Pharmaceutical Benefits Scheme

Post-market Review of

Medicines to treat Pulmonary Arterial Hypertension

ToR 4

Final Report

November 2018

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Abbreviations

Abbreviation	Full Name / Wording
6MWT	Six minute walk test
6MWD	Six minute walk distance
AE	Adverse event
ARD	Absolute risk difference
CI	Confidence Interval
CMI	Consumer medicines information
CO	Cardiac output
CSR	Clinical study report
CTEPH	Chronic thromboembolic pulmonary hypertension
EMA	European Medicines Agency
EQ-5D	EuroQol 5-dimension
EQ-VAS	EuroQol visual analogue scale
ERA	Endothelin receptor antagonist
FC	Functional class
FDA	United States Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HPAH	Heritable pulmonary arterial hypertension
HR	Hazard ratio
IPAH	Idiopathic pulmonary arterial hypertension
IV	Intravenous
LPH questionnaire	Living with pulmonary hypertension questionnaire
MLHF questionnaire	Minnesota living with heart failure questionnaire
mPAP	Mean pulmonary arterial pressure
mRAP	Mean right atrial pressure
NHMRC	National Health and Medical Research Council
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAH-CHD	PAH associated with congenital heart disease
PAH-CTD	PAH associated with connective tissue disease
PAH-HIV	PAH associated with human immunodeficiency virus
PAH-PH	PAH associated with portal hypertension
PAP	Pulmonary artery pressure

PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCWP	Pulmonary capillary wedge pressure
PMR	Post-market review
PDE-5 inhibitor	Phosphodiesterase type 5 inhibitor
PH	Pulmonary hypertension
PI	Product information
PICO	Population, Intervention, Comparator and Outcome
PSD	Public summary document
PVR	Pulmonary vascular resistance
QoL	Quality of life
RAP	Right atrial pressure
RCT	Randomised controlled trial
RR	Relative risk
SC	Subcutaneous
SF-36	36-Item Short Form Health Survey questionnaire
sGC stimulator	Soluble guanylate cyclase stimulator
SmPC	Summary of product characteristics
TGA	Therapeutic Goods Administration
tid	Three times a day
ToR	Term(s) of Reference
US/USA	United States/United States of America
WHO	World Health Organization

Section 4: ToR 4
Review of the comparative effectiveness of PAH medicines

Collate and evaluate evidence on the comparative effectiveness of PAH medicines, including combination use and use in the WHO functional class II patient populations.

4.1 Key findings for ToR 4

Q1. What is the effectiveness and safety of monotherapy with a PAH medicine, compared to placebo/no treatment or another PAH medicine listed on the PBS, in patients with WHO FC I or II PAH?

The key findings from this Review regarding the comparative effectiveness of PAH medicines are:

4.1.1 Effectiveness and safety of monotherapy in WHO FC I or II PAH

4.1.1.1 Endothelin Receptor Antagonists (ERA) versus placebo

Clinical effectiveness

Four randomised controlled trials (RCTs) reported on the effectiveness of an ERA in treating pulmonary arterial hypertension (PAH) compared with placebo in patients with World Health Organization (WHO) Functional Class (FC) I/II PAH:

- ARIES-1&2 used ambrisentan
- EARLY used bosentan
- SERAPHIN used macitentan.

The evidence provided by these trials is summarised in Table 4.1.

Overall, the use of an ERA medication to treat patients with WHO FC I/II PAH is likely to be beneficial.

Table 4.1 Summary of the evidence for the clinical effectiveness of an ERA compared with placebo in patients with WHO FC I/II PAH

Outcome	Included trials No. of patients	Summary of evidence
Clinical worsening	EARLY (bosentan) ARIES-1&2 (ambrisentan) SERAPHIN (macitentan) N=375	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]

Outcome	Included trials No. of patients	Summary of evidence
All-cause mortality	EARLY (bosentan) SERAPHIN (macitentan) N=256	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Improved WHO FC	ARIES-1&2 (ambrisentan) N=101	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Significantly more patients improved their WHO FC after being treated with an ERA compared with receiving a placebo (ARD = 14.0%; 95% CI 4.4, 23.6)
Worsened WHO FC	ARIES-1&2 (ambrisentan) N=101	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Fewer patients taking an ERA had worsening of their WHO FC when compared with receiving a placebo but the 95% CI indicates that there may also be an effect in the opposite direction (RR = 0.25; 95% CI 0.03, 2.20)
Change in 6MWD from baseline	EARLY (bosentan) ARIES-1&2 (ambrisentan) N=154	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Patients taking an ERA had a larger mean improvement in their 6MWD than those taking a placebo, and the difference was clinically important in 2 out of 3 studies (range 25.7−40.0 m walked further) • There was no significant difference in the effectiveness of different ERA medications
Change in haemodynamic parameter from baseline: PVR	EARLY (bosentan) N=156	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Patients taking an ERA had a larger mean improvement in their PVR than those taking a placebo (MD = 23.1% improvement was a clinically important difference)

6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Safety

There is no evidence to evaluate the comparative safety of an ERA medication versus placebo when used to treat patients with WHO FC I/II PAH.

4.1.1.2 PDE-5 inhibitor versus placebo

Clinical effectiveness

Three RCTs were identified that reported on the effectiveness of a PDE-5 inhibitor, as monotherapy, when compared to placebo in patients with WHO FC I/II PAH:

- The PHIRST and Mukhopadhyay 2011 trials used tadalafil
- The SUPER-1 trial used sildenafil.

Neither of these trials reported on all-cause mortality for the subgroup of patients with WHO FC I/II PAH. Two cohort studies were identified that reported on the mortality of patients with WHO FC I/II PAH who were treated with either sildenafil or conventional therapy:

- Sun 2013 enrolled patients with Eisenmenger syndrome who were followed for up to 2 years
- Sastry 2007 collected prospectively acquired survival data from a hospital registry for five years for patients with IPAH of WHO FC II-IV being treated with sildenafil.

The evidence provided by these studies is summarised in Table 4.2.

Overall, there is considerable uncertainty as to whether the use of PDE-5 inhibitor medication to treat patients with WHO FC I/II PAH would be beneficial.

Table 4.2 Summary of the evidence for the clinical effectiveness of a PDE-5 inhibitor versus placebo in patients with WHO FC I/II PAH

Outcome	Included trials No. of patients	Summary of evidence
All-cause mortality	Sun 2013 cohort study (sildenafil) Sastry 2007 cohort study (sildenafil) N=76	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Fewer patients died after treatment with a PDE-5 inhibitor compared with placebo, but the 95% CI indicates that there may also be an effect in the opposite direction (pooled RR = 0.32; 95% CI 0.05, 1.90)
Improved WHO FC	Mukhopadhyay 2011 (tadalafil) N=22	• Low quality evidence (GRADE ⊕⊕⊙⊙) • The same proportion of patients improved their WHO FC taking a PDE-5 inhibitor compared with placebo, but the wide 95% CI indicates that the study was underpowered for this outcome (RR = 1.00; 95% CI 0.07, 15.00)
Worsened WHO FC	Mukhopadhyay 2011 (tadalafil) N=22	• Low quality evidence (GRADE ⊕⊕⊙⊙) • No patients had worsening of their WHO FC during the study period.
Change in 6MWD from baseline	PHIRST (tadalafil) SUPER-1 (sildenafil) N=73	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Patients taking a PDE-5 inhibitor had a larger mean improvement in their 6MWD than those taking a placebo, and the difference was clinically important in 1 study (range 10.8−50.2 m walked further) • No significant difference in the effectiveness of different PDE-5 inhibitors

6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Safety

There was no evidence available to evaluate the comparative safety of PDE-5 inhibitors versus placebo when used to treat patients with WHO FC I/II PAH.

4.1.1.3 Prostanoid versus placebo

There was no evidence available to determine the safety and effectiveness of prostanoids in treating patients with WHO FC I/II PAH.

4.1.1.4 Soluble Guanylate cyclase (sGC) stimulator versus placebo

Clinical effectiveness

Only one RCT was identified that reported on the effectiveness of monotherapy with a sGC stimulator in treating PAH compared with placebo in patients with WHO FC I/II PAH:

- The PATENT-1 trial used riociguat.

The evidence provided by this trial is summarised in Table 4.3.

Overall, there is [redacted] as to whether the use of sGC stimulator medication to treat patients with WHO FC I/II PAH [redacted].

Table 4.3 Summary of the evidence for the clinical effectiveness of a sGC stimulator versus placebo in patients with WHO FC I/II PAH

Outcome	Included trials No. of patients	Summary of evidence
Clinical worsening	PATENT-1 (riociguat) N=107	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
All-cause mortality	PATENT-1 (riociguat) N=107	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Hospitalisation due to worsening PAH	PATENT-1 (riociguat) N=107	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Improved WHO FC	PATENT-1 (riociguat) N=107	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Worsened WHO FC	PATENT-1 (riociguat) N=107	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in 6MWD from baseline	PATENT-1 (riociguat) N=107	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Change in QoL from baseline: EQ-5D[a], LPH[b]	PATENT-1 (riociguat) N=107	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]

Outcome	Included trials No. of patients	Summary of evidence
Change in haemodynamic parameters from baseline: PVR	PATENT-1 (riociguat) N=107	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]

[a] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[b] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQol 5dimension; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; LPH = living with pulmonary hypertension questionnaire; MD = mean difference; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

Safety

There was no evidence available to evaluate the comparative safety of a sGC stimulator versus placebo when used to treat patients with WHO FC I/II PAH.

4.1.2 Evidence of effectiveness and safety of monotherapy in WHO FC III or IV PAH not previously considered by the Pharmaceutical Benefits Advisory Committee (PBAC)

Q2. What is the new evidence concerning the effectiveness and safety of monotherapy with a PAH medicine, compared to the main comparator accepted by the PBAC, in patients with WHO FC III or IV PAH, that has not previously been considered by the PBAC?

There was no new evidence concerning the effectiveness or safety of monotherapy with a PAH medicine, compared to the main comparator accepted by the PBAC, in patients with WHO FC III or IV PAH. The evidentiary basis for PBAC's positive recommendation of the listing of these PAH medicines is summarised in Table 4.4 below.

Table 4.4 Summary of evidence for monotherapy in patients with PAH in WHO FC III or IV

PBAC meeting	PBS restrictions	Head-to-head trials / Indirect comparison	Comparison	Summary of evidence
Bosentan				
December 2003	WHO FC III/IV IPAH and PAH associated with scleroderma	[redacted]	[redacted]	[redacted]
March 2008	WHO FC III/IV PAH-CHD	1 head-to-head RCT comparing bosentan with placebo: • BREATHE-5 [5]	Bosentan vs placebo	• Bosentan was superior in terms of effectiveness but inferior in terms of safety, compared with placebo. • Bosentan was equivalent, in terms of comparative effectiveness and comparative safety in PAH-CHD, to other PBS-listed PAH aetiology groups, eg IPAH and PAH-CTD.

PBAC meeting	PBS restrictions	Head-to-head trials / Indirect comparison	Comparison	Summary of evidence
Ambrisentan				
July 2009	WHO FC III/IV IPAH and PAH-CTD	Indirect comparison of 2 RCTs comparing ambrisentan with placebo: • ARIES-1 [6] (WHO FC III/IV subgroup) • ARIES-2 [6] (WHO FC III/IV subgroup) with 2 RCTs comparing bosentan with placebo: • BREATHE-1 [2] • AC-052-351 [4] via placebo as the common reference	Ambrisentan vs bosentan	• Ambrisentan was non-inferior to bosentan in terms of change in 6MWD. • There was no statistically significant difference between ambrisentan and bosentan with respect to change in BDI, WHO FC and clinical worsening. • The toxicity of ambrisentan appeared non-inferior to bosentan.
Macitentan				
March 2014	WHO FC III/IV IPAH, PAH-CTD and PAH-CHD	Indirect comparison of 1 RCT comparing macitentan with placebo: • SERAPHIN [7] (overall population (i.e. with or without background therapy consisting of other PAH medicines, regardless of WHO FC) and treatment-naïve WHO FC III/IV subgroup) with 4 RCTs comparing bosentan with placebo: • BREATHE-1 [2, 8] • AC-052-351 [3, 4] • EARLY [9] • STRIDE-2 [10] via placebo as the common reference	Macitentan vs bosentan	• Macitentan was non-inferior to bosentan in terms of improvement in 6MWD. • Macitentan was non-inferior in terms of safety when compared to bosentan.
Sildenafil				
November 2006	WHO FC III IPAH and PAH-CTD	Indirect comparison of 1 RCT comparing sildenafil with placebo: • SUPER-1 [11] (overall population i.e. regardless of WHO FC, and WHO III subgroup) with 2 RCTs comparing bosentan with placebo: • BREATHE-1 [2] • AC-052-351 [4] via placebo as the common reference	Sildenafil vs bosentan	• Sildenafil was non-inferior to bosentan in terms of improvement in 6MWD • Sildenafil was no worse than bosentan in terms of toxicity
Tadalafil				
November 2011	WHO FC III IPAH and PAH-CTD	Indirect comparison of 1 RCT comparing tadalafil with placebo:	Tadalafil vs sildenafil	• Tadalafil was non-inferior to sildenafil in terms of improvement in 6MWD.

PBAC meeting	PBS restrictions	Head-to-head trials / Indirect comparison	Comparison	Summary of evidence
		• PHIRST [12-14] (subgroup of no background therapy) with 1 RCT comparing sildenafil with placebo: • SUPER-1 [11, 15-17] via placebo as the common reference		• There were no statistically significant differences between tadalafil and sildenafil with respect to improvement in FC, clinical worsening and haemodynamic parameters. • Tadalafil was non-inferior to sildenafil in terms of safety.
Iloprost				
November 2004	WHO FC III/IV IPAH, PAH-CTD and drug-induced PAH	[redacted]	[redacted]	[redacted]
Epoprostenol				
March 2006	WHO FC III/IV IPAH	Indirect comparison of 2 RCTs comparing epoprostenol with conventional therapy: • BW-46 [19] • BW-35/36 [20] with 2 RCTs comparing bosentan with placebo: • BREATHE-1 [2] • AC-052-351 [3] via placebo/conventional therapy as the common reference	Epoprostenol vs bosentan	• Epoprostenol was no worse than bosentan in terms of improvement in 6MWD. • Epoprostenol was non-inferior to bosentan in terms of safety.
November 2011	WHO FC III (as secondary therapy) and FC IV (as first-line therapy) PAH-CTD	Indirect comparison of 1 RCT comparing epoprostenol with conventional therapy: • VA1A4001 [21] with 1 RCT comparing iloprost with placebo: • AIR [18] (overall population (i.e. regardless of PAH aetiology) and secondary PAH subgroup) via placebo/conventional therapy as the common reference Indirect comparison of 1 RCT comparing epoprostenol with conventional therapy: • VA1A4001 [21]	Epoprostenol vs iloprost Epoprostenol vs bosentan	• Epoprostenol was non-inferior to iloprost in terms of improvement in 6MWD and haemodynamic parameters. • Epoprostenol was non-inferior to bosentan in terms of improvement in 6MWD. • The comparative safety of epoprostenol with iloprost and bosentan was difficult to assess in the absence of head-to head trial data. However, safety profiles of these PAH medicines were well recognised and the safety of epoprostenol was comparable across all subgroups of PAH patients.

PBAC meeting	PBS restrictions	Head-to-head trials / Indirect comparison	Comparison	Summary of evidence
		with 2 RCTs comparing bosentan with placebo: • BREATHE-1 [22] (PAH-CTD subgroup) • AC-052-351 [22] (PAH-CTD subgroup) via placebo/conventional therapy as the common reference		
Riociguat				
March 2014	WHO FC III/IV IPAH, PAH-CTD and PAH-CHD	Indirect comparison of 1 RCT comparing riociguat with placebo: • PATENT-1 [23] (treatment-naïve, WHO FC III/IV subgroup) with 3 RCTs comparing bosentan with placebo: • BREATHE-1 [2] • AC-052-351 [3, 4] • BREATHE-5 [5] via placebo as the common reference	Riociguat vs bosentan	• Riociguat was non-inferior to bosentan in terms of improvement in 6MWD. • The safety profiles of riociguat and bosentan were likely to be dissimilar.

6MWD = 6-minute walk distance; BDI= Borg Dyspnoea Index; FC = functional class; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PAH-CHD = PAH associated with congenital heart disease; RCT = randomised controlled trial; WHO = World Health Organization

Source: Relevant Public summary documents and ratified PBAC minutes

4.1.3 Effectiveness and safety of dual combination therapy

Q3. What is the effectiveness and safety of dual combination therapy involving any combination of an ERA, a PDE 5 inhibitor, a prostanoid, or a sGC stimulator, compared to monotherapy, in:

i) PAH patients, irrespective of disease severity or aetiology;

ii) PAH patients with FC III or IV; and

iii) PAH patients with different disease aetiologies?

4.1.3.1 ERA in addition to PDE-5 inhibitor

Clinical effectiveness

Four RCTs reported on the effectiveness of an ERA in addition to a PDE-5 inhibitor in treating PAH compared with placebo plus a PDE-5 inhibitor in patients with PAH:

- Three trials (EARLY, COMPASS-2 and SERAPHIN) enrolled patients on stable PDE-5 inhibitor monotherapy (sequential combination therapy).
- One trial (AMBITION) enrolled treatment naïve patients (initial combination therapy)
- There were no statistically significant differences in the effectiveness of treatment for patients receiving initial combination therapy versus monotherapy and patients receiving sequential combination therapy versus monotherapy.
- Two RCTs included a subgroup analysis for patients with WHO FC III/IV PAH.
- Two RCTs included a subgroup analysis for patients with different PAH aetiologies.

The evidence provided by these trials is summarised in Table 4.5.

Overall, there is some evidence to suggest that the use of an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy to treat PAH patients is likely to be beneficial. The evidence for patients with WHO FC III/IV PAH and for patients with different PAH aetiologies is more limited, introducing more uncertainty.

Table 4.5 Summary of the evidence for the clinical effectiveness of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	EARLY (bosentan/sildenafil) COMPASS-2 (bosentan/sildenafil) SERAPHIN (macitentan/any PDE-5i) AMBITION (ambrisentan/tadalafil) N=1,124	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
All-cause mortality	EARLY (bosentan/sildenafil) COMPASS-2 (bosentan/sildenafil) SERAPHIN (macitentan/any PDE-5i) AMBITION (ambrisentan/tadalafil) N=1,124	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Hospitalisation due to worsening PAH	SERAPHIN (macitentan/any PDE-5i) AMBITION (ambrisentan/tadalafil) N=761	• High quality evidence (GRADE ⊕⊕⊕⊕) • Significantly fewer patients were hospitalised for worsening PAH with combination therapy compared with monotherapy (pooled RR = 0.67; 95% CI 0.45, 0.98). • There were no significant differences in treatment effectiveness for the different treatment combinations.
Improved WHO FC	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=706	• High quality evidence (GRADE ⊕⊕⊕⊕) • There was little difference in the proportion of patients whose WHO FC improved with combination therapy compared with monotherapy (pooled RR = 1.10; 95% CI 0.85, 1.42). • There were no significant differences in treatment effectiveness for the different treatment combinations.
Worsened WHO FC	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=706	• High quality evidence (GRADE ⊕⊕⊕⊕) • There was no difference in the proportion of patients whose WHO FC worsened with combination therapy compared with monotherapy (pooled RR = 1.00; 95% CI 0.58, 1.73). • There were no significant differences in treatment effectiveness for the different treatment combinations.
Change in 6MWD from baseline	EARLY (bosentan/sildenafil) COMPASS-2 (bosentan/sildenafil) SERAPHIN (macitentan/any PDE-5i) AMBITION (ambrisentan/tadalafil) N=1,046	• Low quality evidence (GRADE ⊕⊕⊙⊙) • In 3 out of 4 studies, patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (range 17.3 m less to 26.3 m walked further). • There were no significant differences in treatment effectiveness for the different treatment combinations.

Outcome	Included trials No. of patients	Summary of evidence
Change in QoL from baseline: SF-36 physical component[a]	SERAPHIN (macitentan/any PDE-5i) N=299	• High quality evidence (GRADE ⊕⊕⊕⊕) • Patients on combination therapy had a larger mean improvement in their QoL than those on monotherapy (MD = 1.4 point improvement; 95% CI 0, 2.9).
Patients with WHO FC III/IV PAH		
Clinical worsening	COMPASS-2 (bosentan/sildenafil) SERAPHIN (macitentan/any PDE-5i) N=351	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
All-cause mortality	SERAPHIN (macitentan/any PDE-5i) N=157	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Patients with different PAH aetiologies		
Clinical worsening in IPAH/HPAH	COMPASS-2 (bosentan/sildenafil) N=226	• High quality evidence (GRADE ⊕⊕⊕⊕) • Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the 95% CI indicates that there may also be an effect in the opposite direction (HR = 0.82; 95% CI 0.55, 1.21).
Clinical worsening in PAH CTD	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=231	• High quality evidence (GRADE ⊕⊕⊕⊕) • Could not calculate RR due to missing numerator in one arm of one study. • Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but this did not quite reach statistical significance (pooled HR = 0.59; 95% CI 0.12, 1.07).
Clinical worsening in PAH-CHD	COMPASS-2 (bosentan/sildenafil) N=20	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (HR = 0.57; 95% CI 0.10, 3.17).

[a] SF-36 physical component summary scores range from 0 to 100. A higher score indicates better QoL.
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; MD = mean difference; PAH = pulmonary arterial hypertension; PAH-CHD = PAH associated with congenital heart disease; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; QoL = quality of life; RR = relative risk; SF-36 = short form 36; WHO = World Health Organization

Safety

Three RCTs reported on the comparative safety of treatment with an ERA plus a PDE-5 inhibitor compared with a PDE-5 inhibitor alone in any patient with PAH:

- COMPASS-2, SERAPHIN and AMBITION
- There were no new safety signals identified.

The evidence provided by these trials is summarised in Table 4.6.

Overall, use of an ERA in addition to a PDE-5 inhibitor could be non-inferior to PDE-5 inhibitor monotherapy in terms of safety when treating PAH patients. The comparative safety of an ERA plus a PDE-5 inhibitor relative to PDE-5 inhibitor monotherapy in the subgroup of patients with IPAH/HPAH and in the subgroup of patients with PAH-CTD appeared to be largely consistent with the comparative safety in the overall PAH population.

