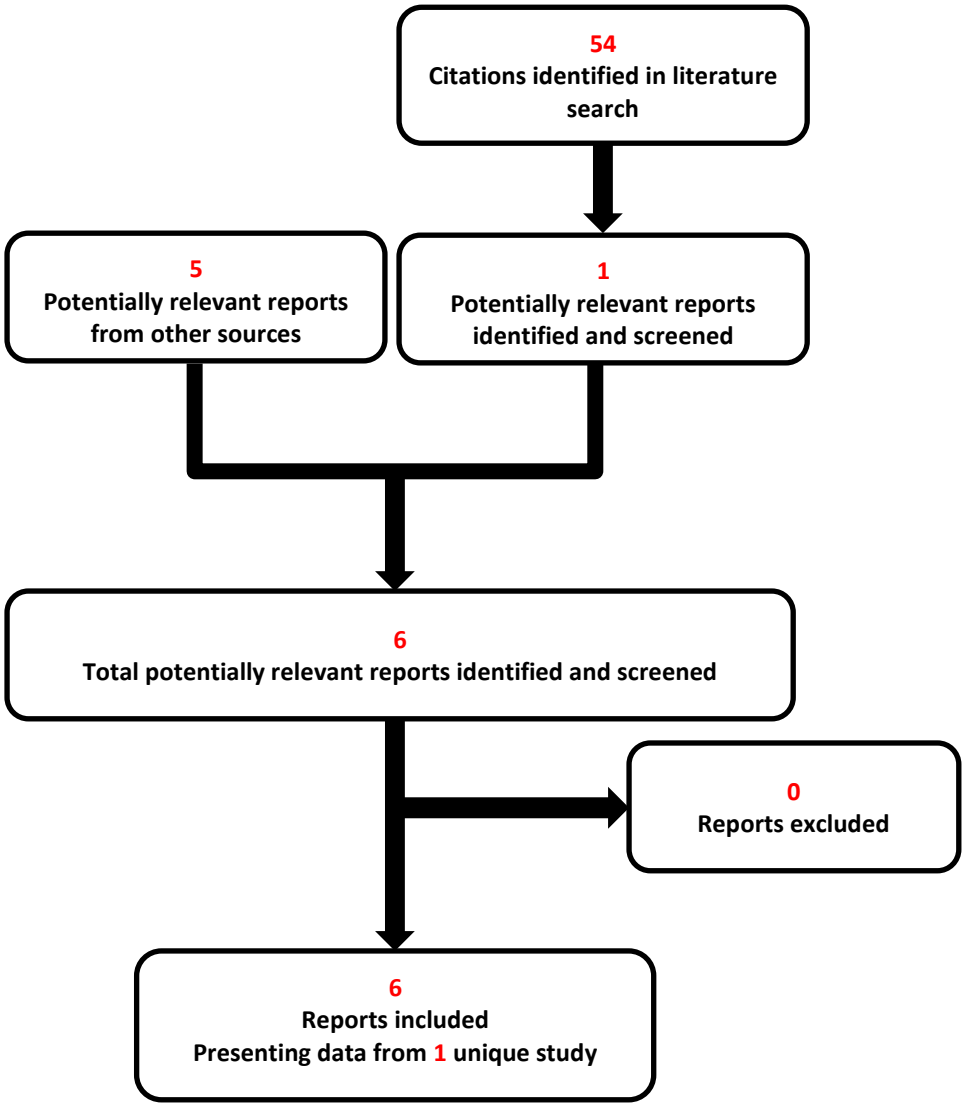


TABLE 5: DETAILS OF INCLUDED STUDIES

		CHEST-1
DESIGNS & POPULATIONS	**Study Design**	Multi-centre, multinational (26 countries), double-blind, placebo-controlled (2:1) RCT
	Locations	Including W. Europe, Japan, USA, Canada
	Randomized (N)	262
	Inclusion Criteria	Age 18 to 80 years; diagnosis of CTEPH, either *inoperable*: PVR > 300 dyn*s*cm^{-5} measured ≥ 90 days after start of full anticoagulation, a PAP_{mean} > 25 mm Hg, and inoperability confirmed by experienced surgeon or central adjudication committee; or *persisting or recurring PH after PEA*: PVR > 300 dyn*sec*cm^{-5}; eligibility + baseline 6MWD test result: 150 m to 450 m; stable doses of unspecific PH co-treatments such as oral anticoagulants, diuretics, digitalis, calcium channel blockers, or supplemental oxygen were permitted. Patients were ideally PAH treatment-naive; however, patients previously exposed to PAH-specific therapies may have been permitted trial entry if they experienced unacceptable adverse reactions or lack of efficacy from past PAH-specific medications. PAH-specific medication must have been stopped ≥ 30 days before baseline right-heart catheterization.
	Exclusion Criteria	*Respiratory:* moderate to severe obstructive lung disease (FEV_1< 60% predicted); severe restrictive lung disease (TLC < 70% predicted); severe congenital abnormalities of the lungs, thorax, and diaphragm; SaO_2 < 88% or PaO_2 < 55 mm Hg, or $PaCO_2$ > 45 mm Hg; *Cardiovascular*: history of uncontrolled arterial hypertension ≤ 90 days before visit 1 and/or SBP > 180 mm Hg and/or DBP > 110 mm Hg at visit 0 and/or visit 1; history of uncontrolled arterial hypertension ≤ last 90 days before visit 1 and/or SBP < 95 mm Hg at visit 0 and/or visit 1; left HF with EF < 40% within last 90 days before visit 1; hypertrophic obstructive cardiomyopathy; severe CAD; symptomatic atherosclerotic disease (e.g., PAD); congenital or acquired valvular or myocardial disease; recurrent thromboembolism; *Hepatic:* hepatic dysfunction or severe insufficiency; *Renal:* eGFR <30 mL/min Pre-treatment with: NO donors (e.g., nitrates), PAH-specific medications; unable to perform a valid 6MWD test or a relative difference of more than 15% between the eligibility and baseline 6MWD test; anticipated life expectancy < 2 years.
DRUGS	**Intervention**	Riociguat 1.0 mg to 2.5 mg orally three times a day (individual dose titration)
	Comparator(s)	matching placebo orally three times a day
DURATION	**Phase**	
	Run-in	4 weeks
	Double-blind	16 weeks
	Follow-up	Safety follow-up after the double-blind phase: 30 days,[a] or Extension phase: ongoing, duration not reported
OUTCOMES	**Primary End Point**	Change from baseline in 6MWD after 16 weeks
	Other End Points	Change from baseline after 16 weeks in: PVR, NT-proBNP, WHO functional class, Borg CR10 Scale or Modified Borg Dyspnea Scale (measured at the end of the 6MWD test), EQ-5D questionnaire, LPH questionnaire; time to clinical worsening

		CHEST-1
NOTES	**Publications**	Ghofrani et al. (2013)[13]

6MWD = six-minute walk distance; AF = atrial fibrillation; BPM = beats per minute; CAD = coronary artery disease; CTEPH = chronic thromboembolic hypertension; DBP = diastolic blood pressure; EF = ejection fraction; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol 5-dimensions questionnaire; ERA = endothelin receptor antagonist; FEV_1 = forced expiratory volume in 1 second; HF = heart failure; HR = heart rate; LPH = Living With Pulmonary Hypertension; NO = nitric oxide; NT-p-BNP = amino terminal pro-brain natriuretic peptide; PAD = peripheral artery disease; PAH = pulmonary arterial hypertension; $PaCO_2$ = arterial partial pressure of carbon dioxide; PaO_2 = arterial partial oxygen pressure; PAP_{mean} = mean pulmonary artery pressure; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; SBP = systemic systolic blood pressure; SaO2 = oxygen saturation; TLC = total lung capacity; WHO = World Health Organization

[a]Safety follow-up for patients who did not proceed to the open-label extension trial (CHEST-2) or who discontinued treatment prematurely.

Note: Five additional reports were included.[7-9,14,15]

Source: CHEST-1 Clinical study report.[7]

3.2 Included Studies

3.2.1 Description of Studies

CHEST-1 was a 16-week multi-centre, multinational (26-country), double-blind, randomized (2:1), placebo-controlled trial stratified by region. It comprised 89 clinical centres worldwide, located predominantly in Western Europe (n = 34) and the Asia–Pacific region (n = 24), but included centres in Canada (n = 5) and the U.S. (n = 9). The primary objective of the trial was to test the efficacy and safety of riociguat compared with placebo in patients with inoperable CTEPH or persistent or recurrent PH following surgery.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

CHEST-1 enrolled patients with WHO FC II or III chronic thromboembolic hypertension (CTEPH) who were either not eligible for surgery (i.e., pulmonary endarterectomy [PEA]) or who had persistent or residual PH post-operatively. Eligible patients were aged ≥ 18 years with a baseline six-minute walk distance (6MWD) test result of between 150 m and 450 m, mean pulmonary artery pressure (PAP_{mean}) > 25 mm Hg and PVR > 300 dyn*s*cm^{-5} at least 90 days after of start of full anticoagulation. Non-specific supportive therapies for PH were permitted, including supplemental oxygen (stable dosing), but specific PH therapies (i.e., nitrates, endothelin receptor antagonists [ERAs], phosphodiesterase inhibitors, or prostacyclin analogues) were not allowed. Patients with uncontrolled systemic hypertension, or severe respiratory, coronary artery, hepatic, or renal disease (eGFR < 30 mL/min) were not eligible to participate.

b) Baseline Characteristics

Baseline characteristics were generally well balanced between groups. Patients enrolled in CHEST-1 were predominantly female (66%) and white (71%), with a mean age of 59 years and body mass index of 27 kg/m^2. The majority had WHO functional II (31%) or III (64%) CTEPH, which was considered inoperable in 72% of patients. Overall, at baseline, patients had a mean 6MWD of 347 m, a PAP_{mean} of 45 mm Hg, and a mean PVR of 787 dyn*s*cm^{-5}. According to the clinical expert consulted by the CADTH Common Drug Review (CDR), this profile of 6MWD and hemodynamic data is consistent with that of CTEPH patients seen in clinical practice. A few patients had had some previous exposure to medications specifically used in PH, namely ERAs (2%), prostacyclins or analogues (10%), or PDE-5 inhibitors (3%). A majority of patients were taking oral anticoagulants (96%) and diuretics (76%) concomitantly. Supplemental oxygen was used as an adjunctive concomitant therapy in almost a quarter of patients (22%).

Small imbalances were noted between riociguat and placebo groups, respectively, in the following baseline characteristics: female sex (68.2% versus 61.4%), smoking history (never: 65.3% versus 53.4%; former: 30.1% versus 38.6%), WHO FC III (61.8% versus 68.2%), CTEPH characterized by post-operative residual PH (30.1% versus 22.7%), 6MWD (342.3 m versus 356.0 m), and PVR (790.7 dyn*s*cm^{-5} versus 779.3 dyn*s*cm^{-5}). However, none of these differences were expected to have a meaningful impact on findings from the efficacy and safety analyses.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Riociguat (n = 173)	Placebo (n = 88)
Age (Years)		
Mean (SD)	59.3 (13.9)	59.2 (12.7)
Proportion ≥ 65 years, n (%)	74 (42.8)	36 (40.9)
Sex, n (%)		
Female	118 (68.2)	54 (61.4)
Race, n (%)		
White	120 (69.4)	65 (73.9)
Black or African American	7 (4.0)	1 (1.1)
Asian	37 (21.4)	20 (22.7)
Other	9 (5.2)	2 (2.3)
Weight (kg)		
Mean (SD)	74.0 (18.5)	76.2 (16.3)
Body Mass Index (kg/m^2)		
Mean (SD)	27.1 (5.8)	27.7 (5.3)
Systemic Blood Pressure (mm Hg)		
Systolic, median (range)	[redacted]	[redacted]
Diastolic, median (range)	[redacted]	[redacted]
WHO Functional Classification, n (%)		
I	3 (1.7)	0
II	55 (31.8)	25 (28.4)
III	107 (61.8)	60 (68.2)
IV	8 (4.6)	2 (2.3)
Missing	0	1 (1.1)
CTEPH Type, n (%)		
Inoperable	121 (69.9)	68 (77.3)
Post-operative, persistent, or residual PH	52 (30.1)	20 (22.7)
6MWD[a] (metres)		
Mean (SD)	342.3 (81.9)	356.0 (74.7)
PVR[a] ($dyn*s*cm^{-5}$)		
Mean (SD)	790.7 (431.6)	779.3 (400.9)
PAP_{mean}[a] (mm Hg)		
Mean (SD)	45.2 (12.8)	44.4 (10.0)
NT-proBNP[a] (pg/mL)		
Mean (SD)	1,508.3 (2,337.8)	1,705.8 (2,567.2)
Borg CR10 Dyspnea Scale[a]		
Mean (SD)	4.3 (2.3)	4.4 (2.2)
LPH Questionnaire[a] (Total Score)		
Mean (SD)	41.5 (21.7)	46.0 (22.6)
EQ-5D Score[a]		
Mean (SD)	0.64 (0.24)	0.66 (0.25)
Prior PH Medication, n (%)		
Endothelin receptor antagonists	5 (2.9)	1 (1.1)
Prostacyclins (including analogues)	17 (9.8)	9 (10.2)

