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Cost-effectiveness of riociguat and bosentan for the treatment of chronic thromboembolic pulmonary hypertension

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Thesis

COST-EFFECTIVENESS OF RIOCIGUAT AND BOSENTAN FOR THE TREATMENT OF CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

by

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DEDICATION

I dedicate this work

To all my mentors, for your investments

To my parents, for your sacrifice and example

To my son and loving wife, for your support and understanding.

You were my biggest cheerleaders; I couldn't have done this without you.

To everyone who dares to dream, your dream can come true.

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I am indebted to my committee members for their time, expertise, and insights. Special thanks to Dr. Alexandra Ward, Dr. Mari-Lynn Drainoni, and Dr. Allan Walkey for serving on my committee, and for reviewing the draft documents. Your feedback and insight made the completion of this project an enjoyable experience. A special thanks to Late Professor James Burgess, for his unwavering support, patience, guidance, and mentorship.

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ABSTRACT

OBJECTIVE: To conduct a cost-effectiveness analysis of riociguat and bosentan in the management of chronic thromboembolic pulmonary hypertension (CTEPH) from a United States payer perspective.

METHODS: A Markov model was developed following the recommendations of the International Society of Pharmacoeconomics and Outcomes Research - Society for Medical Decision Making Modeling Good Research Practices. A cohort of patients with inoperable CTEPH or post-pulmonary endarterectomy CTEPH were simulated over their lifetime. Health outcomes were measured as quality-adjusted life years (QALY). Efficacy and safety data were obtained from BENEFiT and CHEST-1 trials. Drugs costs, associated costs for the management of CTEPH, were obtained from Redbook and published information such as the Healthcare Cost and Utilization Project (HCUPnet) and Centers for Medicare & Medicaid Services Physician Fee Schedule. Deterministic and probabilistic sensitivity analyses were performed to assess the robustness of the model projections.

RESULTS: Riociguat was more effective than bosentan with an incremental cost of $132,065 and an incremental quality-adjusted life year (QALY) of 0.20, corresponding to an incremental cost-effectiveness ratio (ICER) of -$649,380 per QALY (in favor of

riociguat). Riociguat had a lower total discounted lifetime cost compared to bosentan ($2,307,488 versus $2,439,555). Probabilistic sensitivity analyses confirmed dominance of riociguat in 74% of the Monte Carlo simulations.

CONCLUSIONS: Results of this model indicates that riociguat is more effective and less costly than bosentan in the management of patients with inoperable CTEPH or post-pulmonary endarterectomy CTEPH.

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LIST OF ABBREVIATIONS

6MWD	Six-minute walking distance
AEs	Adverse Events
BGR	Brooks-Gelman-Rubin
CEAC	Cost-Effectiveness Acceptability Curve
CENTRAL	Cochrane Central Database of Randomized Trials
CPT	Current Procedural Terminology
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
DMEPOS	Durable Medical Equipment, Prosthetics/Orthotics, and Supplies Fee Schedule
EQ-5D	European Quality of Life Five Scale Dimension
ERAs	Endothelin Receptor Antagonists
FC	Functional Class
FE	Fixed-Effects
HCPCS	Healthcare Common Procedure Coding System
HCUP	Healthcare Cost and Utilization Project
HTA	Health Technology Assessment
ICD	International Classification of Disease
ICER	Incremental Cost-Effectiveness Ratio
ITC	Indirect Treatment Comparison
LOR	Log-odds Ratio

LYG	Life-Years Gained
MD	Mean Difference
mPAP	Mean Pulmonary Artery Pressure
mRAP	Mean Right Atrial Pressure
NICE	National Institute of Health and Care Excellence
NT-proBNP	N-Terminal Pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
PAH	Pulmonary Arterial Hypertension
PEA	Pulmonary Endarterectomy
PSA	Probabilistic Sensitivity Analysis
PVR	Pulmonary Vascular Resistance
QALY	Quality adjusted life-years
QoL	Quality of Life
RCT	Randomized Control Trial
RE	Random-Effects
SD	Standard Deviation
SLR	Systematic Literature Review
STMs	State Transition Models
TPR	Total Pulmonary Resistance
WHO	World Health Organization

BACKGROUND AND SIGNIFICANCE

Chronic thromboembolic pulmonary hypertension (CTEPH) is a secondary form of pulmonary hypertension (PH), defined as an increased pulmonary arterial pressure (>25mm Hg) that is maintained for 6 months after diagnosis of a pulmonary embolism (PE) and is often accompanied by progressive right heart failure.[1] The exact etiology of CTEPH is unclear, but the disease is believed to result from the formation of organized pulmonary artery obstructions after incomplete lysis of pulmonary thromboemboli in patients with venous thromboembolism.[2,3]

Pulmonary endarterectomy (PEA) is the most effective treatment for CTEPH, with a 6-year survival rate of 75%.[4] However, many patients are not candidates for PEA (due either to surgical inaccessibility of the lesions or to severe comorbidities)[1] while others experience residual or recurrent PH after PEA.[5] Until recently, no drug had been approved for treating CTEPH patients with inoperable disease or those with persistent disease post-PEA. Patients are often managed with targeted therapies for pulmonary arterial hypertension (PAH), mostly bosentan, an endothelin receptor antagonists (ERAs), considered to be the standard of care. Other off-label pharmacologic therapies include, phosphodiesterase-5 (PDE5) inhibitors, and prostacyclin analogs.[6] Riociguat, a soluble guanylate cyclase stimulator was approved by the United States (US) Food and Drug Administration and European Medicines Agency for the treatment of CTEPH in October 2013, and January 2014 respectively. Its efficacy and safety was demonstrated in a Phase III, multicenter, randomized, double-blind, placebo-controlled trial.[7] Findings from this trial suggest it is

more efficacious than the off-label bosentan previously considered the standard of care. However, this needs to be confirmed via indirect comparison due to the lack of head-to-head trials.

The objective of this project is to evaluate the cost-effectiveness of riociguat and bosentan in the management of inoperable CTEPH or post-PEA CTEPH in the US setting. This information is crucial as it provides physicians and other health care providers useful and relevant information needed to take informed decisions.

RESEARCH QUESTION

What is the comparative cost-effectiveness of riociguat and bosentan as pharmacological treatments for the management of inoperable CTEPH or post-PEA CTEPH?

METHODOLOGY

Overview

The project utilized a mix of evidence-generation methods including a systematic literature review, an indirect treatment comparison analysis, as well as an economic analysis using the cost-effectiveness framework. Systematic literature reviews, especially of randomized controlled trials, are considered one of highest levels of evidence.[8] They are particularly useful in identifying and generating comparative efficacy and safety evidence in the absence of evidence from head-to-head comparisons of interventions when combined with a meta-analysis.[9] Searches for the systematic literature review were conducted in literature databases (MEDLINE via PubMed, Embase, and Cochrane Central

Register of Clinical Trials) for clinical trials of bosentan and riociguat in CTEPH patients. Efficacy, safety, and quality of life data were retrieved from identified articles (including the phase 3 trials of each treatment) and supplemented by additional literature. In the absence of head-to-head comparisons for the two treatments, Bayesian ITCs (fixed effects) was used to derive comparative efficacy and safety estimates.

Economic evaluations, particularly cost-effectiveness analyses, are important in "identifying, measuring, valuing, and comparing the cost and consequences of two or more courses of action that have the alternative therapies for a specific indication".[10] They are useful particularly in the settings of budget constraints that typifies many healthcare systems. The analysis is based on a Markov-cohort approach. Details of the methodologies are provided in subsequent sections of the document

Conceptual Model

Figure 1. Influence Diagram

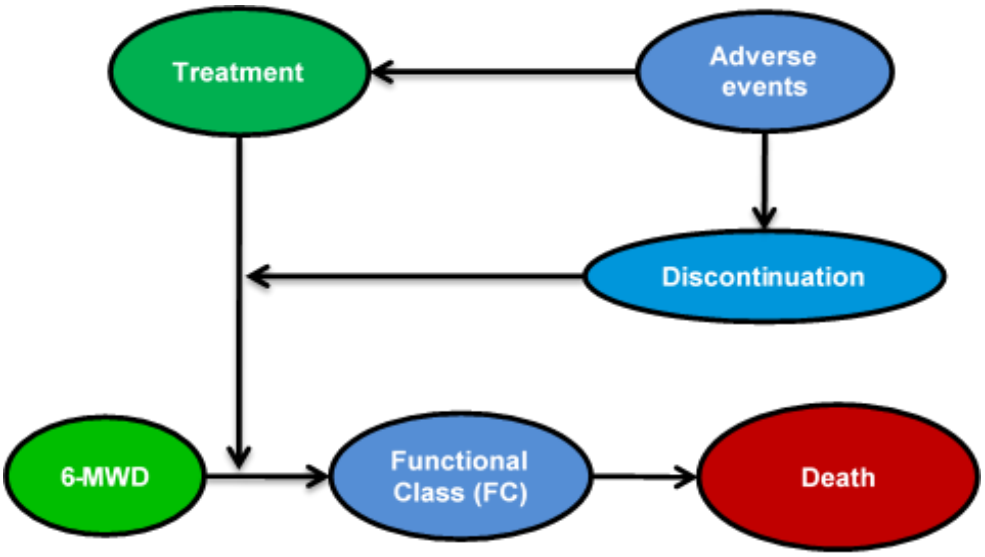
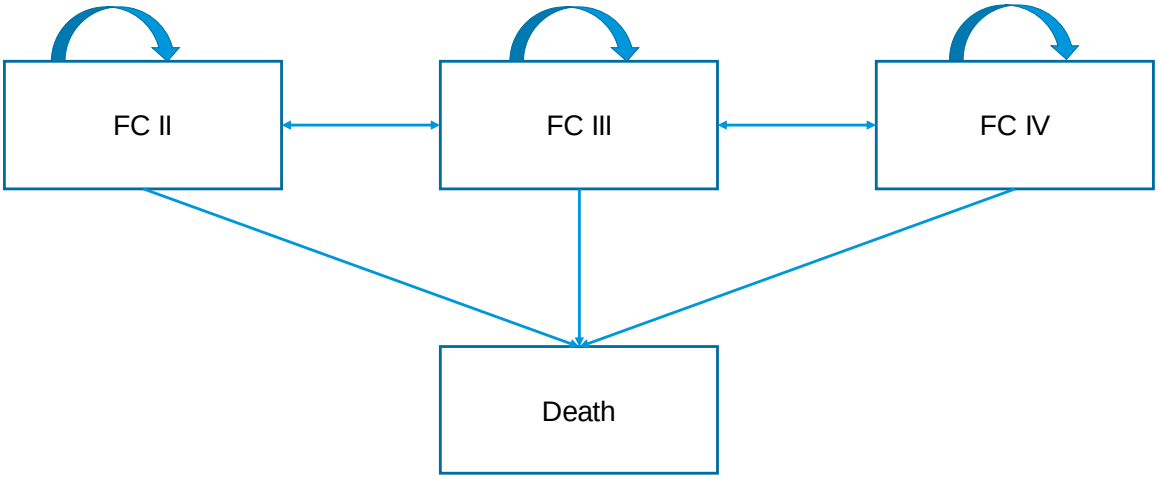