Table 4.6 Summary of the evidence for the safety of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Any AE	COMPASS-2 (bosentan/sildenafil) N=333	• High quality evidence (GRADE ⊕⊕⊕⊕) • The proportion of patients who had any AE was the same for both the combination therapy and monotherapy arms (RR = 0.99; 95% CI 0.93, 1.06).
Serious AEs	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=705	• High quality evidence (GRADE ⊕⊕⊕⊕) • Significantly fewer patients had a serious AE with combination therapy compared with monotherapy (pooled RR = 0.82; 95% CI 0.69, 0.96).
AEs leading to treatment discontinuation	COMPASS-2 (bosentan/sildenafil) AMBITION (ambrisentan/tadalafil) N=705	• High quality evidence (GRADE ⊕⊕⊕⊕) • More patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (pooled RR = 1.47; 95% CI 0.81, 2.66).
Patients with IPAH/HPAH		
Any AE in IPAH/HPAH	AMBITION (ambrisentan/tadalafil) N=204	• High quality evidence (GRADE ⊕⊕⊕⊕) • The proportion of patients who had any AE was the same for both the combination therapy and monotherapy arms (RR = 1.04; 95% CI 0.97, 1.12).
Serious AEs in IPAH/HPAH	AMBITION (ambrisentan/tadalafil) N=204	• High quality evidence (GRADE ⊕⊕⊕⊕) • Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.85; 95% CI 0.58, 1.25).
AEs leading to treatment discontinuation in IPAH/HPAH	AMBITION (ambrisentan/tadalafil) N=204	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • The proportion of patients who had an AE leading to treatment discontinuation was the same for both the combination therapy and monotherapy (RR = 0.98; 95% CI 0.44, 2.20).
Patients with PAH-CTD		
Any AE in PAH-CTD	AMBITION (ambrisentan/tadalafil) N=143	• High quality evidence (GRADE ⊕⊕⊕⊕) • The proportion of patients who had any AE was the same for both the combination therapy and monotherapy arms (RR = 1.02; 95% CI 0.96, 1.07).
Serious AEs in PAH-CTD	AMBITION (ambrisentan/tadalafil) N=143	• High quality evidence (GRADE ⊕⊕⊕⊕) • Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.87; 95% CI 0.60, 1.28).

Outcome	Included trials No. of patients	Summary of evidence
AEs leading to treatment discontinuation in PAH-CTD	AMBITION (ambrisentan/tadalafil) N=143	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.91; 95% CI 0.37, 2.19).

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; HPAH = heritable PAH; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; RR = relative risk

4.1.3.2 ERA in addition to prostanoid

Clinical effectiveness

Two RCTs reported on the effectiveness of an ERA in addition to prostanoid therapy in treating PAH compared with placebo plus a prostanoid:

- BREATHE-2 enrolled treatment-naïve patients with WHO FC III/IV PAH to receive combination therapy or monotherapy
- Han 2017 enrolled treatment-naïve patients with WHO FC III/IV PAH to receive combination therapy or monotherapy

The evidence provided by these trials for patients with WHO FC III/IV PAH is summarised in Table 4.7.

Overall, there is uncertainty as to whether an ERA in addition to prostanoid therapy, relative to prostanoid monotherapy, is beneficial in patients with WHO FC III/IV PAH.

Table 4.7 Summary of the evidence for the clinical effectiveness of an ERA in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
All-cause mortality	BREATHE-2 (bosentan/epoprostenol) N=33	• Low quality evidence (GRADE ⊕⊕⊙⊙) • More patients died from any cause with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (ARD = 13.6%; 95% CI −0.7, 28.0).
Improved WHO FC	BREATHE-2 (bosentan/epoprostenol) N=33	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • More patients improved their WHO FC with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (RR = 1.30; 95% CI 0.62, 2.71).
Change in 6MWD from baseline	BREATHE-2 (bosentan/epoprostenol) Han 2017 (bosentan/iloprost) N=47	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • In 1 out of 2 studies patients on combination therapy had a large clinically important improvement in their 6MWD compared with those on monotherapy (range 6.0 m less to 123.6 m walked further). • Two studies were too small to determine whether the two different treatment combinations differ in their treatment effectiveness.
Change in QoL from baseline: MLHF[a]	Han 2017 (bosentan/iloprost) N=14	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Patients on combination therapy had a larger mean improvement in their QoL than those on monotherapy (MD = 35.34 point improvement was a clinically important difference).
Change in haemodynamic parameters from baseline: CAI, PVR, mPAP	BREATHE-2 (bosentan/epoprostenol) Han 2017 (bosentan/iloprost) N=47	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy and were likely to be clinically important in 1 out of 2 studies (CAI range 10.8−17% improvement; PVR range 9.5−21.5% improvement; mPAP range 6.8−26.3% improvement). • The two studies were too small to determine whether the two different treatment combinations differ in their treatment effectiveness.
Change in haemodynamic parameters from baseline: mRAP, TPR	BREATHE-2 (bosentan/epoprostenol) N=33	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy (mRAP MD = 2.2 mmHg improvement; TPR MD = 13.7% improvement).

[a] MLHF questionnaire total scores range from 0 to 105. A higher score indicates poorer QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CAI = cardiac index; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; MLHF = Minnesota living with heart failure; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; TPR = total pulmonary resistance; WHO = World Health Organization

Safety

Two RCTs reported on the comparative safety of treatment with an ERA plus a prostanoid compared with a prostanoid alone in any patient with PAH:

- BREATHE-2 and Han 2017

- There were no new safety signals identified.

The evidence provided by these trials for patients with WHO FC III/IV PAH is summarised in Table 4.8.

Overall, although there is uncertainty, use of an ERA in addition to a prostanoid could be non-inferior to prostanoid monotherapy when treating patients with WHO FC III/IV PAH.

Table 4.8 Summary of the evidence for the safety of an ERA in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials	Summary of evidence
Patients with WHO FC III/IV PAH		
Any AE	Han 2017 (bosentan/iloprost) N=14	• Low quality evidence (GRADE ⊕⊕⊙⊙) • The proportion of patients who had any AE was similar for both the combination therapy and monotherapy arms, but the 95% CI indicates that there could be an effect favouring either treatment arm (RR = 1.05; 95% CI 0.67, 1.64).
Serious AEs	BREATHE-2 (bosentan/epoprostenol) N=44	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Fewer patients experienced a serious AE with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was likely underpowered for this outcome (RR = 0.75; 95% CI 0.15, 3.85).
AEs leading to treatment discontinuation	BREATHE-2 (bosentan/epoprostenol) N=44	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was likely underpowered for this outcome (RR = 0.50; 95% CI 0.03, 7.26).

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

4.1.3.3 PDE-5 inhibitor in addition to ERA

Clinical effectiveness

Five RCTs reported on the effectiveness of a PDE-5 inhibitor in addition to an ERA in treating PAH patients compared with placebo plus an ERA:

- Four trials (PHIRST, Mainguy 2013, Vizza 2017 and Zhuang 2014) enrolled patients on stable PDE-5 inhibitor monotherapy (sequential combination therapy).
- One trial (AMBITION) enrolled treatment naïve patients (initial combination therapy)
- There were no statistically significant differences in outcomes for patients receiving initial combination therapy versus monotherapy and patients receiving sequential combination therapy versus monotherapy.
- Two RCTs included a subgroup analysis for patients with WHO FC III/IV PAH.
- Three RCTs included a subgroup analysis for patients with different PAH aetiologies.

The evidence provided by these trials for all PAH patients is summarised in Table 4.9.

Overall, there is some evidence to suggest that the use of a PDE-5 inhibitor in addition to an ERA to treat PAH patients, relative to ERA monotherapy, is likely to be beneficial. The evidence for patients with WHO FC III/IV PAH, and for patients with either IPAH/HPAH or PAH-CTD is more limited.

Table 4.9 Summary of the evidence for the clinical effectiveness of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	AMBITION (tadalafil/ambrisentan) PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=694	• High quality evidence (GRADE ⊕⊕⊕⊕) • Significantly fewer patients experienced clinical worsening with combination therapy compared with monotherapy (pooled RR = 0.53; 95% CI 0.38, 0.73). • There were no significant differences in treatment effectiveness for the different treatment combinations, but the point estimate for Vizza 2017 showed the opposite effect.
All-cause mortality	AMBITION (tadalafil/ambrisentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=682	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Fewer patients died from any cause with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (pooled RR = 0.64; 95% CI 0.18, 2.36) • There were no significant differences in treatment effectiveness for the different treatment combinations, but the point estimate for Vizza 2017 showed the opposite effect.
Hospitalisation due to worsening PAH	AMBITION (tadalafil/ambrisentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=607	• High quality evidence (GRADE ⊕⊕⊕⊕) • Significantly fewer patients were hospitalised with combination therapy compared with monotherapy (pooled RR = 0.42; 95% CI 0.25, 0.70). • There were no significant differences in treatment effectiveness for the different treatment combinations.
Improved WHO FC	AMBITION (tadalafil/ambrisentan) PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=691	• High quality evidence (GRADE ⊕⊕⊕⊕) • There was little difference in the proportion of patients whose WHO FC improved with combination therapy compared with monotherapy (pooled RR = 1.11; 95% CI 0.77, 1.60). • The PHIRST study showed a trend favouring the opposite effect to the other 3 studies.
Worsened WHO FC	AMBITION (tadalafil/ambrisentan) PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=691	• High quality evidence (GRADE ⊕⊕⊕⊕) • Fewer patients on combination therapy had worsening of their WHO FC compared with monotherapy, but the result did not quite reach statistical significance (pooled RR = 0.60; 95% CI 0.34, 1.05). • There were no significant differences in treatment effectiveness for the different treatment combinations.

Outcome	Included trials No. of patients	Summary of evidence
Change in 6MWD from baseline	AMBITION (tadalafil/ambrisentan) PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) Mainguy 2013 (sildenafil/PDE-5 inhibitor) N=726	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • In 4 out of 5 studies, patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, and the difference could be clinically important in 1 study (range 2.4 m less to 36.1 m walked further). • The Vizza 2017 study showed a trend favouring the opposite effect to the other 4 studies, but this difference may not be statistically significant.
Change in haemodynamic parameters from baseline: PVR, mPAP	Zhuang 2014 (tadalafil/ambrisentan) N=124	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those patients receiving monotherapy (PVR MD = 13.9% improvement; mPAP MD = 8.5% improvement).
Patients with WHO FC III/IV PAH		
Change in 6MWD from baseline	PHIRST (tadalafil/bosentan) Zhuang 2014 (tadalafil/ambrisentan) N=109	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Patients on combination therapy had a larger mean improvement in their 6MWD than those patients receiving monotherapy, but the difference was not clinically important (range 13.5−20.1 m walked further). • There were no significant differences in treatment effectiveness for the different treatment combinations.
Patients with IPAH/HPAH		
Change in 6MWD from baseline	PHIRST (tadalafil/bosentan) Vizza 2017 (sildenafil/bosentan) N=120	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (range 8.6−13.6 m walked further). • There were no significant differences in treatment effectiveness for the different treatment combinations.
Patients with PAH-CTD		
Clinical worsening	AMBITION (tadalafil/ambrisentan) N=147	• High quality evidence (GRADE ⊕⊕⊕⊕) • Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the result just failed to reach statistical significance (HR = 0.51; 95% CI 0.25, 1.01)
Change in 6MWD from baseline	PHIRST (tadalafil/bosentan) Vizza 2017 (sildenafil/bosentan) N=55	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Patients on combination therapy had a wide range of change in their 6MWD compared with those on monotherapy, but the difference was not clinically important (range 34.1 m less to 20.7 m walked further). • There were no significant differences in treatment effectiveness for the different treatment combinations.

6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; MD = mean difference; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; RR = relative risk; WHO = World Health Organization

Safety

Four RCTs reported on the comparative safety of treatment with a PDE-5 inhibitor plus an ERA compared with an ERA alone in any patient with PAH:

- PHIRST, AMBITION, Vizza 2017 and Zhuang 2014
- There were no new safety signals identified.

The evidence provided by these trials for all PAH patients is summarised in Table 4.10.

Overall, the use of a PDE-5 inhibitor in addition to an ERA appears non-inferior to ERA monotherapy when treating PAH patients overall, although there is possible safety concern for serious adverse events (AEs) in the subgroup of patients with PAH-CTD.

Table 4.10 Summary of the evidence for the safety of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Any AE	PHIRST (tadalafil/bosentan) Vizza 2017 (sildenafil/bosentan) N=190	• High quality evidence (GRADE ⊕⊕⊕⊕) • The proportion of patients who had any AE was similar for both the combination therapy and monotherapy arms (pooled RR = 1.00; 95% CI 0.79, 1.27). • There were no significant differences in treatment effectiveness for the different treatment combinations.
Serious AEs	AMBITION (tadalafil/ambrisentan) Vizza 2017 (sildenafil/bosentan) N=482	• High quality evidence (GRADE ⊕⊕⊕⊕) • The proportion of patients who had a serious AE was similar for both the combination therapy and monotherapy arms (pooled RR = 0.99; 95% CI 0.76, 1.29). • There were no significant differences in treatment effectiveness for the different treatment combinations.
AEs leading to treatment discontinuation	AMBITION (tadalafil/ambrisentan) Zhuang 2014 (tadalafil/ambrisentan) N=503	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • More patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (pooled RR = 1.65; 95% CI 0.35, 7.81). • There were no significant differences in treatment effectiveness for the different treatment combinations.
Patients with PAH-CTD		
Any AE	AMBITION (tadalafil/ambrisentan) N=146	• High quality evidence (GRADE ⊕⊕⊕⊕) • The proportion of patients who had any AE was similar for both the combination therapy and monotherapy arms (RR = 1.04; 95% CI 0.97, 1.11).
Serious AEs	AMBITION (tadalafil/ambrisentan) N=146	• High quality evidence (GRADE ⊕⊕⊕⊕) • More patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 1.28; 95% CI 0.80, 2.04).

Outcome	Included trials No. of patients	Summary of evidence
AEs leading to treatment discontinuation	AMBITION (tadalafil/ambrisentan) N=146	• High quality evidence (GRADE ⊕⊕⊕⊕) • Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.75; 95% CI 0.34, 1.65).

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; RR = relative risk

4.1.3.4 PDE-5 inhibitor in addition to prostanoid

Clinical effectiveness

One RCT reported on the effectiveness of a PDE-5 inhibitor in addition to a prostanoid in treating PAH compared with placebo plus a prostanoid:

- PACES-1 enrolled patients receiving long-term intravenous epoprostenol therapy to receive combination therapy with sildenafil plus epoprostenol or epoprostenol alone.

The evidence provided by this trial for all PAH patients is summarised in Table 4.11.

Overall, the use of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy, to treat PAH patients is likely to be beneficial.

Table 4.11 Summary of the evidence for the clinical effectiveness of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	PACES-1 (sildenafil/epoprostenol) N=265	• High quality evidence (GRADE ⊕⊕⊕⊕) • Significantly fewer patients experienced clinical worsening of their PAH with combination therapy compared with monotherapy (RR = 0.33; 95% CI 0.15, 0.70).
All-cause mortality	PACES-1 (sildenafil/epoprostenol) N=265	• High quality evidence (GRADE ⊕⊕⊕⊕) • Significantly fewer patients died from any cause with combination therapy compared with monotherapy (ARD = −5.3%; 95% CI −9.2, −1.5).
Hospitalisation due to worsening PAH	PACES-1 (sildenafil/epoprostenol) N=265	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Fewer patients were hospitalised with combination therapy compared with monotherapy, but the 95% CI indicates that there may also be an effect in the opposite direction (RR = 0.71; 95% CI 0.30, 1.71).
Change in 6MWD from baseline	PACES-1 (sildenafil/epoprostenol) N=265	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (MD = 28.8 m walked further; 95% CI 13.9, 43.8).
Change in haemodynamic parameters from baseline: PVR, mPAP, mRAP	PACES-1 (sildenafil/epoprostenol) N=265	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy and this improvement may be clinically important PVR and mRAP (PVR MD = 20.8% improvement; mPAP MD = 7.5% improvement; mRAP MD = 2.1 mmHg improvement).

6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; RR = relative risk

Safety

One RCT reported on the effectiveness of a PDE-5 inhibitor in addition to prostanoid therapy in treating PAH compared with placebo plus a prostanoid:

- PACES-1
- There were no new safety signals identified.

The evidence provided by this trial is summarised in Table 4.12.

Overall, the use of a PDE-5 inhibitor in addition to a prostanoid is likely to be non-inferior to prostanoid monotherapy in terms of safety when treating PAH patients.

Table 4.12 Summary of the evidence for the safety of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials	Summary of evidence
All PAH patients		
Any AE	PACES-1 (sildenafil/epoprostenol) N=265	• High quality evidence (GRADE ⊕⊕⊕⊕) • The proportion of patients who had any AE was similar for both the combination therapy and monotherapy arms (RR = 0.95; 95% CI 0.90, 1.00).
Serious AEs	PACES-1 (sildenafil/epoprostenol) N=265	• High quality evidence (GRADE ⊕⊕⊕⊕) • Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.73; 95% CI 0.48, 1.10).
AEs leading to treatment discontinuation	PACES-1 (sildenafil/epoprostenol) N=265	• High quality evidence (GRADE ⊕⊕⊕⊕) • Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.49; 95% CI 0.20, 1.17).

AE = adverse event; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; WHO = World Health Organization

4.1.3.5 Prostanoid in addition to an ERA

Clinical effectiveness

Two RCTs reported on the effectiveness of a prostanoid in addition to an ERA in treating PAH compared with a placebo plus an ERA:

- COMBI enrolled patients with WHO FC III IPAH (who were already being treated with bosentan) to receive combination therapy with the addition of iloprost or continue bosentan monotherapy.
- STEP enrolled patients with PAH who were already being treated with bosentan to receive combination therapy with the addition of iloprost or continue bosentan monotherapy.
    - Nearly all included patients had WHO FC III/IV PAH; one patient randomised to monotherapy had WHO FC II PAH.

The evidence provided by these trials for patients with WHO FC III/IV PAH is summarised in Table 4.13.

Overall, there is limited evidence to suggest that the use of a prostanoid in addition to an ERA, relative to ERA monotherapy, to treat patients with WHO FC III/IV PAH may be beneficial. This finding would be stronger if it were replicated in additional research.

Table 4.13 Summary of the evidence for the clinical effectiveness of a prostanoid in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
Clinical worsening	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=105	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.39; 95% CI 0.04, 3.45).
All-cause mortality	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=105	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • There were no deaths during the study period.
Hospitalisation due to worsening PAH	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=105	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Fewer patients were hospitalised with combination therapy compared with monotherapy, but the 95% CI indicates that there may also be an effect in the opposite direction (pooled ARD = −5.5%; 95% CI −18.9, 7.8).
Improved WHO FC	STEP (iloprost/bosentan) N=65	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Significantly more patients improved their WHO FC with combination therapy compared with monotherapy (RR = 5.67; 95% CI 1.36, 23.61).
Worsened WHO FC	STEP (iloprost/bosentan) N=65	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Fewer patients on combination therapy had worsening of their WHO FC compared with monotherapy, but the difference was not statistically significant (ARD = −3.0%; 95% CI −8.9, 2.8).
Change in 6MWD from baseline	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=105	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (range 10−26 m walked further).
Change in QoL from baseline: EQ-VAS[a]	COMBI (iloprost/bosentan) N=40	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Patients on combination therapy had a larger mean improvement in their QoL than those on monotherapy (MD = 10 point improvement was a clinically important difference).
Change in haemodynamic parameters from baseline: CAI, PVR, mPAP	STEP (iloprost/bosentan) N=65	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy (PVR MD = 30.4% improvement was a clinically important difference; mPAP clinically important MD = 15.6% improvement).

[a] EQ-VAS scores range from 0 to 100. A higher score represents better QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CAI = cardiac index; CI = confidence interval; EQ-VAS = EuroQoL visual analogue scale; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; WHO = World Health Organization

Safety

Two RCTs reported on the comparative safety of treatment with a prostanoid in addition to an ERA compared with an ERA alone in patients with WHO FC III/IV PAH:

- COMBI and STEP
- There were no new safety signals identified.

The evidence provided by these trials is summarised in Table 4.14.

Overall, there is considerable uncertainty as to whether the use of a prostanoid in addition to an ERA is likely to be as safe as ERA monotherapy in patients with WHO FC III/IV PAH.

Table 4.14 Summary of the evidence for the safety of a prostanoid in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
Any AE	COMBI (iloprost/bosentan) STEP (iloprost/bosentan) N=107	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • More patients experienced an AE with combination therapy compared with monotherapy, but the 95% CI indicates there was an effect in the opposite direction (pooled RR = 2.40; 95% CI 0.15, 37.41).
Serious AEs	STEP (iloprost/bosentan) N=67	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) • Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be an effect in the opposite direction (RR = 0.65; 95% CI 0.23, 1.85).
AEs leading to treatment discontinuation	COMBI (iloprost/bosentan) N=40	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • More patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the difference was not statistically significant (ARD = 5.2%; 95% CI −4.8, 15.3).

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

4.1.3.6 sGC stimulator in addition to an ERA

Clinical effectiveness

One RCT reported on the effectiveness of a sGC stimulator in addition to an ERA in treating PAH when compared with a placebo plus an ERA in patients with PAH:

- PATENT-1 enrolled WHO FC I-IV PAH patients with or without background ERA or prostanoid therapy, to receive riociguat or placebo.
- A subgroup analysis for pre-treated patients with WHO FC III/IV PAH was also undertaken
  - 12/87 (14%) patients in this subgroup were treated with a prostanoid instead of an ERA.

The evidence provided by this trial is summarised in Table 4.15.

Overall, there is very limited evidence indicating that the use of a sGC stimulator in addition to an ERA, relative to ERA monotherapy, [redacted] for PAH patients. The evidence for patients

with WHO FC III/IV PAH showed a similar [redacted] effect. This finding would be stronger if it were replicated in additional research.

Table 4.15 Summary of the evidence for the clinical effectiveness of a sGC stimulator in addition to an ERA, relative to ERA monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
All-cause mortality	PATENT-1 (riociguat/ERA) N=167	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Hospitalisation due to worsening PAH	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Improved WHO FC	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Worsened WHO FC	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Change in 6MWD from baseline	PATENT-1 (riociguat/ERA) N=167	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Change in QoL from baseline: EQ-5D[a], LPH[b]	PATENT-1 (riociguat/ERA) N=167	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in haemodynamic parameters from baseline: PVR	PATENT-1 (riociguat/ERA) N=148	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Patients with WHO FC III/IV PAH		
Clinical worsening	PATENT-1 (riociguat/ERA) N=120	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]

Outcome	Included trials No. of patients	Summary of evidence
All-cause mortality	PATENT-1 (riociguat/ERA) N=120	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Hospitalisation due to worsening PAH	PATENT-1 (riociguat/ERA) N=120	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Improved WHO FC	PATENT-1 (riociguat/ERA) N=120	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Worsened WHO FC	PATENT-1 (riociguat/ERA) N=120	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in 6MWD	PATENT-1 (riociguat/ERA) N=120	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in QoL: EQ-5D[a], LPH[b]	PATENT-1 (riociguat/ERA) N=120	• High quality evidence (GRADE ⊕⊕⊕⊕) [redacted]
Change in haemodynamic parameters: PVR	PATENT-1 (riociguat/ERA) N=103	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]

[a] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[b] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQol 5 dimension; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; LPH = living with pulmonary hypertension; MD = mean difference; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

Safety

There is no evidence to evaluate the comparative safety of a sGC stimulator in addition to an ERA, relative to ERA monotherapy, when used to treat patients with PAH.