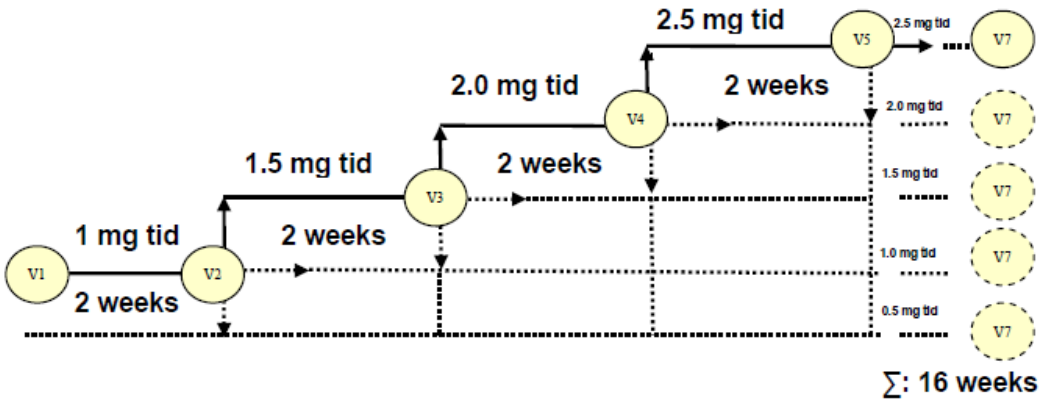
Characteristic	Riociguat (n = 173)	Placebo (n = 88)
PDE-5 inhibitors	3 (1.7)	4 (4.5)
Non-specific, Concomitant PH Medication		
Calcium channel blockers	34 (19.7)	17 (19.3)
Digitalis glycosides	18 (10.4)	8 (9.1)
Oral anticoagulants	165 (95.4)	85 (96.6)
Loop or high-ceiling diuretics	106 (61.3)	54 (61.4)
Thiazides or low-ceiling diuretics	28 (16.2)	11 (12.5)
Adjunctive Supplemental Oxygen		
Prior therapy	37 (21.4)	18 (20.5)
Concomitant therapy	38 (22.0)	19 (21.6)

6MWD = six-minute walk distance; COPD = chronic obstructive pulmonary disease; CTEPH = chronic thromboembolic pulmonary hypertension; EQ-5D = EuroQol 5-dimensions questionnaire; LPH = Living With Pulmonary Hypertension; NR = not reported; PAP_{mean} = mean pulmonary artery pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; SD = standard deviation; WHO = World Health Organization.
[a]ITT analysis set.
Note: Safety analysis set data presented unless otherwise indicated.
Source: CHEST-1 Clinical Study Report.[7]

3.2.3 Interventions

Following an initial 4-week pre-treatment (run-in) phase, patients were randomized (2:1) to either riociguat (1.0 mg to 2.5 mg) orally three times a day, or matching placebo added to usual care for a total of 16 weeks. An individual dose titration protocol was employed during the first eight weeks post-randomization, during which a 1.0 mg dose was initiated and subsequently titrated by 0.5 mg increments every two weeks as indicated by systemic systolic blood pressure readings until the target (maximum) dose of 2.5 mg three times a day or maximally tolerated dose was achieved. At the end of this eight-week titration period, patients were continued for another eight weeks on a dose-maintenance phase (Figure 2). Dose reductions for safety reasons were permitted throughout the 16 weeks of the trial, while dose increases were limited to the eight-week titration phase. During the trial, non-specific supportive therapies for PH were permitted, including supplemental oxygen (stable dosing), but specific PH therapies (i.e., nitrates, ERAs, phosphodiesterase inhibitors, or prostacyclin analogues) were not allowed.

FIGURE 2: TITRATION SCHEME — RIOCIGUAT (1.0 MG TO 2.5 MG) GROUP



Source: Clinical Study Report.[7]

3.2.4 Outcomes

The primary efficacy outcome in CHEST-1 was the change from baseline in 6MWD after 16 weeks. By contrast, the CDR systematic review protocol identified the key efficacy outcomes as survival, hospitalization, clinical worsening, change in WHO functional class, and health-related quality of life by validated scale; the 6MWD was relegated to "other" outcome status (Table 7). Time to clinical worsening was a composite outcome, which the manufacturer defined as the time to first occurrence of any one of seven events described in Table 8.

TABLE 7: EFFICACY OUTCOMES IN CHEST-1 VERSUS CADTH COMMON DRUG REVIEW SYSTEMATIC REVIEW PROTOCOL

CHEST-1[7]	CDR Systematic Review Protocol
Primary	**Key**
• 6MWD: change from baseline after 16 weeks	• Survival • Hospitalization • Clinical worsening • Change in WHO functional class • HRQoL measured by a validated scale
Secondary	**Other**

• Change from baseline after 16 weeks in:
  ○ PVR
  ○ NT-proBNP
  ○ WHO functional class[a]
  ○ Borg CR10 Scale[b] or Modified Borg Dyspnea Scale[b]
  ○ EQ-5D questionnaire
  ○ LPH questionnaire[c]
  ○ "Additional hemodynamic parameters"
• Time to clinical worsening[d]
	• 6MWD
	• Cardiopulmonary exercise testing (i.e., peak VO_2)
	• Change in PH symptoms
	• Change in:
	  ○ PVR
	  ○ PAP_{mean}
	  ○ BNP/NT-proBNP
	• Use of supplemental oxygen

6MWD = six-minute walk distance; AE = adverse event; BNP = brain natriuretic peptide; CDR = CADTH Common Drug Review; CTEPH = chronic thromboembolic hypertension; EQ-5D = EuroQol 5-dimensions questionnaire; HRQoL = health-related quality of life; LPH = Living With Pulmonary Hypertension questionnaire; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PAP_{mean} = mean pulmonary artery pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; peak VO_2 = maximal oxygen consumption; WHO = World Health Organization.

[a]Classification system for monitoring changes in functional capacity in PH based on the New York Heart Association (NYHA) classification system for heart failure.[1]

[b]Subjective scale used to rate intensity of breathlessness.

[c]Disease-specific quality of life instrument.

[d]Defined in Table 8.

None of the outcomes in CHEST-1 have been specifically validated in CTEPH; however, the 6MWD and the LPH questionnaire have been validated in PAH with associated minimal clinically important differences (MCIDs) of 33 m and 7 points, respectively (Table 15). The MCID for the EQ-5D, which has been tested in several conditions, ranges from 0.033 to 0.074.[16] It should be noted that some uncertainty exists with respect to how well change from baseline in 6MWD predicts clinical outcomes.[17]

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

Efficacy Outcome
Death (all-cause mortality)
Heart/lung transplantation
Rescue pulmonary endarterectomy due to persistent worsening of PH[a]
Hospitalization due to persistent worsening of PH[b,c]
Start of new PH-specific treatment due to worsening PH: *Includes endothelin receptor antagonists, prostacyclin analogues, PDE-5 inhibitors*
Persistent decrease of more than 15% from baseline or more than 30% compared with the last study-related measurement in 6MWD due to worsening PH:[b] *The persistence of the decrease has to be confirmed by a second measurement performed after 14 days. In case the period between first occurrence of the event and Visit 7/Termination Visit is less than 14 days, the decrease needs to be confirmed at Visit 7/Termination Visit*
Persistent worsening of functional class due to deterioration of PH:[c] *Patients who deteriorate from class II or III to class IV: The persistence of worsening has to be confirmed by a second measurement performed after 14 days. In case the period between first occurrence of the event and Visit 7/Termination Visit is less than 14 days, the decrease needs to be confirmed at Visit 7*

6MWD = six-minute walking distance; PDE-5 = phosphodiesterase-5; PH = pulmonary hypertension.
Source: CHEST-1 Clinical Study Report.[7]
[a]Although only patients considered as technically inoperable or with persisting or recurrent PH after PEA were allowed entry into the trial, it could not be excluded that, in exceptional cases, patients whose PH considerably deteriorated would undergo rescue PEA. In this case, respective events were considered as an event of special interest.
[b]Transient deteriorations of clinical status requiring hospitalization (e.g., treatment with short-term intravenous diuretics, positive inotropic drugs, or non-invasive ventilation) and allowing patients discharge within 48 hours, were not considered as persistent with respect to the event of special interest definition.
[c]In case of clinical deterioration, the investigator was to carefully assess if the deterioration of the patient's condition (e.g., worsening functional class) was related to the underlying PH or could be explained by an alternative cause (e.g., transient infection, musculoskeletal disease, surgical, or medical intervention [other than PH-related], exacerbation of a concomitant lung disease, medication non-compliance). Only persistent clinical deteriorations caused by the underlying PH were considered as events of special interest.

For a more detailed description of these outcomes and information on validity and MCIDs, see APPENDIX 5: VALIDITY OF OUTCOME MEASURES.

Safety data (including adverse events, serious adverse events, and withdrawals due to adverse events [WDAEs]) were collected according to regulatory requirements throughout the trial. In addition, the following adverse events were identified in the systematic review protocol as being of special interest: anemia, bleeding events, hypotension, orthostatic hypotension, presyncope, syncope, peripheral edema, acute renal failure, and gastritis.

3.2.5 Statistical Analysis

CHEST-1 was a randomized controlled trial (RCT) designed to test the superiority of riociguat (1.0 mg to 2.5 mg orally three times a day) versus matching placebo on the primary efficacy outcome of change from baseline in 6MWD. The sample size for the trial was contingent on demonstrating the superiority of riociguat versus placebo on the primary efficacy outcome. Assuming a standard deviation of 70 m, a power of 90%, and a two-sided significance level of 5%, with a 2:1 randomization, then 174 and 87 patients (in the treated and placebo groups, respectively) would be required to detect a placebo-adjusted difference of 30 m. Thus, in total, 261 patients valid for the efficacy analysis were needed;

allowing for a small invalidity rate of approximately 3%, a total of 270 randomized patients would be required.

Outcomes were analyzed based on the intention-to-treat (ITT) principle. Assuming normally distributed data, between-group comparisons on the change in the primary efficacy outcome (i.e., 6MWD) from baseline to 16 weeks were performed using analysis of covariance (ANCOVA) with baseline 6MWD as a covariate and treatment group and region as main effects. The mean difference was reported with 95% confidence intervals. A test of normality (the Shapiro-Wilk test for normality) was conducted on the ANCOVA residuals. If the data were determined to not be distributed normally (i.e., reject the Shapiro-Wilk null hypothesis that the data are normally distributed), then analyses of the change from baseline in 6MWD were also conducted using non-parametric testing (Wilcoxon test, stratified by region). The same approach was used to compare the change from baseline to 16 weeks in the following secondary efficacy outcomes: PVR, NT-proBNP, EQ-5D, and LPH questionnaire. The changes from baseline to 16 weeks in WHO FC and Borg CR10 Scale (or Modified Borg Dyspnea Scale) were tested using the stratified Wilcoxon test. The composite end point of time to clinical worsening (Table 8) over the 16-week study period was analyzed by stratified log-rank test, while Kaplan-Meier estimates were used for the proportion of patients experiencing the event, thereby taking into account the timing of the event relative to treatment initiation. Mantel–Haenszel weighting stratified by region was used in a sensitivity analysis conducted to estimate the between-group difference in event incidence.

A hierarchical testing procedure was used to adjust for multiplicity (i.e., type I error associated with multiple pairwise statistical comparisons). The pre-specified sequence for formal testing of treatment differences between riociguat and placebo on a series of seven secondary efficacy outcomes could proceed only if a statistically significant treatment difference favouring riociguat was initially detected on the primary efficacy outcome (i.e., 6MWD) at the two-sided 5% level. The order of subsequent statistical testing for secondary outcomes was:

- PVR
- NT-proBNP
- WHO FC
- Time to clinical worsening
- Borg CR10 Scale (or Modified Borg Dyspnea Scale)
- EQ-5D
- LPH questionnaire.

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

Subgroup analyses were conducted on the primary efficacy outcome (6MWD) only. These pre-specified subgroups included baseline WHO FC (I and II; III and IV); region; baseline 6MWD (< 320 m, ≥ 320 m, < 380 m, ≥ 380 m); gender; age (< 65 years, ≥ 65 years); race; operability status (inoperable, post-operable). The possibility of a treatment-by-region interaction was the only subgroup analysis finding that was to be targeted for further investigation.

Last observation carried forward (LOCF) was used to impute missing values of patients who discontinued study medication prematurely. If a patient did not complete the trial due to death or withdrawal due to clinical worsening (without termination visit), the worst possible value was imputed for the 6MWD, Borg CR10 Scale (or Modified Borg Dyspnea Scale), EQ-5D, and LPH questionnaire; for WHO FC, the worst

possible score (IV) was used in the case of withdrawal due to clinical worsening, while the worst possible score plus one (V) was used in the case of death. LOCF was also used for missing PVR and NT-proBNP values.

a) Analysis Populations

The primary analysis set for performing efficacy analyses in CHEST-1 was the ITT set, defined by the manufacturer as all randomized patients who received at least one dose of treatment. It should be noted that a true ITT set consists of all randomized patients regardless of treatment received; thus, the ITT set in CHEST-1 must be considered a modified ITT set. The safety analysis set was defined in the same way as the ITT set.