Figure 2. Markov Model Health States Transitions[a]



[a] Health States are based on the functional classification systems (the New York Heart Association Functional Classification/ World Health Organization Functional Assessment Classification)

Table 1. New York Heart Association Functional Classification

Class	Symptoms
Class I	No symptoms with ordinary physical activity.
Class II	Symptoms with ordinary activity. Slight limitation of activity.
Class III	Symptoms with less than ordinary activity. Marked limitation of activity.
Class IV	Symptoms with any activity or even at rest.

Adapted from Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Introduction. Chest. 2004; 126:7S–10S

Table 2. World Health Organization Functional Assessment Classification

Class	Symptoms
Class I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Adapted from Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Introduction. Chest. 2004; 126:7S–10S

Systematic Literature Review Methods

MEDLINE- (via PubMed), EMBASE-indexed literature published as of March 2016 were systematically reviewed to identify randomized controlled trials evaluating bosentan and riociguat. The review was limited to studies published in English. The search algorithm included a combination of medical subject headings (MeSH) terms and free-text terms for CTEPH and study designs of interest. The complete search strategy for each database can be found in Appendix A.

Citations returned from the searches of the electronic databases were screened in two rounds. In the first round, identified titles/abstracts were screened using the predefined inclusion and exclusion criteria specified in Table 3. Titles/abstracts that could not be definitively excluded were accepted at this round and the full publication retrieved for further review. The second round of screening involved review of the full text of articles deemed relevant during the first round.

In addition to identifying RCTs for the interventions being compared, references of existing systematic literature reviews and meta-analyses of bosentan and riociguat as it relates to the management of chronic thromboembolism were reviewed. The primary purpose of reviewing the references of these articles is to identify potentially relevant literature.

Table 3. Inclusion and Exclusion Criteria

Inclusion Criteria	
Population	Patients with CTEPH
Intervention/Comparators	Bosentan or riociguat
Outcomes	Any efficacy, quality of life outcome, or safety outcome
Study Design	Randomized controlled trials (RCT) Phase II/III (including subgroup analyses and post-hoc analyses)
Exclusion Criteria	
Population	Studies of non-CTEPH patients Studies with mixed population where outcomes are not reported separately for the CTEPH population
Intervention/ Comparators	Studies that did not evaluate bosentan or riociguat
Outcomes	Studies lacking relevant data on any of the outcomes of interest
Study Design	Narrative reviews, guidelines, commentary, letters to the editor, conference proceedings, no abstract to inform decision (for conference abstracts) Animal or *in vitro* studies Pharmacokinetic or pharmacodynamic studies

Abbreviations: CTEPH=Chronic thromboembolic pulmonary hypertension

Indirect Treatment Comparison Methods

Assessing feasibility of Indirect Treatment Comparison

Prior to conducting the indirect treatment comparison (ITC), the relevant trials were assessed to determine if they can be connected in an evidence network. The following elements were reviewed to determine if the trials are sufficiently similar, or if any dissimilarity are serious enough to preclude an indirect comparison.

- Comparability of patient populations, and confounding factors in relation to the patient population
- Similarity of treatments (including background and/or concomitant treatments)
- Differences in the definition, measurement and reporting of outcomes
- Study design, including the quality of methods employed in the trial

Once a connected network was established, the extent of clinical heterogeneity based on key elements of the two trials were then reviewed and assessed.

Overview of the Bayesian Algebraic Model

In the absence of direct, head-to-head evidence comparing treatments A and B (e.g., a log-odds ratio [LOR] or a mean difference [MD] between treatments; call this comparison d_{AB}), an unbiased estimate from RCTs comparing treatments A and C and from RCTs comparing B and C can be derived[11]:

$$d_{AB} = d_{AC} - d_{BC} \qquad \text{(Equation 1)}$$

The assumption being made is that the same d_{AB} that is estimated by the AB trials would

be estimated in the BC and AC trials, only if all three treatments had been included in them. If this assumption is correct, indirect evidence can be used not only instead of direct evidence, but also to supplement it.

Consider a hypothetical situation with four treatments (A, B, C, and D) investigated in several pairwise trials. Functional parameters d_{BC}, d_{BD}, and d_{CD} can then be expressed in terms of the basic parameters d_{AB}, d_{AC}, and d_{AD}:

$$d_{BC} = d_{AC} - d_{AB}$$

$$d_{BD} = d_{AD} - d_{AB} \qquad \text{(Equation 2)}$$

$$d_{CD} = d_{AD} - d_{AC}$$

For the purposes of this example, assume the outcome is binary in nature (e.g. treatment discontinuations), although similar logic applies for continuous outcomes. The data consist of the numerators r_{jk} (numbers successfully treated) and denominators n_{jk} for trials *j*=1,2… and treatments *k* = A,B,C,D. If we take p_{jk} as the probability of success on treatment *k* in trial *j*, then the numerators r_{jk} come from a binomial distribution with denominators n_{jk} and probabilities p_{jk}. The likelihood contribution of each arm is thus:

$$r_{jk} \sim B_{in}(p_{jk}, n_{jk}) \qquad \text{(Equation 3)}$$

The role of the model is to relate the probabilities p_{jk} to the basic parameters, if necessary, via the functional parameters. The RE model can be expressed in the form of a logistic regression (Equation 4):

$$\text{Logit}(p_{jk}) = \mu_{jb} \qquad \text{if k=b, b=A, B, C}$$

$\mu_{jb} + \delta_{jbk}$ if k alphabetically "after" b (Equation 4)

Where μ_{jb} represents the LOR of success for treatment *b* in study *j* and δj_{XY}—the LOR for treatment Y relative to treatment X in trial *j*—is drawn from a normal distribution, $\delta j_{XY} \sim N(d_{XY}, \sigma^2)$, with a mean d_{XY} and variance σ^2 to be calculated from the data.

The formulas for continuous outcomes are simpler, using an identity link instead of a logit link. Let λ_{jk} represent the observed mean change in the outcome on treatment *k* in trial *j*, with variance σ_{jk}.[12,13]

$$\lambda_{jk} \sim (\theta_{jk}, \sigma_{jk}) \quad \text{(Equation 5)}$$

$$\theta_{jk} = \mu_{jb} \quad \text{if k=b, b=A, B, C}$$

$$\mu_{jb} + \delta_{jbk} \quad \text{if } k \text{ alphabetically "after" } b \quad \text{(Equation 6)}$$

For comparison-level data (e.g., log-hazard ratios), the logic is similar, and an identity link is also employed.[13] Thus, this procedure allows the estimation of relative effectiveness (in the form of log-odds or log-hazard ratios) of each pair of treatments. It also allows for the estimation of the underlying probabilities of events for individual treatments (p_k), or a similar treatment-specific statistic in the case of other outcomes. While all analyses will, as noted above, either be based in log-odds due to the logit link, or utilize log-hazard ratios as inputs, all outputs were in terms of odds ratios and mean differences.

All Bayesian indirect treatment comparison (ITC) analyses involved a 50,000-run-in iteration phase and a 50,000-iteration phase for parameter estimation. Analyses were conducted using OpenBUGS v3.2.2 and R3.3.0.

Model Convergence

Convergence was confirmed by inspection of the ratios of Monte Carlo error to the standard deviations of the posteriors (<5% generally implies adequate convergence) and examinations of the three-chain Brooks-Gelman-Rubin (BGR) plots.[14,15]

Investigation of Statistical Heterogeneity

Statistical heterogeneity is defined as the instance where a set of true relative treatment effects varies across studies; in other words, the observed treatment effects vary more than would be expected due to sampling error. Statistical heterogeneity between the same comparisons are typically evaluated using the I-squared (I^2) statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Typically, I^2 values of 25%, 50%, and 75% are considered low, moderate, and high.[16] Only two RCTs (one for each intervention of interest) form the evidence network for the analyses, hence investigation of statistical heterogeneity using the I-squared statistics was not applicable.