4.1.3.7 sGC stimulator in addition to a PDE-5 inhibitor

Clinical effectiveness

One RCT reported on the effectiveness of a sGC stimulator in addition to PDE-5 inhibitor in treating PAH when compared with placebo plus a PDE-5 inhibitor:

- PATENT-PLUS enrolled WHO FC III/IV PAH patients receiving stable sildenafil therapy to additional receive either riociguat or placebo.
- No subgroup analyses were performed.

The evidence provided by this trial is summarised in Table 4.16.

Overall, there is insufficient evidence to determine whether the use of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy, is likely to be beneficial for PAH.

Table 4.16 Summary of the evidence for the clinical effectiveness of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
All-cause mortality	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • No patients died during the study period.
Improved WHO FC	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • Fewer patients improved their WHO FC with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (RR = 0.50; 95% CI 0.09, 2.73).
Worsened WHO FC	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • No patients had worsening of their WHO FC during the study period.
Change in 6MWD from baseline	PATENT-PLUS (riociguat/sildenafil) N=18	• Very low quality evidence (GRADE ⊕⊙⊙⊙) • Patients on combination therapy had a smaller mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important (MD = 23 m less).

6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

Safety

One RCT reported on the comparative safety of treatment with a sGC stimulator in addition to a PDE-5 inhibitor, compared with a PDE-5 inhibitor alone, in patients with PAH:

- PATENT-PLUS
- There were no new safety signals identified.

The evidence provided by this trial is summarised in Table 4.17.

Overall, there is considerable uncertainty whether the use of a sGC stimulator in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy, would cause additional harm to PAH patients.

Table 4.17 Summary of the evidence for the safety of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy

Outcome	Included trials No. of patients	Summary of evidence
Patients with WHO FC III/IV PAH		
Any AE	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • More patients experienced an AE with combination therapy compared with monotherapy, but the 95% CI indicates that the study was underpowered for this outcome (RR = 1.50; 95% CI 0.85, 2.64).
Serious AEs	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • More patients experienced a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that the study was underpowered for this outcome (ARD = 16.7%; 95% CI −4.4, 37.8).
AEs leading to treatment discontinuation	PATENT-PLUS (riociguat/sildenafil) N=18	• Low quality evidence (GRADE ⊕⊕⊙⊙) • More patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the difference was not statistically significant (ARD = 8.3%; 95% CI −7.3, 24.0).

AE = adverse event; ARD = absolute risk difference; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

4.1.3.8 sGC stimulator in addition to a prostanoid

Clinical effectiveness

One RCT reported on the effectiveness of a sGC stimulator in addition to a prostanoid when compared with placebo plus a prostanoid in patients with PAH:

- PATENT-1 enrolled PAH patients with or without background ERA or prostanoid therapy, to receive riociguat or placebo
- Due to the small size of the sGC stimulator ± prostanoid group, no further subgroup analysis was undertaken

The evidence provided by this trial is summarised in Table 4.18.

Overall, there is considerable uncertainty as to whether the use of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy to treat PAH patients is likely to be beneficial.

Table 4.18 Summary of the evidence for the clinical effectiveness of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy

Outcome	Included trials No. of patients	Summary of evidence
All PAH patients		
Clinical worsening	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]

Outcome	Included trials No. of patients	Summary of evidence
All-cause mortality	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Hospitalisation due to worsening PAH	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Improved WHO FC	PATENT-1 (riociguat/prostanoid) N=27	• Very low quality evidence (GRADE ⊕⊙⊙⊙) [redacted]
Worsened WHO FC	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Change in 6MWD from baseline	PATENT-1 (riociguat/prostanoid) N=27	• Low quality evidence (GRADE ⊕⊕⊙⊙) [redacted]
Change in QoL from baseline: EQ-5D[a], LPH[b]	PATENT-1 (riociguat/prostanoid) N=27	• Moderate quality evidence (GRADE ⊕⊕⊕⊙) [redacted]
Change in haemodynamic parameters from baseline: PVR	PATENT-1 (riociguat/prostanoid) N=27	• Very low quality evidence (GRADE ⊕⊙⊙⊙) [redacted]

[a] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[b] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQol 5 dimension; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; LPH = living with pulmonary hypertension; MD = mean difference; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

Safety

There is no evidence to evaluate the comparative safety of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy, when used to treat patients with PAH.

4.1.4 Effectiveness and safety of triple combination therapy

Q4. What is the effectiveness and safety of triple combination therapy involving any combination of an ERA, a PDE 5 inhibitor, a prostanoid, or a sGC stimulator, compared to dual combination therapy, in:

i) PAH patients, irrespective of disease severity or aetiology;

ii) PAH patients with FC III or IV; and

iii) PAH patients with different disease aetiologies?

There was no comparative evidence concerning the effectiveness and safety of triple combination therapy with PBS-listed PAH medicines relative to dual combination therapy in any patients with PAH.

4.1.5 Extended assessment of safety

Results from a total of four RCTs and 19 observational studies were presented in the Review for extended safety assessment of PAH medicines. The key findings are:

- No clear safety signal has been identified on the basis of the safety data from included trials and studies.
- In paediatric patients, sildenafil had a worse safety profile than placebo. AEs occurring more frequently in patients receiving sildenafil, included pyrexia, increased erection, and upper respiratory tract infections. The occurrence of pyrexia, vomiting, and nausea appeared to be dose-related.
- The proportion of patients with ocular adverse events was generally low and comparable between sildenafil, at its recommended dose (i.e. 20 mg three times a day (tid)), and placebo, but with some AEs reported only in patients receiving sildenafil, eg retinal haemorrhage (1.4%).
- Monotherapy with tadalafil was inferior to placebo in terms of safety, with a higher incidence of overall AEs, diarrhoea, nausea, nasopharyngitis, upper respiratory tract infections, myalgia, flushing, dyspepsia and pain in the extremities.
- The included observational studies followed patients for 2 years and above, which reflects the typical prolonged use of PAH medicines in clinical practice. For individual PAH medicines, the safety results from observational studies generally agreed with each other and with the safety results from RCT(s) and post-marketing data included in the product information (PI) documents.
- Limited data from studies in paediatric PAH patients suggested that, for both bosentan and sildenafil, the safety profile in children with PAH was generally consistent with that in adults.

The potential new safety signals identified by comparing the Therapeutic Goods Administration (TGA) approved PI with the European Medicines Agency (EMA) Summary of Product

Characteristics (SmPC) and the United States Food and Drug Administration (FDA) product label include:

- Use of bosentan in patients with chronic obstructive pulmonary disease (increase in minute ventilation, decreased oxygen saturation and dyspnoea).
- AEs of penile haemorrhage and haematospermia in patients receiving PDE-5 inhibitors (both sildenafil and tadalafil).
- Potential for vaso-occlusive crises in patients receiving sildenafil for PH secondary to sickle cell anaemia.
- Intracerebral haemorrhage in tadalafil-treated patients.
- Increased mortality and serious AEs in patients receiving riociguat in treating PH associated with idiopathic interstitial pneumonias.

There was evidence from a long-term observational study suggesting increased mortality with higher sildenafil doses. Sildenafil is not indicated for use in paediatric patients, according to the TGA PI. The FDA product label communicates an apparently lesser strength of warning: use of sildenafil, particularly chronic use, is not recommended in children (namely there may be situations in which the benefit-risk profile of sildenafil may be acceptable in individual children; for example, when other treatment options are limited and sildenafil can be used with close monitoring). The EMA SmPC states that sildenafil is indicated for the treatment of children aged 1-17 years of age with PAH, but only at a recommended low dose. The international guidelines do not reach consensus regarding the use of sildenafil in paediatric PAH patients.

4.1.6 Stakeholder views

- Stakeholders suggest the review should include a review of recent clinical evidence as clinical guidelines may not reflect the most recent evidence.
- Stakeholders are concerned that recent standards of clinically relevant endpoints may be used to re-evaluate evidence previously considered by PBAC. Stakeholders note a shift from short-term functional changes to improvements in long-term outcomes in measuring treatment outcomes.
- Composite endpoints to measure PAH disease progression should include morbidity and mortality measures.
- Stakeholders note there are few RCTs assessing the comparative efficacy and safety of PAH treatments, but provide available evidence for ambrisentan and epoprostenol that is yet to be considered by PBAC, with inclusion of studies pertaining to combination use and use in the FC II patient population.

4.1.7 Consumer Views

- Consumers on combination therapy advised they tended to be using various double and triple combinations of endothelin receptor antagonists with PDE-5 inhibitors and prostacyclins.
- Some consumers participated in drug trials, including for bardoxolone methyl (Catalyst trial) and oral trepostinil, a prostacyclin analogue.

- There were reports of patients in the Pulmonary Hypertension Association Australia using selexipag.
- Consumers advised that they usually stay on the same medicines and add a further medicine to address worsening symptoms.
- Consumers swapped medicines to alleviate side effects or because they proved ineffective.
- Consumers pointed out that continuous intravenous administration of epoprostenol, while effective, leads to considerable inconvenience and additional cost for accessories and dressings. In addition there is a risk of catheter-related infection.
- Some consumers reported preferring the nebulised prostacyclins which although had more frequent dosing, were less invasive.
- Generally consumers found that PAH medicines did not impact on other medicines.
- Some advised they could not take cold/flu medicines or antihistamines or anti-inflammatory medicines.

4.2 Introduction

The Australian Government Department of Health commissioned a systematic literature review of the PAH medicines currently listed on the PBS, particularly the combination use and use in the WHO functional class II patient populations (Term of Reference 4 of the Post-Market Review of PAH medicines). For detailed background information regarding this PAH Post-Market Review, refer to the Background section.

The aim of ToR 4 of this review was to update the evidence base for the eight PAH medicines listed on the PBS, as monotherapy, for the treatment of WHO FC III-IV and to assess the effectiveness and safety of PAH medicines outside the PBS restrictions; i.e. for the treatment of patients with WHO FC I or II PAH as well as the combination use of these medicines. Any new safety signals associated with the listed PAH medicines - that had not been previously noted by the PBAC - were also of interest.

4.3 Methodology

This section outlines the methodology that underpinned the evidence review undertaken to address ToR 4. Throughout Chapter 4, new studies that add to the existing evidence base are discussed in light of findings previously submitted to the PBAC, with consideration of whether the new evidence provides support for previous PBAC decision making and whether the new evidence supports the use of PAH medicines in PAH patients with less severe disease (i.e. WHO FC I-II) and the use of combination therapy with PAH medicines.

4.3.1 Identification of relevant studies

4.3.1.1 Research questions

Outlined below are the research questions that were formulated and used to guide the review:

1. What is the effectiveness and safety of monotherapy with a PAH medicine, compared to placebo/no treatment or another PAH medicine listed on the PBS, in patients with WHO FC I or II PAH?

2. What is the new evidence concerning the effectiveness and safety of monotherapy with a PAH medicine, compared to the main comparator accepted by the PBAC, in patients with WHO FC III or IV PAH, that has not previously been considered by the PBAC?

3. What is the effectiveness and safety of dual combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator, compared to monotherapy, in: i) PAH patients, irrespective of disease severity or aetiology; ii) PAH patients with FC III or IV; and iii) PAH patients with different disease aetiologies?

4. What is the effectiveness and safety of triple combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator, compared to dual combination therapy, in: i) PAH patients, irrespective of disease severity or aetiology; ii) PAH patients with FC III or IV; and iii) PAH patients with different disease aetiologies?

The PICO (Population, Intervention, Comparator, Outcomes) study selection criteria for each of the research questions are shown in Table 4.19 to Table 4.22.

Table 4.19 Study selection criteria for systematic review of PAH medicines: research question 1

PICO component	Description	
Population	Patients with WHO FC I or II PAH	
Intervention	Monotherapy with a PAH medicine currently listed on the PBS[a]	
Comparators	Placebo/no treatment or another PAH medicine currently listed on the PBS[a]	
Outcomes	Effectiveness	Study-defined clinical worsening[b] Mortality Hospitalisation WHO FC 6MWD Quality of life Lung transplant Atrial septostomy Initiation of other PAH medicine(s) Haemodynamic parameters
	Safety	Adverse events
Study design	Effectiveness	Randomised trials or systematic reviews of randomised trials. If there was no evidence obtainable from these study designs, then the search expanded to include nonrandomised or observational studies (cohort or case-control) and systematic reviews of these.
	Safety	Randomised trials, large nonrandomised or observational studies (cohort, case-control, cross-sectional, or case series), or systematic reviews of randomised and/or nonrandomised/observational studies
Language	English only	
Research question: What is the effectiveness and safety of monotherapy with a PAH medicine, compared to placebo/no treatment or another PAH medicine listed on the PBS, in patients with WHO FC I or II PAH?		

[a] Including macitentan, ambrisentan, bosentan, sildenafil, tadalafil, iloprost, epoprostenol and riociguat
[b] Representing a composite of death, PAH-related hospitalisation, lung transplantation, atrial septostomy, initiation of other PAH medicine(s), deterioration of functional class, and/or worsening of 6MWD. The definition the composite outcome differed between studies.
6MWD = 6-minute walk distance; FC = functional class; PAH = pulmonary arterial hypertension; PBS = Pharmaceutical Benefits Scheme; WHO = World Health Organization

Table 4.20 Study selection criteria for systematic review of PAH medicines: research question 2

PICO component	Description	
Population	Patients with WHO FC III or IV PAH	
Intervention	Monotherapy with a PAH medicine currently listed on the PBS[a]	
Comparators	The main comparator previously accepted by the PBAC	
Outcomes	Effectiveness	Study-defined clinical worsening[b] Mortality Hospitalisation WHO FC 6MWD Quality of life Lung transplant Atrial septostomy Initiation of other PAH medicine(s) Haemodynamic parameters
	Safety	Adverse events
Study design	Effectiveness	Randomised trials or systematic reviews of randomised trials. If there was no evidence obtainable from these study designs and the previous evidence assessed by the PBAC was nonexperimental, then the search expanded to include nonrandomised or observational studies (cohort or case-control) and systematic reviews of these.
	Safety	Randomised trials, large nonrandomised or observational studies (cohort, case-control, cross-sectional, or case series), or systematic reviews of randomised and/or nonrandomised/observational studies
Language	English only	
Research question: What is the new evidence concerning the effectiveness and safety of monotherapy with a PAH medicine, compared to the main comparator accepted by the PBAC, in patients with WHO FC III or IV PAH, that has not previously been considered by the PBAC?		

[a] Including macitentan, ambrisentan, bosentan, sildenafil, tadalafil, iloprost, epoprostenol and riociguat
[b] Representing a composite of death, PAH-related hospitalisation, lung transplantation, atrial septostomy, initiation of other PAH medicine(s), deterioration of functional class, and/or worsening of 6MWD. The definition the composite outcome differed between studies.
6MWD = 6-minute walk distance; FC = functional class; PAH = pulmonary arterial hypertension; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; WHO = World Health Organization

Table 4.21 Study selection criteria for systematic review of PAH medicines: research question 3

PICO component	Description
Population	Patients with PAH irrespective of disease severity or aetiology. Subgroups: i) with FC III or IV; or ii) with different disease aetiologies
Interventions	Dual combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator currently listed on the PBS[a]
Comparator	Monotherapy with a PAH medicine currently listed on the PBS[b]
Outcomes	Effectiveness: Study-defined clinical worsening[c]; Mortality; Hospitalisation; WHO FC; 6MWD; Quality of life; Lung transplant; Atrial septostomy; Initiation of other PAH medicine(s); Haemodynamic parameters Safety: Adverse events
Study design	Effectiveness: Randomised trials or systematic reviews of randomised trials. If there was no evidence obtainable from these study designs, then the search expanded to include nonrandomised or observational studies (cohort or case-control) and systematic reviews of these. Safety: Randomised trials, large nonrandomised or observational studies (cohort, case-control, cross-sectional, or case series), or systematic reviews of randomised and/or nonrandomised/observational studies
Language	English only
Research question: What is the effectiveness and safety of dual combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator, compared to monotherapy, in: i) PAH patients, irrespective of disease severity or aetiology; ii) PAH patients with FC III or IV; and iii) PAH patients with different disease aetiologies?	

[a] ERA refers to macitentan, ambrisentan or bosentan. PDE-5 inhibitor refers to sildenafil or tadalafil. Prostanoid refers to iloprost or epoprostenol. sGC stimulator refers to riociguat

[b] Including macitentan, ambrisentan, bosentan, sildenafil, tadalafil, iloprost, epoprostenol and riociguat

[c] Representing a composite of death, PAH-related hospitalisation, lung transplantation, atrial septostomy, initiation of other PAH medicine(s), deterioration of functional class, and/or worsening of 6MWD. The definition the composite outcome differed between studies.

6MWD = 6-minute walk distance; ERA = endothelin receptor antagonist; FC = functional class; PAH = pulmonary arterial hypertension; PBS = Pharmaceutical Benefits Scheme; PDE-5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase; WHO = World Health Organization

Table 4.22 Study selection criteria for systematic review of PAH medicines: research question 4

PICO component	Description	
Population	Patients with PAH irrespective of disease severity or aetiology. Subgroups: i) with FC III or IV; or ii) with different disease aetiologies	
Intervention	Triple combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator currently listed on the PBS[a]	
Comparator	Dual combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator currently listed on the PBS[a]	
Outcomes	Effectiveness	Study-defined clinical worsening[b] Mortality Hospitalisation WHO FC 6MWD Quality of life Lung transplant Atrial septostomy Initiation of other PAH medicine(s) Haemodynamic parameters
	Safety	Adverse events
Study design	Effectiveness	Randomised trials or systematic reviews of randomised trials. If there was no evidence obtainable from these study designs, then the search expanded to include nonrandomised or observational studies (cohort or case-control) and systematic reviews of these.
	Safety	Randomised trials, large nonrandomised or observational studies (cohort, case-control, cross-sectional, or case series), or systematic reviews of randomised and/or nonrandomised/observational studies
Language	English only	
Research question: What is the efficacy and safety of triple combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator, compared to dual combination therapy, in: i) PAH patients, irrespective of disease severity or aetiology; ii) PAH patients with FC III or IV; and iii) PAH patients with different disease aetiologies?		

[a] ERA refers to macitentan, ambrisentan or bosentan. PDE-5 inhibitor refers to sildenafil or tadalafil. Prostanoid refers to iloprost or epoprostenol. sGC stimulator refers to riociguat

[b] Representing a composite of death, PAH-related hospitalisation, lung transplantation, atrial septostomy, initiation of other PAH medicine(s), deterioration of functional class, and/or worsening of 6MWD. The definition the composite outcome differed between studies.

6MWD = 6-minute walk distance; ERA = endothelin receptor antagonist; FC = functional class; PAH = pulmonary arterial hypertension; PBS = Pharmaceutical Benefits Scheme; PDE-5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase; WHO = World Health Organization

4.3.1.2 Literature sources and search strategies

The peer reviewed literature was searched for studies which investigated the effectiveness and/or safety of the medicines currently listed on the PBS for the treatment of PAH. No restriction was placed on the time period searched because the search terms included the specific drug names. The initial literature search was conducted on 4th October 2017 and updated on 5th December 2017. The search covered the following databases: PubMed, Embase.com and the Cochrane Library. Search terms are described in Table 4.23 and Table 4.24.

Table 4.23 Search terms for evidence to inform the systematic review questions (Pubmed and Cochrane Library)

Element of clinical question	Pubmed/Medline search terms
Population	"pulmonary arterial hypertension" OR PAH OR "pulmonary artery hypertension" OR "primary pulmonary hypertension" OR IPAH OR FPAH OR HPAH OR CTEPH OR PVH OR POPH OR "pulmonary venous hypertension" OR "portopulmonary hypertension" OR "chronic thromboembolic pulmonary hypertension" OR "hypertension, pulmonary"[MesH]
Intervention	Macitentan OR Opsumit OR ambrisentan OR Letairis OR Volibris OR Pulmonext OR bosentan OR Traceleer OR iloprost OR Ventavis OR Ilomedine OR epoprostenol OR Flolan OR Veletri OR sildenafil OR Viagra OR Revatio OR tadalafil OR Cialis OR Adcirca OR riociguat OR Adempas
Comparator (if applicable)	-
Outcomes (if applicable)	-
Limits	Article type: Clinical Study OR Clinical Trial OR Controlled Clinical Trial OR Comparative Study OR Observational Study OR Pragmatic Clinical Trial OR Randomized Controlled Trial OR Systematic Reviews OR Meta-Analysis OR Technical Report

MeSH = Medical Subject Heading, based on a Medline/PubMed platform

Table 4.24 Search terms for evidence to inform the systematic review questions (Embase PICO search)

Element of clinical question	Embase search terms
Population	'pulmonary hypertension'/exp +19 synonyms:all
Intervention	macitentan/exp + 6 synonyms:all ambrisentan/exp +7 synonyms:all bosentan/exp + 11 synonyms:all iloprost/exp + 18 synonyms:all prostacyclin/exp + 17 synonyms:all sildenafil/exp + 28 synonyms:all tadalafil/exp + 17 synonyms:all riociguat/exp + 10 synonyms:all
Comparator (if applicable)	-
Outcomes (if applicable)	-
Limits	controlled study OR clinical trial OR clinical article OR major clinical study OR randomized controlled trial (topic) OR randomized controlled trial OR controlled clinical trial OR retrospective study OR prospective study OR clinical trial (topic) OR double blind procedure OR multicentre study OR cohort analysis OR systematic review OR phase 3 clinical trial (topic)

Relevant papers had their reference lists pearled for other studies potentially missed in the database searches. No restriction was placed on the time period searched because the search terms include the specific drug names.

In addition to literature obtained through the above databases, the WHO clinical trials registry was searched for potentially relevant clinical studies. The submissions provided by the sponsors, prior to the listing of their drugs on the PBS, were also cross-checked for relevant trials.

4.3.1.3 Inclusion/exclusion criteria

In general, studies were excluded from the evidence base if they:

- Did not address the research questions;
- Did not provide information on the pre-specified target population, intervention or comparator;
- Were studies recruiting a mixed population (eg including both FC I/II PAH and FC III/IV PAH, with or without background therapy with PAH medicine(s) etc) which did not provide results of effectiveness analysis stratified by the appropriate subgroup(s) of patients of interest*;
- Were studies investigated a mixture of PAH therapies in the intervention arm and/or in the comparator arm which did not provide results by PAH regimen;
- Were studies where the administration and/or dosage of a PAH medicine is not approved or recommended by the TGA, i.e. intravenous use of iloprost (approved administration: inhaled) and ambrisentan 2.5 mg once daily (od) (recommended dose: 5-10 mg od);
- Were studies where a PAH medicine was not used for the purpose of treatment (eg one dose PAH medicine to examine its acute haemodynamic effects);
- Did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes;
- Did not have the appropriate study design (see below);
- Were studies in languages other than English; or
- Were only available in abstract form (i.e. conference abstract).