3.3 Patient Disposition

In CHEST-1, a total of 262 patients were randomized (2:1): 174 to riociguat and 88 to placebo; one patient was randomized in error to the riociguat group and did not receive the study drug. This same patient was the reason for the modified ITT set. The number of patients who discontinued treatment prematurely was slightly higher in the riociguat (14 [8.0%]) group compared with the placebo (5 [5.7%]) group, but the clinical expert consulted by CDR confirmed that this observation was not unexpected. The most common reasons for discontinuation were adverse event (RIO: 4 [2.3%] versus PB: 2 [2.3%]) and death (RIO: 2 [1.1%] versus PB: 2 [2.3%]) (Table 9).

TABLE 9: PATIENT DISPOSITION

	CHEST-1	
	Riociguat	Placebo
Screened, N	**446**	
Randomized, N (%)	**174 (39.0)**	88 (19.7)
Discontinued treatment, N (%)	**14 (8.0)**	5 (5.7)
Primary reason:		
Adverse event	4 (2.3)	2 (2.3)
Death	2 (1.1)	2 (2.3)
Lack of efficacy	2 (1.1)	1 (1.1)
Non-compliance with study drug	1 (0.6)	0
Protocol violation	3 (1.7)	0
Withdrawal by patient	2 (1.1)	0
ITT set, N	**173 (99.4)**	88 (100)
Safety set, N	**173 (99.4)**	88 (100)

ITT = intention-to-treat.
Source: CHEST-1 Clinical Study Report.[7]

3.4 Exposure to Study Treatments

The mean duration of treatment was 108.2 ± 21.2 days in the riociguat group compared with 110.2 ± 14.8 days in the placebo group; this corresponded to a median of 113 days each for the riociguat (range: 2 to 130 days) and placebo (range: 14 to 126 days) groups.

At the end of 16 weeks, 123 (76.9%) riociguat-treated patients (n = 160 [92.5%] still on treatment at study end point) were taking the highest dose of 2.5 mg, while 20 (12.5%), 10 (6.3%), 6 (3.8%), and 1 (0.6%) were taking 2.0 mg, 1.5 mg, 1.0 mg, and 0.5 mg, respectively. [redacted]

[redacted] A decrease in systemic systolic blood pressure or other "safety issue" comprised the most common reasons why a dose was either maintained (during the titration period only) or reduced.

3.5 Critical Appraisal

3.5.1 Internal Validity

Overall, the trial was adequately designed and executed with appropriate blinding, allocation concealment, and randomization. Interactive voice response system (IVRS) was used for treatment allocation and dosage titration (whether assigned riociguat or placebo); in the case of placebo assignment, a sham titration protocol was employed. Study medication and packaging were identical in appearance. The multiple criteria established for determining operability status (per experienced surgeon or central adjudication committee) and thus, trial eligibility, were deemed adequate by the clinical expert consulted by CDR. One patient was randomized in error (riociguat group) and did not receive a single dose of study medication; the ITT analysis set therefore actually represents a modified ITT analysis set, since this individual's data were excluded. However, this error in randomization likely had little or no impact on the findings of the study. Participant follow-up was > 90% complete at the end of the double-blind phase.

During its review of riociguat,[9] the FDA recalculated the treatment difference estimate for the primary efficacy outcome using non-parametric methods due to the non-normality of the 6MWD data. The FDA further indicated that the treatment difference estimates provided for the secondary efficacy outcomes would have been more appropriately reported using non-parametric (as opposed to parametric) methods. Nonetheless, there was general concordance between the parametric and non-parametric statistical tests, including for the primary outcome of change from baseline in 6MWD.

During the trial, both the Borg CR10 Scale and Modified Borg Dyspnea Scale were used to assess the same outcome. This occurred as a result of an amendment that was filed after the trial launched to replace the Modified Borg Dyspnea Scale with the Borg CR10 Scale. For consistency, both instruments were retained, such that patients randomized before the amendment (Amendment 3) used the Modified scale, while those entering the trial thereafter used the Borg CR10. It is unclear why the decision was made to replace the original scale; no explicit rationale could be found within the submission. It was not reported how many patients were using the Borg CR10 Scale and how many were using the Modified Borg Dyspnea Scale, as patients were analyzed together. It is also unclear to what extent the use of these two scales to assess the same outcome (i.e., dyspnea) may have introduced bias and in what direction; moreover, the possibility exists that any such bias may go undetected through the dilutional effect of analyzing the two symptom-scale cohorts together.

During a pre-submission meeting, the FDA had recommended against using a single active treatment arm in CHEST-1, favouring instead multiple, parallel, active dosing arms.[14]This was because a single, undifferentiated dosing arm would obfuscate the effects of dose and time on efficacy and safety outcomes.[14] Nonetheless, the single-arm design was retained, along with the potential confounding effects of dose and time.

Pre-specified subgroup analyses examining the consistency of the findings from the primary analysis of the primary efficacy outcome (i.e., 6MWD) included two different subgroup thresholds in baseline 6MWD: < or ≥ 320 m, and < or ≥ 380 m. It is unclear, however, how these specific thresholds were derived; there does not appear to be a rationale given in the submission. Input from the clinical expert consulted by CDR indicated there is a lack of consensus in the research community on the best way to

conduct sensitivity analyses around the 6MWD; it would therefore seem appropriate for the manufacturer to explicitly state how these distances were selected. For example, if these thresholds were derived from data collected prospectively during the trial or during screening, a risk of bias favouring riociguat could not be ruled out.

3.5.2 External Validity

The forced titration protocol (targeting a final dose of 2.5 mg three times a day) used during the first eight weeks of the trial was considered too aggressive by the FDA medical reviewer, who cited concerns about an excess risk of hypotension in vulnerable patients against the findings from an FDA analysis that showed a flat exposure-response curve (i.e., no incremental efficacy) at doses above 1.5 mg three times a day in the corresponding PAH trial (PATENT-1), in which an additional 1.5 mg three times a day fixed-dose arm was explored.[14] There was also some doubt about the implementation of such a dosing strategy in clinical practice.[14] In fact, the clinical expert consulted by CDR shared these hypotension concerns, indicating that in clinical practice, such titrations would proceed more slowly than every two weeks. During the final eight-week dose-maintenance phase of the trial, dose escalations were not permitted at all. This meant that patients for whom a dose reduction may have been made for safety reasons could not be subsequently re-challenged at the higher, previous dose. As a result of this restriction in dosing, there may be some divergence from the approach taken in clinical practice.

Usual care was not explicitly described in the submission. This impedes a determination of whether usual care (i.e., pharmacological and non-pharmacological treatments) delivered under the auspices of CHEST-1 was comparable to that delivered in the Canadian clinical practice setting.

Rescue PEA performed due to persistent worsening of PH was a component outcome within the composite end point of clinical worsening. However, the clinical expert consulted by CDR indicated this was not a relevant intervention in the context of Canadian clinical practice.

In the event of clinical deterioration during the trial, alternative therapy could be instituted at the discretion of the investigator, and riociguat treatment discontinued. The subjectivity inherent in this type of remediation is, on the one hand, consistent with the subjective nature of decision-making in clinical practice; however, in the context of a multinational trial, such freedom of intervention introduces the possibility of practice variation, which may diverge from Canadian clinical practice.

The entire trial was 16 weeks in duration, including an initial eight-week forced titration; the target or maximally tolerated dose achieved at the end of the eight weeks was then maintained for a further eight weeks. Although the trial was considered long enough to demonstrate a difference in its primary outcome (i.e., 6MWD), a similarly designed previous 16-week trial examining the use of bosentan in CTEPH[18] likely spent proportionately more time at target dose since the bosentan target dose of 125 mg twice daily was designed to be achieved after an initial four weeks at 62.5 mg twice daily. Moreover, according to the clinical expert consulted by CDR, there is a movement afoot in PH research to design trials that capture more clinically important outcomes, such as mortality and morbidity, rather than traditional surrogates (i.e., change from baseline in 6MWD) alone. Although CHEST-1 did include clinical worsening as a secondary outcome, the trial was underpowered (i.e., too short in duration and/or too few patients) to be able to detect any statistically significant changes. It should be noted that the MCID for the change in 6MWD was derived from studies of PAH patients, not CTEPH patients specifically. Furthermore, there remains uncertainty around the predictive ability of change from baseline in the 6MWD as a surrogate for clinical outcomes.[17] Thus, the primary evidence for efficacy of riociguat in CTEPH largely hinges upon the assumption that the 6MWD as a surrogate correlates well with clinical

events. Since a clear correlational relationship has not been established, there is a risk of concluding that a clinically meaningful treatment difference favouring riociguat exists when, in fact, it may not.

Only a small number (n = 24 [9.2%]) of North American patients were represented in the trial, of which nine (3.4%) were from Canada.; the majority of patients were based in Europe (n = 157 [60.2%]), including more than 40% from Western Europe. According to the clinical expert consulted by CDR, the clinical management of PH is more similar in approach between Canada and Western Europe than it is between Canada and the US. Hence, the limited number of Canadian study centres is unlikely to have an important effect on the generalizability of the study.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (see section 2.2, Table 4) are reported here. Subgroup data are reported only for the 6MWD (section 3.6.6), the trial's primary efficacy outcome, because comparative statistics were not performed on the other subgroups of interest identified in the systematic review protocol. As described in the statistical analysis (section 3.2.5), the ITT analysis was performed on changes occurring from baseline to week 16; however, in the case of missing values (e.g., premature discontinuation), data were imputed for the "last (post-baseline) visit." Therefore, for the ITT analyses of efficacy described below, "week 16" includes actual week 16 data and imputed data for those patients lacking week 16 data. A summary of the results of the hierarchical step-down testing procedure for the secondary efficacy outcomes can be found in Table 13.

3.6.1 Survival

Survival was not studied as an efficacy outcome in the trial. However, "death" was included as a component within the composite end point of clinical worsening. (Refer to section 3.6.3.)

3.6.2 Hospitalization

Hospitalization was not studied in isolation as an efficacy outcome; rather, it was included as a component within the composite end point of clinical worsening as "hospitalization due to PH." (Refer to section 3.6.3.)

3.6.3 Clinical Worsening

Clinical worsening, a secondary efficacy outcome in the trial, was a composite outcome whose seven components are described in section 3.2.4.

During the trial, the overall number of patients who experienced the composite outcome of clinical worsening was small and similar between the riociguat (4 [2.3%]) and placebo (5 [5.7%]) groups. The difference between groups in clinical worsening was not statistically significant either for incidence or time to event.

Of the individual components of interest (as defined by the systematic review protocol) in the composite outcome, one (1.1%) patient from the placebo group was hospitalized due to PH while no patients were hospitalized due to PH from the riociguat group. Two (1.2%) deaths occurred in the riociguat group compared with 3 (3.4%) in the placebo group (Table 11). Cardiac failure was the cause of death in 1 (0.6%) patient in the riociguat group and 2 (2.3%) in the placebo group. Cardiopulmonary failure (0 versus 1 [1.1%]) and a combination of renal failure, anemia, and catheter site hemorrhage (1 [0.6%] versus 0) accounted for the remaining deaths.

3.6.4 Change in WHO Functional Class

Change in WHO FC was a secondary efficacy outcome in the trial. A statistically significant change in WHO FC was observed from baseline to last visit, indicating that a greater proportion of patients improved than worsened with riociguat treatment than with placebo (*P* = 0.0026) (Table 10). This pattern seemed to be consistent over time from visit to visit. Nonetheless, the largest proportion of patients in both treatment groups (riociguat: 62% and placebo: 78%) remained unchanged with respect to WHO FC.