Consistency

Consistency is defined as an agreement between direct and indirect sources of evidence. In the evidence networks, there are no instances of a comparison benefiting from both direct and indirect evidence. Subsequently, it is not possible to assess inconsistency.[16–18]

Statistical Models

A fixed-effects (FE) indirect treatment comparison model[19–22] was conducted to generate

comparative effectiveness and safety estimates using data from the RCTs of each intervention of interest (bosentan and riociguat). Fixed-effects models assumes that "there is no variation in relative treatment effects across studies for a particular pairwise comparison; and any difference is due to sampling error".[23]

Random-effects (RE) models on the other hand, assumes that the "true relative effects across studies are exchangeable (i.e., the prior position of expecting underlying effects to be similar but not identical) and can be described as a sample from a normal distribution whose mean is the pooled relative effect and whose standard deviation reflects the heterogeneity.[23,24] RE models are not appropriate in this case due to the nature of the network and the lack of adequate data to estimate a random-effects variance (network with only two trials, one for each intervention of interest).[12,23,24]

Cost-Effectiveness Model Methods

Overview

The economic evaluation is based on a Markov model which follows the recommendations of the International Society of Pharmacoeconomics and Outcomes Research - Society for Medical Decision Making Modeling Good Research Practices. Costs and health benefits were discounted at 3.5% annual rate.[25] Sensitivity analyses were performed as appropriate. The model was programmed in TreeAge® Pro Software 2011.

Markov models (or State Transition Models [STMs]) are one of the common models used in economic evaluations. This approach frames decision problems in terms of distinct, mutually exclusive health states, and conceptualizes the transition of patients among

these states during fixed intervals in time. In addition, "it assumes the interactions between individuals are not relevant, and the population of interest is a closed cohort".[26] The main advantage of this approach is its simplicity, the ease of analyses and communication using user-friendly software such as TreeAge® or Microsoft Excel®. However, it does not have the flexibility required to respond to the broad variations in the patient population and is limited by the Markov assumption of no memory. Details of the model elements are presented below.

Population

The population of interest are patients with inoperable CTEPH or with persistent or recurrent pulmonary hypertension following pulmonary endarterectomy.

Comparators

The model evaluated the cost-effectiveness of riociguat monotherapy compared to bosentan monotherapy.

Setting

The cost-effectiveness analysis is based on the US market and conducted from the economic perspective of the government payer. Therefore, only direct costs are assessed.

Time Horizon

The model projects costs and outcomes up to the patient lifetime (assumed to be a maximum of 41 years or death). The time horizon is broken into four-month cycles to correspond to the duration of the CHEST-1 trial,[7] the primary source of data, and to

enable changes in patient health status and resource use to be captured.

Discount Rate and Currency Year

Discounting adjusts current costs and benefits to be worth more than those occurring in the future because the assumption is that there is an opportunity cost to spending money now instead of later. Costs and health benefits are discounted at 3.5% annual rate. Currency year is 2016 US dollars.

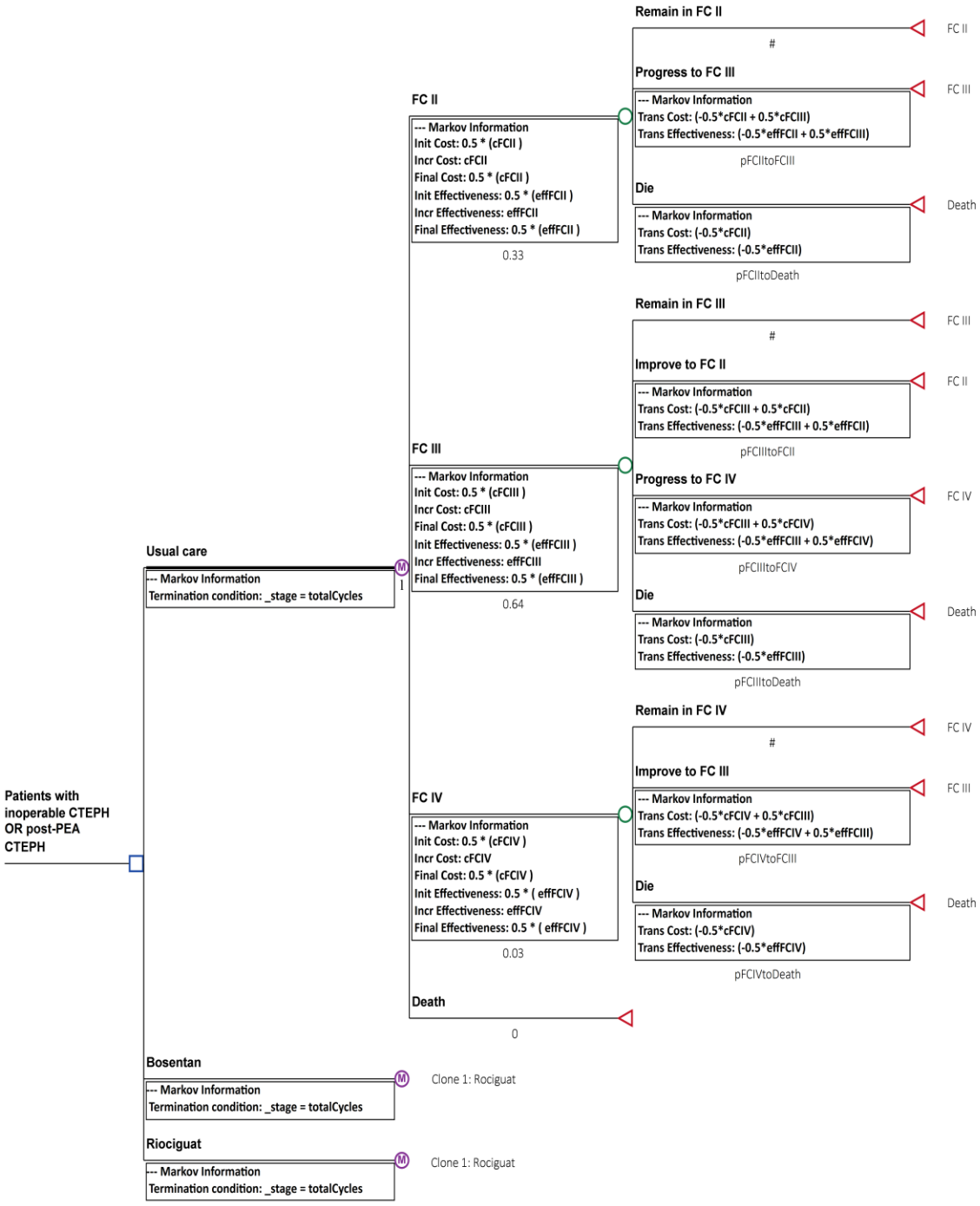
Model Outcomes

The model collects the following health outcomes: QALYs, and costs. The ICER, which is the incremental cost per QALY gained, is regarded as the primary cost-effectiveness outcome measure in health economics. This measure reflects the cost to gain each additional QALY when using riociguat versus bosentan.

Model Diagram

A diagram showing the decision nodes and Markov health states is shown below

Figure 3. TreeAge Model Diagram



Model Inputs

Mortality

Data on mortality included in the model were based on the primary trial publications for each intervention, as well as age- and gender-specific background mortality derived from the United States Life Tables 2013.[27] The mortality rates were then converted to a probability using well-established methods.[28,29]

- Converting probability to rates: $\frac{-\ln(1-p)}{t}$
- Converting rates to probabilities: $1 - exp^{(-rt)}$

  Where *p* is the probability, *t* is time, and *r* is rate.

Functional class-specific mortality rates were not identified in the literature, and were not included in the model. The combined mortality rate for the overall population was used. Of note, mortality rates were not significantly different between riociguat and bosentan compared to placebo/standard of care in the primary trials,[7,30,31] or in the indirect treatment comparison, as such the relative mortality rates between riociguat and bosentan were not applied in the model.

Adverse Events

Adverse event (AEs) rates for riociguat and bosentan were identified from their respective phase III trials and the product labels.[7,30,31] Only the most relevant AE for each intervention were included in the model, specifically liver toxicity. No data on disutilities were identified, hence they were not considered in the model. Disutilities are likely to already be accounted for in the data capturing utilities by FC. (Table 12 and Table 13)

Treatment Discontinuation

Discontinuation rates for riociguat and bosentan were identified from the CHEST-1 trial and BENEFiT study respectively (See table below). The overall discontinuation rate was not significantly different between both treatments based on the ITC (Table 15), hence this variable was not included in the model.

Table 4. Treatment Discontinuation Rate and Adverse Event Rate

Parameter	Riociguat	Bosentan	Source
Discontinuation Rate (Mean, SD)	1.2%, 0.12%	3.00%, 0.30%	CHEST-1 Trial[7] BENEFiT Trial[30]
Liver Function Abnormalities	0%	7%	

Costs and Resources Use

Costs used in the model were derived from a mix of sources – public, as well as subscription-based sources like RedBook[32] and adjusted to 2016 US dollars where applicable. A micro-costing approach was used.[25]

Table 5. Treatment Dosing and Cost

Drug	Dosage	Cost/Day Cost/month	Source
Riociguat	Initiate treatment at 1 mg taken three times a day. Increase dosage by 0.5 mg at intervals of no sooner than 2-weeks as tolerated to a maximum of 2.5 mg t.i.d[33b]	$231.46 $6,943.86	Red Book[32]
Bosentan	125mg b.i.d or 250mg total[31]	$184.98 $5,549.40	Red Book[32]

In addition to the active interventions, CTEPH patients receive supportive care which

[b] The 2.5mg dose was assumed.

could include supplemental oxygen, warfarin, furosemide, and digoxin. Details of the associated costs are provided below.