Study types that were considered for inclusion in the systematic review differed for the evaluation of effectiveness and safety.

<u>Effectiveness</u>

- Randomised controlled trials (RCTs);
- Large nonrandomised or observational comparative studies (eg cohort or case-control) <u>only if</u> a higher level of evidence is absent; and
- Systematic reviews of evidence with the above study designs.

Systematic reviews would have been included if they posed the same question and used the same criteria for selecting trials/studies as required for this current review, and the assessors were satisfied that the systematic review had adequately considered the risk of bias in the included primary studies.

* Safety results comparing the PAH medicines with their comparators in the appropriate subgroup(s) were presented in relevant research question sections (Section 4.4.1 to Section 4.4.4). If the safety data on the relevant subgroup(s) were not available, the systematic review reports the safety results in the overall mixed population as part of the extended assessment of safety of PAH medicines in Section 4.4.5.

Where adequate evidence was available of a higher quality (i.e. studies with designs where bias is minimised), lower quality evidence was not considered.

Safety

- RCTs;
- Large nonrandomised or observational studies;
- Systematic reviews of evidence with any study design.

In order to detect potential safety signals that had not been noted by the PBAC, the reviewer read the full article of any observational study with a sample size of ≥10 patients. Short-term (follow-up of <2 years) studies were included only if they identified AEs not reported or under-reported by RCTs or in the TGA-approved PI. Observational studies with longer follow-up (≥2 years) which fulfilled the PICO criteria were included in the literature review had ≥50 patients receiving PAH medicines in the studies or if they had reported new safety signals.

It was considered that routine AE reporting would be the source of AE data and that where relevant, PI for the PAH medicine affected would be updated to include these. Regulatory agencies are responsible for reviewing the AE reports and in some cases publish the outcome of these reviews. Websites of regulatory agencies, including the TGA, the FDA and the EMA, were searched for any safety concerns from post-marketing drug safety surveillance which might incur regulatory recall actions undertaken to mitigate risk, eg alterations of the product label, hazard alert, or suspension or cancellation of the product.

4.3.2 Search results and selection of evidence

A PRISMA flowchart (Figure 4.1) provides a graphic depiction of the results of the literature search and the application of the study selection criteria as stated in Section 4.3.1 [24].

Studies were selected by a single reviewer with a second reviewer assessing 10 per cent of the most relevant citations. Relevance was determined by the algorithm within Rayyan software[†].

Studies were excluded from the review if they could not be retrieved or if they met the study selection criteria but contained insufficient or inadequate data for data extraction and synthesis. These excluded studies are listed in Appendix 4B. A list of short-term observational studies which did not detect any new safety signals and, therefore, were excluded from extended assessment of the safety of PAH medicines can be provided on demand.

[†] https://rayyan.qcri.org/

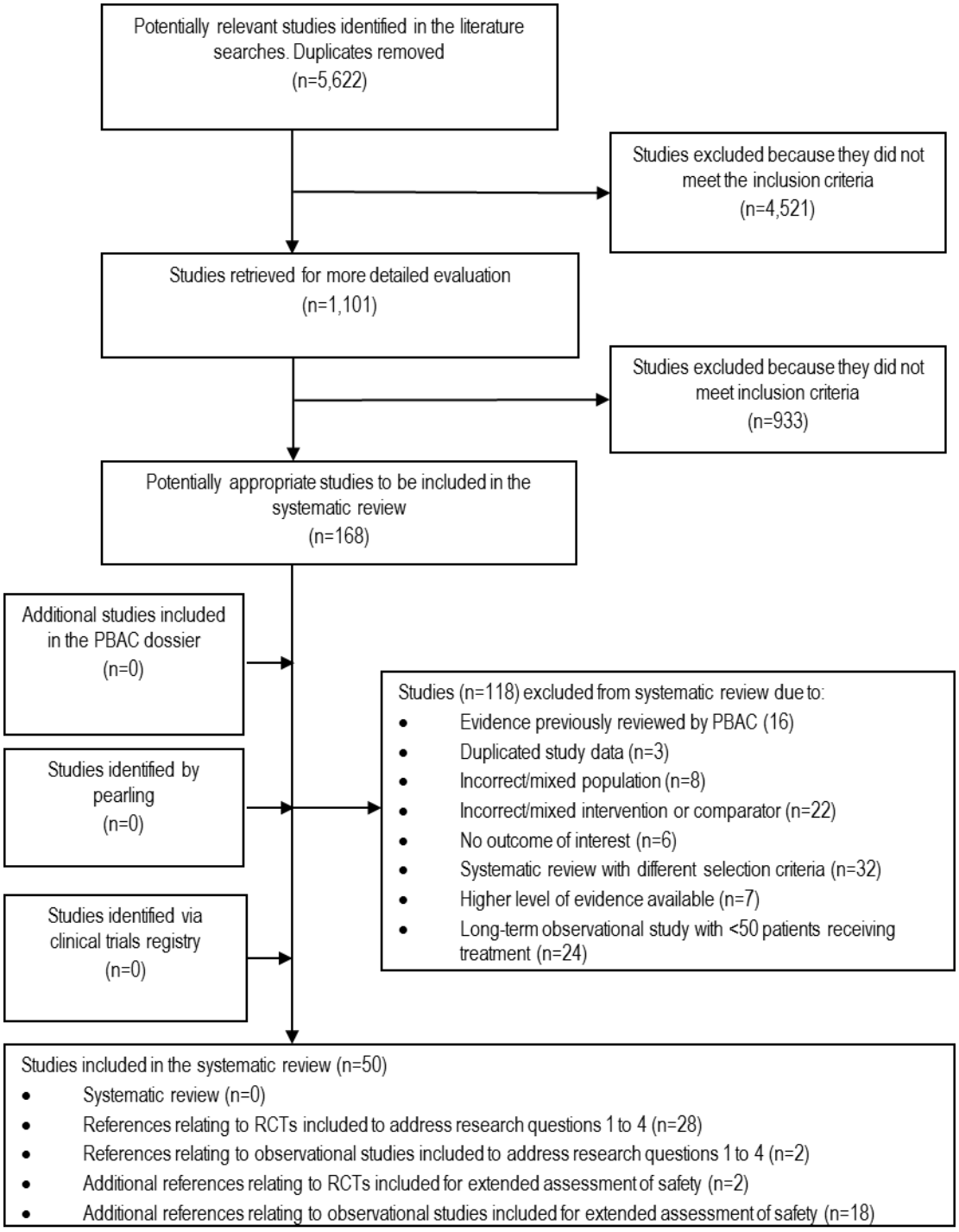


Figure 4.1 Summary of the process used to identify and select studies for the assessment of PAH medicines

PICO = Population, Intervention, Comparator and Outcome; RCT = randomised controlled trial

A profile of each included study is given in Appendix 4A. This study profile describes the study ID, authors, publication year, study design and study quality (level of evidence and risk of bias), study location, setting, length of follow-up of patients, study population characteristics, description of the intervention, description of the comparator and the relevant outcomes assessed. Key study characteristics are also summarised in a shorter format in Section 4.3.4. In studies where a PAH medicine was given at different doses, data were extracted only for the arm with the dose that is recommended by the TGA-approved PI.

4.3.3 Critical appraisal

Individual studies were critically appraised in terms of the risk of bias associated with their study design (National Health and Medical Research Council (NHMRC) levels of evidence, see Table 4.25) and their execution. The Cochrane Collaboration's tool for assessing risk of bias[25] was used to appraise the RCTs. Observational studies were assessed using Cochrane's Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool[26]. Systematic reviews would have been assessed using the AMSTAR 2 checklist[27].

Table 4.25 Designations of levels of interventional evidence

Level	Intervention[a]
I[b]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[c] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[d] ▪ Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

[a] Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence [28] and in the accompanying Glossary.
[b] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.
[c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).
[d] Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).
Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence that is practically achievable; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.
Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.
Note C: Each individual study that is attributed a "level of evidence" should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.
Source: Merlin et al 2009[29]

4.3.4 Clinical evidence included in the systematic review

4.3.4.1 Clinical evidence addressing questions 1 to 4

There were no systematic reviews identified that posed the same questions and used the same criteria for selecting trials/studies determined *a priori* for this current review. The review was therefore reliant on primary research evidence.

A total of 30 references were included in this literature review which reported comparative effectiveness and/or safety of PAH medicines versus their comparators in the appropriate populations of interest as specified in Tale 4.19 to Table 4.22. They were related to a total of 19 RCTs (level II evidence) and two comparative observational studies (level III-2 evidence and level III-3 evidence). A summary of the key features of these studies is presented in Table 4.26.

Of the 19 included RCTs, PBAC has reviewed data from six trials (ARIES-1, ARIES-2, PATENT-1, PHIRST, SERAPHIN and SUPER-1) on the overall population and/or on the subgroup of patients in line with the PBS restrictions requested by the PAH submissions, i.e. WHO FC III or IV patients without background therapy with other PAH medicines (see Table 4.4 in the "4.1 Key findings for ToR 4" section). Trial results presented in this literature review were of patient populations outside the PBS target patients, namely patients receiving monotherapy with a PAH medicine for treatment of WHO FC I-II PAH (research question 1) and patients on PAH dual or triple combination therapy (research questions 3 and 4).

Table 4.26 Key features of the included evidence addressing research questions

Study ID Study period Location	Study design Duration of follow-up Risk of bias	N[a] WHO FC PAH aetiology	Intervention(s)[b] Comparator Background therapy	Relevant RQ Overall population or subgroup	Outcomes
Randomised controlled trials (RCTs)					
AMBITION[30-32] 2010-2014 US, Canada, Europe, Australia, Japan	RCT, DB 1.7 years Low	N=500 WHO FC II-III IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-HIV, or PAH-DT	AMB 10 mg od + TAD 40 mg od AMB 10 mg od + PBO TAD 40 mg od + PBO No background therapy	RQ 3 Overall population	- Clinical worsening - Hospitalisation - Change in WHO FC - Mortality - Change in 6MWD
ARIES-1[6, 33, 34] 2003-2006 US, Mexico, South America, Australia, Europe	RCT, DB 12 weeks Low-to-moderate	N=134 WHO FC I-IV IPAH, PAH-CTD, PAH-HIV, or PAH-DT	AMB 5 mg od PBO No background therapy	RQ 1 Subgroup of patients with WHO FC I-II PAH (n=46)	- Clinical worsening - Change in 6MWD - Change in WHO FC
ARIES-2[6, 33, 34] 2003-2006 Europe, Israel, South America	RCT, DB 12 weeks Low-to-moderate	N=128 WHO FC I-IV IPAH, PAH-CTD, PAH-HIV, or PAH-DT	AMB 5 mg od PBO No background therapy	RQ 1 Subgroup of patients with WHO FC I-II PAH (n=55)	- Clinical worsening - Change in WHO FC - Change in 6MWD

Study ID Study period Location	Study design Duration of follow-up Risk of bias	N[a] WHO FC PAH aetiology	Intervention(s)[b] Comparator Background therapy	Relevant RQ Overall population or subgroup	Outcomes
BREATHE-2[35] No later than 2004[c] US, Europe	RCT, DB 16 weeks Low-to-moderate	N=33 WHO FC III-IV[d] IPAH or PAH-CTD	BOS 125 mg bid + EPO 12-16 ng/kg/min PBO + EPO 12-16 ng/kg/min	RQ 3 Overall population	- Mortality - Change in WHO FC - Change in 6MWD - Haemodynamic parameters[e] - Adverse events
COMBI[36] 2004 Germany	RCT, OL 12 weeks High	N=40 WHO FC III IPAH	ILO 5 µg 6 times daily No treatment Background therapy with BOS 125 mg bid (100%)	RQ 3 Overall population	- Clinical worsening - Mortality - Change in 6MWD - QoL (EQ-VAS) - Adverse events
COMPASS-2[37] 2006-2012 US, Europe, Brazil, Saudi Arabia	RCT, DB 3.2 years Low-to-moderate	N=334 WHO FC II-IV IPAH, PAH-CTD, PAH-CHD, HPAH, or PAH-DT	BOS 125 mg bid PBO Background therapy with SIL ≥20 mg tid (100%)	RQ 3 Overall population	- Clinical worsening - Mortality - Change in WHO FC - Change in 6MWD - Adverse events
EARLY[9] 2004-2006 US, Europe, Brazil	RCT, DB 26 weeks Low	N=185 WHO FC II IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-HIV, or PAH-DT	BOS 125 mg bid PBO Background therapy with SIL (16%)	RQ 1 Subgroup of patients without background therapy (n=156) Q3 Subgroup of patients with background therapy (n=29)	- Clinical worsening - Mortality - Change in 6MWD - Haemodynamic parameters[e]
Han 2017[38] 2012-2015 China	RCT, OL 13 weeks High	N=14 WHO FC III-IV IPAH or CTEPH[f]	BOS 125 mg bid + ILO 10 µg 4-6 times daily ILO 10 µg 4-6 times daily No background therapy	RQ 3 Overall population	- Change in 6MWD - QoL (MLHF) - Haemodynamic parameters[e] - Adverse events
Mainguy 2013[39] 2009-2011 Canada	RCT, DB, cross-over 4 weeks Low-to-moderate	N=20 WHO FC II-III IPAH, HPAH, PAH-CTD, PAH-CHD	SIL 20 mg tid PBO Background therapy with ERA (90%) Background therapy with EPO (10%)	RQ 3 Overall population	- Change in 6MWD
Mukhopadhyay 2011[40] No later than 2011[c]	RCT, DB, cross-over 6 weeks	N=28 WHO II-III PAH-CHD	TAD 40 mg od PBO	RQ 1 Subgroup of patients with	- Change in WHO FC

Study ID **Study period** **Location**	**Study design** **Duration of follow-up** **Risk of bias**	**N[a]** **WHO FC** **PAH aetiology**	**Intervention(s)[b]** **Comparator** **Background therapy**	**Relevant RQ** **Overall population or subgroup**	**Outcomes**
India	Low-to-moderate		No background therapy	WHO FC I-II PAH (n=22)	
PACES-1[41] 2003-2006 US, Canada, Europe, Israel	RCT, DB 16 weeks Low	N=267 WHO FC I-IV IPAH or PAH-CTD	SIL 20-80 mg tid PBO Background therapy with EPO 3-181/kg/min (100%)	RQ 3 Overall population	- Clinical worsening - Mortality - Hospitalisation - Change in 6MWD - Haemodynamic parameters[e] - Adverse events
PATENT-1[23, 42, 43] 2008-2012 US, Canada, Mexico, Asia, Europe, South America, Australia	RCT, DB 12 weeks Low-to-moderate	N=380 WHO FC I-IV IPAH, PAH-CTD, PAH-CHD, PAH-PH, or PAH-DT	RIO up to 2.5 mg tid PBO Background therapy with ERA (44%) Background therapy with PRO (6%)	RQ 1 Subgroup of patients with WHO FC I-II PAH, without background therapy (n=107) RQ3 Subgroup of patients with background therapy (n=194)	- Clinical worsening - Mortality - Hospitalisation - Change in WHO FC - Change in 6MWD - QoL (LPH, EQ-5D) - Haemodynamic parameters[e] - Adverse events
PATENT-PLUS[44] 2010-2013 Europe	RCT, DB 12 weeks Low	N=18 WHO FC I-IV IPAH, PAH-CTD, PAH-CHD or PAH-PH	RIO up to 2.5 mg tid PBO Background therapy with SIL 20 mg tid (100%)	RQ 3 Overall population	- Change in WHO FC - Change in 6MWD - Adverse events
PHIRST[12, 13, 45] 2005-2007 US, Canada, Europe, Japan	RCT, DB 16 weeks Low-to-moderate	N=161 WHO FC I-IV IPAH, HPAH, PAH-CTD, PAH-CHD, or PAH-DT	TAD 40 mg od PBO Background therapy with BOS up to 125 mg bid (54%)	RQ 1 Subgroup of patients with WHO FC I-II PAH, without background therapy (n=21) RQ3 Subgroup of patients with background therapy (n=87)	- Clinical worsening - Change in WHO FC - Change in 6MWD - Adverse events
SERAPHIN[7, 46, 47] 2008-2012 US, Canada, Europe, Asia, South America, Australia	RCT, DB 2.5 years Low-to-moderate	N=492 WHO FC I-IV IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-HIV, or PAH-DT	MAC 10 mg od PBO Background therapy with PDE-5 inhibitor (61%) Background therapy with PRO (4%)	RQ 1 Subgroup of patients with WHO FC I-II PAH, without background therapy (n=100)	- Clinical worsening - Mortality - Hospitalisation - Change in 6MWD - QoL (SF-36) - Adverse events

Study ID Study period Location	Study design Duration of follow-up Risk of bias	N[a] WHO FC PAH aetiology	Intervention(s)[b] Comparator Background therapy	Relevant RQ Overall population or subgroup	Outcomes
				RQ 3 Subgroup of patients with background therapy (n=308)	
STEP[48] 2004 USA	RCT, DB 12 weeks Low	N=67 WHO FC III-IV[d] IPAH or associated PAH	ILO 5 µg 6-9 times daily PBO Background therapy with BOS 125 mg bid (100%)	RQ 3 Overall population	- Clinical worsening - Change in WHO FC - Change in 6MWD - Haemodynamic parameters[e] - Adverse events
SUPER-1[11] 2002-2003 US, Mexico, South America, Europe, Asia, South Africa, Australia	RCT, DB 12 weeks Low-to-moderate	N=139 WHO FC I-IV IPAH, PAH-CTD or PAH-CHD	SIL 20 mg tid PBO No background therapy	RQ 1 Subgroup of patients with WHO FC I-II PAH (n=56)	- Change in 6MWD
Vizza 2017[49] 2006-2012 US, Europe, Australia, Israel, China	RCT, DB 12 weeks Low-to-moderate	N=103 WHO FC II-IV IPAH, HPAH or PAH-CTD	SIL 20 mg tid PBO Background therapy with BOS 62.5-125 mg bid (100%)	RQ 3 Overall population	- Clinical worsening - Mortality - Hospitalisation - Change in WHO FC - Change in 6MWD - Adverse events
Zhuang 2014[50] 2011-2013 China	RCT, DB 16 weeks Low-to-moderate	N=124 WHO FC II-IV IPAH, HPAH, PAH-CTD, PAH-CHD, or PAH-DT	TAD 40 mg od PBO Background therapy with AMB 10 mg od (100%)	RQ 3 Overall population	- Clinical worsening - Mortality - Hospitalisation - Change in WHO FC - Change in 6MWD - Haemodynamic parameters[e] - Adverse events
Observational studies					
Sun 2013[51] 2005-2011 China	Retrospective and prospective cohort 3.0 years Moderate	N=121 WHO FC I-IV PAH-CHD	SIL daily dose of 60-100 mg Conventional therapy No background therapy	RQ 1 Subgroup of patients with WHO FC I-II PAH (n=76)	- Mortality
Sastry 2007[52] 1999-2006 India	Historical control study Up to 5 years Moderate-to-high	N=178 WHO II-IV IPAH	SIL 25-50 mg tid Conventional therapy No background therapy	RQ 1 Subgroup of patients with WHO FC I-II PAH (n=79)	- Mortality

[a] Number of patients in the control arm and those in the active treatment arm where a PAH medicine was given at the recommended dose regimen.
[b] Only including the active treatment arm where a PAH medicine was given at the recommended dose regimen. The dose presented was the target dose. Patients could have received a PAH medicine at a lower initial dose.

[c] Publication year. Information on the study period was not available.
[d] The name New York Heart Association FC, instead of WHO FC, was used in the study. However, the description for each class in these two FC classifications is generally similar.
[e] Haemodynamic parameters include cardiac index, pulmonary arterial pressure, pulmonary vascular resistance, pulmonary capillary wedge pressure and right atrial pressure.
[f] The bosentan monotherapy arm was excluded from the review, given that a non-trivial proportion of patients (28.6% (2 out of 7)) in this treatment group had CTEPH, not PAH.
6MWD = 6-minute walk distance; AMB = ambrisentan; bid = twice daily; BOS = bosentan; CTEPH = chronic thromboembolic pulmonary hypertension; DB = double-blinded; EPO = epoprostenol; EQ-5D = EuroQoL 5 dimensions; EQ-VAS = EuroQoL visual analogue scale; ERA = endothelin receptor antagonist; FC = functional class; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; ILO = iloprost; LPH = Living with pulmonary hypertension; MLHF = Minnesota living with heart failure; od = once daily; PDE-5 = phosphodiesterase type 5; OL = open-label; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PAH-DT = drug/toxin-induced pulmonary arterial hypertension; PAH-HIV = pulmonary arterial hypertension associated with human immunodeficiency virus infection; PAH-PH = pulmonary arterial hypertension associated with portal hypertension; PBO = placebo; PRO = prostanoid; QoL = quality of life; RCT = randomised controlled trial; RQ = research question; SF-36 = 36-Item Short Form Survey; SIL = sildenafil; TAD = tadalafil; tid = three times a day; WHO = World Health Organization

Patients in three of the 19 trials (AMBITION, COMPASS-2 and SERAPHIN) were followed up for >1.5 years; whilst the other 16 RCTs had a short follow-up period of ≤6 months. More than half of the RCTs commenced >10 years ago; since then the management of PAH has changed with the development of targeted medical therapies and overall improvements in surgical treatment options and general supportive care.

The two open-label trials (COMBI and Han 2017) had a high risk of bias. The remaining 17 RCTs were double-blinded. Five of these had a low risk of bias (AMBITION, EARLY, PACES-1, PATENT-PLUS, and STEP) and 12 had a low-to-moderate risk of bias (ARIES-1, ARIES-2, BREATHE-2, COMPASS-2, Mainguy 2013, Mukhopadhyay 2011, PATENT-1, PHIRST, SERAPHIN, SUPER-1, Vizza 2017 and Zhuang 2014).

None of the trials solely compared PAH monotherapy with placebo/no treatment or another PAH medicine in a population of patients with WHO FC I/II PAH. Data from relevant subgroups from eight RCTs (ARIES-1, ARIES-2, EARLY, Mukhopadhyay 2011, PATENT-1, PHIRST, SERAPHIN and SUPER-1) were therefore analysed to address research question 1. Of these trials, EARLY was the only study that solely included patients with WHO FC I/II PAH and randomisation was stratified according to background sildenafil use. This trial had low risk of bias and confounding. In the other seven RCTs which involved a mixed population of WHO FC I/II and III/IV, baseline WHO FC was not a stratification factor. Therefore, the patient characteristics at baseline might not be comparable between intervention and control arms in the WHO FC I/II, no background therapy subgroup, thereby introducing the risk of biased findings.