TABLE 10: CHANGE IN WHO FUNCTIONAL CLASS FROM BASELINE TO LAST VISIT

Change (Number of Classes[a])	Riociguat n (%)	Placebo n (%)
–2	4 (2.3)	0
–1	53 (30.6)	13 (14.9)
0	107 (61.8)	68 (78.2)
1	7 (4.0)	3 (3.4)
2	1 (0.6)	3 (3.4)
3	1 (0.6)	0
Treatment comparison	Riociguat versus placebo	
P value (stratified Wilcoxon test)	0.0026	

Last visit = last observed value (not including follow-up) for patients who completed the study or withdrew, except imputed worst value in case of death (WHO functional class V) or clinical worsening (WHO functional class IV) without a termination visit or a measurement at that termination visit.
[a]A negative (–) sign indicates improvement in functional class.
Source: CHEST-1 Clinical Study Report.[7]

3.6.5 Quality of Life

Quality of life was a secondary efficacy outcome in the trial. Two quality-of-life instruments — one disease-specific, one general — were used: the Living With Pulmonary Hypertension and EQ-5D questionnaires.

a) Living With Pulmonary Hypertension

After 16 weeks, a statistically significant improvement in the LPH total score was observed from baseline favouring riociguat (mean difference: –5.8; 95% confidence interval [CI], –10.5 to –1.1). However, the test conducted on the normality of the ANCOVA residuals was found to be statistically significant (*P* = 0.0001), indicating the LPH data were not normally distributed. Accordingly, non-parametric testing was subsequently employed, as per the statistical analysis plan, the result of which indicated no statistically significant difference between groups (*P* = 0.1220) (Table 11).

b) EQ-5D

After 16 weeks, a statistically significant improvement in EQ-5D utility score was observed from baseline favouring riociguat (mean difference: 0.1; 95% CI, 0.1 to 0.2). This difference is also clinically significant based on an MCID ranging from 0.03 to 0.05. However, as with the LPH questionnaire, the test conducted on the normality of the ANCOVA residuals from the EQ-5D data was found to be statistically significant (*P* = 0.0001), indicating that the data were not normally distributed. Non-parametric testing produced a similar statistically significant between-group difference (*P* < 0.0001) (Table 11). However, because of pre-specified hierarchical testing rules to adjust for multiplicity, the results of this analysis could not be considered statistically significant in the adjusted analysis.

3.6.6 Change in Six-Minute Walk Distance

The change from baseline in 6MWD — the trial's primary outcome — was identified as a secondary outcome in the systematic review. After 16 weeks, a statistically significant increase in the 6MWD was observed from baseline favouring riociguat treatment (adjusted least-squares [LS] mean difference: 45.7 m; 95% CI, 24.7 m to 66.6 m) (Table 11). However, the test conducted on the normality of the ANCOVA residuals was found to be statistically significant ($P = 0.0001$), indicating that the 6MWD data were not normally distributed. Non-parametric testing was subsequently employed, as per the statistical analysis plan, which also indicated a statistically significant between-group difference in the change from baseline in 6MWD ($P < 0.0001$). The FDA, in its statistical review of the data,[9] cited concerns about a treatment estimate being obtained from an analysis intended for normally distributed data (i.e., ANCOVA), and so opted to recalculate the treatment effect using non-parametric statistics. The FDA's revised 6MWD estimate was 39 m (95% CI, 25 m to 54 m). The MCID for the 6MWD has been reported in the PAH literature[19] as being 33 m; hence, the treatment difference — whether taken from the investigator's analysis (45.7 m) or the FDA (39 m) reanalysis — was clinically meaningful.

a) Subgroup Analyses

The manufacturer conducted several pre-specified subgroup analyses on the primary outcome, including by age (< 65 years versus ≥ 65 years), baseline 6MWD (< 320 m versus ≥ 320 m; < 380 m versus ≥ 380 m), and baseline WHO functional class (FC I and II versus FC III and IV). In the systematic review protocol, three additional subgroups of interest were identified (i.e., prior use of PH medication, baseline PVR, and baseline PAP_{mean}); however, none of these subgroups were analyzed in CHEST-1.

In the two subgroup analyses by age and baseline 6MWD, respectively, the results were consistent with those of the primary analysis findings in that riociguat treatment led to a statistically significantly greater improvement in 6MWD compared with placebo, regardless of the age or baseline 6MWD subgroup. Thus, no treatment by subgroup interactions was noted for these subgroups (6MWD < 320 m and ≥ 320 m: $P = 0.93$; 6MWD < 380 m and ≥ 380 m: $P = 0.78$; age < 65 years and ≥ 65 years: $P = 0.90$).[20] However, in the case of baseline WHO FC, there was no statistically significant difference from baseline in 6MWD after 16 weeks between riociguat and placebo in patients who were categorized as WHO FC I or II at baseline (mean difference: 25.5 m; 95% CI, –8.9 m to 59.8 m), which contrasts with the findings from the primary analysis. By comparison, in patients who were categorized as WHO FC III or IV at baseline, results were found to be consistent with those of the primary analysis: statistically significant improvement from baseline in 6MWD with riociguat versus placebo. The treatment by subgroup interaction ($P = 0.21$) was not statistically significant, however.[20]

3.6.7 Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (peak VO_2) was not studied as an efficacy outcome in the trial.

3.6.8 Change in Pulmonary Hypertension Symptoms

The change in PH symptoms, as assessed by the Borg CR10 Scale or Modified Borg Dyspnea Scale, was a secondary efficacy outcome in the trial. A statistically significant difference for the change from baseline in the Borg scale in favour of riociguat ($P = 0.0035$) was reported (Table 11). However, because of pre-specified hierarchical testing rules to adjust for multiplicity, the results of this analysis could not be considered statistically significant in the adjusted analysis.

3.6.9 Change in Pulmonary Vascular Resistance

The change in PVR was a secondary efficacy outcome in the trial. After 16 weeks, a statistically significant reduction in PVR was observed from baseline favouring riociguat treatment over placebo (adjusted LS mean difference: –246.4 dyn*s*cm^{-5}; 95% CI, –303.3 dyn*s*cm^{-5} to –189.5 dyn*s*cm^{-5}). However, the test conducted on the normality of the ANCOVA residuals was found to be statistically significant (P = 0.0001), indicating that the PVR data were not normally distributed. However, subsequent analysis using a non-parametric test (per the statistical analysis plan) indicated the observed, statistically significant between-group difference was upheld (Wilcoxon test P < 0.0001). The size of the improvement from baseline in PVR (approximately 30%) was considered clinically meaningful by the clinical expert consulted by CDR.

3.6.10 Change in Mean Pulmonary Artery Pressure

The change in mean pulmonary artery pressure (PAP_{mean}) was a secondary efficacy outcome in the trial. After 16 weeks, a statistically significant reduction in PAP_{mean} was observed from baseline favouring riociguat treatment versus placebo (adjusted LS mean difference: –5.0 mm Hg; 95% CI, –6.8 mm Hg to –3.2 mm Hg). However, the test for normality of the ANCOVA residuals was found to be statistically significant (P = 0.0231), indicating that the PAP_{mean} data were not normally distributed. Subsequent non-parametric testing, per the statistical analysis protocol, suggested the observed statistically significant between-group difference was upheld (Wilcoxon test P < 0.0001). The improvement from baseline observed in PAP_{mean} was considered by the clinical expert consulted by CDR as being supportive of the improvements observed in 6MWD and PVR.

3.6.11 N-terminal Prohormone of Brain Natriuretic Peptide

The change in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) from baseline to week 16 was a secondary outcome. A statistically significant reduction in NT-proBNP was observed from baseline to week 16 favouring riociguat treatment over placebo (adjusted LS mean difference: –444.0 pg/mL; 95% CI, –843.0 pg/mL to –45.0 pg/mL). However, the test conducted on the normality of the ANCOVA residuals was found to be statistically significant (P = 0.0001), indicating that the NT-proBNP data were not normally distributed. Non-parametric testing was subsequently employed, per the statistical analysis protocol, the result of which upheld the observed statistically significant between-group difference (Wilcoxon test P < 0.0001). The improvement from baseline observed in NT-proBNP was considered by the clinical expert consulted by CDR as being supportive of the improvements observed in 6MWD, PVR, and PAP_{mean}.

3.6.12 Use of Supplemental Oxygen

New concomitant adjunctive supplemental oxygen begun after the initiation of study drug was captured as a safety outcome and only presented as a descriptive statistic. It was prescribed in 10 (5.8%) patients in the riociguat group compared with 4 (4.5%) in the placebo group.

TABLE 11: EFFICACY OUTCOMES

	CHEST-1	
Primary: 6MWD	**Riociguat n = 173**	**Placebo n = 88**
Change From Baseline to Week 16 (metres)		
Adjusted[a] LS mean of change	**42.8**	–2.9
Mean difference (95% CI)	45.7 (24.7, 66.6)	
P value[b]	< 0.0001	
FDA Recalculation[9]		
Median difference (95% CI)	39 (25, 54)	
Clinical Worsening		
Number of patients with clinical worsening, n (%):	**4 (2.3)**	5 (5.7)
Hospitalization due to PH, n (%)	**0**	1 (1.1)
Start of new PH treatment, n (%)	**2 (1.2)**	1 (1.1)
Decrease in 6MWD due to PH, n (%)	**1 (0.6)**	2 (2.3)
Persistent worsening of functional class due to PH, n (%)	**0**	1 (1.1)
Death, n (%)	**2 (1.2)**	3 (3.4)
P value[b]	0.1724	
P value (Mantel–Haenszel[c])	0.2180	
Hemodynamic Parameters[d]		
Pulmonary Vascular Resistance (dyn*s*cm^{-5})		
N (%)	151 (87.3)	82 (93.2)
Adjusted[a] LS mean of change	–214.5	32.0
Mean difference (95% CI)	–246.4 (–303.3, –189.5)	
P value[b]	< 0.0001	
Mean Pulmonary Artery Pressure (mm Hg)		
N (%)	156 (90.2)	84 (95.5)
Adjusted[a] LS mean of change	–4.2	0.7
Mean difference (95% CI)	–5.0 (–6.8, –3.2)	
P value[b]	< 0.0001	
HRQoL[d]		
LPH Total Score		
N (%)	**170 (98.3)**	86 (97.7)
Adjusted[a] LS mean of change	**–8.2**	–2.5
Mean difference (95% CI)	–5.8 (–10.5, –1.1)	
P value[b]	0.1220	
EQ-5D Utility Score		
N (%)	**172 (99.4)**	87 (98.9)
Adjusted[a] LS mean of change	**0.08**	–0.06
Mean difference (95% CI)	0.1 (0.1, 0.2)	
P value[b]	< 0.0001	

	CHEST-1	
Change in Symptom Score		
Borg CR10 Scale[e]		
N (%)	**173 (100)**	88 (100)
Adjusted[a] LS mean of change	**–0.83**[f]	0.17[f]
Mean difference (95% CI)	NR	
P value[b]	0.0035	

CI = confidence interval; EQ-5D = EuroQol 5-dimensions questionnaire; HRQoL = health-related quality of life; LPH = Living With Pulmonary Hypertension questionnaire; PH = pulmonary hypertension.
[a]Adjustments for baseline value, treatment group, and region.
[b]Wilcoxon log-rank test, stratified by region, and performed if test of normality was statistically significant.
[c]Sensitivity test for the difference in incidences stratified by region.
[d]Change from baseline to week 16[e;]patients enrolled before Amendment 3 completed the Modified Borg Dyspnea Scale.
[f]Mean change from baseline.
Source: CHEST-1 Clinical Study Report.[7]

3.7 Harms

Only those harms identified in the review protocol (see section 2.2) are reported here. (For detailed harms data, see APPENDIX 4: DETAILED OUTCOME DATA.)

3.7.1 Adverse Events

Adverse events appeared to occur at a slightly higher frequency in the riociguat (RIO) (91.9%) group compared with the placebo (PB) (86.4%) group. The most commonly occurring adverse events in riociguat-treated patients were headache (RIO: 24.9% versus PB: 13.6%) and dizziness (RIO: 22.5% versus PB: 12.5%) followed by dyspepsia (RIO: 17.9% versus PB: 8.0%), peripheral edema (15.6%, 20.5%), nasopharyngitis (RIO: 15.0% versus PB: 9.1%), nausea (RIO: 11.0% versus PB: 8.0%), diarrhea (RIO: 9.8%, PB: 4.5%), vomiting (RIO: 9.8% versus PB: 3.4%), and hypotension (RIO: 9.2% versus PB: 3.4%) (Table 12).

3.7.2 Serious Adverse Events

SAEs were frequent in both groups (RIO: 19.7% versus PB: 15.9%), with no particular pattern of concentration for individual AEs; however, SAEs were most often classified as cardiac disorders (RIO: 5.8% versus PB: 6.8%) or respiratory, thoracic, and mediastinal disorders (RIO: 6.4% versus PB: 2.3%) (Table 12).

3.7.3 Withdrawals Due to Adverse Events

WDAEs occurred in five patients (2.9%) in the riociguat group and two patients (2.3%) in the placebo group. The most common reason for permanent WDAE was due to cardiac disorders (RIO: 1 [0.6%] versus PB: 2 [2.3%]) (Table 12). During weeks 8, 12, and 16, dose reductions occurred in three patients (1.8%), four patients (2.5%), and one patient (0.6%) respectively in the riociguat group, compared with 0, 1 (1.2%), and zero patients in the placebo group.

3.7.4 Notable Harms

The following harms of interest were pre-specified in the review protocol following consultation with the clinical expert involved in the review: peripheral edema (RIO: 27 [15.6%] versus PB: 18 [20.5%]), blood pressure-related events (RIO: 24 [13.9%] versus PB: 7 [8.0%]) including hypotension (RIO: 16 [9.2%] versus PB: 3 [3.4%]), bleeding events (RIO: 23 [13.3%] versus PB: 10 [11.4%]), anemia (RIO: 6 [3.5%] versus PB: 1 [1.1%]), gastritis (RIO: 6 [3.5%] versus PB: 0), and acute renal failure (RIO: 1 [0.6%] versus PB: 0) (Table 12).