Table 6. Supportive Care - Oxygen

Drug	Volume	Cost per 3 months	Data Source
Oxygen	26% across all functional classes.[c]		DMEPOS Fee Schedule July 2013 File
	Uptake FC II: 6%	$332.3	
	Uptake FC III: 30%	$332.3	
	Uptake FC IV: 63%	$332.3	

Table 7. Other Supportive Care – warfarin, furosemide, digoxin

Drug	Volume	% of patients receiving	Cost/Day, Cost/month	Data Source
Warfarin	5 mg/day	27.57%	$0.66860, $20.06	Red Book[32]
Furosemide	100 mg/day	55.07%	$0.715, $21.45	Red Book[32]
Digoxin	125 mcg/day	11.92%	$1.42200, $42.66	Red Book[32]

Other costs and resource use associated with the management of CTEPH are noted in the tables below. They include liver function test (for patients on bosentan), and costs of routine care by FC [comprising hospitalization, visits to specialist and primary care physician, and diagnostic testing]. The annual rates of accessing these resources were obtained from an European study by Schweikert et al 2014[34] in the absence of US data.

[c] 1,360 litres/day for FCI-III. 2,122 litres/day for FC IV

Table 8. Laboratory Tests

	Liver Function Test	Total Costs USD
Riociguat	0	$0
Bosentan	1	$11.13

Table 9. Routine Care by FC

FC	Cost per Month	Data Source
FC II	$0	NICE PAH Assessment Report 2007
FC III	$304.8	NICE PAH Assessment Report 2007
FC IV	$709.4	NICE PAH Assessment Report 2007

A micro-costing approach was used to estimate costs, hence the aggregate routine care cost data identified from the literature were not used in the model.

Table 10. Ongoing Resource Use

Resource	Mean ± SD	Median	Source
Hospitalizations/year	1.8 ± 2.2	1.0	Schweikert 2014,[34] EU data
Hospitalization days/year	14.8 ± 26.1	7.8	
Specialist visits/year	1.3 ± 1.4	0.9	
Primary Care Doctor visits/year	2.8 ± 4.2	0.7	
Diagnostic tests/year	8.4 ± 5.9	7.8	

Table 11. Unit Costs for Resource Use

Resource	Unit Cost USD	Source
Average length of stay	Mean: 6.5 days, SE: 0.262 Median: 4.0 days ICD 9 code: 416.8	Healthcare Cost and Utilization Project (H.CUPnet)[35]
Hospitalization – per Episode	Mean charges: $70,139, SE $5,532 Median charges: $34,414 Mean costs: $19,216, SE $1,764 Median costs new: $9,479 ICD 9 code: 416.8	
Specialist Nurse/PAs	99201 – 1st visit Non-facility limiting charge: $48.11 99201 – other visits (same as 1st visit)	Centers for Medicare & Medicaid Services Physician Fee Schedule[36]
Visit to Primary Care Doctor	99202 – 1st visit Non-facility limiting charge: $82.14 99212 – other visits Non-facility limiting charge: $47.72	
Visit to Specialist - Pulmonologist	99204 – 1st visit Non-facility limiting charge: $181.50 99214 – other visits Non-facility limiting charge: $118.13	
ECG	$55.94 HCPSC Code: 93005	Current Procedural Terminology, Fourth Edition ("CPT®"), Addendum B, July 2016[37]
VQ Scan	$441.36 HCPSC Code: 78582	
CT Scan Thorax	$112 [HCPSC Code: 712500 w/o dye] $236.86 [HCPSC Code: 71260 with] $347.72 [HCPSC Code: 71270 with or w/o dye]	
CT - Pulmonary Angiogram of the Chest	$236.86 HCPSC Code: 71275	
Liver Function Test	$11.13 HCPSC Code: 80076	

The charge-to-cost conversion was not necessary since costs were available in the HCUP

data source. The mean cost for hospitalization per episode was used in the model.

Utilities

Quality of life data were estimated based on the EuroQol-5D (EQ-5D) baseline scores reported in the CHEST-I study, adjusted based on other values identified from the literature. (see Table 12 and Table 13 below).

Table 12. Utilities from EQ-5D

Functional Class	Mean, SD	Source
FC II	0.72, 0.21	A combination of CHEST-1 trial[7] and other sources noted in Table 13 below
FC III	0.64, 0.26	
FC IV	0.41, 0.26	

Estimates of utilities by FC from other published studies were also identified, although these were specific to PAH and not CTEPH.

Table 13. Additional Utilities by FC Values from Published Studies

Functional class	Keogh 2007[38]	Kirsch 2000[39] 2 year	Kirsch 2000[39] 10 year	Olschewski 2002[40]
FC II	0.67, 0.10	0.78, 0.031	0.76, 0.023	0.75, 0.193
FC III	0.60, 0.10	0.55, 0.045	0.50, 0.044	0.61, 0.254
FC IV	0.52, 0.09	0.37, 0.051	0.28, 0.051	0.44, 0.291

Values are mean, SD

Efficacy of Treatment

Transition probabilities for each intervention was derived by applying the relative effects from an indirect treatment comparison analyses,[41] which estimated the comparative impact of bosentan and riociguat on the improvement and worsening in FC, to the

baseline probabilities for FC improvement and worsening with supportive care alone. Please note that the population for the analyses were subjects with PAH. These data were used in the absence of CTEPH-specific data.

Subjects could remain in their starting functional class, improve (i.e. transition to a lower FC), or worsen (i.e., transition to a higher FC) during a treatment cycle. Subjects were only allowed to move one FC at a time. I assumed that interventions resulted in improvements in FC during the first cycle. This assumption is based on the lack of long-term data and on the fact that the impact of each intervention on FC change were evaluated in the primary trials during the 12- to 16-week study duration. Evidence from the trial publications also indicate that the interventions reduces the risk of FC worsening.[7,30] Transition probabilities used in the model were identified from an indirect treatment comparison[41] mentioned earlier in this section, and are noted below:

Supportive care

- Probability of FC improvement: 0.10
- Probability of FC worsening: 0.12

Relative risk of FC improvement versus supportive care (95% CrI)

- Bosentan: 2.05 (1.25, 3.32)
- Riociguat: 1.49 (0.90, 2.46)

Relative risk of FC worsening versus supportive care (95% CrI)

- Bosentan: 0.46 (0.18, 1.04)
- Riociguat: 0.22 (0.07, 0.63)

Sensitivity Analysis

Sensitivity analyses were conducted to qualify and quantify the uncertainty surrounding some of the model parameters.[42] Deterministic (one-way) sensitivity analyses were conducted by systematically varying model parameters one at a time. A probabilistic sensitivity analysis was also conducted to account for multivariate and stochastic uncertainty in the model. The uncertainty in the individual parameters were characterized by using the appropriate distributions for certain model parameters. The probabilistic sensitivity analysis was conducted as a sampling Monte Carlo simulation in Treeage with 100,000 replications.

The following distributions were applied:

- Costs: Gamma distribution
- Transition probabilities and utilities: Beta distribution
- Relative risk of worsening or improving: Log –normal distribution

Table 23 summarizes additional information on the variables, and distributions included in the PSA.

RESULTS

Systematic Literature Review

The MEDLINE (via PubMed), EMBASE, and CENTRAL searches yielded a total of 128 records (25 from MEDLINE, 72 from EMBASE, and 31 from CENTRAL), with some overlap between the databases. After removing duplicate articles, 95 unique records were identified and screened, of which 41 were selected for further review in the full text. Ultimately 12 records were identified as relevant (list provided below). A diagram summarizing the flow and attrition of records identified from the database searches through the two stages of screening is presented in Appendix B. A list of articles identified from the literature review is presented below.

1. Confalonieri M, Vassallo FG, Scarduelli C, et al. A preliminary open label controlled trial with bosentan in patients affected by chronic thromboembolic pulmonary hypertension (CTEPH) [Abstract]. *Proceedings of the American Thoracic Society.* 2006:A167 [Poster D169].

2. D'Armini AM, Ghofrani HA, Kim NH, Mayer E, Simonneau G, Wilkins MR. Riociguat for the treatment of inoperable CTEPH or persistent/recurrent PH after pulmonary endarterectomy (PEA): A responder analysis from the phase III CHEST-1 study [Abstract]. *European Respiratory Society Annual Congress, 2013 Sept 7–11, Barcelona, Spain.* 2013;42(Suppl 57):543s [P2598].

3. Ghofrani H, Grimminger F, Hoeper M, et al. Riociguat for the treatment of inoperable

chronic thromboembolic pulmonary hypertension: A randomized, double-blind, placebo-controlled study (CHEST-1). *Chest.* 2012;142(4).

4. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *New England Journal of Medicine.* 2013;369(4):319–329.

5. Ghofrani HA, Grimminger F, Hoeper MM, et al. Impact of riociguat on health-related quality of life (HRQoL) in patients with chronic thromboembolic pulmonary hypertension (CTEPH). *European Respiratory Journal.* 2013;42.

6. Jais X, D'Armini AM, Jansa P, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. *Journal of the American College of Cardiology.* 2008;52(25):2127–2134**.**

7. Jais X, Ghofrani A, Hoeper MM, Lang I, Mayer E, Pepke-Zaba J. Bosentan for inoperable chronic thromboembolic pulmonary hypertension (CTEPH): a randomized, placebo-controlled trial - BENEFIT [Abstract]. *American Thoracic Society International Conference, May 18–23, 2007, San Francisco, California, USA.* 2007: Poster #D82.

8. Jansa P, Ghofrani HA, Hoeper MM, et al. Comparison of hemodynamic parameters in patients with inoperable and persistent/recurrent chronic thromboembolic

pulmonary hypertension (CTEPH) in the Phase III CHEST-1 study. *European Heart Journal.* 2013;34:187.