Eleven trials compared PAH dual therapy with monotherapy (AMBITION, BREATHE-2, COMBI, COMPASS, Han 2017, Mainguy 2013, PACES-1, PATENT-PLUS, STEP, Vizza 2017 and Zhuang 2014). Results of these trials, in addition to the subgroups of patients with background therapy from four RCTs (EARLY, PATENT-1, PHIRST and SERAPHIN), addressed research question 3. SERAPHIN was the only RCT that included a mixture of subjects with and without background therapy, with randomisation that was not stratified by this factor. As data on baseline characteristics were not provided in the subgroup of patients with background therapy across the treatment arms, results of the subgroup analyses from SERAPHIN are subject to bias and confounding. The majority of the

included trials examined sequential combination therapy in PAH patients who had already been stabilised on background monotherapy, with only three RCTs (AMBITION, BREATHE-2 and Han 2017) comparing upfront combination therapy *versus* monotherapy in treatment-naïve patients.

There were no RCTs identified that fitted the selection criteria determined *a priori* for research question 2 (new evidence comparing PAH monotherapy *versus* the PBAC-accepted main comparator for treatment of WHO FC III/IV) and research question 4 (triple therapy *versus* dual therapy).

Two observational studies were identified by the systematic review which reported long-term survival data in PAH patients receiving sildenafil in addition to conventional therapy and in those treated with conventional therapy only. One of these had concurrent controls (Sun 2013) and the other had a historical control group (Sastry 2007). Mortality results of the WHO FC I/II subgroup from these two studies were presented to address research question 1 as none of the identified RCTs (higher level of evidence) provided survival data associated with a PDE-5 inhibitor as monotherapy relative to no treatment/placebo in patients with WHO FC I/II PAH. However, the WHO FC I/II subgroup results should be interpreted with caution due to the potential for confounding, as no information on the patient characteristics of this subgroup was provided in the study report. Although mortality data for the WHO FC III/IV PAH subgroup were also reported by Sun 2013 and Sastry 2007, the studies did not fulfil the selection criteria for Research question 2, given that 'conventional therapy' was not the main comparator accepted by the PBAC when it recommended the listing of sildenafil. An indirect comparison of sildenafil with the main comparator bosentan, *via* no treatment/placebo as the reference group, could not be performed in the review due to the absence of corresponding long-term survival data for bosentan.

4.3.4.2 Other clinical evidence included for the extended assessment of safety

Table 4.27 summarises the key features of clinical evidence included for extended assessment of safety of PAH medicines.

Three RCTs recruiting a mixed population - Mukhopadhyay 2011[40], PHIRST[45] and SUPER-1[53] - had their clinical effectiveness results reported for the appropriate subgroups of interest, but had their safety results reported as a mixed population. These data were not previously reviewed by the PBAC.

There was one RCT involving paediatric patients with WHO FC I-IV PAH which did not provide results of the clinical effectiveness analysis stratified by baseline FC: STARTS-1[54]. This trial was included in the systematic review as supplementary evidence for the extended assessment of the safety of PAH medicines in the overall PAH population.

No short-term observational studies identified by the literature review detected important safety signals which had not already been noted by the PBAC/TGA. Safety results of PAH medicines were reported by 43 long-term observational studies, of which 24 were small studies (<50 patients receiving PAH medicines) without new safety signals reported. Thus, a total of 19 observational studies were included for an extended assessment of the safety of PAH medicines. Although the

study by Sastry et al (2007) included a cohort of patients treated with sildenafil in addition to conventional therapy and a historical control group receiving conventional therapy only, the results of AEs were not reported for the control group. This study, therefore, is a non-comparative study for evaluation of safety. The remaining 18 studies were uncontrolled case series in study design. The safety of PAH medicines in paediatric patients was investigated in two observational studies (STARTS extension study and Hislop 2011). The other 17 studies recruited adults only or predominantly.

Table 4.27 Key features of the included evidence for assessment of extended safety

Study ID Study period Location	Study design Duration of follow-up	N[a] WHO FC PAH aetiology	Intervention[b] Comparator Background therapy
Randomised controlled trials (RCTs)			
Mukhopadhyay 2011[40] No later than 2011[c] India	RCT, DB, cross-over 6 weeks Low-to-moderate	N=28 WHO II-III PAH-CHD	TAD 40 mg od PBO
PHIRST[45] 2005-2007 US, Canada, Europe, Japan	RCT, DB 16 weeks	N=74[c]/161 WHO FC I-IV IPAH, HPAH, PAH-CTD, PAH-CHD, or PAH-DT	TAD 40 mg od PBO Background therapy with BOS up to 125 mg bid (54%)
STARTS-1[54] 2003-2008 North, South, and Central America, Asia, Europe	RCT, DB 16 weeks	N=234 WHO FC I-IV IPAH, HPAH or PAH-CHD	SIL at weight-based low, median or higher doses[d] PBO
SUPER-1[53] 2002-2003 US, Mexico, South America, Europe, Asia, South Africa, Australia	RCT, DB 12 weeks	N=139 WHO FC I-IV IPAH, PAH-CTD or PAH-CHD	SIL 20 mg tid PBO
Observational studies			
ARIES extension study[55] No later than 2009[c] US, Mexico, South America, Australia, Europe, Israel	Prospective case series 2 years	N=383 WHO I-IV IPAH, PAH-CTD, PAH-HIV or PAH-DT	AMB 2.5 mg, 5 mg or 10 mg od Combination with SIL and/or PRO (18%)
Dickinson 2009[56] 1998-2006 Netherlands	Retrospective case series 2.6 years	N=111 WHO II-IV IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-PH, PAH-HIV, PAH-DT or PAH associated with Gaucher disease Type 1	EPO (dose not stated)
EARLY extension study[57] 2004-2011 US, Europe, Brazil	Prospective case series 4.3 years	N=173 WHO FC I-III IPAH, PAH-CTD, PAH-CHD or PAH-HIV	BOS 125 mg bid Combination with SIL and/or PRO (17%-46%)
Hislop 2011[58] 2002-2008 UK	Retrospective case series 2.6 years	N=101 WHO FC unknown IPAH or PAH-CHD	BOS 15-125 mg bid, according to body weight[e] Combination with SIL and/or EPO (34%-63%)

Study ID **Study period** **Location**	**Study design** **Duration of follow-up**	**N[a]** **WHO FC** **PAH aetiology**	**Intervention[b]** **Comparator** **Background therapy**
Kallen 2008[59] 2004-2006 US	Retrospective case series 4 years	N=195 WHO FC unknown PAH aetiology not specified	EPO (dose not stated)
Keogh 2011[60] 2004-2007 Australia	Prospective case series 2.1 years	N=528 WHO FC II-IV IPAH or PAH-CTD	BOS (dose not stated) Combination with SIL or PRO (11%)
Kitterman 2012[61] 2006-2010 US	Prospective case series 2 years	N=1,146 WHO FC I-IV IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-PH, PAH-DT, PAH-HIV, other associated PAH or PVOD	EPO or TRE (dose not stated)
McLaughlin 2002[62] 1991-2001 US	Case series (unclear if retrospective or prospective) 2.6 years	N=162 WHO FC III-IV IPAH, HPAH or PAH-DT	EPO dose titrated to a maximum tolerated dose
Oudiz 2004[63] 1987-2000 US	Retrospective and prospective case series 3.6 years	N=192 WHO FC unknown IPAH, PAH-CTD, PAH-CHD, PAH-PH or PAH-HIV	EPO (dose not stated)
PACES extension study[64] 2003-2009 US, Canada, Europe, Israel	Prospective case series 3.2 years	N=265 WHO I-IV IPAH or PAH-CTD	SIL 20-80 mg tid +EPO (dose not stated)
PATENT extension study[65] 2009-2014 North America, South America, Asia, Europe, Australia	Prospective case series 2.7 years	N=396 WHO FC I-IV IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-PH, PAH-DT	RIO up to 2.5 mg tid Combination with ERA and/or PRO (50%-55%)
Provencher 2006[66] 1999-2004 France	Retrospective case series 2.0 years	N=103 WHO FC III-IV IPAH	BOS 125 mg bid Combination with PRO (44%)
Sastry 2007[52] 1999-2006 India	Historical control study Up to 5 years	N=178 WHO FC II-IV IPAH	SIL 25-50 mg tid Conventional therapy
Sitbon 2002[67] 1992-2001 France	Retrospective case series 2.2 years	N=178 WHO FC III-IV IPAH, HPAH or PPAH-DT	EPO dose adjusted based on clinical symptoms, exercise capability, and haemodynamic measurements
Sitbon 2016[68] 2007-2013 France	Retrospective case series 2.5 years	N=97 WHO FC II-IV IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-DT, PAH-PH or PAH-HIV	BOS/AMB+SIL/TAD BOS 125 mg bid AMB 5 mg or 10 mg od SIL 20 or 40 mg tid TAD 20 or 40 mg od Combination with PRO or SEL (29%)

Study ID Study period Location	Study design Duration of follow-up	N[a] WHO FC PAH aetiology	Intervention[b] Comparator Background therapy
STARTS extension study [69] 2004-2011 North, South, and Central America, Asia and Europe	Prospective case series 4.1 years	N=329 WHO FC I-IV IPAH, HPAH or PAH-CHD	SIL dose adjusted according to clinical response and tolerability
Vachiéry 2017 [70] 2008-2013 Europe, Canada, Australia	Prospective case series 2.2 years	N=998 WHO FC I-IV IPAH, HPAH or associated PAH	AMB 5 mg or 10 mg od Combination with other PAH medicines (32% at baseline)
VA1A4001 extension study[71] No later than 2009[c] North America	Prospective case series Up to 3 year	N=97 WHO FC II-IV PAH-CTD	EPO dose up-titrated from 2 mg/kg/min based on tolerability
Vis 2013[72] 2005-2010 Netherlands	Case series (unclear if retrospective or prospective) 3.9-4 years	N=64 WHO FC II-IV PAH-CHD	BOS 125 mg bid Combination with sildenafil (2%)

[a] Number of patients in the control arm and those in the active treatment arm where a PAH medicine was given at the recommended dose regimen.
[a] Only including the active treatment arm where a PAH medicine was given at the recommended dose regimen. The dose presented was the target dose. Patients could have received a PAH medicine at a lower initial dose.
[c] Subgroup of patients with no background therapy
[d] Low dose: 10 mg in patients >20 kg (no patients ≤ 20 kg received the low dose). Median dose: 10 mg in patients 8-20 kg; 20 mg in patients 20-45 kg; 40 mg in patients >45 kg. High dose: 20 mg in patients 8-20 kg; 40 mg in patients 20-45 kg; 80 mg in patients >45 kg
[e] 15 mg bid for a body weight of <10 kg; 31.5 mg bid for weight of 10-20 kg; 62.5 mg bid for weight of 20-40 kg; 125 mg bid for weight of >40 kg
AMB = ambrisentan; bid = twice daily; BOS = bosentan; DB = double-blinded; EPO = epoprostenol; FC = functional class; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; od = once daily; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PAH-DT = drug/toxin-induced pulmonary arterial hypertension; PAH-HIV = pulmonary arterial hypertension associated with human immunodeficiency virus infection; PAH-PH = pulmonary arterial hypertension associated with portal hypertension; PBO = placebo; PRO = prostanoid; PVOD = pulmonary veno-occlusive disease; RCT = randomised controlled trial; SEL = selexipag; SIL = sildenafil; TAD = tadalafil; tid = three times a day; TRE = treprostinil; WHO = World Health Organization

4.2.4.3 Information from regulatory agencies included for the extended assessment of safety

The TGA's Database of Adverse Event Notifications includes details of reports for each medicine, but not of any reviews or revisions to the PI or consumer medicines information (CMI) that may have arisen out of such reports. The TGA's Medicines Safety Update announcements (also published in Australian Prescriber) do not cover minor changes to product safety warnings and other information. Other than information in the current PI and CMI, no information pertaining to updated safety of PAH medicines has been published by the TGA that could be reviewed for this extended assessment.

A new FDA database of Drug Safety Labeling Changes is available and searchable information starts from January 2016. This database replaces the Medwatch system of alerts. A search for sildenafil (as Revatio) returned results relating to the FDA's warnings in 2012 and 2014 about paediatric use. No other results were returned for PAH medicines within the scope of this post-market review. A search of the FDA's Medwatch drug safety alerts indicates that information prior to 2016 is no longer searchable - an archived version of the site exists, but the search function did

not return the pages containing changes to safety information that were found through a manual search of the archived Medwatch drug safety monthly reports. Time did not permit comprehensive handsearching of these reports. In the absence of systematic information for changes to FDA-approved information, current PI was checked for statements concerning the AEs.

The EMA publishes variations and updates to PI on its website, for products that are centrally authorised. The EMA website includes a history of all changes ('variations') made since authorisation for each product. The variation history was reviewed for each listed PAH medicine (except epoprostenol which is not centrally authorised) to determine what amendments have been made to safety information, focusing on the last 10 years (2008-2018).

4.3.5 Outcome measures

Clinical worsening events and mortality were two important patient-relevant outcomes for the assessment of PAH medicines. They were both rated as critical outcomes according to the GRADE Working Group grades of evidence[1].

A total of 13 RCTs reported results of clinical worsening in the relevant population of interest. The inclusion of clinical worsening as an outcome in these RCTs followed the Dana Point 2008 Task Force guidelines[73] which recommend a composite primary endpoint is used for future RCTs in PAH, including mortality as well as measurable "hard" morbidity events related to PAH progression. The EMA[74] also suggested the use of all-cause mortality and time to PAH-related morbidity "provided that clear, non-equivocal and prospective definitions are provided". The definitions of clinical worsening across the trials included in this review are summarised in Table 4.28. Although in most of the included RCTs clinical worsening usually represented a combination of death, PAH-related hospitalisation, lung transplant, atrial septostomy, initiation of new PAH medicine(s), deterioration of WHO CF or worsening of 6-minute walk distance (6MWD), this composite outcome was heterogeneously defined across the trials. The inconsistent definition of clinical worsening, as well as the varying trial duration, hinders a meaningful comparison of the efficacy of PAH medicines in terms of preventing combined mortality/morbidity events across clinical trials.

Table 4.28 Definition of clinical worsening

Study ID	Any death	Disease progress				
		LT	AS	PAH-hospital-isation	Start of new therapy	Others
AMBITION	✓	✓	✓	✓	Parenteral prostanoid	• >15% decrease in 6MWD from baseline and WHO FC III or IV symptoms at 2 consecutive visits; or • Any decrease in 6MWD from baseline and WHO FC III symptoms assessed at 2 clinic visits
ARIES-1	✓	✓	✓	✓	✓	Study discontinuation due to ≥ 2 early escape criteria: • ≥20% decrease in 6MWD; • increase in WHO FC; • worsening right ventricular failure; • progressing hepatic or renal failure; • systolic blood pressure <85 mmHg
ARIES-2	✓	✓	✓	✓	✓	
COMBI	✓	–	–	Right-heart failure	–	• Deterioration in WHO FC; or • Decrease in 6MWD by ≥20% or <150 metres
COMPASS-2	✓	✓	✓	✓	IV prostanoid	• Moderate or marked worsening of PAH symptoms and the initiation of SC or inhaled prostanoid or use of bosentan; or • No change or mild worsening of PAH symptoms, accompanied by decrease in 6MWD of > 20% from the previous visit or >30% from baseline and by the initiation of SC or inhaled prostanoid or use of bosentan
EARLY	✓	–	–	✓	–	One of the following: • Appearance or worsening of right-heart failure; • Decrease of ≥10% from baseline in 6MWD; or • Decrease of ≥5% from baseline in 6MWD and ≥ 2 points increase in Borg dyspnoea index
PACES-1	✓	✓	–	✓	Bosentan	Change in epoprostenol dose of ≥10% due to clinical deterioration
PATENT-1	✓	✓	✓	✓	✓	• Decrease in 6MWD of >15% from baseline or >30% from the last measurement • Persistent worsening of WHO FC; or • Modification of a pre-existing prostanoid treatment due to worsening PAH
PHIRST	✓	✓	✓	✓	✓	Worsening of WHO FC
SERAPHIN	✓	✓	✓	–	SC or IV prostanoid	All of the following: • ≥15% decrease in 6MWD from baseline; • Need for additional treatment for PAH; and • Worsening of symptoms of PAH.
STEP	PAH-related	✓	✓	Any	✓	Early study discontinuation due to worsening PAH
Vizza 2017	✓	✓	–	✓	✓	–
Zhuang 2014	✓	✓	✓	✓	✓	Worsening of WHO FC

6-MWD = 6-minute walk distance; AS = atrial septostomy; FC = functional class; IV = intravenous; LT = lung transplant; PAH = pulmonary arterial hypertension; SC = subcutaneous; WHO = World Health Organization

Mortality is the other clinically important endpoint. However the generally short duration of study follow-up of the included RCTs was insufficient for a reliable assessment of this endpoint in PAH patients.

The 6MWD, which assesses the treatment effect of PAH medicines on exercise capacity, is measured in almost all PAH studies. Change in 6MWD has been previously accepted by the PBAC as an appropriate surrogate outcome. Nevertheless, the validity of the 6MWD, as a surrogate for survival, remains a subject of debate in the literature[75]. The EMA guidelines on PAH[74] point out that there is uncertainty regarding the suitability of 6MWD as a primary endpoint given that it is influenced by age, gender, height, weight and degree of motivation and that improvement in performance has been shown not to correlate with survival. The EMA accepts the 6MWD as a primary endpoint for PAH trials *only* if the proposed indication is restricted to improvement in exercise capacity and states that the 6MWD should be used in conjunction with other efficacy endpoints when the indication claims an effect on clinical worsening. There are numerous references that propose a minimum clinically important difference in 6MWD of between 35 m and 50 m[76-80]. Non-inferiority thresholds of -35 m and -50 m in 6MWD were used previously in the context of PBS reimbursement applications and have been accepted by the PBAC (ambrisentan Public Summary Document (PSD), July 2009 PBAC meeting; epoprostenol PSD, November 2011 PBAC meeting). The Six Minute Walk Test (6MWT) was rated as an important outcome according to the GRADE Working Group grades of evidence[1].

The diagnosis of PAH needs to be confirmed by right cardiac catheterisation with appropriate haemodynamic measurements. Haemodynamic measures, including pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), cardiac index, pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP) etc, may play an important role during the early development of the drug to elucidate the mechanism of action or to define the dose-response relationship[74]. These parameters have been included in some clinical trials, usually as secondary or tertiary outcomes, for assessment of the treatment effect of PAH medicines. The haemodynamic parameters are less patient-relevant, and, therefore, were rated as not important outcomes according to the GRADE Working Group grades of evidence[1].

Other effectiveness outcomes of interest included hospitalisation, change in WHO FC, quality of life (QoL), lung transplant, atrial septostomy and initiation of other PAH medicine(s). Safety was assessed by the reporting of AEs. All the above outcomes were rated as important outcomes according to the GRADE Working Group grades of evidence[1].

4.3.6 Synthesis of evidence

Effectiveness and safety results were extracted for the appropriate populations, interventions and comparators as specified for each research question (Table 4.19 to Table 4.22). Where the studies included a mixed population and the published papers did not provide data for the subgroup of interest, the PBAC dossier was searched for relevant previous submissions, commentaries and/or PBAC minutes. Data sourced from confidential PBAC documents were highlighted throughout the literature review in different colours according to distinct sponsors for redaction when the report is sent to pharmaceutical companies for feedback.

Descriptive statistics were extracted or calculated for all relevant outcomes in the individual studies – including numerator and denominator information, means and standard deviations, medians and inter-quartile ranges.

Relative effect measures (relative risks (RRs) or hazard ratios (HRs)), absolute risk differences (ARDs), and associated 95% confidence intervals (CIs) were calculated from individual comparative studies containing count data. Mean differences and 95% CIs were extracted or calculated for normally distributed continuous outcomes in individual studies.

Meta-analyses were conducted, where appropriate, and tested for heterogeneity. The DerSimonian and Laird random-effects model was used to estimate pooled risk ratios with their 95% CIs for event data. Forest plots were created. When there were no events in one treatment group, we used a 0.5 continuity correction. Trials with no events in either arm were excluded. Pooled effects on continuous variables were presented as weighted mean differences with corresponding 95% CI.

For research question 1, only direct evidence was presented. No RCTs were identified to address research questions 2 and 4. For research question 3, if direct studies which compare combination therapy with PBS-listed PAH medicines against PAH monotherapy as specified in Table 4.21 were not available, pairwise indirect comparisons using Bucher method[81] had been considered. However, no meaningful indirect comparison could be performed, given the lack of transitivity across included trials according to the guidance given in version 5 of the *PBAC Guidelines*[‡] (eg heterogeneities in WHO FC, PAH aetiology, history of previous PAH therapy, outcome measure, length of follow-up and study period) and the limited direct evidence on the comparative treatment effect of two PAH medicines.

Statistical analysis were undertaken using the biostatistical computer package, Stata version 14.

When a quantitative synthesis was not possible, eg summarised using inconsistent statistics (eg mean and median), the review findings were synthesised into an overall narrative that addresses each of the review questions.

For comparative studies, the overall quality of the evidence per individual health outcome was rated, across the studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias using Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[1]. This was done to provide an indication of the confidence in the estimate of the effect in the context of Australian clinical practice (see Section 4.5).

‡ Source: https://pbac.pbs.gov.au/

4.4 Results of the literature review

4.4.1 Research question 1

What is the effectiveness and safety of monotherapy with a PAH medicine, compared to placebo/no treatment or another PAH medicine listed on the PBS, in patients with WHO FC I or II PAH?

4.4.1.1 ERA versus placebo

Four RCTs reported on the effectiveness of an ERA in treating PAH compared with placebo in patients with WHO FC I/II PAH: two trials for ambrisentan and one each for bosentan and macitentan. There were no significant differences in the effectiveness of the different ERA medicines for any outcome.

The EARLY[9] double-blind trial randomised WHO FC II PAH patients with and without background sildenafil therapy to receive bosentan or placebo for 6 months. The PAH aetiology and haemodynamic factors were evenly distributed between the two randomised groups. As randomisation was stratified according to background therapy, and only a small proportion of patients received sildenafil as background therapy (15% in the bosentan group and 16% in the placebo group), the risk of incomparable baseline parameters for the treatment-naïve subgroup is low. A pre-specified subgroup analysis of treatment-naïve patients was available from the clinical study report (CSR) (highlighted in blue below).

Two double-blind trials (ARIES-1 and ARIES-2[6]) randomised PAH patients of any WHO FC to receive ambrisentan or placebo for 12 weeks. The baseline characteristics of the randomised groups were similar. However, as randomisation was not stratified by WHO FC, patients with WHO FC I/II PAH may have a different distribution of baseline characteristics between trial arms, resulting in imbalances in disease severity markers between the two treatment arms. A post hoc subgroup analysis for patients with WHO FC I/II PAH was conducted by Chin et al (2014)[33].