TABLE 12: HARMS

	CHEST-1	
	Riociguat	Placebo
AEs		
Patients with ≥ 1 AEs, N (%)	159 (91.9)	76 (86.4)
Most common AEs (≥ 5%):		
Headache	43 (24.9)	12 (13.6)
Dizziness	39 (22.5)	11 (12.5)
Dyspepsia	31 (17.9)	7 (8.0)
Peripheral edema	27 (15.6)	18 (20.5)
Nasopharyngitis	26 (15.0)	8 (9.1)
Nausea	19 (11.0)	7 (8.0)
Diarrhea	17 (9.8)	4 (4.5)
Vomiting	17 (9.8)	3 (3.4)
Hypotension	16 (9.2)	3 (3.4)
Constipation	10 (5.8)	1 (1.1)
INR increased	10 (5.8)	4 (4.5)
Upper respiratory tract infection	10 (5.8)	4 (4.5)
Cough	9 (5.2)	16 (18.2)
Dyspnea	8 (4.6)	12 (13.6)
Back pain	7 (4.0)	5 (5.7)
Insomnia	4 (2.3)	6 (6.8)
Blood creatinine increased	3 (1.7)	5 (5.7)
Pain in extremity	3 (1.7)	5 (5.7)
SAEs		
Patients with ≥ 1 SAEs, N (%)	34 (19.7)	14 (15.9)
Most common SAEs (≥ 1%):		
Right ventricular failure	6 (3.5)	3 (3.4)
Syncope	4 (2.3)	3 (3.4)
Hemoptysis	3 (1.7)	0
Catheter site hemorrhage	2 (1.2)	0
Chronic renal failure	2 (1.2)	0
Gastritis	2 (1.2)	0
Pulmonary hypertension	2 (1.2)	0
Respiratory failure	2 (1.2)	0
Anemia	1 (0.6)	1 (1.1)
Atrial flutter	1 (0.6)	1 (1.1)
Bronchitis	1 (0.6)	1 (1.1)
Chronic obstructive pulmonary disease	1 (0.6)	1 (1.1)
Dyspnea	1 (0.6)	1 (1.1)
Bipolar I disorder	0	1 (1.1)
Cardiac arrest	0	2 (2.3)
Cardiopulmonary failure	0	1 (1.1)
Deep vein thrombosis	0	1 (1.1)
Gastric ulcer	0	1 (1.1)
Infection	0	1 (1.1)
Injury	0	1 (1.1)
Light chain analysis increased	0	1 (1.1)
Renal impairment	0	1 (1.1)
WDAEs		
WDAEs, N (%)	5 (2.9)	2 (2.3)

	CHEST-1	
	Riociguat	**Placebo**
Most common WDAEs (≥ 1%):		
Right ventricular failure	1 (0.6)	2 (2.3)
Cardiac arrest	0	1 (1.1)
Notable Harms		
Peripheral edema	27 (15.6)	18 (20.5)
Blood pressure–related:[b]	24 (13.9)	7 (8.0)
Blood pressure decreased	3 (1.7)	1 (1.1)
Presyncope	2 (1.2)	0
Syncope	4 (2.3)	3 (3.4)
Hypotension	16 (9.2)	3 (3.4)
Orthostatic hypotension	1 (0.6)	0
Bleeding events[c]	23 (13.3)	10 (11.4)
Anemia	6 (3.5)	1 (1.1)
Gastritis	6 (3.5)	0
Acute renal failure	1 (0.6)	0

AE = adverse event; INR = international normalized ratio; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a]One patient had multiple contributing factors listed: renal failure, anemia, catheter site hemorrhage.
[b]Numbers denote number and percentage of patients with events per treatment group. Multiple mentions per patient are possible.
[c]Bleeding events included hemorrhage, but not laboratory adverse events.
Source: CHEST-1 Clinical Study Report.[7]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was drawn from one phase III (CHEST-1) double-blind, randomized (2:1), placebo-controlled trial comprising 262 patients with WHO FC II or III CTEPH, which was either inoperable or characterized by post-operative residual PH. Patients were randomly assigned riociguat (1.0 mg initially) orally three times a day or matching placebo for 16 weeks. During the first eight weeks, an individual dose titration protocol was used to target a final dose of 2.5 mg three times a day or the maximally tolerated dose; the remaining eight weeks comprised a dose-maintenance phase.

4.2 Interpretation of Results

4.2.1 Efficacy

The primary efficacy outcome in CHEST-1 — identified as a secondary outcome in the systematic review protocol — was the change in 6MWD from baseline to 16 weeks. A statistically significant increase in 6MWD was observed favouring riociguat (adjusted LS mean difference: 45.7 m; 95% CI, 24.7 m to 66.6 m). The FDA's recalculated median difference of 39 m (95% CI, 25 m to 54 m) was performed after statistical testing revealed that the data on which the original estimate was based were not normally distributed. The MCID for the 6MWD has been reported as being 33 m among patients with PAH[19] (no CTEPH-specific MCID was identified). Hence, it would appear that the treatment difference, whether taken from the original (45.7 m) or the FDA (39 m) reanalysis, was clinically meaningful. As noted previously (and in APPENDIX 5: VALIDITY OF OUTCOME MEASURES), change in 6MWD as an outcome has several limitations, most notably its modest-to-poor validity as a surrogate for clinical events, such as mortality and morbidity. Nevertheless, change in 6MWD remains the most commonly used primary efficacy outcome in PH studies. The clinical expert involved in the CDR review indicated that despite its limitations as an outcome, 6MWD remains an important marker of patients' functioning and should be considered alongside other key clinical outcomes.

The manufacturer conducted several pre-specified subgroup analyses on the primary outcome, including by age (< 65 years versus ≥ 65 years), baseline 6MWD (< 320 m versus ≥ 320 m; and < 380 m versus ≥ 380 m), and baseline WHO functional class (FC I and II versus FC III and IV). Results were largely consistent with the primary analysis, with the exception of the baseline WHO FC I and FC II subgroup analysis. In that analysis, there did not appear to be a treatment difference between riociguat and placebo. This finding is not unexpected, as patients with less functional limitation (especially those in WHO FC I) and not receiving treatment (other than placebo) would have less difficulty walking farther in six minutes than their counterparts whose functional limitation was more severe (WHO FC III or IV). Thus, detecting a difference in 6MWD between riociguat and placebo would be more difficult among patients categorized with less functional limitation.

Survival and hospitalizations were identified in the systematic review protocol as key efficacy outcomes; however, they were not analyzed as individual outcomes in the trial, but as components of the composite end point of clinical worsening (Table 8). The proportion of patients who experienced clinical worsening was small and not statistically different between treatment groups (RIO: 2.3% versus PB: 5.7%). This finding is not surprising: rates of clinical worsening would be expected to be low during a study of only 16 weeks' duration, and the study did not have sufficient power to detect differences in this outcome between treatment groups.

Change in WHO FC was a secondary efficacy outcome in the trial. A statistically significant change in WHO FC was observed from baseline to last visit, indicating that a (statistically significant) greater proportion of patients improved than worsened from baseline with riociguat treatment than with placebo (P = 0.0026). Nevertheless, most patients (62% with riociguat and 78% with placebo) experienced no change in WHO FC. Yet, given the difficult-to-treat and progressive natural history of CTEPH and PH in general, treatments that delay worsening and that may improve patient functional status by one or more categories may be meaningful for patients.

The observed superiority of riociguat versus placebo in improving exercise capacity and FC was strengthened by the statistically significant improvements in hemodynamic parameters (change from baseline in PVR and PAP_{mean}) and NT-proBNP. These changes were considered by the clinical expert consulted by CDR to be supportive of the primary outcome, particularly the magnitude of the change in PVR, which represented about a 30% reduction from baseline.

The PH-specific LPH questionnaire and the EQ-5D were suggestive of the superiority of riociguat (versus placebo) in improving HRQoL, especially with an observed between-group difference of 0.1 (95% CI, 0.1 to 0.2) on the EQ-5D, which exceeds the upper range of the MCID on the instrument (i.e., 0.074). However, because of the step-down hierarchical analysis plan used in CHEST-1, statistical testing was stopped prior to testing these outcome measures. Therefore, it remains to be determined what the impact of riociguat is on HRQoL.

Clinical practice guidelines for the medical management of CTEPH are limited in terms of the guidance provided, reflecting the paucity of available evidence for treating this subtype of PH.[1,3] European guidelines[1] make only a cursory mention of the available classes of ERAs, phosphodiesterase-5 (PDE-5) inhibitors, and prostanoids — commonly employed in PAH — as potential monotherapy options in CTEPH. Canadian guidelines[3] go a step further in identifying a specific drug within each class where there exists some supportive trial evidence; however, no one class or drug is favoured over another.

According to the clinical expert involved in the review, bosentan (an endothelin receptor antagonist) is currently the most widely used oral drug in treating CTEPH. In a published double-blind, placebo-controlled RCT in CTEPH, the BENEFiT trial (N = 157),[18] from which data for bosentan were drawn for the manufacturer's submitted ITC (see APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY for details), bosentan was compared against placebo in a sample of CTEPH patients. BENEFiT's patients appeared fairly comparable to patients in CHEST-1 with respect to baseline characteristics; however, BENEFiT's patients tended to be slightly older (mean age: 63 years) than those from CHEST-1 (mean age: 59 years) and had also been permitted to have lower systemic SBP to qualify for trial inclusion compared with CHEST-1 (i.e., ≥ 85 mm Hg[21] versus ≥ 95 mm Hg, respectively). Both trials were similarly designed (with the exception of an individualized dose titration protocol, which was only used in CHEST-1), of similar duration, and with similar outcomes. While both CHEST-1 and BENEFiT showed improvements in PVR, only CHEST-1 showed a statistically significant improvement in change from baseline in 6MWD.[7,18]

In support of its pharmacoeconomic (PE) submission, the manufacturer submitted a systematic review and ITC of treatments for CTEPH, the full appraisal of which can be found in APPENDIX 7: SUMMARY AND APPRAISAL OF MANUFACTURER SUBMITTED NETWORK META-ANALYSIS. Briefly, a total of three studies were included in the ITC, from which the manufacturer compared riociguat with bosentan and sildenafil through a common placebo or standard therapy comparator using the Bucher method. The main efficacy outcomes included change in 6MWD, PVR, NT-proBNP, Borg Dyspnea Scale, and WHO FC

while specific harms outcomes included mortality, headache, hepatic dysfunction, and nasopharyngitis. Of the analyses performed, only two active comparisons yielded statistically significant differences: riociguat performed better than bosentan on the 6MWD and had a lower risk of hepatic dysfunction than bosentan. In addition to the methodological limitations highlighted in the Appendix, it is notable that several clinically important adverse events identified by the FDA reviewer,[14] the clinical expert consulted by CDR, and the Health Canada reviewer[15] were not specifically compared in this ITC, in particular the risk of hypotension. Other adverse event concerns identified by the reviewers, but not specifically examined in the ITC included the risk of bleeding or anemia,[14,15] upper gastrointestinal tract dysfunction,[15] and acute renal failure;[14] these adverse event concerns were also identified by the clinical expert consulted by CDR along with peripheral edema. According to the manufacturer,[22] these particular adverse event data are not available in the public domain; thus, they were not included in the ITC. By contrast, neither regulatory reviewer nor the consulting clinical expert identified headache, hepatic dysfunction, or nasopharyngitis as safety outcomes of interest. Because of the essentiality of harms inputs to the outcome of a cost-consequence analysis, identifying the most clinically relevant harms is integral to accurately estimating or appreciating the net value of therapy.

Although CHEST-1 was considered long enough to demonstrate a difference in its primary outcome (i.e., 6MWD), a 16-week RCT is nonetheless limited in terms of the information it can provide on long-term efficacy (especially mortality, morbidity and disease progression outcomes) and safety. According to the clinical expert consulted by CDR, there is a movement afoot in PH research to design trials that capture more clinically important outcomes, such as mortality and morbidity, rather than traditional surrogates alone. Although CHEST-1 did study clinical worsening as a composite secondary outcome, which was composed of several hard clinical end points, the trial was not powered to be able to detect any statistically significant changes.

North American (9%) and Canadian (3%) patients represented a small proportion of the trial population. The majority of patients were European (60%), including a large portion (40%) from Western Europe. Despite the limited data from North America, the clinical expert consulted by CDR indicated that the approach to the clinical management of PH is more similar between Canada and Western Europe than it is between Canada and the US. Therefore, the clinical expert expressed confidence in the generalizability of the trial's findings to Canadian clinical practice.

4.2.2 Harms

Adverse events were common in CHEST-1 in both groups (RIO: 91.9% versus PB: 86.4%). Headache (RIO: 24.9% versus PB: 13.6%), dizziness (RIO: 22.5% versus PB: 12.5%), and dyspepsia (RIO: 17.9% versus PB: 8.0%) were the most commonly reported adverse events associated with riociguat treatment. Blood pressure–related events, which were of particular interest to the CDR systematic review, occurred more often with riociguat treatment than placebo (RIO: 13.9% versus PB: 8.0%), and were driven mainly by hypotension events (RIO: 9.2% versus PB: 3.4%).