9. Kim NH, D'Armini A, Grunig E, et al. Hemodynamic assessment of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) in the phase iii chest-1 study. *American Journal of Respiratory and Critical Care Medicine.* 2013;187.

10. Lang IM. Bosentan for inoperable chronic thromboembolic pulmonary hypertension (CTEPH) and post -pulmonary endarterectomy pulmonary hypertension: a subgroup analysis of the randomized, placebo-controlled trial - BENEFiT. *Clinical research in cardiology.* 2007;96(11):779–780.

11. Mayer E, D'Armini AM, Ghofrani HA, et al. Efficacy of riociguat in patients with inoperable CTEPH vs persistent/recurrent PH after pulmonary endarterectomy (PEA): Results from the phase III CHEST-1 study. *European Respiratory Journal.* 2013;42.

12. Papke-Zaba J, Mayer E, Simmoneau G, Rubin LJ, Lang I, Hoeper MM. Bosentan for inoperable chronic thromboembolic pulmonary hypertension: a randomised, placebo-controlled trial - BENEFiT [Abstract]. *Thorax.* 2007;62(Suppl iii):A15.

Evidence Network

The evidence network consists of two randomized controlled trials, BENEFiT (bosentan), and CHEST-1 (riociguat) identified from the systematic literature review.

The BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic

pulmonary hypertension) was a 16-week, phase 3, double-blind, randomized, placebo-controlled study investigating the efficacy and safety of bosentan in patients with chronic thromboembolic pulmonary hypertension who were considered either inoperable or had persistent/recurrent pulmonary hypertension after pulmonary endarterectomy (≥6 months after PEA).[30]

Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1) is a 16-week, phase 3, double-blind, multicenter, randomized, placebo-controlled study investigating the efficacy and safety of riociguat in patients with chronic thromboembolic pulmonary hypertension who were considered by experienced surgeons to be ineligible for surgery or who had persistent or recurrent pulmonary hypertension after pulmonary endarterectomy.[7]

The network formed from these two trials are shown below. Placebo is acting as a common comparator for both treatments.

Figure 4. Evidence Network of Trials

Table 14. Characteristics and Findings of CHEST-1 and BENEFiT Trials

	BENEFit		CHEST-1	
	Placebo n=80	**Bosentan n=77**	**Placebo n=88**	**Riociguat n=173**
Baseline Characteristics				
Age (yrs)*	63.1 ± 10.3	63.0 ± 12.9	59 ± 13	59 ± 14
Females, %	58.8	71.4	61	68
PVR (dyn·s·cm^{-5})*	787 ± 333	778 ± 323	779 ± 401	791 ± 432
6MWD (m)*	344.5 ± 82.6	340.0 ± 85.3	356 ± 75	342 ± 82
WHO FC (I/II/III/IV)	0/22/56/2	0/22/51/3	0/25/60/2	3/55/107/8
mPAP (mmHg)*	47.4 ± 12.5	44.2 ± 10.4	44 ± 10	45 ± 13
mRAP (mmHg)*	8.4 ± 6.0	8.3 ± 6.1	9 ± 6	9 ± 5
BDI*	4.1 ± 2.3	4.4 ± 2.0	4.0 ± 2.0	4.0 ± 2.0
NT-proBNP (ng/l)*	1405 ± 1882	1481 ± 1833	1706 ± 2567	1508 ± 2388
Outcomes at 12/16 weeks				
6MWD change (m)	0.8 (-18.1, 19.7)[#]	2.9 (-12.9, 18.8)[#]	-6 ± 84	39 ± 79
WHO FC	9 improved 64 no change 7 worsened	11 improved 64 no change 2 worsened	13 improved 68 no change 6 worsened	57 improved 107 no change 9 worsened
BDI change	0.2 (-0.3, 0.6)[#]	-0.4 (-0.8, 0.0)[#]	0.2 ± 2.4	-0.8 ± 2
PVR change (dyn·s·cm^{-5})	30 (-25, 85)[#]	-146 (-207, –85)[#]	23 ± 274	-226 ± 248
NT-proBNP (ng/l)[##]	-622 (-1018, -225), 0.0034		-444 (-843, -45), <0.001	
mRAP (mmHg)[##]	-0.8 (-2.6, 1.0), 0.6277		-0.6 (-1.7, 0.6), 0.4	

	BENEFit		CHEST-1	
	Placebo n=80	**Bosentan n=77**	**Placebo n=88**	**Riociguat n=173**
mPAP (mmHg)[##]	-2.5 (-5.0, 0.0), 0.0652		-5 (-7, -3), <0.001	
Safety, n (%)				
Clinical worsening	5 (6.3)	3 (3.9)	5 (6)	4 (2)
Elevated LFTs >3 ULN	3 (3.8)	11 (14.5)	0	0
Death	1 (1)	1 (1)	3 (3)	2 (1)
Headache	(1.3)	(6.5)	12 (14)	43 (25)

Abbreviations: mPAP=mean pulmonary artery pressure; mRAP=mean right atrial pressure; NT-proBNP=N-terminal pro-brain natriuretic peptide; PEA=pulmonary endarterectomy; PVR=pulmonary vascular resistance; SD=standard deviation; TPR=total pulmonary resistance; WHO=World Health Organization.

*Mean ± SD; [#] n (95% confidence interval); [##] Mean treatment effects (95% confidence interval)

Indirect treatment Comparison Analyses

Results of the Bayesian fixed-effects ITC analyses are shown below.

Table 15. Summary of Indirect Treatment Comparison Results

	Effect Measure	Estimate (95% CrI)
Primary Analyses		Riociguat vs. Bosentan
Efficacy Outcomes		
Change in 6MWD	Mean Difference	42.2 (9.8, 74.8)¥
Change in NT proBNP (pg/mL)	Mean Difference	242.8 (-238.9, 725)
Change in PVR (dyn*sec*cm-5)	Mean Difference	-72.9 (-181.3, 36)
Change in Borg CR 10 Scale score	Mean Difference	-0.4 (-1.3, 0.5)
Odds of being in WHO FC II or better vs. FC III/worse	Odds Ratio	1.15 (0.51, 2.61)
Safety Outcomes		
Headache	Odds Ratio	0.31 (0.01, 2.69)
Hepatic Abnormalities	Odds Ratio	0.04 (0.00, 0.94)¥
Any AEs	Odds Ratio	0.83 (0.27, 2.45)
Discontinuations due to AEs	Odds Ratio	3.24 (0.28, 58.03)
Mortality	Odds Ratio	0.29 (0.00, 18.43)
Subgroup Analyses		
Inoperable CTEPH		
Change in 6MWD	Mean Difference	43.5 (1.4, 85.6)¥
Change in PVR	Mean Difference	-156.3 (-293.6, -19.6)¥
Post-PEA CTEPH		
Change in 6MWD	Mean Difference	37.1 (-10.4, 84.3)
Change in PVR	Mean Difference	131.5 (-34.9, 297.3)

AE = adverse event; CTEPH = chronic thromboembolic pulmonary hypertension; FC = functional classification. ¥ Statistically conclusive result

There were statistical differences between riociguat and bosentan with regards to change in 6MWD and occurrence of hepatic abnormalities at 12–16 weeks in the overall population i.e. combination of subjects with inoperable disease and those with post-PEA CTEPH.

In the subgroup analyses, treatment with riociguat led to significantly higher improvements in 6MWD, and significant reduction in PVR in subjects with inoperable CTEPH, compared to bosentan. Results for subjects with persistent or recurrent CTEPH post-PEA were not statistically different.

Cost-Effectiveness Analyses

Base Case Analyses

These analyses estimated the outcomes for a cohort of CTEPH patients receiving riociguat monotherapy or bosentan monotherapy over their lifetimes. Costs and outcomes were discounted by 3.5%.

Model Assumptions

All assumptions in the base-case analysis of the model are summarized in Table 16.

Table 16. Assumptions

Domain	Assumption	Explanation/Implication
Population	A fixed cohort of patients was analyzed.	1. Characteristic of Markov cohort models 2. Incident CTEPH cases were not considered
Treatment effect and haemodynamics	Impact of hemodynamics was not included in the model.	1. There is limited data showing the relationship between hemodynamics and health-economic impact in pulmonary hypertension. 2. It was difficult to justify the impact of haemodynamics on health-economic outcomes based on available data.
Transition probabilities	Derived by combining the relative risk of FC improvement or worsening (on placebo/usual care) with the same sets of risks for riociguat and bosentan. Data from a surrogate disease (PAH) was applied in the absence of CTEPH-specific data	1. CTEPH-specific data was not identified from the literature search 2. Treatment effect may have been over- or underestimated. This impact is likely to be small considering there might be common mechanisms behind both diseases.
Disutilities	Not applied due to lack of evidence	1. Disutility data on the specific AEs were not identified from the literature search 2. Utility decrement associated with treatment may have been underestimated. Rates of adverse events were generally low and the utility decrement would have been marginal. As such, the impact of the underestimation is likely to be very small

AE = adverse event; CTEPH = chronic thromboembolic pulmonary hypertension; FC = functional classification; RCT = randomized controlled trial, RR = relative risk

Costs

Costs associated with CTEPH for riociguat and bosentan are presented by drug costs,

supportive care costs, oxygen costs, and cost of LFTs (Table 17). Patients on bosentan had the highest discounted total life time cost at $2,439,555 per patient. The majority of this cost is made up of drug costs, $2,089,113. Total cost for riociguat was $2,307,489 of which $1,960,552 were drug cost.