The SERAPHIN[7] double-blind long-term trial randomised PAH patients of any WHO FC to receive macitentan or placebo for up to 54 months. Patients were also permitted to have background therapy with a PDE-5 inhibitor (61% of patients) or a prostanoid (4% of patients). Although the baseline characteristics of the randomised groups were similar, the lack of stratification based on WHO FC, may have resulted in imbalances in disease severity in the WHO FC I/II subgroup. The mean duration of study treatment was 85.3 weeks and 103.9 weeks for the patients receiving placebo and macitentan, respectively. Post hoc subgroup analyses of patients with WHO FC I/II PAH for several relevant outcomes were reported in the CSR (highlighted in blue below).

The EARLY trial had a low risk of bias, whereas the ARIES and SERAPHIN trials had a low-to-moderate risk of bias. The increased bias risk was mainly due to the lack of stratification for WHO FC. There was also a large variation in the duration of the trials; varying from 12 weeks to 115 weeks, as described above.

a. Study-defined clinical worsening

EARLY, SERAPHIN and the post hoc subgroup analysis of the ARIES1/ARIES2 trials reported on the proportion of patients who had clinical worsening during the study period. The definitions of clinical worsening in the three trials varied but all included death and progression of PAH (see Section 4.3.5 for further details).

Two of the trials reported the HR for patients with WHO FC I/II experiencing clinical worsening while taking an ERA drug compared with placebo (Table 4.29). In the EARLY trial, patients receiving bosentan were [redacted] to have clinical worsening than patients who received a placebo over the 26-week study period. Over a longer time-period (median 115 weeks), patients treated with macitentan in the SERAPHIN trial were [redacted] to have clinical worsening than patients receiving a placebo.

Table 4.29 The effectiveness of an ERA compared with placebo in preventing clinical worsening in patients with WHO FC I/II PAH

Study ID	ERA Follow-up period	n/N (%)		HR (95%CI)
		ERA	Placebo	
EARLY, CSR	Bosentan 26 weeks	[redacted]	[redacted]	[redacted]
ARIES-1&2[33]	Ambrisentan (10 mg) 12 weeks	0/50 (0%)	3/51 (6%)	Not reported
SERAPHIN, March 2014 submission	Macitentan (10 mg) Median 115 weeks	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; ERA = endothelin-receptor antagonist; FC = functional class; HR = hazard ratio; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; WHO = World Health Organization

A meta-analysis of the RR of having clinical worsening when being treated with an ERA compared with placebo was performed (Figure 4.2). Despite the disparity in the duration of treatment and follow-up between the four studies, there was no heterogeneity between studies [redacted] Overall, patients treated with an ERA had [redacted] of having a clinical worsening event compared with those taking a placebo.

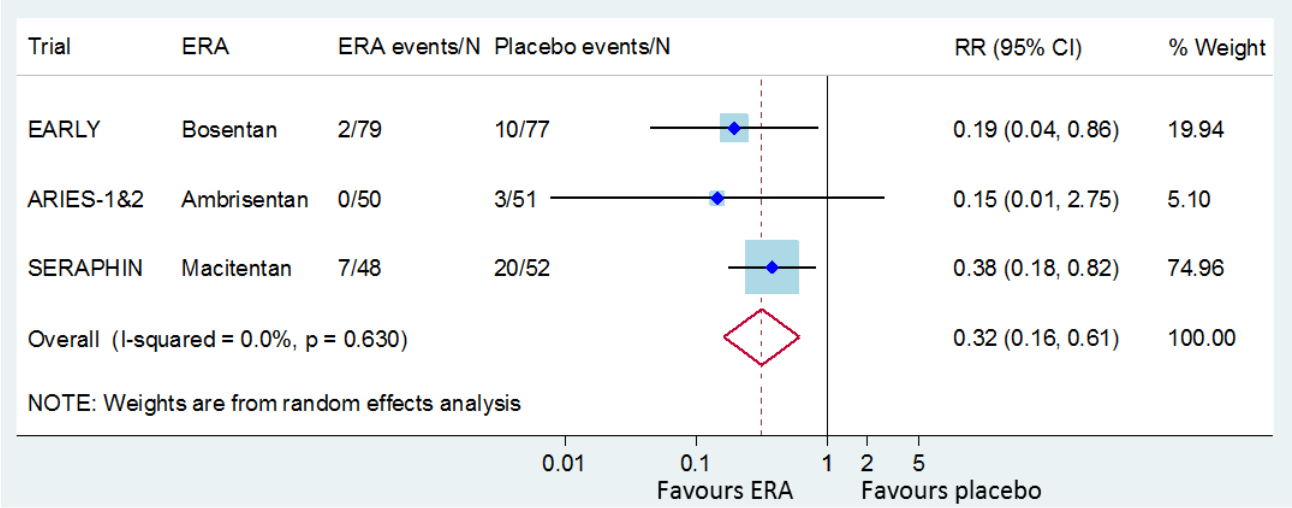


Figure 4.2 Forest plot showing the RR of having a clinical worsening event while being treated with an ERA compared with placebo in patients with WHO FC I/II PAH

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

b. All-cause mortality

Two RCTs reported on the proportion of patients who died from any cause during the study period (Table 4.30). The EARLY trial did not report the HR (ARD = [redacted]). In the SERAPHIN trial, over a median of 129 weeks of treatment, patients receiving macitentan were [redacted] to die from any cause compared with patients in the placebo group (ARD [redacted]). The number needed to treat (NNT) is equivalent to the inverse of the ARD (1/ARD). Thus, [redacted] people in the EARLY trial and [redacted] people in the SERAPHIN trial needed to be treated by an ERA to prevent one additional death compared with [redacted]

Of the patients who died in the SERAPHIN trial [redacted] died due to PAH, with patients receiving the placebo [redacted] to die from PAH than those receiving macitentan during the study period (ARD = [redacted]).

Table 4.30 Mortality rates for an ERA compared with placebo in patients with WHO FC I/II PAH

Study ID	ERA Study period	n/N (%)		HR (95% CI)
		ERA	Placebo	
EARLY CSR	Bosentan 6 months (all-cause)	[redacted]	[redacted]	NR
SERAPHIN, March 2014 submission	Macitentan (10 mg) Median 129 weeks all-cause due to PAH	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; HR = hazard ratio; n = number of patients with events; N = number of patients; NR = not reported; PAH = pulmonary arterial hypertension; WHO = World Health Organization

[redacted]

Figure 4.3 Forest plot showing the RR of all-cause mortality for ERA compared with placebo in patients with WHO FC I/II PAH

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

c. Hospitalisation due to worsening PAH

None of the three RCTs reported on the number of patients with WHO FC I/II PAH who were hospitalised.

d. Change in WHO FC from baseline

The ARIES-1&2 trials reported the number of patients with WHO FC I/II PAH who changed FC during treatment (Table 4.31). The patients treated with ambrisentan were more likely to improve their WHO FC than those receiving a placebo (ARD = 14.0%; 95% CI 4.4, 23.6; p = 0.0056) but the RR was not calculable. Patients receiving ambrisentan were also 4-times less likely to experience a decrease in WHO FC than those receiving a placebo (ARD = −5.8%; 95% CI −14.2, 2.5; p = 0.169). Thus, eight patients need to be treated with ambrisentan for one additional patient to improve in WHO FC, and 18 to prevent harm (worsening WHO FC) to one additional patient compared with placebo. However, these differences did not reach statistical significance.

Table 4.31 The effectiveness of an ERA compared with placebo in improving WHO FC in patients with WHO FC I/II PAH

Study ID ERA	Change in WHO FC	n/N (%)		RR (95% CI)
		ERA	Placebo	
ARIES-1&2[33] Ambrisentan	Improved	7/50 (14%)	0/51 (0%)	Not calculable
	Worsened	1/50 (2%)	4/51 (8%)	0.25 (0.03, 2.20)

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

e. Change in 6MWD from baseline

The SERAPHIN trial did not report on the mean difference in 6MWD for the treatment-naïve WHO FC I/II PAH subgroup. After 6 months of bosentan treatment, treatment-naïve patients in the EARLY study had a mean increase in 6MWD of 25.7 m (Table 4.32), which is unlikely to be clinically meaningful (see Section 4.3.5). The ARIES trials depicted the data for this patient subgroup in a graph (Figure 4.4), which shows that the 6MWD significantly improved in both ambrisentan-treated groups by more than 40 m (a clinically important distance) compared with the placebo group over the 12-week treatment period.

Table 4.32 The effectiveness of an ERA compared with placebo in improving 6MWD in patients with WHO FC I/II PAH

Study ID ERA	N Follow-up period	Mean baseline 6MWD (95% CI), metres		Mean change from baseline (95% CI), metres		Mean difference (95% CI), metres
		ERA	Placebo	ERA	Placebo	
EARLY CSR and Galiè et al. 2008[9] Bosentan	N=149 6 months	[redacted]	[redacted]	[redacted]	[redacted]	25.7 (3.8, 47.6)

6MWD = 6-minute walk distance; CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; n = number of events; N = number of patients; WHO = World Health Organization

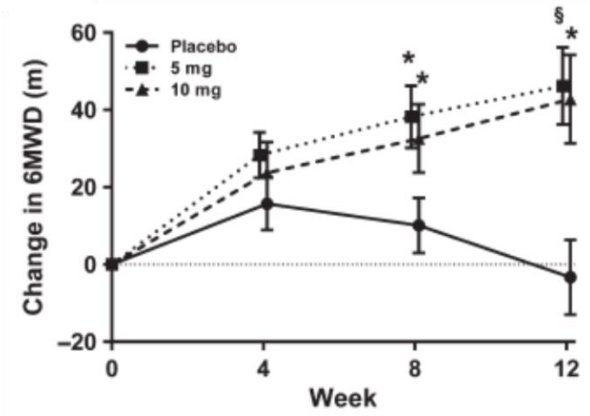


Figure 4.4 The change in 6MWD from baseline to 12 weeks in patients with WHO FC I/II PAH by ambrisentan dose or placebo (ARIES-1&2)

* $p < 0.05$; § $p < 0.001$
Note: The 10 mg ambrisentan dose versus placebo is the relevant comparison for this review
6MWD = 6-minute walk distance; FC = functional class; PAH = pulmonary arterial hypertension; WHO = World Health Organization
Source: Chin et al. (2014)[33]

f. Change in QoL from baseline

No QoL outcomes were reported for WHO FC I/II PAH patients.

g. Change in haemodynamic parameters from baseline

The ARIES-1&2 and SERAPHIN trials did not report on the mean difference in haemodynamic parameters for treatment-naïve patients with WHO FC I/II PAH. After 6 months of bosentan treatment in the EARLY study, treatment-naïve patients with WHO FC I/II PAH had a statistically

significant mean placebo-adjusted decrease in PVR of 23.1% (Table 4.33). As the normal laboratory PVR in adults is <250 dyn*sec*cm^{-5}, [redacted] seen in the ERA group [redacted], but due to the [redacted] group, the overall placebo-adjusted mean difference of 23.1% may be clinically important.

Table 4.33 The effectiveness of an ERA compared with placebo in improving PVR in patients with WHO FC I/II PAH

Study ID ERA	N Follow-up period	Mean baseline PVR[a] (95% CI), dyn*sec*cm^{-5}		Mean change from baseline (95% CI), dyn*sec*cm^{-5} [% change from baseline]		Mean % difference (95% CI)
		ERA	Placebo	ERA	Placebo	
EARLY CSR and Galiè et al. 2008[9] Bosentan	N=156 6 months	[redacted]	[redacted]	[redacted]	[redacted]	−23.1% (−35.1, −8.9) p<0.0001

[a] A decrease in PVR indicates improvement in haemodynamic parameters
CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; WHO = World Health Organization

h. Comparative safety

None of the four RCTs reported on the comparative safety of monotherapy with an ERA versus placebo in patients with WHO FC I/II PAH. Hence, the AEs that were observed in the broader PAH populations are discussed in Section 4.4.5.

4.4.1.2 PDE-5 inhibitor *versus* placebo

Three RCTs were identified that reported on the effectiveness of PDE-5 inhibitor, as monotherapy, in treating PAH compared with placebo in patients with WHO FC I/II PAH. Tadalafil was used in the PHIRST[12] and Mukhopadhyay 2011[40] trials, and sildenafil in the SUPER-1 trial[11].

The PHIRST double-blind trial randomised PAH patients of any WHO FC to receive tadalafil or placebo for 16 weeks. Background use of bosentan was permitted for patients taking a stable dose for a minimum of 12 weeks before screening. The randomisation was stratified for baseline walk distance (<325 m or >325 m), PAH aetiology (IPAH, HPAH and anorexigen use versus other types of PAH) and for bosentan use. As the baseline characteristics for the treatment-naïve WHO FC I/II tadalafil versus placebo subgroups were not reported, and patients were not stratified by WHO FC, there remains the possibility that these patients may have different distributions of baseline characteristics resulting in imbalances in disease severity markers. A post hoc subgroup analysis for treatment-naïve patients with WHO FC I/II PAH was conducted by Barst et al. (2011)[45].

The Mukhopadhyay 2011 trial was a double-blind crossover RCT that enrolled patients with PAH-CTD and mostly WHO FC II (22/28). Patients were randomised to receive either tadalafil or a matching placebo for 6 weeks, followed by a 2-week washout period before crossing over to the other treatment for 6 weeks.

The SUPER-1 double-blind trial randomly assigned patients with symptomatic IPAH, PAH-CTD or PAH-CHD of any WHO FC to either placebo or sildenafil for 12 weeks. The randomisation was stratified with respect to the baseline 6MWD (<325 m or ≥325 m) and PAH aetiology, but not by WHO FC. Thus, differences in the baseline characteristics of patients with WHO FC I/II PAH included in the post hoc subgroup analysis cannot be excluded. Data for the change in 6MWD for patients with WHO FC I/II PAH was reported in the November 2016 PBAC submission (highlighted in purple below).

The PHIRST trial had a moderate risk of bias due to the post hoc analysis for the WHO FC I/II subgroup. The remaining two trials had a low-to-moderate risk of bias. The trials varied in duration from 6 weeks for the Mukhopadhyay 2011 crossover RCT to 12 and 16 weeks for the SUPER-1 and PHIRST trials, respectively.

None of these trials reported on all-cause mortality for the subgroup of patients with WHO FC I/II PAH. Two cohort studies (Sun 2013[51] and Sastry 2007[52]) that reported on the mortality of patients with WHO FC I/II PAH who were treated with either sildenafil or conventional therapy were identified and included for this outcome. Sun 2013 enrolled patients with Eisenmenger syndrome who were followed for up to 2 years. Conventional therapy mainly consisted of digoxin, oral anticoagulants and diuretics. The baseline data from enrolled patients were collected retrospectively from medical files. Overall, the baseline characteristics were well balanced between groups and there was a moderate risk of bias.

Sastry 2007 collected survival data from patients with IPAH of WHO FC II-IV being treated with sildenafil prospectively from a hospital registry for five years. Patients treated with conventional therapy (including digoxin, oral anticoagulants, diuretics and calcium channel blockers) prior to the availability of sildenafil in India acted as an historical control. The baseline characteristics of the intervention and historical control groups were similar for the whole cohort, except the duration of symptoms was much longer in the control group (median 24 months versus 12 months). No information was provided for the WHO FC II subgroup. Overall, this study has a moderate-to-high risk of bias. The authors reported the mortality rates among patients with WHO FC II IPAH.

a. Study-defined clinical worsening

None of the three RCTs reported on the number of patients with WHO FC I/II PAH who had clinical worsening.

b. All-cause mortality

The Sun 2013 observational study reported on all-cause mortality over a 48-month follow-up period (Table 4.34). No patients with WHO FC I/II PAH receiving sildenafil died during this time but five patients receiving conventional therapy did (ARD = −13.9%; 95% CI −2.6, −25.2; p = 0.015). The Sastry 2007 study, also conducted over a 48-month period, reported that patients with WHO FC II IPAH in the historical conventional treatment group were twice as likely to die than those receiving treatment with a PDE-5 inhibitor (ARD = −14.9%; 95% CI −37.8, 8.0; p = 0.159). Thus, the two studies found that seven to eight patients need to be treated with a PDE-5 inhibitor to

prevent one additional death compared with the conventional therapy control groups. The pooled RR estimate showed that patients treated with conventional drugs were 3-times more likely to die than those treated with a PDE-5 inhibitor (Figure 4.5), but it was not statistically significant.

Table 4.34 Mortality rates for PDE-5 inhibitors compared with conventional therapy in patients with WHO FC I/II PAH

Study ID PDE-5 inhibitor	Study period	n/N (%)		RR (95% CI)
		PDE-5 inhibitor	Conventional therapy	
Sun 2013[51] Sildenafil	48 months	0/40 (0%)	5/36 (14%)	0 (not calculable)
Sastry 2007[52] Sildenafil	48 months	10/60 (17%)	6/19 (32%)	0.53 (0.22, 1.26)

CI = confidence interval; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; RR = relative risk; WHO = World Health Organization

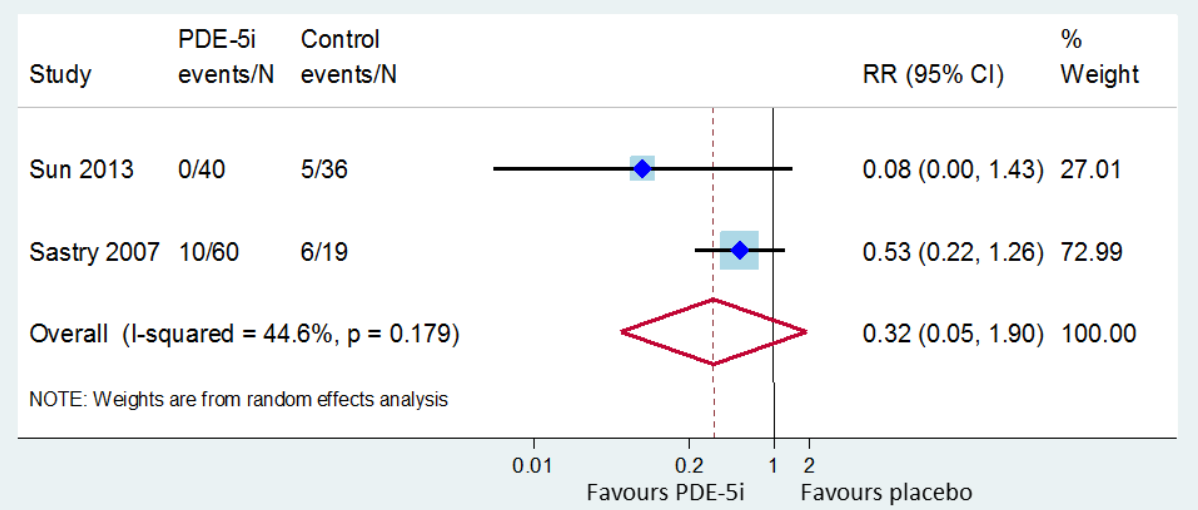


Figure 4.5 Forest plot showing the RR of all-cause mortality for PDE-5 inhibitors compared with conventional therapy in patients with WHO FC I/II PAH

CI = confidence interval; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; RR = relative risk; WHO = World Health Organization

c. Hospitalisation due to worsening PAH

None of the three RCTs reported on the number of patients with WHO FC I/II PAH who were hospitalised.

d. Change in WHO FC from baseline

Only the Mukhopadhyay 2011 crossover RCT reported on a change in WHO FC. There was no difference between the two treatment arms (Table 4.35). One patient improved in WHO FC during the tadalafil phase and one patient improved in WHO FC during the placebo phase. No patient experienced a worsening of WHO FC.

Table 4.35 The effectiveness of PDE-5 inhibitors compared with placebo in improving WHO FC in patients with WHO FC I/II PAH

Study ID Follow-up period PDE-5 inhibitor	Change in WHO FC	n/N (%)		RR (95% CI)
		PDE-5 inhibitor	Placebo	
Mukhopadhyay 2011[40] 6 weeks Tadalafil	Improved	1/22 (5%)	1/22 (5%)	1.00 (0.07, 15.00)
	Worsened	0/22 (0%)	0/22 (0%)	Not calculable

CI = confidence interval; FC = functional class; n = number of events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; RR = relative risk; WHO = World Health Organization

e. Change in 6MWD from baseline

The PHIRST and SUPER-1 trials reported on the change in 6MWD for patients with WHO FC I/II PAH. The patients in the PHIRST trial being treated with tadalafil showed a placebo-adjusted improvement of 10.8 m over the 16-week trial period (Table 4.36). Although this distance is not clinically relevant, the importance of this change cannot be determined in the absence of reported baseline levels of 6MWD. The placebo-adjusted improvement for WHO FC I/II PAH patients treated with sildenafil at the end of the 12-week trial period in the SUPER-1 trial was clinically important (about 50 m; Table 4.36, Figure 4.6).

Table 4.36 The effectiveness of PDE-5 inhibitors compared with placebo in improving 6MWD in patients with WHO FC I/II PAH

Study ID	PDE-5 inhibitor Follow-up period	Mean ± SD baseline 6MWD, metres		Mean ± SD change from baseline (95% CI), metres		Mean difference, metres
		PDE-5i	Placebo	PDE-5i	Placebo	
PHIRST[45]	Tadalafil 16 weeks	NR	NR	n=10 23.6 (17.8, 49.5)	n=11 12.8 (–34.8, 38.1)	10.8
SUPER-1[a], November 2006 submission	Sildenafil 12 weeks	n=30 392.0 ± 58.7	n=22 375.1 ± 60.5	n=30 58.5 ± 58.6 (33.8, 83.2)	n=22 8.3 ± 33.1 (–4.1, 20.7)	50.2

[a] One patient in the placebo group was omitted from this analysis because they were WHO FC I, all other patients were WHO FC II

6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; NR = not reported; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; SD = standard deviation; WHO = World Health Organization

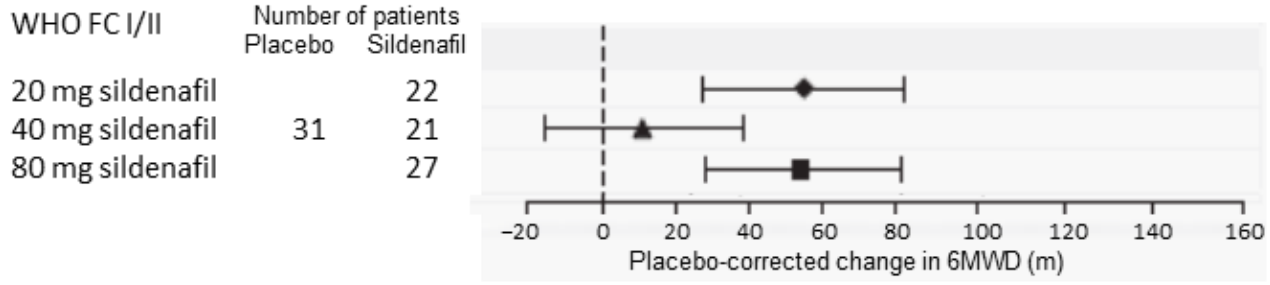


Figure 4.6 Forest plot showing the change in 6MWD from baseline to 12 weeks in patients with WHO FC I/II PAH by sildenafil dose or placebo (SUPER-1)

Note: The 20 mg sildenafil dose versus placebo is the relevant comparison for this review
6MWD = 6-minute walk distance; FC = functional class; PAH = pulmonary arterial hypertension; WHO = World Health Organization
Source: Galiè et al. (2005)[11] (1 patient in the placebo group was WHO FC I all other patients were FC II)

f. Change in QoL from baseline

No QoL outcomes were reported for patients with WHO FC I/II PAH.

g. Change in haemodynamic parameters from baseline

The three trials did not report haemodynamic outcomes for patients with WHO FC II PAH.

h. Comparative safety

No studies were identified that reported on the safety of monotherapy with a PDE-5 inhibitor compared with placebo in WHO FC I/II PAH patients.