Serious adverse events were also common (RIO: 19.7% versus PB: 15.9%), and most often classified as cardiac disorders (RIO: 5.8% versus PB: 6.8%) or respiratory, thoracic, and mediastinal disorders (RIO: 6.4% versus PB: 2.3%). WDAEs were infrequent (RIO: 2.9% versus PB: 2.3%).

Following the completion of CHEST-1,[7] patients were enrolled in an open-label extension trial called CHEST-2.[8] Patients who received riociguat during CHEST-1 were continued on the same dose they received on their last day of follow-up in CHEST-1 while patients who had received placebo during CHEST-1 were initiated on riociguat using the same, 8-week dose titration protocol used in CHEST-1. At the time of the March 2013 safety update, 237 (90.8%) participants were enrolled in CHEST-2, 155 (89.6%) from the former riociguat treatment group and 82 (93.2%) from placebo. No new safety signals were identified from this limited snapshot of observational data. Because this safety update of CHEST-2 data was performed more than one year ago, CDR was interested in obtaining a more recent safety update; however, the manufacturer confirmed that none was available (see Appendix 6: Summary of Open-Label Extensions Study for details).

The FDA, in a pre-submission meeting with the manufacturer,[14] had expressed some concerns about the proposed single-dose treatment arm of the trial. Specifically, the regulator had indicated a preference for a design that included a broader dosage range (i.e., multiple, parallel, active arms) in order to reduce the risk of confounding on dose effect and time from dose titrations performed for safety reasons (e.g., reductions).[14] Likewise, concern was raised about the forced titration dosing algorithm[14] in which doses were escalated by 0.5 mg three times a day increments every two weeks based on the trough systolic arterial blood pressure (SBP) remaining at, or above, 95 mm Hg. The FDA questioned whether this titration protocol might be overly aggressive compared with the approach used in clinical practice. For example, the algorithm did not take into account the magnitude of SBP lowering achieved at the current dose, such that dose escalation at the next visit would necessarily proceed regardless the magnitude of reduction in SBP achieved, as long as the SBP ≥ 95 mm Hg; likewise, the FDA considered the window for holding a dose constant too narrow.[14] Either scenario was felt to potentially place patients at higher risk for symptomatic hypotension. Despite these concerns, the original design was retained. When it came time for the FDA to review the clinical data for riociguat, the medical reviewer reiterated similar concerns about the dosing strategy (i.e., single active treatment arm, aggressivity of dosing protocol) and the risk of hypotension and related sequelae. With approximately 40% of the trial patients ≥ 65 years, concerns were raised about the risk of occult coronary, cerebral, or peripheral vascular disease and the known association of these diseases with poor tolerance to hypotension.[14] The reviewer also cited an FDA exposure-response analysis of accompanying PAH trial (PATENT-1) data, which suggested a potential lack of incremental efficacy in doses exceeding 1.5 mg three times a day. The FDA also noted that a number of patients — about 25% in CHEST-1 — did not tolerate the 2.5 mg three times daily target dose, likely because of hypotensive effects.[14]

5. CONCLUSIONS

In a single adequately designed RCT, riociguat was shown to improve the primary efficacy outcome of change from baseline in 6MWD compared with placebo in patients with WHO FC II or III CTEPH who were either not eligible for surgery or who had persistent or residual PH symptoms post-operatively. The improvement in 6MWD with riociguat treatment is augmented by the accompanying improvements noted in hemodynamic parameters and in WHO FC. Although survival and hospitalization were identified as key outcomes in the systematic review protocol, they were only studied as components of the secondary composite outcome of clinical worsening, which was underpowered to detect statistically significant differences between treatments. Riociguat treatment was more commonly associated with headache, dizziness, dyspepsia, nasopharyngitis, diarrhea, vomiting, and hypotension versus placebo. Serious adverse events were frequent in both groups and most often classified as "cardiac" or "respiratory, thoracic, and mediastinal" disorders. WDAEs were infrequent and similar between groups. Five deaths occurred during the trial: two in the riociguat group and three in the placebo group. No additional safety signals were identified from the data in the open-label extension trial (CHEST-2). How well riociguat compares with other drugs used in CTEPH is uncertain, as the data from the ITC submitted by the manufacturer are limited; comparisons of tolerability are further hampered by the omission of relevant safety outcomes (e.g., hypotension) from the analysis.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by Canadian Agency for Drugs and Technologies in Health staff based on the input provided by patient groups.

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

The Pulmonary Hypertension Association of Canada (PHA Canada) is a charitable organization established by patients, caregivers, parents and family members collectively referred to as "Canadians living with PH." PHA Canada aims to end isolation, provide education, support pulmonary hypertension (PH) patients and their caregivers, and create a united Canadian PH community. PHA Canada receives funding from its Corporate Committee members, including Actelion Pharmaceuticals, Bayer Inc., GlaxoSmithKline, McKesson Specialty Pharmacy, Pfizer Canada, Shoppers Drug Mart Specialty Health, 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.

2. Condition and Current Therapy-Related Information

PHA Canada compiled the information for this submission by requesting it from patients with chronic thromboembolic pulmonary hypertension (CTEPH) and their caregivers, as well as from stories gathered and heard during the organization's five years of work with the PH community.

PH has a significant impact on the lives of patients. Usually unknown to the patient prior to diagnosis, it is a shock and 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.

With PH, day-to-day life is made difficult, exhausting, and challenging. Symptoms, which can fluctuate from day to day, include difficulty breathing with any exertion, dizziness with chest constriction or with sudden exertion, fatigue, swelling of feet and ankles, syncope, and chest pain. Difficulty breathing, peripheral edema, and dizziness and syncope are the most important to control. 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, or lift medium weight loads (e.g., groceries, children), and complete household chores. Patients can struggle with even basic tasks such as bathing, dressing, or preparing meals. As a result, patients 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, patients commonly experience depressed mood, anxiety, and feelings of helplessness and hopelessness as they are faced with a serious illness with a high risk of death within a few years. As PH is most often an invisible disease, patients often face social stigma, as exemplified when parking in a handicapped spot and receiving comments of "abusing the system."

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 and financial responsibilities, and become the main providers for any children. Caregivers also attend doctors' appointments, help with managing side effects and medications, provide psychosocial support, and advocate for the patient. As a result, caregivers often face emotional and physical burnout and relationships sometimes become victim to the strains of the patient–caregiver dynamic.

Currently, there is no drug therapy specifically for CTEPH. For these patients, the best option for relief is pulmonary thromboendarterectomy (PTE) surgery. There are currently no options for patients with inoperable CTEPH, or for patients post-PTE surgery who continue to have residual CTEPH.

Patients are sometimes prescribed sildenafil and bosentan, which are medications approved for the treatment of pulmonary arterial hypertension. Patients see a measure of improvement with these off-label medications, but they continue to struggle with their symptoms — particularly shortness of breath and fatigue — which prevent them from participating in many daily activities. A major challenge with these medications is insurance coverage, as they require special authority from doctors and approval through a lengthy bureaucratic process. Patients may also use diuretics, blood thinners, and supplemental oxygen. High deductibles and additional costs for associated medications make the cost of living with CTEPH quite high.

3. Related Information About the Drug Being Reviewed

Patients with no experience with Adempas hope it will enable them to lead a somewhat more normal life, closer to the one they lived prior to developing the disease. They expect the drug will help overcome some of the tiredness, difficulty breathing, and other physical limitations. One patient remarked that a 20% improvement over the way she is currently feeling would be significant for her. Most patients are willing to tolerate some measure of side effects, such as headaches and nausea, as long as their overall condition is stabilized and the benefits (ability to perform day-to-day tasks and ability to function with less shortness of breath) outweigh the side effects.

Individuals already taking Adempas (through a clinical trial, compassionate supply, or paying for the drug out-of-pocket) remarked that this medication has been life-changing. Patients felt the drug was effective at managing shortness of breath and increasing overall physical exertion ability with little-to-no side effects (some headaches and occasional heartburn were reported). Patients reported that taking the Adempas three times a day was no easier or more difficult than taking any other eight-hourly medication. Long term, patients were hopeful that as long as they developed no major adverse effects from the medication, they would continue to experience improved quality of life due to the drug controlling the major symptoms of their CTEPH.

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:	February 11, 2014
Alerts:	Weekly search updates until (date of CDEC meeting)
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
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.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
oemezd	Ovid database code; Embase 1974 to present, updated daily
/	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

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(riociguat* or Adempas* or BAY 63-2521 or BAY63-2521 or BAY 632521).ti,ot,ab,sh,hw,rn,nm.
2	625115-55-1.rn,nm.
3	1 or 2
4	3 use pmez
5	*riociguat/
6	(riociguat* or Adempas* or BAY 63-2521 or BAY63-2521 or BAY 632521).ti,ab.
7	5 or 6
8	7 use oemezd
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
24	remove duplicates from 23
25	(comment or newspaper article or editorial or letter or note).pt.
26	24 not 25

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	February 3 to 7, 2014
Keywords:	Adempas (riociguat), pulmonary hypertension
Limits:	No date or language limits used

Relevant websites from the following sections of the Canadian Agency for Drugs and Technologies in Health 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
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
No potentially relevant reports were excluded	

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 13: SECONDARY EFFICACY VARIABLES: SUMMARY OF HIERARCHICAL TESTING

Variable[a]	Treatment Effect ANCOVA *P* Value	Shapiro-Wilk Test *P* Value[b]	Stratified Wilcoxon Test *P* Value	Statistically Significant	Statistically Significant in Hierarchical Testing
6MWD (Primary)	< 0.0001	0.0001	**< 0.0001**	Yes	Yes
PVR	< 0.0001	0.0001	**< 0.0001**	Yes	Yes
NT-proBNP	0.0293	0.0001	**< 0.0001**	Yes	Yes
WHO functional class	–	–	**0.0026**	Yes	Yes
Time to clinical worsening	0.2180[c]	–	**0.1724**[d]	No	No
Borg CR10 Scale[e]	–	–	**0.0035**	Yes	No
EQ-5D questionnaire	0.0002	0.0001	**< 0.0001**	Yes	No
LPH questionnaire	0.0165	0.0001	**0.1220**	No	No

ANCOVA = analysis of covariance; 6MWD = six-minute walk distance; EQ-5D = EuroQol 5-dimensions questionnaire; LPH = Living With Pulmonary Hypertension questionnaire; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; PVR = pulmonary vascular resistance; WHO = World Health Organization.
Note: *P* values used to determine statistical significance are given in bold.
[a]Variables are ordered in the sequence of testing.
[b]Test of normality of the data.
[c]Mantel–Haenszel estimate *P* value for incidence of clinical worsening.
[d]Stratified log-rank test *P* value for time to clinical worsening.
[e]Patients enrolled before CHEST-1 analysis plan Amendment 3 used the Modified Borg Dyspnea Scale.
Source: CHEST-1 Clinical Study Report.[7]

TABLE 14: CHANGE IN WORLD HEALTH ORGANIZATION FUNCTIONAL CLASS

Visit	WHO Functional Class	Riociguat (n = 173)	Placebo (n = 88)
Baseline	n		
	I		
	II		
	III		
	IV		
Last Visit	n		
	I		
	II		
	III		
	IV		
	V[a]		
Change From Baseline at Last Visit	n		
	–2		
	–1		
	0		
	1		
	2		
	3		
P value (stratified Wilcoxon test)			

WHO = World Health Organization.
[a]V represented an imputed worst value in case of death.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

The objective of this section is to describe outcomes measures used in CHEST-1 and report minimal clinically important difference (MCID) estimates where available.

Findings

A summary of the scales and other outcome measures from CHEST-1 is presented in Table 15.

TABLE 15: SUMMARY OF OUTCOMES USED IN CHEST-1

Instrument	Description	Validated in CTEPH	Validated in PAH	MCID	Comments
6MWD[19,23-32]	Total distance walked in 6 minutes. Submaximal test to assess exercise capacity. Widely used in studies and clinical practice. Accepted by regulatory agencies.	No	Yes	33.0 m (range: 25.1 to 38.6 m)	Baseline 6MWD correlated with outcomes in PAH.[33] Absolute 6MWD during treatment is correlated with outcomes in PAH. Change in 6MWD moderately to poorly correlated with outcomes in PAH.[17,33,34] Ceiling effect in patients with less severe disease.[35]
Clinical worsening[36,37]	Composite outcome includes various components designed to measure PH morbidity and mortality (see Table 8 for definition in CHEST-1). May also be reported as time to clinical worsening.	No	No[a]	Unknown	Recommended as a key outcome for use in PAH studies by 2008 Dana Point and 2013 NICE clinical trial design task forces.[38] Rescue PEA performed due to PH persistent worsening component not a relevant intervention in the context of Canadian clinical practice.
Borg dyspnea score[39-41]	Borg CR10: Open scale. Ranges from 0 [no dyspnea] to 10 [max. dyspnea] points), with ability for subject to assign scores above 10. Modified Borg Dyspnea Scale: 11-point scale (ranges from 0 [no dyspnea] to 10 [max. dyspnea] points).	No	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 six-minute treadmill walk test.[39-41]

Instrument	Description	Validated in CTEPH	Validated in PAH	MCID	Comments
EQ-5D[42]	Generic HRQoL instrument applied to wide range of health conditions and treatments. Two parts: health states and VAS. Index score generated using multi-attribute utility function to the descriptive system.	No	No	Unknown in CTEPH General: ranges 0.033 to 0.074[16]	Different utility functions for US and UK. Scores < 0 represent health states that are valued by society as being worse than dead; scores 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Well validated in different diseases.
WHO functional class[43]	PH severity classification system based on NYHA HF classification (Table 2).	No	No	Unknown	
Living with PH questionnaire[2,3]	PH-specific HRQoL scale derived from MLHFQ. 6-point Likert scale (21 items) range: 0 (no) to 5 (very much). Total score range: 0 to 105; higher score indicates worse HRQoL.	No	Yes	Physical and emotional sub-scales: change of 3 points. Total score: change of 7 points.	