Table 17. Component of Costs for each Treatment Strategy

Costs ($)	Riociguat	Bosentan
Drug costs	$1,960,552	$2,089,113
Supportive care costs	$12490	$12,490
Oxygen costs	$7,548	$8,988
Follow-up costs (PCP + Pulmonologist)	$10,311	$10,311
Cost of LFT	$0	$2,066
Cost of Investigations	$19,332	$19,332
Cost of Hospitalization	$297,255	$297,255
Total	**$2,307,489**	**$2,439,555**

QALYs

Heath outcomes are presented in terms of QALYs. As shown in Incremental Results

Results are also presented as incremental gains in QALYS, costs and the ICERs, defined as the incremental average costs divided by the incremental total QALYs. Riociguat had the greatest impact on patient's QoL due the marginally higher utility values associated with improved FC, compared to bosentan.

Table 18, patients who received riociguat had the highest discounted QALYs over their

lifetime at 14.07 compared to 13.87 for bosentan.

Incremental Results

Results are also presented as incremental gains in QALYS, costs and the ICERs, defined as the incremental average costs divided by the incremental total QALYs. Riociguat had the greatest impact on patient's QoL due the marginally higher utility values associated with improved FC, compared to bosentan.

Table 18. Incremental Results (Costs, QALYs) and ICER

	LifeTime Costs	Incremental Cost	LifeTime Effectiveness	QALYs	Incremental QALYs	ICER
Bosentan	$2,439,555	Reference	41.60	13.87	Reference	Reference
Riociguat	$2,307,489	-$132,066	42.21	14.07	0.20	-$649,380

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year, Ref = reference

Note: Lifetime effectiveness is converted to QALYs by dividing by 3.

Deterministic Sensitivity Analysis

The purpose of a deterministic sensitivity analysis is to identify parameters that could influence on model results. Results of the 1-way deterministic sensitivity analyses, including the base, low and high values used for each of the relevant variables, and the corresponding ICER values are shown in Table 19. Impact of variations in QALYs for each FC was not evaluated as they resulted in clinically implausible scenarios e.g. using a high input value for QALY of FC III such that the value becomes higher than that of FCII patients.

Table 19. Results of Deterministic Analysis for Riociguat versus Bosentan

Parameter	Main Case Input Value	Low Input Value	ICER from Low Input Value	High Input Value	ICER from High Input Value
Discount Rate	3.5%	0	-$613,384	5%	-$666,412
Markdown for Drugs*	1	0	-$17,236	0.5	-$333,308

FC = Functional Classification; ICER = incremental cost-effectiveness ratio

* applied only to riociguat and bosentan. Drugs used as supportive care (e.g. warfarin, digoxin) were not marked down

Probabilistic Sensitivity Analysis

The probabilistic analyses were run for 100,000 replications where values for specific variables were drawn repeatedly from a probability distributions specified *a priori* for select variables, specifically QALYs, probabilities for FC improvement or worsening, drug costs (bosentan, riociguat), and cost of hospitalization. The incremental cost-effectiveness curves for riociguat compared to bosentan at a $50,000 and $100,000 per QALY gained thresholds are shown in Figure 5 and Figure 6 respectively. As show in both figures, riociguat resulted in a more favorable ICER compared to bosentan in 74% of the Monte Carlo simulations (quadrant IV of the incremental cost-effectiveness plane). The remaining iterations (26%) where in quadrant III and mostly below the $50,000 or $100,000 WTP thresholds.

Figure 5. Incremental Cost-effectiveness for Riociguat vs. Bosentan, WTP $50,000

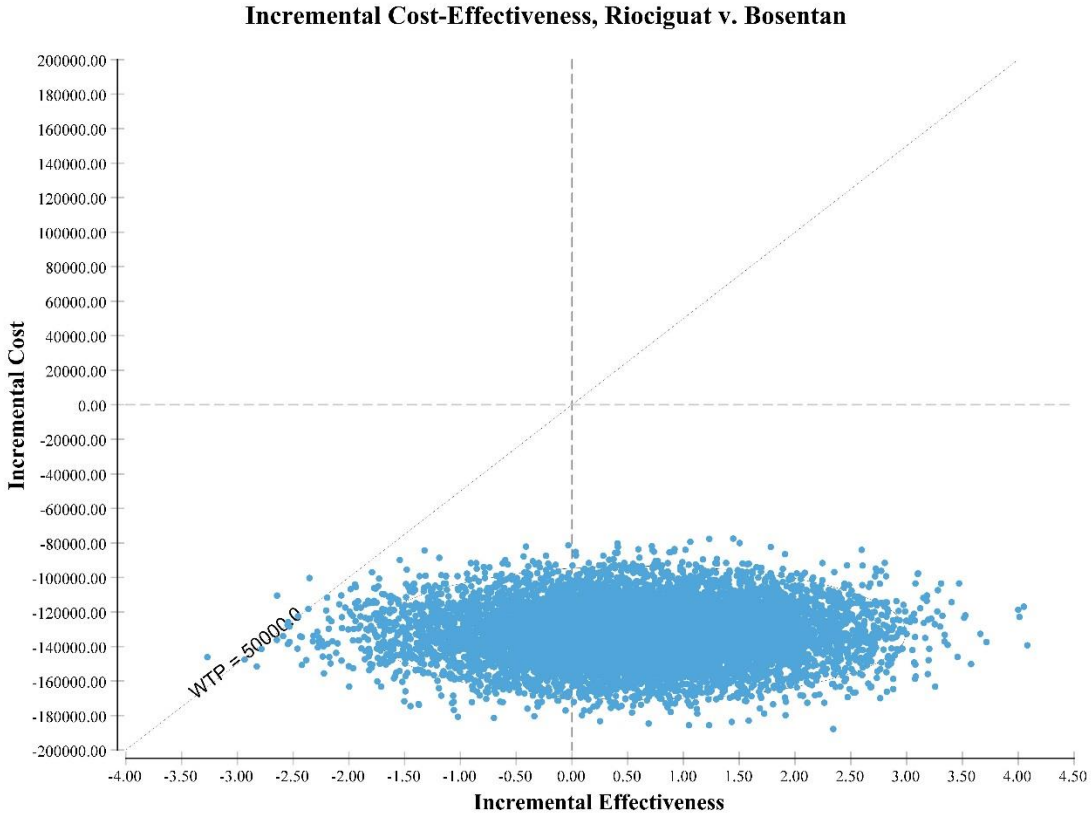
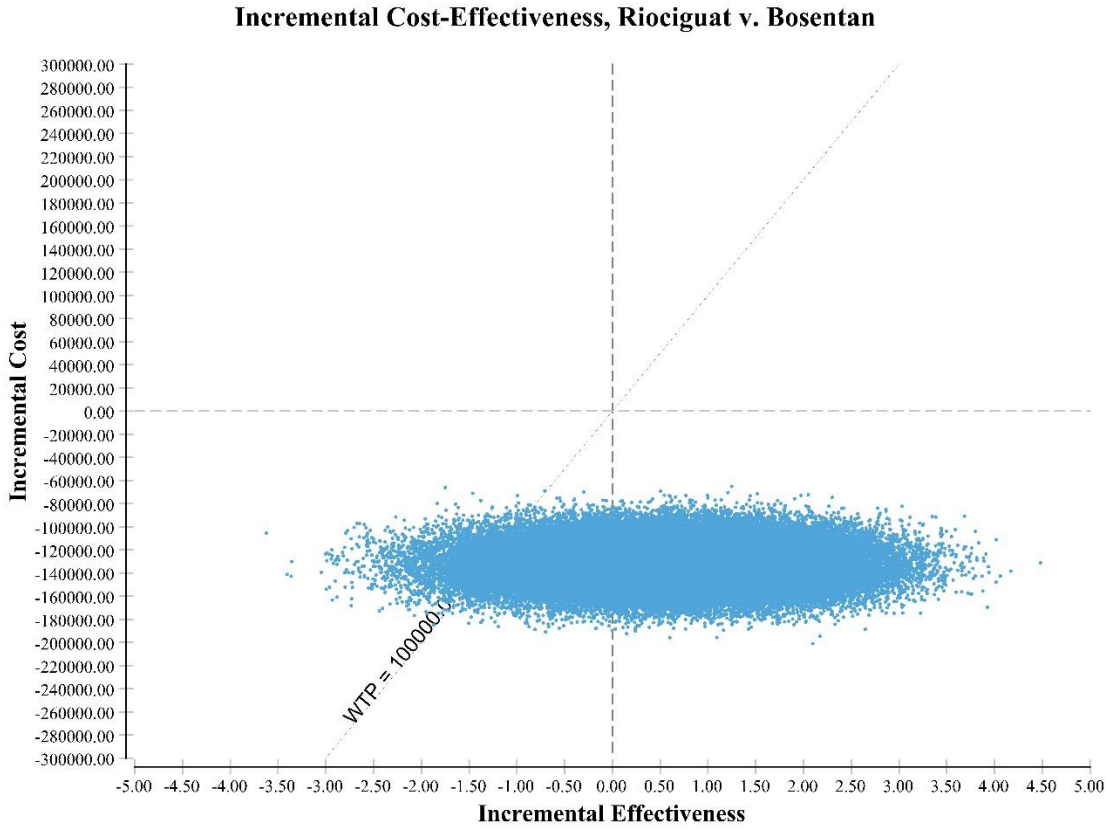
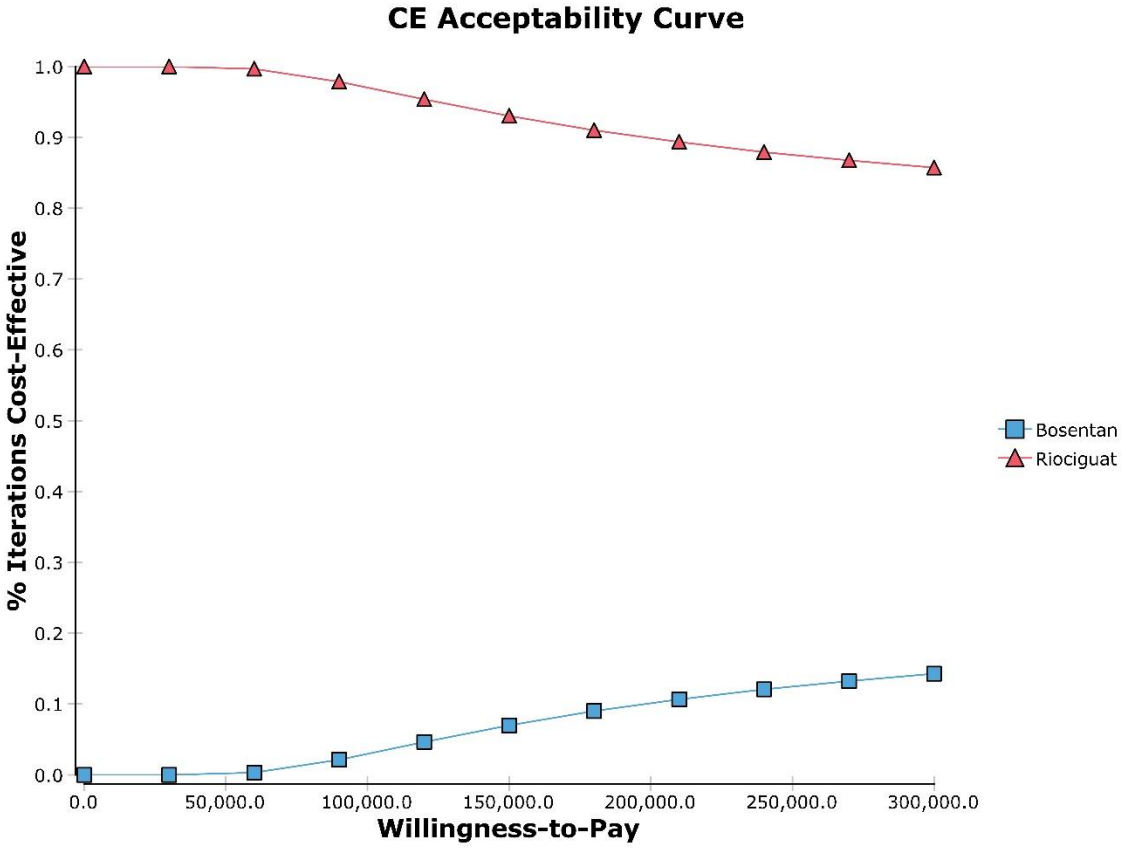