4.4.1.3 Prostanoid *versus* placebo

No studies were identified that reported on the effectiveness or safety of monotherapy with a prostanoid compared with placebo in WHO FC I/II PAH patients.

4.4.1.4 sGC stimulator *versus* placebo

Only one RCT was identified that reported on the effectiveness of monotherapy with a sGC stimulator in treating PAH compared with placebo in patients with WHO FC I/II PAH. The PATENT-1[23] double-blind trial, with a low-to-moderate risk of bias, randomised PAH patients of *any* WHO FC to receive riociguat or placebo for 12 weeks. Background use of an ERA or prostanoid was permitted. Approximately 44% of included patients were using an ERA medicine (primarily bosentan) and 6% a prostanoid (primarily inhaled iloprost) at baseline. The baseline characteristics for the treatment-naïve WHO FC I/II riociguat and placebo subgroups were well balanced with respect to age, gender, WHO FC and haemodynamic parameters, but the proportion of patients having different PAH aetiologies was not reported. The CSR reported data for treatment-naïve patients with WHO FC I/II PAH (highlighted in green below).

a. Study-defined clinical worsening

In the PATENT-1 study, clinical worsening was defined as all-cause mortality, heart/lung transplantation, atrial septostomy, start of new PAH treatment (ERA, prostanoid or PDE-5 inhibitor), modification of a pre-existing prostanoid treatment, hospitalisation due to PAH, persistent decrease in 6MWD, or persistent worsening of WHO FC due to worsening of PAH.

[redacted] with WHO FC I/II PAH who was not receiving background therapy in the riociguat group and [redacted] in the placebo group experienced clinical worsening during the trial period (Table 4.37). Thus, there was [redacted] between the two treatment arms. The ARD of [redacted] indicated that [redacted] patients would need to be treated with [redacted] to prevent one additional patient experiencing clinical worsening compared with [redacted]

Table 4.37 The effectiveness of a sGC stimulator compared with placebo in preventing clinical worsening in patients with WHO FC I/II PAH

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator	Placebo	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

b. All-cause mortality

[redacted] with WHO FC I/II PAH who was not receiving background therapy in the [redacted] (Table 4.38; ARD = [redacted]

Table 4.38 Mortality rates for a sGC stimulator compared with placebo in patients with WHO FC I/II PAH

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator	Placebo	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

c. Hospitalisation due to worsening PAH

[redacted] with WHO FC I/II PAH receiving monotherapy were hospitalised due to PAH during the trial period (Table 4.39).

Table 4.39 Hospitalisation due to PAH for a sGC stimulator compared with placebo in patients with WHO FC I/II PAH

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator	Placebo	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

d. Change in WHO FC from baseline

[redacted] patients in the [redacted] group experienced worsening of their WHO FC compared with the [redacted] group (ARD = [redacted] (Table 4.40). [redacted] group also showed an improvement in WHO FC over those in the [redacted] group, but this did not reach statistical significance (ARD = [redacted]). Thus, [redacted] patients need to be treated with [redacted] to prevent harm (worsening of WHO FC) to one additional patient compared with [redacted].

Table 4.40 The effectiveness of a sGC stimulator compared with placebo in improving WHO FC in patients with WHO FC I/II PAH

Study ID sGC stimulator	Change in WHO FC	n/N (%)		RR (95% CI)
		sGC stimulator	Placebo	
PATENT-1 CSR Riociguat	Improved	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

e. Change in 6MWD from baseline

The patients being treated with riociguat showed a placebo-adjusted improvement of [redacted] m in 6MWD over the 12-week trial period but the result was not statistically significant or clinically important (given the baseline distance walked) (Table 4.41).

Table 4.41 The effectiveness of a sGC stimulator compared with placebo in improving 6MWD in patients with WHO FC I/II PAH

Study ID sGC stimulator	N Follow-up period	Mean ± SD baseline 6MWD, metres		Mean ± SD change from baseline, metres		Mean difference (95% CI), metres
		sGC stimulator	Placebo	sGC stimulator	Placebo	
PATENT-1 CSR Riociguat	N=107 Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6MWD = 6 minute walk distance; CI = confidence interval; CSR = clinical study report; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; SD = standard deviation; sGC = soluble guanylate cyclase; WHO = World Health Organization

f. Change in QoL from baseline

The self-reported health-related QoL of patients receiving riociguat compared with placebo was measured using the EuroQol 5 dimension (EQ-5D) questionnaire and the Living with pulmonary hypertension (LPH) questionnaire.

The EQ-5D questionnaire contains five domains: mobility, self-care, pain/discomfort, usual activities and anxiety/depression. In PATENT-1, the EQ-5D utility scores were generated on the basis of the answers to the five questions (each with 3 categories), by applying a multi-attribute utility function. The EQ-5D utility score had a range of possible values from –0.59 (worst outcome) to 1.00 (best outcome). Results of change in EQ-5D utility scores from Trial PATENT-1 indicated that there was [redacted] in QoL in the riociguat group and the [redacted] in the placebo group (Table 4.42). This difference may [redacted]. The minimal clinically important difference in EQ-5D utility score ranged from 0.033 to 0.074 in the literature[82].

The LPH questionnaire was adapted from the Minnesota living with heart failure (MLHF) questionnaire for use in patients with PAH. The LPH questionnaire comprises 21 items, responded to on a 6-point Likert scale ranging from 0 'No' to 5 'Very much'. A total score ranging from 0 to 105 is calculated by summing the responses to all 21 questions. A higher LPH score represents that patients are more affected by their medical condition (poorer QoL). In PATENT-1, the scores for the LPH questionnaire showed an approximate [redacted] in QoL in the riociguat group and a 1-point improvement in the placebo group (Table 4.42). The minimally important difference for the LPH scale has been previously determined to be 7 points for the total score[83]. Thus, although there was [redacted] in the QoL for patients taking a placebo compared with those on active treatment, the changes in QoL observed in this study mostly [redacted]

Table 4.42 The effectiveness of a sGC stimulator compared with placebo in improving QoL in patients with WHO FC I/II PAH

Study ID sGC stimulator	N Follow-up period	Mean ± SD baseline QoL		Mean change from baseline ± SD		Mean difference, points
		sGC stimulator	Placebo	sGC stimulator	Placebo	
PATENT-1 CSR Riociguat	N=107 Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[b] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
CSR = clinical study report; EQ-5D = EuroQoL 5 dimensions; FC = functional class; LPH = living with pulmonary hypertension; N = number of patients; PAH = pulmonary arterial hypertension; QoL = quality of life; RR = relative risk; SD = standard deviation; sGC = soluble guanylate cyclase; WHO = World Health Organization

g. Change in haemodynamic parameters from baseline

In the PATENT-1 trial, treatment-naïve patients with WHO FC I/II PAH randomised to riociguat treatment had a mean baseline PVR [redacted] than those who were randomised to placebo. Thus, any confounding of the treatment effect would favour [redacted]. However, the

treatment-naïve patients with WHO FC I/II PAH had a mean placebo-adjusted [redacted] in PVR of [redacted] after 12 weeks of riociguat treatment (Table 4.43). As the normal laboratory PVR in adults is <250 dyn*sec*cm^{-5}, and the [redacted].

Table 4.43 The effectiveness of a sGC stimulator compared with placebo in improving PVR in patients with WHO FC I/II PAH

Study ID sGC stimulator	N Follow-up period	Mean ± SD baseline PVR[a], dyn*sec*cm^{-5}		Mean ± SD change from baseline, dyn*sec*cm^{-5} (% change from baseline)		Mean difference, dyn*sec*cm^{-5} (% change)
		sGC stimulator	Placebo	sGC stimulator	Placebo	
PATENT-1 CSR Riociguat	N=107 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] A decrease in PVR indicates improvement in haemodynamic parameters
CSR = clinical study report; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; SD = standard deviation; sGC = soluble guanylate cyclase; WHO = World Health Organization

h. Comparative safety

The RCT did not report on the comparative safety of monotherapy with a sGC stimulator versus placebo in patients with WHO FC I/II PAH. Hence, the AEs that were observed in the broader PAH population are discussed in Section 4.4.5.

4.4.2 Research question 2

What is the new evidence concerning the effectiveness and safety of monotherapy with a PAH medicine, compared to the main comparator accepted by the PBAC, in patients with WHO FC III or IV PAH, that has not previously been considered by the PBAC?

There was no new evidence concerning the effectiveness and safety of monotherapy with a PAH medicine, compared to the main comparator accepted by the PBAC, in patients with WHO FC III or IV PAH.

4.4.3 Research question 3

What is the effectiveness and safety of dual combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator, compared to monotherapy, in: i) PAH patients, irrespective of disease severity or aetiology; ii) PAH patients with FC III or IV; and iii) PAH patients with different disease aetiologies?

4.4.3.1 ERA in addition to PDE-5 inhibitor

Four RCTs reported on the effectiveness of an ERA in addition to a PDE-5 inhibitor in treating PAH compared with placebo plus a PDE-5 inhibitor in patients with PAH.

The EARLY[9] double-blind trial randomised WHO FC II PAH patients with and without background sildenafil therapy to receive bosentan or placebo for 26 weeks. Patients had been diagnosed with IPAH, PAH-CHD, PAH-CTD or PAH-HIV. The PAH aetiology and haemodynamic factors were evenly distributed between the two randomised groups. Randomisation was stratified according to background therapy. Therefore, even though only a small proportion of patients received sildenafil as background therapy (15% in the bosentan group and 16% in the placebo group), the risk of incomparable baseline parameters for these patients is low. Pre-specified subgroup analysis of patients receiving background sildenafil therapy was available from the CSR (highlighted).

The COMPASS-2[37] double-blind trial randomised PAH patients who were on stable sildenafil therapy to receive bosentan or placebo for up to end of study. The mean ± SD duration of follow-up duration was 39.7 ± 22.6 months for the placebo group and 38.0 ± 21.9 months for the bosentan group. Overall, 172/334 patients, (51% from the placebo group and 52% from the bosentan group), did not complete the study. Of these patients, 63 (37%) did not experience a primary end-point event, resulting in 20% missing information for the primary end-point of clinical worsening and 22% for the secondary end-point of time to death from any cause. Pre-specified subgroup analysis for patients with FC III/IV PAH, and patients with different PAH aetiologies were also conducted.

The SERAPHIN[7] double-blind long-term trial randomised PAH patients of any WHO FC to receive macitentan or placebo for up to 54 months. Patients were also permitted to have background therapy with a PDE-5 inhibitor (61% of patients) or a prostanoid (4% of patients). The baseline characteristics of the randomised groups were similar, the lack of stratification based on background therapy and WHO FC may have resulted in imbalances in disease severity in individual treatment arms for these subgroups. The mean duration of study treatment was 85.3 weeks and 103.9 weeks for the patients receiving placebo and macitentan, respectively. Post hoc subgroup analyses of patients with WHO FC III/IV PAH for several relevant outcomes were reported in the March 2014 submission to PBAC (highlighted).

The AMBITION[30] double-blind trial randomised patients with WHO FC II/III PAH to receive combination therapy with ambrisentan plus tadalafil, or monotherapy with ambrisentan plus placebo, or tadalafil plus placebo. The mean duration of use of the randomly assigned study medication from the start of therapy to the final assessment visit was 74 weeks (79 weeks in the combination-therapy group and 69 weeks in the pooled-monotherapy group). Patients were diagnosed with IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-HIV or drug/toxin-induced PAH, and were stratified according to PAH aetiology and WHO FC. Overall, 13% of patients withdrew from the study before having a primary end-point event.

The EARLY and AMBITION trials had a low risk of bias, and the COMPASS and SERAPHIN trials had a low-to-moderate risk of bias. The increased risk was mainly due to the lack of stratification for background therapy and WHO FC in the SERAPHIN trial, and the high rate of discontinuation in the COMPASS trial. There was also a large variation in the duration of the trials; varying from 26 weeks to 169 weeks, as described above.

a. Study-defined clinical worsening

The composite endpoint of clinical worsening included death and symptomatic disease progression in all four trials, with other components varying across trials (see Section 4.3.5 for further details).

a.i PAH patients, irrespective of disease severity or aetiology

All four RCTs reported on the proportion of PAH patients, irrespective of disease severity or aetiology, who had clinical worsening while taking both an ERA and a PDE-5 inhibitor drug compared with a placebo plus a PDE-5 inhibitor drug (Table 4.44). In the EARLY trial, patients receiving bosentan and sildenafil were [redacted] to have clinical worsening than patients who received only sildenafil over the 26-week study period, but the study was underpowered to detect a statistically significant difference. There was also a lack of statistical significance in the modest 20% reduced likelihood of clinical worsening seen in the bosentan and sildenafil combination therapy group in the COMPASS-2 trial compared with the sildenafil monotherapy group over a mean duration of follow-up of 169 weeks.

Over a 74-week period, patients treated with ambrisentan and tadalafil in the AMBITION trial were significantly less likely, by almost 2-times, to have clinical worsening than patients receiving tadalafil alone. Over 104 weeks in the SERAPHIN trial, patients treated with macitentan and a PDE-5 inhibitor were [redacted] to have clinical worsening than patients receiving a PDE-5 inhibitor alone.

Table 4.44 The effectiveness of an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in preventing clinical worsening in all PAH patients

Study ID	Follow-up period ERA/PDE-5i	n/N (%)		HR (95% CI)
		ERA + PDE-5i	PDE-5i	
EARLY CSR	26 weeks Bosentan/sildenafil	[redacted]	[redacted]	[redacted]
COMPASS-2[37]	EOS: mean 169 weeks Bosentan/sildenafil	68/159 (43%)	90/175 (51%)	0.83 (0.61, 1.14), p=0.251
SERAPHIN [a] Pulido et al. (2013)[7] and March 2014 submission	EOT: median 115 weeks Macitentan/any PDE-5i	50/154 (33%)	68/154 (44%)	[redacted]
AMBITION[30]	FAV: mean 74 weeks, ITT Ambrisentan/tadalafil	60/302 (20%)	45/151 (30%)	0.55 (0.37, 0.81), p=0.002

[a] Small proportion of patients (4%) receiving prostanoids or receiving doublet background therapy
CI = confidence interval; CSR = clinical study report; EOS = end of study; EOT = end of treatment; ERA = endothelin receptor antagonist; FAV = final assessment visit; HR = hazard ratio; ITT = intention-to-treat; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor

A meta-analysis of the RR of PAH patients having clinical worsening when being treated with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone was performed despite the disparity in the duration of treatment and follow-up between the four studies (Figure 4.7). There

was no heterogeneity between studies [redacted] Overall, patients treated with an ERA and a PDE-5 inhibitor were [redacted] to have a clinical worsening event compared with those treated with a PDE-5 inhibitor alone.

Figure 4.7 Forest plot showing the RR of having a clinical worsening event while being treated with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonists; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

a.ii PAH patients with FC III or IV

Two studies reported the HR for patients with WHO FC III/IV PAH experiencing clinical worsening while taking an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone (Table 4.45). In the COMPASS-2 trial, patients receiving bosentan and sildenafil were almost as likely to have clinical worsening as patients who received a PDE-5 inhibitor alone over the 169-week study period. Over a median treatment period of 115 weeks in the SERAPHIN trial, patients with WHO FC III/IV PAH treated with macitentan and a PDE-5 inhibitor were [redacted] to have clinical worsening than patients receiving a PDE-5 inhibitor alone.

Table 4.45 The effectiveness of an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in preventing clinical worsening in patients with WHO FC III/IV PAH

Study ID	Follow-up period ERA/PDE-5i	n/N (%)		HR (95% CI)
		ERA + PDE-5i	PDE-5i	
COMPASS-2[37]	EOS: mean 169 weeks Bosentan/sildenafil	44/88 (50%)	62/106 (59%)	0.90 (0.61, 1.33)
SERAPHIN [a], March 2014 submission	EOT: median 115 weeks Macitentan/any PDE-5 inhibitor	[redacted]	[redacted]	[redacted]

[a] Small proportion of patients (4%) receiving prostanoids or receiving doublet background therapy
CI = confidence interval; EOS = end of study; EOT = end of treatment; ERA = endothelin receptor antagonist; FC = functional class; HR = hazard ratio; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; WHO = World Health Organization

A meta-analysis of the RR of patients with WHO FC III/IV PAH having clinical worsening when being treated with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone in patients with WHO FC III/IV PAH was performed (Figure 4.8). There was moderate heterogeneity between the two studies [redacted]

Figure 4.8 Forest plot showing the RR of experiencing clinical worsening with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone in patients with WHO FC III/IV PAH

CI = confidence interval; ERA = endothelin receptor antagonists; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk; WHO = World Health Organization

a.iii PAH patients with different disease aetiologies

Two studies reported the HR for patients with different PAH aetiologies experiencing clinical worsening while taking an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone (Table 4.46). Both the COMPASS-2 and the AMBITION trials reported on PAH-CTD patients treated with

an ERA and a PDE-5 inhibitor compared with a PDE-5 inhibitor alone, but only the AMBITION study found a statistically significant effect, a 60% decrease in events favouring combination over monotherapy over a 74-week period. PAH-CTD patients in the COMPASS-2 trial were on combination therapy were just as likely to have an event as those on monotherapy over the 169-week study period. Meta-analysis of the HRs of patients with PAH-CTD having clinical worsening when being treated with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone was performed (Figure 4.9). There was moderate heterogeneity between the two studies, and the pooled point estimate, which favoured treatment with an ERA and a PDE-5 inhibitor, showing a 40% reduction in the likelihood of having an event, over a PDE-5 inhibitor alone, failed to reach clinical significance (pooled HR = 0.59; 95% CI 0.12, 1.07).

The COMPASS-2 study also reported on patients with either IPAH or HPAH, and on patients with PAH-CHD. The point estimate showed a 20% and 40% reduction, respectively, in the likelihood of having an event while receiving combination therapy compared with monotherapy over the 169-week study period, but these differences did not reach statistical significance.

Table 4.46 The effectiveness of an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in preventing clinical worsening in patients with different PAH aetiologies

Study ID ERA/PDE-5i	Follow-up period PAH aetiology	n/N (%)		HR (95% CI)
		ERA + PDE-5i	PDE-5i	
COMPASS-2[37] Bosentan/sildenafil	EOS: mean 169 weeks IPAH/HPAH or PAH-DT PAH-CTD PAH-CHD	44/107 (41%) 22/43 (51%) 2/9 (22%)	60/119 (50%) 26/45 (58%) 4/11 (36%)	0.82 (0.55, 1.21) 0.90 (0.51, 1.60) 0.57 (0.10, 3.17)
AMBITION[31] Ambrisentan/tadalafil	FAV: mean 74 weeks PAH-CTD	20/103 (19%)	NR/40	0.40 (0.20, 0.77)

CI = confidence interval; EOS = end of study; ERA = endothelin receptor antagonist; FAV = final assessment visit; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; n = number of patients with events; N = number of patients; NR = not reported; PAH = pulmonary arterial hypertension; PAH-CHD = PAH associated with congenital heart disease; PAH-CTD = PAH associated with connective tissue disease; PAH-DT = drug/toxin-induced pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor

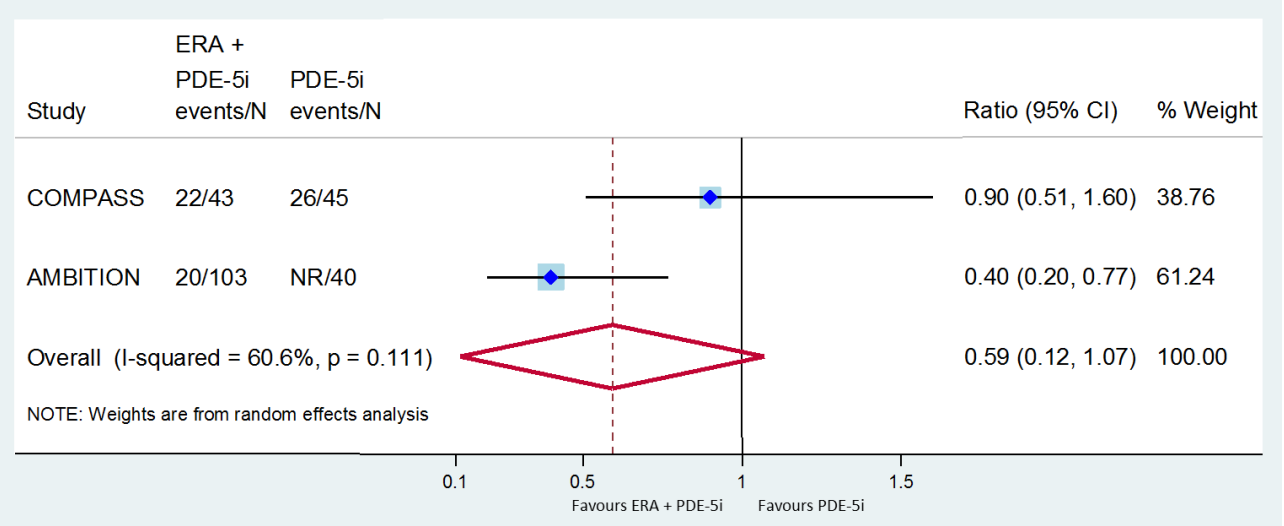


Figure 4.9 Forest plot showing the HR of experiencing clinical worsening with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone in patients with PAH-CTD

CI = confidence interval; ERA = endothelin receptor antagonists; HR = hazard ratio; N = number of patients; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor

b. All-cause mortality

b.i PAH patients, irrespective of disease severity or aetiology

All four RCTs reported on the proportion of PAH patients, irrespective of disease severity or aetiology, who died while taking both an ERA and a PDE-5 inhibitor compared with a placebo plus a PDE-5 inhibitor (Table 4.47). In the EARLY trial, [redacted] died over the 26-week study period, and a HR was not reported. [redacted]

Table 4.47 Mortality rates for an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in all PAH patients

Study ID	ERA/PDE-5i Follow-up period	n/N (%)		HR (95% CI)
		ERA + PDE-5i	PDE-5i	
EARLY CSR	Bosentan/sildenafil 26 weeks	[redacted]	[redacted]	NR
COMPASS-2[37]	Bosentan/sildenafil EOS: mean 169 weeks	33/159 (21%)	44/175 (25%)	0.86 (0.54, 1.34), p=0.4974
SERAPHIN [a], March 2014 submission	Macitentan/any PDE-5i EOS: median 129 weeks	[redacted]	[redacted]	[redacted]
AMBITION[32]	Ambrisentan/tadalafil FAV: mean 74 weeks, ITT	18/302 (6%)	15/151 (10%)	0.54 (0.27, 1.07), p=0.07

[a] Small proportion of patients (4%) receiving prostanoids or receiving doublet background therapy
CI = confidence interval; CSR = clinical study report; EOS = end of study; EOT = end of treatment; ERA = endothelin receptor antagonist; FAV = final assessment visit; HR = hazard ratio; ITT = intention-to-treat; n = number of patients with events; N = number of patients; NR = not reported; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor

A meta-analysis of the RR of patients with PAH who died while being treated with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone was performed (Figure 4.10). There was low heterogeneity between the studies [redacted]

Figure 4.10 Forest plot showing the RR of mortality while being treated with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonists; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

b.ii PAH patients with FC III or IV

The SERAPHIN trial reported that patients with WHO FC III/IV PAH taking ERA:PDE-5 inhibitor combination therapy were [redacted] to die than those taking PDE-5 inhibitor monotherapy over the study period, but [redacted] (Table 4.48).