6MWD = six-minute walk distance; CTEPH = chronic thromboembolic pulmonary hypertension; EQ-5D = EuroQol 5-dimensions questionnaire; HF = heart failure; HRQoL = health-related quality of life; MCID = minimal clinically important difference; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NICE = National Institute for Health and Care Excellence; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; pts = points; SF-36 = Short Form Health Survey 36-item; WHO = World Health Organization.

[a]Clinical worsening has not been formally validated, but it has been recommended as an outcome for use in PAH studies by the 2008 Dana Point and the 2013 NICE clinical trial design task forces to more accurately reflect disease progression.

Six-Minute Walk Distance

The six-minute walk distance (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 hypertension (PH) and is used in most pulmonary arterial hypertension (PAH) trials as a primary outcome.[24,27,44-46] 6MWD is also used in clinical practice and is widely accepted by regulatory agencies. The main advantage of the 6MWD test 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).[24] 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.[33] However, change in 6MWD is a surrogate outcome and has demonstrated moderate to poor correlation with key clinical outcomes in PAH.[17,33,34] 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.[28-30] Furthermore, in multi-centre trials experience and technical skills may vary between sites, and the

correlations between the 6MWD and CPET might improve over time with increasing experience.[31] 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] or World Health Organization [WHO] functional class II, baseline 6MWD > 450 m).[47] Despite these limitations, improvement in function, as reflected by 6MWD, remains clinically valuable in PH.

Saouti et al.[48] and Reesnik et al.[49] both reported a positive correlation between 6MWD and survival for patients with inoperable CTEPH. Saouti et al.[48] reported a significantly lower survival rate in patients with a 6MWD less than 298 m as compared to patients with a 6MWD greater than 298 m. Reesnik et al.[49] determined that 6MWD results decreased in proportion to NYHA functional class and were correlated with hemodynamic improvements in CTEPH patients after one year. Mathai et al., using distributional and anchor-based methods of estimating a MCID, reported a change of 33.0 m (range 25.1 to 38.6 m) compared with placebo for patients with PAH.[19] No MCID was identified for patients with CTEPH.

Clinical Worsening

Clinical worsening events include death; heart or lung transplantation; rescue pulmonary endarterectomy (PEA) due to persistent worsening of PH; initiation of new PH medications; hospitalization; persistent decrease of > 15% in 6MWD from baseline or > 30% compared with the last 6MWD measurement due to worsening PH; and persistent worsening of WHO FC due to deterioration of PH as a single outcome. The composite (combined) outcome of clinical worsening events may improve precision (increased statistical power would make it easier to detect a therapeutic benefit) and offer a more global assessment of the patient and his or her clinical state by including non-fatal but important morbid events in the course of disease.[36] Therefore, it is likely a clinically relevant outcome. However, there are limitations using composite outcomes in PH studies:[36]

- Confounding may occur if a component outcome occurs at a different rate versus others in the composite outcome, especially during a trial of short duration.
- Including outcomes such as hospitalization in a composite outcome may be a problem because they may, at least partially, be driven by social or non-medical factors, which may disproportionately influence a composite that also contains more direct measures of disease progression (death).
- A composite outcome driven by individual outcomes with centre-specific availability (lung transplantation and atrial septostomy) may pose difficulty in multi-centre trials.
- In a composite outcome, each of the components has equal clinical implications.
- There is no standardized definition for clinical worsening and the component end points vary across PAH trials.

In a recent assessment of survival in an observational study, Frost et al. suggested that clinical worsening was highly predictive of subsequent mortality and was meaningful as a primary end point in clinical trials of PAH.[37]

No CTEPH-specific information was identified regarding clinical worsening.

Borg Dyspnea Score and Borg CR10

The Borg CR10 is a categorical scale from 0 to 10 where 0 represents normal breathing and 10 represents maximum dyspnea.[50] However, patients may report a score greater than 10 to describe their own sensation of dyspnea with greater precision than a 10-point score would allow, thus making this an open scale. The modified Borg dyspnea score is a version of the CR10.[50] The modified Borg dyspnea score is a scale from 0 to 10, where 0 represents no dyspnea and 10 represents maximal

dyspnea. It is obtained at the end of the 6MWD test and reflects the maximum degree of dyspnea at any time during the walk test. Although it is a subjective assessment scale for assessing the intensity of breathlessness, it has been shown to be reliable for quantifying dyspnea in trial patients with chronic obstructive pulmonary disease (COPD) who have undergone a six-minute treadmill walk test.[39-41] No studies have clearly addressed the MCID of the score.

No CTEPTH-specific information was identified regarding the Borg dyspnea score.

EuroQoL Questionnaire

The EuroQoL 5-Dimensions Questionnaire (EQ-5D)[42,51] is a generic quality-of-life (QoL) instrument that may be applied to a wide range of health conditions and treatments. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[42,51] The second part is a 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS which best represents their health on that day.

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

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference-weighted health index score based on the descriptive system
- A self-reported assessment of health status based on the EQ VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. The EQ-5D demonstrated convergent validity with the Medical Research Council Dyspnea Scale in both primary and specialist care settings within the UK and US and across five EU countries.[52] The MCID for the EQ-5D ranges from 0.033 to 0.074.[16]

No CTEPH-specific information was identified regarding the EQ-5D.

WHO Functional Classification for Pulmonary Hypertension

The WHO FC system for PH was adapted from the NYHA classification (Table 2). The WHO FC system is used widely in clinical practice and as an outcome in clinical trials. One study reported clinicians' assessment of functional class varied widely in PAH, especially when classifying patients as functional class II or III.[43] The intraclass correlation coefficient was approximately 0.6. In one instance, 53% of clinicians classified a patient as functional class II and 47% classified the patient as functional class III. Thus, despite wide use of the WHO classification system, interrater agreement may be poor.

No CTEPH-specific information was identified regarding WHO FC.

Living With Pulmonary Hypertension Questionnaire

The Living With Pulmonary Hypertension (LPH) Questionnaire was derived from the Minnesota Living with Heart Failure Questionnaire for use in PH populations. The instrument comprises 21 questions (items) that are responded to on a 6-point Likert scale ranging from 0 (No) to 5 (Very much). The responses to all 21 questions are summed for a total score ranging from 0 to 105. A physical dimension score (range 0 to 40, 8 items) and an emotional dimension score (range 0 to 25, 5 items) can also be calculated. A higher score on all LPH scores indicates that patients are more affected by their PH.[23]

In terms of clinical validity, according to Bonner et al., the LPH physical and total scores were able to differentiate between patients of different severity levels based on WHO functional class or 6MWD.[23] The LPH emotional score, however, did not demonstrate the same differentiation. There was high correlation between the Borg scores and the LPH physical score. A change of 3 points for the sub-scales (range: 1.48 to 4.71) and 7 points (range: 4.41 to 11.02) for the total score were indicated as the MCID values for PAH.[23]

APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDY

Objective

The objective of this section is to summarize the results of CHEST-2, the open-label extension study to CHEST-1.[8] The following summary is based on unpublished data provided by the manufacturer on the open-label extension phase.

Findings

Study Design

After completion of the 16-week double-blind CHEST-1 trial, a multi-centre, multinational open-label long-term extension study was initiated to evaluate the safety and tolerability of riociguat (1 mg, 1.5 mg, 2 mg, or 2.5 mg three times a day) in patients with chronic thromboembolic pulmonary hypertension (CTEPH). The aim was to collect additional information to evaluate safety and tolerability. The trial recruited 237 patients and these patients were treated with their individual optimal dose (between 0.5 mg and 2.5 mg three times a day) of open-label riociguat.

Patients who received riociguat during CHEST-1 were continued on the same dose they received on their last day of follow-up in CHEST-1, while patients who had received placebo during CHEST-1 were initiated on riociguat using the same, eight-week dose titration protocol used in CHEST-1. Efficacy outcomes evaluated in the open-label extension stage included the change from baseline (week 0 in CHEST-1) for the following: six-minute walk distance (6MWD), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), World Health Organization functional class (WHO FC), Borg CR10 score, EuroQoL 5-Dimensions Questionnaire (EQ-5D) score, Living With Hypertension Questionnaire (LPH) score, use of health care resources, and time to clinical worsening. Safety outcomes evaluated included adverse events, mortality, laboratory parameters, vital signs, electrocardiogram parameters, and blood-gas analysis.

At the time of the March 2013 safety update, 237 participants were enrolled in CHEST-2: 155 from the former riociguat treatment group and 82 from placebo. The majority of the patients were female (153 [64.6%]). The mean age of patients was 59.1 years. The majority of patients were white (165 [69.6%]).[53]

Results

The mean duration of treatment was 582.2 days (590.4 in the former riociguat group and 566.6 in the former placebo group). Adverse event results are presented in Table 16. There were eight treatment discontinuations due to treatment-emergent adverse events. Four discontinuations were determined to be related to riociguat and one event resulted in death. Eight deaths were reported between May 2012 and March 2013 (safety cut-offs 1 and 2). The causes of death were cardiac arrest (n = 2), cardiac failure (n = 1), sudden death (n = 1), unspecified cause of death (n = 1), thyroid cancer (n = 1), multi-organ failure (n = 1), and pneumonia and neoplasm (n = 1).

TABLE 16: RESULTS SUMMARY FOR OPEN-LABEL EXTENSION

Number (%)	Former Riociguat	Former Placebo	Total
Patients evaluable for AEs	155	82	237
Patients with AEs	152 (98.1)	78 (95.1)	230 (97.0)
Patients with SAEs	65 (41.9)	38 (46.3)	103 (43.5)
Patients with any AE-related death	9 (5.8)	4 (4.9)	13 (5.5)
Patient with any TEAE	150 (96.8)	78 (95.1)	228 (96.2)
Any serious TEAE	63 (40.6)	37 (45.1)	100 (42.2)
Discontinuation due to TEAE	3 (1.9)	5 (6.1)	8 (3.4)
Discontinuation due to serious TEAE	3 (1.9)	4 (4.9)	7 (3.0)
Deaths reported between safety cut-offs 1 and 2	6	2	8

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Manufacturer's submission.[8]

TABLE 17: MOST FREQUENTLY REPORTED TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS

Number (%)	Former Riociguat	Former Placebo	Total
Any event	63 (40.6)	37 (45.1)	100 (42.2)
Atrial fibrillation	2 (1.3)	3 (3.7)	5 (2.1)
Cardiac arrest	4 (2.6)	1 (1.2)	5 (2.1)
Cardiac catheterization	4 (2.6)	1 (1.2)	5 (2.1)
Gastrointestinal hemorrhage	4 (2.6)	1 (1.2)	5 (2.1)
Pneumonia	5 (3.2)	3 (3.7)	8 (3.4)
Pulmonary hypertension	6 (3.9)	6 (7.3)	12 (5.1)
Right ventricular failure	8 (5.2)	4 (4.9)	12 (5.1)
Syncope	10 (6.5)	7 (8.5)	17 (7.2)

Manufacturer's submission.[8]

Summary

The goal of the study was to evaluate the long-term safety and efficacy of riociguat. Design limitations (open-label, no control group) limit its usefulness for providing any further information on the risk of harm for riociguat. No new safety concerns were identified in the open-label extension phase.

APPENDIX 7: SUMMARY AND APPRAISAL OF MANUFACTURER SUBMITTED NETWORK META-ANALYSIS

Objective

The objective of this review is to summarize the methods and results and conduct a critical appraisal of the manufacturer-provided network meta-analysis[54] (NMA) comparing the efficacy and safety of riociguat with sildenafil and bosentan.

Summary of Network Meta-analysis

Rationale

The manufacturer indicated that the systematic review and NMA were undertaken because none of the identified randomized controlled trials (RCTs) were designed to assess the comparative efficacy of riociguat, sildenafil, and bosentan.

Methods

a) Eligibility Criteria

The manufacturer conducted a systematic review to investigate the epidemiologic, clinical, quality of life, and economic burden of illness of chronic thromboembolic pulmonary hypertension (CTEPH).