Figure 6. Incremental Cost-effectiveness for Riociguat vs. Bosentan, WTP $100,000



The cost-effectiveness acceptability curve shown in Figure 7 is generated from the PSA and shows the likelihood of riociguat being cost-effective at various willingness to pay thresholds. Riociguat is cost-effective compared to bosentan at multiple willingness to pay thresholds ($50,000, $100,000, and $150,000) with the probability of it being cost-effective decreasing as the WTP thresholds increases.

Figure 7. Cost-effectiveness Acceptability Curves for Riociguat versus Bosentan



DISCUSSION

This Markov model was developed to evaluate the cost-effectiveness of pharmacologic therapies, riociguat and bosentan for inoperable or post-PEA CTEPH. The model calculates costs and outcomes associated with CTEPH over the lifetime of an average 59-year-old American based on changes in FC. Riociguat emerged as the most attractive treatment strategy with a marginally higher QALY and lower life-time costs. The differences in life-time costs appear to the mostly driven by the additional costs of LFTs for patients on bosentan (bosentan is associated with elevations in LFTs) and the small difference in drug costs. Results of the ITC indicates that compared to bosentan, riociguat significantly improved 6-MWD, the primary outcome of the CHEST-1 and BENEFiT trials. There were no significant differences between both drugs with regards to hemodynamic parameters such as NT-proBNP, mPAP, and mRAP.

A review of the literature for published studies evaluating the comparative cost-effectiveness of riociguat and bosentan in CTEPH yielded four documents. One study was conducted in a US setting; the remaining three were conducted in a Canadian, Turkish, and Russian setting respectively. The US study was a Markov cohort-based cost-utility analyses from a US third-party payer perspective published as a meeting abstract. Details of the model such as time horizon, discount factors were not reported in the abstract. Authors reported that riociguat was cost-effective at a threshold of $100,000/QALY after the first year of treatment, and it dominates bosentan by the second year of treatment

onwards – specific values were not reported.[43]

The Turkish study was also reported as a meeting abstract. It evaluated the cost-effectiveness of riociguat for inoperable or post-PEA CTEPH patients over life time (set at 30 years) from a Turkish payer's perspective. Total cost (2014 dollars) of riociguat-treated patients was $1,558 higher compared to bosentan; and riociguat was associated with increments of 1.0034 LYs compared to bosentan. The ICER of riociguat per LYs gained compared to bosentan was 6,750 USD. Riociguat was deemed cost-effective compared to bosentan with ICER values below the willingness-to-pay threshold (3-times GDP per capita – 32,346 USD) for Turkey.[44] Similar to the first two studies, the Russian study was based on a Markov model. The difference in costs between riociguat and standard practice (comprised on bosentan monotherapy with addition of sildenafil therapy when patients progressed) was 60 646.15 RUB per patient per year in favor of the riociguat. Riociguat costs were lower in 94.4% of sensitivity analysis. Authors concluded that riociguat was more cost-effective.[45]

The fourth study was documented in a Common Drug Review Pharmacoeconomic report developed by the Canadian Agency for Drug and Technologies in Health (CADTH) as part of its evaluation of the evidence submitted by riociguat's manufacturer.[46] This report documents a cost-utility analyses conducted from a Canadian Public Payer perspective over a lifetime (considered to be 20 years). Costs and health outcomes occurring one year post-treatment were discounted at an annual rate of 5% according to the CADTH

guidelines, and costs were reported in 2013 Canadian dollars. Riociguat dominated brand name bosentan – it had lower drug cost (–$58,409) and was more effective.

One criticism noted by the CADTH was that the model was likely to have double counted the potential benefit of riociguat on mortality since it assumed that mortality increased by worsening FC, but mortality also increased by treatment (independent of FC status).

Though conducted in different settings with different assumptions, findings from these studies indicate that riociguat is cost-effective compared to bosentan as a pharmacologic therapy for patients with inoperable CTEPH or post-PEA CTEPH. The findings align with the results of the current analyses.

Riociguat is the only drug approved for the management of CTEPH, while bosentan is mostly used off-label. This impacts the ability of bosentan to compete on price. As time goes by, and in the absence of other approved agents, or approved agents that are most cost-effective, riociguat uptake may increase, and it will may become the standard of care. It will be interesting to see how the cost-effectiveness profile changes over time given the aforementioned. Given that CTEPH is considered a rare disease and that life expectancy for patients, particularly those in FC IV, may not exceed several years, the benefit of riociguat may be as a first-line pharmacologic therapy.

There are some limitations to this economic model. Inputs for the model were sourced from published literature, using data specific to CTEPH where available. Data for a surrogate disease, PAH, was used in instances where CTEPH-specific data was

unavailable. Similarly, health care resource use data from the UK were used in the absence of US-specific data and model inputs where supplemented with assumptions as necessary. This could have impacted the model outcomes although this impact is likely to be small. Use of CTEPH-specific data will be helpful to generate more robust results. However, the model provides some insight into the cost-effectiveness of riociguat, and the impact of uncertainties around specific model parameters on model predictions to be evaluated. Similarly, data from a well-conducted and appropriately powered direct head-to-head trial of riociguat and bosentan will provide less biased estimate of the relative efficacy and safety as compared to an indirect treatment comparison.

A micro-costing approach was used for the cost inputs. Micro-costing is a cost estimation method that allows for precise assessment of the economic costs of health interventions. It is quite useful in deriving precise estimates of costs for interventions. However, it is not without drawbacks. For example, it is more complex and time consuming compared to other methods such as gross-costing or the use of aggregate costs identified from the published literature. Costs estimates calculated using micro-costing may not be generalizable to all settings (even within a country) due to other factors such as variation in discounts, or special price arrangements.

CONCLUSION

Taken together, the results of the ITC and the economic evaluation indicate that riociguat monotherapy is a more effective and less costly pharmacologic therapy than bosentan monotherapy for the management of inoperable CTEPH or post-PEA CTEPH.