From the articles identified for inclusion in the systematic review, randomized controlled trials were assessed for inclusion in the NMA. The authors performed a feasibility assessment to determine which of the five clinical trials identified (four identified from the literature, plus the manufacturer-provided CHEST-1 data) could be included for analysis in the NMA. The heterogeneity of the patient populations and clinical time points was assessed. After assessment, two trials were excluded from the analysis due to population heterogeneity, leaving three clinical trials to be included in the NMA.

b) Intervention and Comparators

The included interventions and doses were riociguat 0.5 mg to 2.5 mg three times a day, sildenafil, and bosentan. (Dose information was not clearly described for sildenafil or bosentan.) These were compared with placebo or standard therapy.

c) Outcomes

The main outcomes of interest for the NMA included a mean difference between treatments in change in six-minute walk distance (6MWD), pulmonary vascular resistance (PVR), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), or Borg dyspnea scale. Relative treatment differences were estimated for WHO functional class (at study end point), mortality, headache, hepatic dysfunction, nasopharyngitis, adverse events, and withdrawal due to adverse events.

d) Analysis

The quality of the included studies was assessed using the National Institute for Health and Care Excellence checklist for study quality assessment. This scale does not provide a numerical value of quality assessment but rather indicates if randomization, concealment, prognostic similarity between groups, double blinding, imbalances in dropouts between groups, non-reporting of outcomes, and intention-to-treat (ITT) analysis were present, absent, or unclear. A table of the quality assessment results was provided.

Indirect comparisons were undertaken using fixed-effects Bayesian meta-analyses to compare all treatments of interest. This model assumes that all included studies share one true effect size. Analysis was also undertaken using the Bucher indirect treatment comparison (ITC) method. The authors indicated that, given the simplicity of the network, the Bayesian and Boucher results should be identical. Both sets of results were presented in the NMA. Analyses were performed for five efficacy and six safety outcomes (11 outcomes for riociguat versus bosentan and eight outcomes for riociguat versus sildenafil).

Subgroup analyses were performed between riociguat and bosentan for two outcomes (6MWD and PVR). The subgroups examined were patients with inoperable CTEPH and patients with persistent or recurrent CTEPH after pulmonary endarterectomy.

Results

Results of the Network Meta-analysis

The key end point in the included trials was change in 6MWD from baseline. The reported results were similar between the mixed treatment comparison and Boucher methods.

TABLE 18: OUTCOMES USED IN INDIRECT TREATMENT COMPARISON

Outcome (Change from Baseline)	Number of Patients	Number of Studies	Effect Measure
Efficacy			
6MWD	420	3	Mean difference
NT-proBNP	390	3	Mean difference
PVR	389	3	Mean difference
Borg CR10 score	420	3	Mean difference
WHO FC	418	2	Odds ratio
Safety			
Any AE	418	2	Odds ratio
Discontinuation due to AEs	418	2	Odds ratio
Headache	437	3	Odds ratio
Hepatic dysfunction	418	2	Odds Ratio
Nasopharyngitis	418	2	Odds ratio
Mortality	418	2	Odds ratio

6MWD = six-minute walk distance; AE = adverse event; NT-proBNP = N-terminal of the prohormone brain natriuretic peptide; PVR = pulmonary vascular resistance; WHO FC = World Health Organization functional class
Source: Manufacturer's submission.[54]

Bucher Method Analysis

The analysis of indirect comparisons using the Bucher method identified significant differences in the efficacy of riociguat when compared with bosentan for 6MWD. There were no significant differences in the efficacy of riociguat when compared with sildenafil. For safety outcomes, the odds of experiencing hepatic dysfunction were significantly lower when comparing riociguat with bosentan. Further detail is presented in Table 19. *P* values were not presented in the NMA.

TABLE 19: SUMMARY OF INDIRECT COMPARISON RESULTS USING BUCHER METHOD

Comparison	Estimate	95% CrI
Change in 6MWD		
Riociguat versus placebo	MD = 44.4	23.3 to 65.7; S
Riociguat versus bosentan	MD = 42.3	9.8 to 74.8; S
Riociguat versus sildenafil	MD = 26.9	–16.3 to 70.1; NS
Change in NT-proBNP		
Riociguat versus placebo	MD = –366.5	–796.0 to 64.3; NS
Riociguat versus bosentan	MD = 243.0	–239.1 to 725.1; NS
Riociguat versus sildenafil	MD = –89.0	–696.4 to 520.3; NS
Change in PVR		
Riociguat versus placebo	MD = –248.6	–319.6 to –177.4; S
Riociguat versus bosentan	MD = –72.8	–181.4 to 35.9; NS
Riociguat versus sildenafil	MD = –51.8	–233.1 to 129.6; NS
Change in Borg CR10 Score		
Riociguat versus placebo	MD = –1.0	–1.6 to –0.4; S
Riociguat versus bosentan	MD = –0.4	–1.3 to 0.5; NS
Riociguat versus sildenafil	MD = –0.1	–1.6 to 1.4; NS
WHO Functional Class		
Riociguat versus placebo	OR = 2.19	1.29 to 3.71; S
Riociguat versus bosentan	OR = 1.15	0.51 to 2.61; NS
Any AE		
Riociguat versus placebo	OR = 1.57	0.64 to 3.76; NS
Riociguat versus bosentan	OR = 0.84	0.28 to 2.48; NS
Discontinuation Due to AEs		
Riociguat versus placebo	OR = 1.42	0.28 to 11.50; NS
Riociguat versus bosentan	OR = 2.53	0.23 to 27.73; NS
Headache		
Riociguat versus placebo	OR = 2.27	1.16 to 4.76; S
Riociguat versus bosentan	OR = 0.41	0.04 to 3.97; NS
Riociguat versus sildenafil	OR = 0.87	0.06 to 12.73; NS
Hepatic Dysfunction		
Riociguat versus placebo	OR = 0.21	0.01 to 2.72; NS
Riociguat versus bosentan	OR = 0.04	0.00 to 0.94; S
Nasopharyngitis		
Riociguat versus placebo	OR = 1.67	0.76 to 3.93; NS
Riociguat versus bosentan	OR = 0.76	0.11 to 5.10; NS
Mortality		
Riociguat versus placebo	OR = 0.31	0.04 to 2.11; NS
Riociguat versus bosentan	OR = 0.32	0.01 to 8.86; NS

6MWD = six-minute walk distance; AE = adverse event; CrI = credible interval; MD = mean difference; NS = not significant; NT-proBNP = N-terminal of the prohormone brain natriuretic peptide; OR = odds ratio; PVR = pulmonary vascular resistance; S = significant; WHO = World Health Organization
Source: Manufacturer's submission.[54]

The large credible interval reported for NT-proBNP is likely a result of the small sample size of the sildenafil trial. No significant difference was identified in reduction of Borg dyspnea score between treatments; however, there appears to be a trend toward higher improvements in Borg score for riociguat compared with bosentan. There was no statistically significant difference in the odds of experiencing any adverse event when taking riociguat compared with bosentan. No comparison was made with sildenafil for this outcome. There was a statistically significant reduction in the odds of developing hepatic dysfunction when taking riociguat as compared with bosentan.

Subgroup Analyses

Two subgroups were identified (inoperable CTEPH and recurrent CTEPH following endarterectomy) and analyses were done to compare riociguat and bosentan for 6MWD and PVR. The Boucher ITC results are presented in Table 20 and Table 21.

TABLE 20: SUMMARY OF INDIRECT COMPARISON RESULTS USING BOUCHER METHOD — INOPERABLE CTEPH

Comparison	Estimate	95% CrI
6MWD		
Riociguat versus placebo	MD = 51.8	26.2 to 77.5; S
Riociguat versus bosentan	MD = 43.5	1.4 to 85.6; S
PVR		
Riociguat versus placebo	MD = –290.2	–379.8 to –200.3; S
Riociguat versus bosentan	MD = –156.5	–293.0 to –20.0; S

6MWD = six-minute walk distance; CrI = credible interval; MD = mean difference; NS = not significant; PVR = peripheral vascular resistance; S = significant.
Source: Manufacturer's submission.[54]

TABLE 21: SUMMARY OF INDIRECT COMPARISON RESULTS USING BOUCHER METHOD — POST-PEA CTEPH

Comparison	Estimate	95% CrI
6MWD		
Riociguat versus placebo	MD = 25.3	–11.5 to 62.3; NS
Riociguat versus bosentan	MD = 37.0	–10.2 to 84.2; NS
PVR		
Riociguat versus placebo	MD = –142.5	–241.4 to –43.0; S
Riociguat versus bosentan	MD = 131.1	–34.5 to 296.8; NS

6MWD = six-minute walk distance; CrI = credible interval; MD = mean difference; NS = not significant; PEA = pulmonary endarterectomy; PVR = peripheral vascular resistance; S = significant.
Source: Manufacturer's submission.[54]

For patients with inoperable CTEPH, treatment with riociguat resulted in significantly greater improvement in 6MWD and PVR from baseline compared with bosentan. For the post-surgical CTEPH subgroup, the differences in 6MWD and PVR from baseline were not significantly different between treatments.

Critical Appraisal of Network Meta-analysis

The quality of the manufacturer's network meta-analysis was assessed according to the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[55] Details and commentary for each of the relevant items identified by the ISPOR group are provided in **TABLE 22.**

Limitations

No information was provided on the assessment of clinical, methodological, and statistical heterogeneity among the three included studies for the ITC/NMA with regard to, for example, patient characteristics (age, gender, and race); disease duration; previous treatments; and best supportive care; etc.

In the absence of an appropriate assessment of the assumptions relating to the use of the ITC/NMA, it is difficult to assess the potential impacts of potential heterogeneities among the three trials on the evaluation of comparative efficacy and safety between riociguat and its two comparators. Therefore, it is unknown to what extent the study findings would be valid based on the simple Bucher method.

Only three studies were included in the network and all had relatively small sample sizes, with the sildenafil trial including only 19 participants in both arms of the study. Moreover, the extremely small number of trials (i.e., only three trials for three comparisons) included in the ITC/NMA further comprised the strength of the network, leaving the analysis results highly unreliable.

Strengths

Some strengths of the manufacturer-provided NMA include quality assessment of the included studies; inclusion of a network diagram; clear and comprehensive literature search methods; and duplicate study screening, selection, and data extraction.

TABLE 22: CRITICAL APPRAISAL BASED ON ISPOR NETWORK META-ANALYSIS CHECKLIST[55]

Checklist Item	Details and Comments
Are the rationale for the study and the study objectives stated clearly?	• Rationale was not clearly stated
Does the methods section include the following? • Description of eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction (validity/quality assessment of individual studies)	• Literature search methods, search terms, and dates are presented • Search strategy is presented • Inclusion criteria for the systematic review are presented • Critical appraisal was performed and results presented but not discussed • Duplicate study selection, appraisal, and data extraction occurred
Are the outcome measures described?	• Outcome measures were described
Is there a description of methods for analysis/synthesis of evidence? Do the methods described include the following? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• Description of analysis methods and models, description of statistics used, and justification provided • Studies were assessed for heterogeneity in patient population and outcome evaluation time points before inclusion in the analysis • Did not describe whether bias was identified or how it was dealt with is identified • Fixed-effects Bayesian meta-analysis and Boucher ITC method were used for all outcomes

Checklist Item	Details and Comments
Are sensitivity analyses presented?	• Sensitivity analyses were not conducted
Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Network diagram was presented • Study characteristics and trial inclusion/exclusion criteria were presented in an appendix • Patient characteristics from the studies were not provided
Does the study describe an assessment of model fit? Are competing models being compared?	• The NMA used fixed-effects Bayesian and Boucher models • Random effects modelling was not used because no two studies investigated the same comparison
Are the results of the evidence synthesis (ITC/MTC) presented clearly?	• Tables with results for the pairwise comparisons were presented • Forest plots were presented for individual studies and pairwise comparisons
Sensitivity/scenario analyses	• Sensitivity analyses were not conducted
Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis • External validity • Implications of results for target audience	• Forest plots were provided summarizing individual study outcome results • Robustness of the analysis may have been limited due to the small sample sizes of the included clinical trials • Heterogeneity may exist between trials due to the incomplete description of concomitant medications treatment during the trials and the incomplete description of what constituted standard care • No discussion of implications for target audience

ISPOR = International Society of Pharmacoeconomics and Outcomes Research; NMA = network meta-analysis; MTC = mixed treatment comparison.
Source: Jansen et al., 2011.[55]

Summary

Due to the absence of head-to-head trials to include in its analysis that compared riociguat with sildenafil or with bosentan, the manufacturer undertook a systematic review and used the identified RCTs to perform a NMA. Overall, the efficacy of riociguat was superior only to bosentan for change in 6MWD and odds of hepatic dysfunction. There were no significant differences found with respect to changes in PVR, NT-proBNP, or Borg dyspnea scale, or the odds ratios for relative treatment differences in WHO functional class, mortality, headache, nasopharyngitis, adverse events, or withdrawal due to adverse events. Some important limitations of the NMA include the small number of patients in the included studies, the small number of trials, and lack of sensitivity analyses.

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