APPENDICES

APPENDIX A. SEARCH ALGORITHMS FOR SYSTEMATIC LITERATURE REVIEW

Table 20. MEDLINE via PubMed

Search	MEDLINE Search Algorithm	Hits
#1	CTEPH OR "Chronic thromboembolic pulmonary hypertension"	1,240
#2	"bosentan" [Supplementary Concept] OR Bosentan OR "riociguat" [Supplementary Concept] OR riociguat	2,352
#3*	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]	3,763,628
#4	#1 AND #2 AND #3	69
#5	Letter [pt] OR editorial[pt] OR review[pt]	3,374,162
#6	animals [mh] NOT humans [mh]	4,188,108
#7	#4 NOT #5 NOT #6: Filters: Humans, English	25

* Adapted from Chapter 6: Searching for studies. In: Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions.* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

Table 21. Embase via Embase.com

Search	Embase Search Algorithm	Hits
#1	'chronic thrombo embolic pulmonary hypertension'/exp OR 'chronic thrombo embolic pulmonary hypertension' OR cteph	2,138
#2	'bosentan'/exp OR 'riociguat'/exp	7,060
#3**	random* OR factorial OR crossover OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocate* OR volunteer* OR 'crossover-procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp	1,851,990
#5	#1 AND #2 AND #3	132
#6	'letter':it OR 'editorial':it OR 'review':it	3,514,134
#7	#3 NOT #4 AND [humans]/lim AND [english]/lim	72

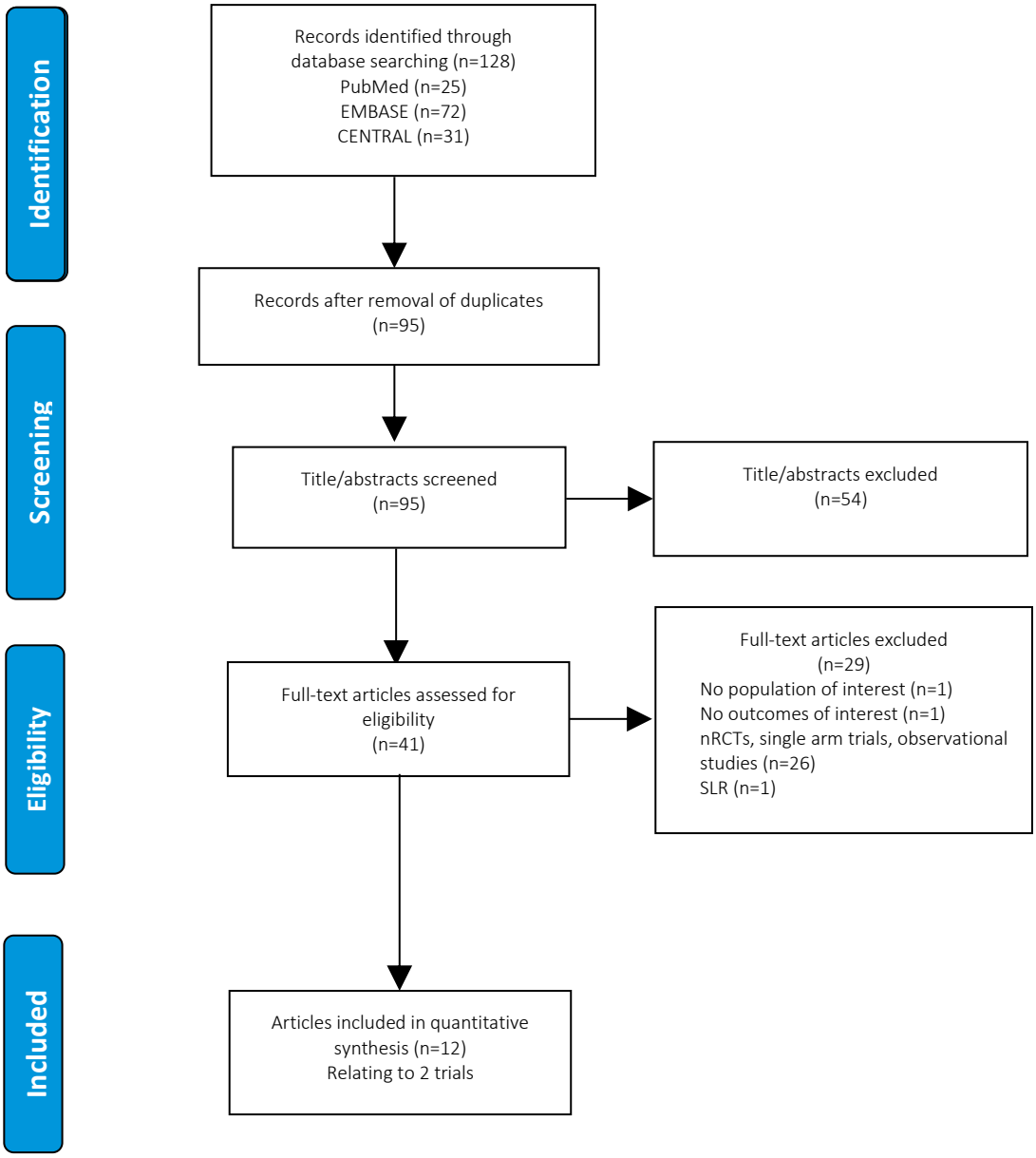
** Adapted from Chapter 6: Searching for studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

Table 22. CENTRAL via Cochrane Library

Search	Cochrane Search Algorithm	Hits
#1	Chronic thromboembolic pulmonary hypertension	81
#2	bosentan or riociguat	352
#3	#1 AND #2	38
#4	Cochrane Central Register of Controlled Trials : Issue 2 of 12, February 2016	31

APPENDIX B. PRISMA DIAGRAM

Figure 8. Attrition diagram for Systematic Literature Review



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 2009;6(6):e1000097. doi:10.1371/journal.pmed1000097

APPENDIX C. MODEL PARAMETERS

Table 23. Details of Distributions used in the Probabilistic Sensitivity Analysis

Variable	Distribution	Parameters
effFCIV_Dist	Beta	subtype: 2, alpha: ((0.426^2)*(1-0.426)/(0.259^2)), beta: (0.426*(1-0.426)/(0.259^2))-((0.426^2)*(1-0.426)/(0.259^2))
effFCIII_Dist	Beta	subtype: 2, alpha: ((0.630^2)*(1-0.630)/(0.259^2)), beta: (0.630*(1-0.630)/(0.259^2))-((0.630^2)*(1-0.630)/(0.259^2))
effFCII_Dist	Beta	subtype: 2, alpha: ((0.705^2)*(1-0.705)/(0.205^2)), beta: (0.705*(1-0.705)/(0.205^2))-((0.705^2)*(1-0.705)/(0.205^2))
pFCworsening_Dist	Beta	subtype: 2, alpha: (((0.12)^2)*(1-(0.12))/((0.012)^2)-(0.12)), beta: ((1-(0.12))*(((1-(0.12))*(0.12))/((0.012)^2)-1))
pFCimprovement_Dist	Beta	subtype: 2, alpha: (((0.10)^2)*(1-(0.10))/((0.01)^2)-(0.10)), beta: ((1-(0.10))*(((1-(0.10))*(0.10))/((0.01)^2)-1))
CostHospitalization_PerEpis_Dist	Gamma	alpha: ((19216)^2)/((187677.5624)^2), lambda: (19216)/((187677.5624)^2)
DrugCostBos_Dist	Gamma	alpha: (($184.98*2*30.42*3)^2)/((($184.98*2*30.42*3)^0.5)^2), lambda: ($184.98*2*30.42*3)/((($184.98*2*30.42*3)^0.5)^2)
DrugCostRio_Dist	Gamma	alpha: (($115.7311*3*30.42*3)^2)/((($115.7311*3*30.42*3)^0.5)^2), lambda: ($115.7311*3*30.42*3)/((($115.7311*3*30.42*3)^0.5)^2)

Table 24. Monte-Carlo Simulation Statistics (PSA) for Riociguat vs. Bosentan

Attribute	Statistics	Bosentan	Riociguat
Cost	Mean	2430595.53	2298424.12
Cost	Std Deviation	2789679.29	2789702.48
Cost	Minimum	2086803.68	1962474.98
Cost	*2.5%*	*2120533.13*	*1989019.99*
Cost	10%	2128434.22	1996553.65
Cost	Median	2143638.39	2011393.35
Cost	90%	2163153.25	2030524.38
Cost	97.5%	3620787.85	3480859.10
Cost	Maximum	151751798.29	151625266.70
Cost	Sum	243059553058.05	229842412017.84
Cost	Size (n)	100000.00	100000.00
Cost	Variance	7782310564216.58	7782439941943.00
Cost	Variance/Size	77823105.64	77824399.42
Cost	SQRT[Variance/Size]	8821.74	8821.81
Effectiveness	Mean	41.55*	42.16*
Effectiveness	Std Deviation	8.96	9.45
Effectiveness	Minimum	6.48	5.72
Effectiveness	*2.5%*	*21.93*	*21.27*

Attribute	Statistics	Bosentan	Riociguat
Effectiveness	10%	28.99	28.79
Effectiveness	Median	42.60	43.41
Effectiveness	90%	52.39	53.51
Effectiveness	***97.5%***	***55.75***	***56.73***
Effectiveness	Maximum	60.66	61.10
Effectiveness	Sum	4154962.82	4216397.78
Effectiveness	Size (n)	100000.00	100000.00
Effectiveness	Variance	80.31	89.39
Effectiveness	Variance/Size	0.00	0.00
Effectiveness	SQRT[Variance/Size]	0.03	0.03
Net Monetary Benefit	**Mean**	**-353114.12**	**-190225.23**
Net Monetary Benefit	Std Deviation	2824360.60	2828337.68
Net Monetary Benefit	Minimum	-149104603.46	-148945367.91
Net Monetary Benefit	2.5%	-1654989.19	-1518037.65
Net Monetary Benefit	10%	-800442.22	-682884.19
Net Monetary Benefit	Median	-38712.91	132159.92
Net Monetary Benefit	90%	468024.23	656596.28
Net Monetary Benefit	97.5%	640080.63	820848.65
Net Monetary Benefit	Maximum	906695.80	1048939.83

Attribute	Statistics	Bosentan	Riociguat
Net Monetary Benefit	Sum	-35311412087.34	-19022523211.58
Net Monetary Benefit	Size (n)	100000.00	100000.00
Net Monetary Benefit	Variance	7977012794655.19	7999494010076.36
Net Monetary Benefit	Variance/Size	79770127.95	79994940.10
Net Monetary Benefit	SQRT[Variance/Size]	8931.41	8943.99

* Effectiveness values will be divided by 3 to obtain the QALYs, which will be 13.85, and 14.05 for Bosentan and Riociguat respectively.

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