Table 4.48 Mortality rates for an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in patients with WHO FC III/IV PAH

Study ID	ERA/PDE-5i Follow-up period	n/N (%)		HR (95% CI)
		ERA + PDE-5i	PDE-5i	
SERAPHIN [a], March 2014 submission	Macitentan/any PDE-5i EOS: median 129 weeks Death due to PAH All-cause mortality	[redacted]	[redacted]	[redacted]

[a] Small proportion of patients (4%) receiving prostanoids or receiving doublet background therapy

CI = confidence interval; EOS = end of study; ERA = endothelin receptor antagonist; FC = functional class; HR = hazard ratio; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; WHO = World Health Organization

c. Hospitalisation due to worsening PAH

c.i PAH patients, irrespective of disease severity or aetiology

Two RCTs reported on the proportion of PAH patients, irrespective of disease severity or aetiology, who were hospitalised due to worsening PAH while taking both an ERA and a PDE-5 inhibitor compared with a placebo plus a PDE-5 inhibitor (Table 4.49). The pooled RR shows a statistically significant difference favouring combination therapy over monotherapy with those on combination having a 30% reduction in the likelihood of being hospitalised for worsening PAH; there was low heterogeneity between the two studies (Figure 4.11).

Table 4.49 Hospitalisation due to PAH for an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in all patients with PAH

Study ID Author year	Follow-up period ERA/PDE-5i	n/N (%)		HR (95% CI)
		ERA + PDE-5i	PDE-5i	
SERAPHIN[a] Channick et al. (2015)[46]	EOT: median 115 weeks Macitentan/any PDE-5i	35/154 (23%)	48/154 (31%)	NR
AMBITION[30]	FAV: mean 74 weeks, ITT Ambrisentan/tadalafil	24/302 (8%)	23/151 (15%)	0.44 (0.25, 0.79), p=0.004

[a] Small proportion of patients (4%) receiving prostanoids or receiving doublet background therapy
CI = confidence interval; EOT = end of treatment; ERA = endothelin receptor antagonist; FAV = final assessment visit; HR = hazard ratio; ITT = intention-to-treat; n = number of patients with events; N = number of patients; NR = not reported; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor

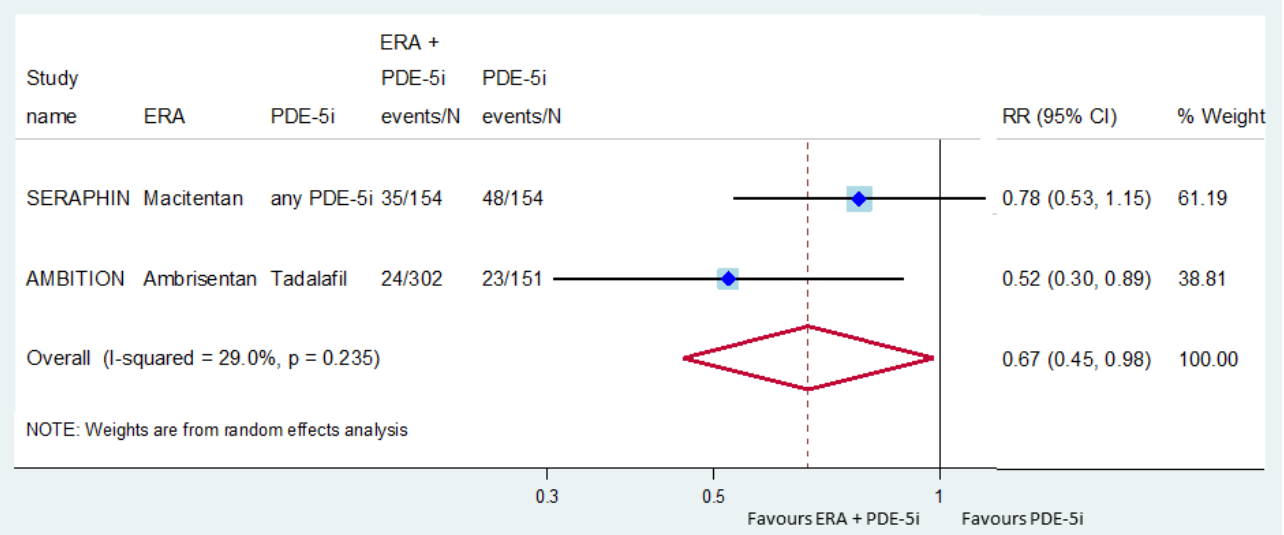


Figure 4.11 Forest plot showing the RR of being hospitalised due to worsening PAH while being treated with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonists; N = number of patients; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

d. Change in WHO FC from baseline

d.i PAH patients, irrespective of disease severity or aetiology

Two RCTs reported on the proportion of PAH patients, irrespective of disease severity or aetiology, whose PAH WHO FC either improved or worsened while taking both an ERA and a PDE-5 inhibitor compared with a placebo plus a PDE-5 inhibitor (Table 4.50). There was no significant difference in the proportion of patients receiving ERA plus PDE-5 inhibitor combination therapy compared with PDE-5 inhibitor monotherapy whose WHO FC improved or worsened over a 16-24 week period. The pooled estimates also showed no difference between the two therapy groups. There was no heterogeneity between the two studies (Figure 4.12).

Table 4.50 The effectiveness of an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in improving WHO FC in all PAH patients

Study ID Follow-up period ERA/PDE-5i	Change in WHO FC	n/N (%)		RR (95% CI)
		ERA + PDE-5i	PDE-5i	
COMPASS-2[37] 16 weeks Bosentan/sildenafil	Improved	25/159 (16%)	28/175 (16%)	0.98 (0.69, 1.61)
	Worsened	13/159 (8%)	17/175 (10%)	0.84 (0.42, 1.68)
AMBITION[30] 24 weeks Ambrisentan/ tadalafil	Improved	94/252 (37%)	39/120 (33%)	1.15 (0.85, 1.55)
	Worsened	12/252 (5%)	7/120 (6%)	1.35 (0.55, 3.33)

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk; WHO = World Health Organization

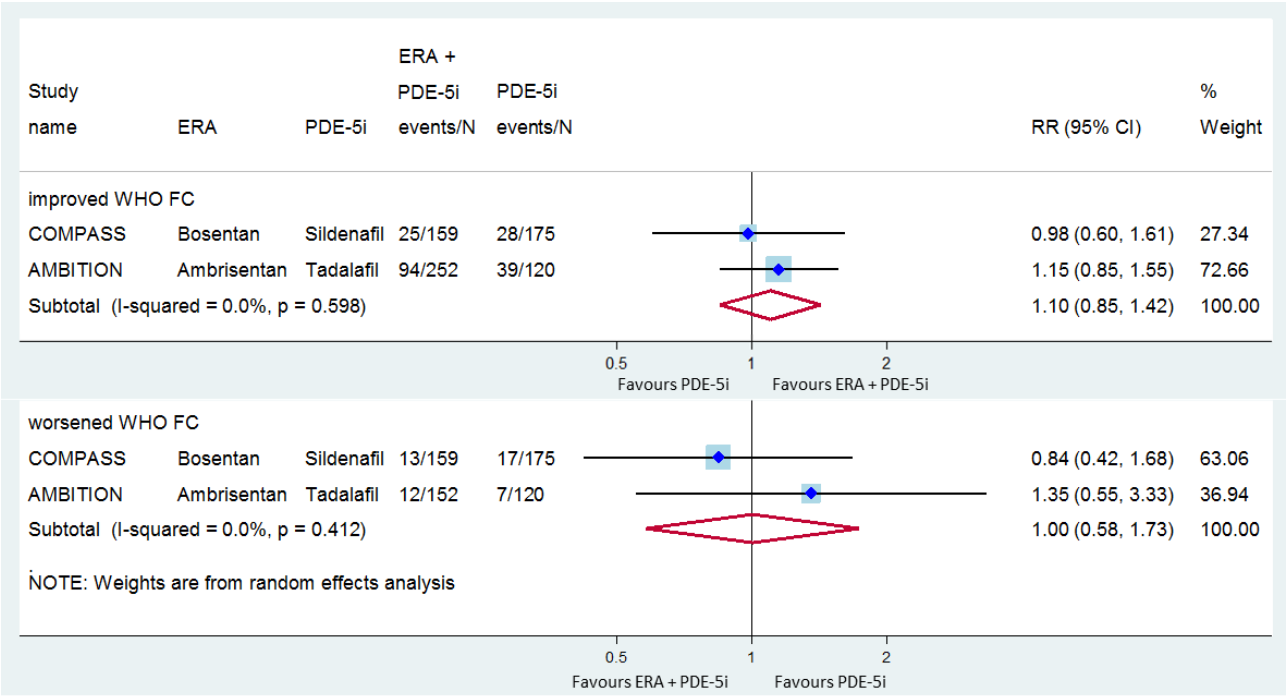


Figure 4.12 Forest plot showing the RR of improving or worsening in WHO FC while being treated with an ERA and a PDE-5 inhibitor compared with PDE-5 inhibitor alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonists; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk; WHO = World Health Organization

e. Change in 6MWD from baseline

e.i PAH patients, irrespective of disease severity or aetiology

All four RCTs reported on the change in 6MWD in patients receiving ERA + PDE-5 inhibitor combination therapy compared to those receiving PDE-5 inhibitor monotherapy over the study period (Table 4.51). All studies, except the EARLY study, showed a greater improvement in patients receiving combination therapy than those on monotherapy. In the EARLY study, one patient out of 14 in ERA+PDE-5 inhibitor subgroup died, and was deemed to have 6MWD of 0 m. This had a large impact on the small subgroup, hence, the median difference in 6MWD, which favoured combination therapy, may be a more accurate reflection of the study outcome. The mean difference reached statistical significance in two RCTs but it was not clinically important in any of them (see Section 4.3.5).

Table 4.51 The effectiveness of an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in improving 6MWD in all PAH patients

Study ID ERA/PDE-5i	N Time point	Mean ± SD (95% CI) baseline 6MWD, metres		Mean change from baseline ± SD (95% CI), metres		Mean difference (95% CI), metres
		ERA + PDE-5i	PDE-5i	ERA + PDE-5i	PDE-5i	
EARLY [a] Galiè et al. (2008)[9] and CSR WHO FC II Bosentan/ sildenafil	N=28 26 weeks	Mean: [redacted] Median: [redacted]	Mean: [redacted] Median: [redacted]	Mean: [redacted] Median: [redacted]	Mean: [redacted] Median: [redacted]	Mean: −17.3 (−105.7, 71.1) Median: 5.0 (−43.1, 53.9)
COMPASS-2[37] Bosentan/ sildenafil	N=334 16 weeks	363.1 ± 78.5	357.6 ± 73.1	7.2 ± 66.0	−14.6 ± 80.4	21.8 (5.9, 37.8)
SERAPHIN[7] Macitentan/any PDE-5i[b]	N=308 26 weeks	364 ± 96.7	360 ± 110.5	17.9 ± 82.3	−7.8 ± 84.8	25.7
AMBITION[30] Ambrisentan/tadalafil	N=374 24 weeks	357.0 (IQR 292.0–425.3)	363.3 (IQR 287.0–421.5)	49.0 (IQR 4.6–85.8)	22.7 (IQR −8.3–66.0)	26.3, p=0.003

[a] 1/14 patients in ERA+PDE-5i subgroup died, and was deemed to have 6MWD of 0, thus median may be more informative for this subgroup
[b] Small proportion of patients receiving prostanoids or receiving doublet background therapy
6MWD = 6-minute walk distance; CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; HR = hazard ratio; IQR = interquartile range; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; SD = standard deviation; WHO = World Health Organization

f. Change in QoL from baseline

f.i PAH patients, irrespective of disease severity or aetiology

The SERAPHIN study reported on the change in QoL in patients receiving ERA + PDE-5 inhibitor combination therapy compared to those receiving PDE-5 inhibitor monotherapy over a 26-week period (Table 4.52). Mehta et al (2017)[47] converted the domain and component summary scores to norm-based scores based on the 1998 US general population (scale 0−100). A higher SF-36 score denotes better QoL. The authors reported that the minimum clinically important difference varies across diseases with the generally accepted threshold being 2−3 norm-based points for the physical component score and three for mental component score. In the absence of a norm-based PAH-specific minimal important difference, a three-point threshold was used. Although there was an improvement in the SF-36 scores of most domains for patients receiving combination therapy over those receiving monotherapy, the difference were not clinically important. Thus, the norm-based difference only reached clinical importance for the SF-36 domain for vitality (score 3.1). The physical functioning and role-physical domains may be of clinical importance as the norm-based difference between combination therapy and monotherapy was >2.

Table 4.52 The effectiveness of an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in improving QoL in all PAH patients

Study ID Questionnaire	ERA/PDE-5 inhibitor Follow-up period	Domain	Median monotherapy-corrected norm-based change from baseline (95% CI)
SERAPHIN [a] Mehta et al. 2017[47] SF-36	Macitentan/any PDE-5 inhibitor 26 weeks ERA + PDE-5 inhibitor (n=150) Placebo + PDE-5 inhibitor (n=149)	SF-36 summary components [b]	
		Physical component	1.4 (0.0, 2.9)
		Mental component	1.5 (-0.5, 3.8)
		SF-36 domains [b]	
		Physical functioning	2.1 (0.0, 4.2)
		Role-physical	2.4 (0.0, 2.4)
		Bodily pain	0.8 (0.0, 4.6)
		General health	1.4 (0.0, 2.4)
		Vitality	3.1 (0.0, 3.1)
		Social functioning	0.0 (0.0, 5.5)
		Role emotional	0.0 (0.0, 3.9)
		Mental health	1.4 (0.0, 2.8)

[a] Small proportion of patients (4%) receiving prostanoids or receiving doublet background therapy
[b] SF-36 component summary scores and domain scores range from 0 to 100. A higher score indicates better QoL.
CI = confidence interval; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; QoL = quality of life; SF-36 = short form 36

g. Change in haemodynamic parameters from baseline

None of the studies reported on haemodynamic outcomes for the subgroups of interest.

h. Comparative safety

Three RCTs reported on the comparative safety of treatment with an ERA plus a PDE-5 inhibitor compared with a PDE-5 inhibitor alone in any patient with PAH.

McLaughlin et al (2015)[37] reported on the number of patients who had any AE, serious AEs and AEs that led to discontinuation of double-blind treatment over the study period from the COMPASS-2 trial. The mean exposure period to the double-blind study drug was 26.4 ± 20.99 months for bosentan and 30.7 ± 24.31 months for the placebo.

The number of patients who had oedema-related AEs, haemoglobin decrease-related AEs, hypotension-related AEs and abnormal liver function-related AEs during combination therapy compared with those receiving monotherapy from the SERAPHIN trial was presented to PBAC in the March 2014 submission.

Galie et al (2015)[30] reported the number of serious AEs and the number of AEs leading to discontinuation of blinded treatment from the AMBITION trial.

h.i PAH patients, irrespective of disease severity or aetiology

The important AEs reported in the COMPASS-2, SERAPHIN and AMBITION trials are listed in Table 4.53. In the COMPASS-2 trial, the proportion of patients who had any AE was the same for both the combination therapy and monotherapy arms. However, meta-analysis of the COMPASS-2 and

AMBITION trials showed significantly more patients in the monotherapy arm had a serious AE compared to those in the combination therapy arm (Figure 4.13). Conversely, patients in the combination therapy arms had more AEs that led to treatment discontinuation than those in the monotherapy arm, but the difference was not statistically significant (Figure 4.13). In the SERAPHIN trial, [redacted] patients receiving combination therapy had a haemoglobin decrease-related AE compared with those receiving monotherapy. On the other hand [redacted] patients in the monotherapy arm had abnormal liver function-related AEs compared with those in the combination therapy arm. [redacted] of patients who had oedema-related or hypotension-related AEs [redacted] in the two treatment arms.

Table 4.53 The comparative safety of an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in all patients with PAH

Study ID ERA./PDE-5i Follow-up period	Adverse events	n/N (%)		HR or RR (95% CI)
		ERA + PDE-5i	PDE-5i	
COMPASS-2[37] Bosentan/ sildenafil 104 weeks	Any AE Serious AEs AEs leading to discontinuation	144/159 (91%) 73/159 (46%) 39/159 (25%)	159/174 (91%) 102/174 (59%) 22/174 (13%)	RR = 0.99 (0.93, 1.06) RR = 0.78 (0.63, 0.97) RR = 1.94 (1.20, 3.12)
SERAPHIN [a], March 2014 submission Macitentan/any PDE-5 inhibitor 12 weeks	Oedema-related AEs Haemoglobin decrease-related AEs Hypotension-related AEs Abnormal liver function-related AEs	[redacted]	[redacted]	[redacted]
AMBITION[30] Ambrisentan/ tadalafil 24 weeks	Serious AEs AEs leading to discontinuation	92/252 (37%) 31/252 (12%)	50/120 (42%) 14/120 (12%)	RR = 0.88 (0.67, 1.14) RR = 1.05 (0.58, 1.91)

[a] Small proportion of patients (4%) receiving prostanoids or receiving doublet background therapy
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; HR = hazard ratio; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk

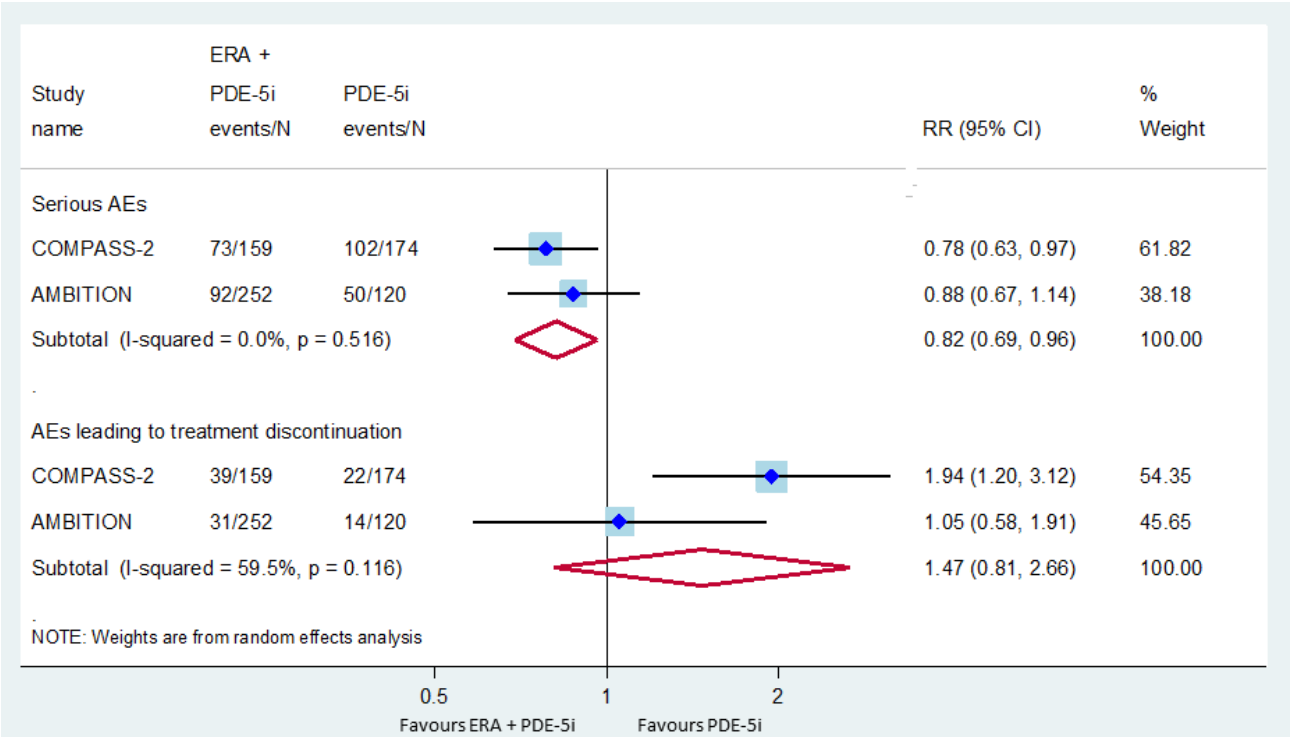


Figure 4.13 Forest plot showing the RR of having a serious AE or an AE leading to treatment discontinuation while being treated with an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor alone in all PAH patients

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonists; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

h.iii PAH patients with different disease aetiologies

In the AMBITION trial, the proportion of patients with either IPAH/HPAH or PAH-CTD who had any AE, a serious AE or an AE leading to treatment discontinuation were similar in the combination therapy and monotherapy arms (Table 4.54).

Table 4.54 The comparative safety of an ERA in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in patients with either IPAH/HPAH or PAH-CTD

Study ID ERA./PDE-5i Follow-up period	Adverse events	n/N (%)		RR (95% CI)
		ERA + PDE-5i	PDE-5i	
AMBITION[30] Ambrisentan/tadalafil 24 weeks	IPAH/HPAH Any AE Serious AEs AEs leading to discontinuation PAH-CTD Any AE Serious AEs AEs leading to discontinuation	 130/134 (97%) 44/134 (33%) 15/134 (11%) 102/103 (99%) 45/103 (44%) 14/103 (14%)	 65/70 (93%) 27/70 (39%) 8/70 (11%) 39/40 (98%) 20/40 (50%) 6/40 (15%)	 1.04 (0.97, 1.12) 0.85 (0.58, 1.25) 0.98 (0.44, 2.20) 1.02 (0.96, 1.07) 0.87 (0.60, 1.28) 0.91 (0.37, 2.19)

[a] Small proportion of patients (4%) receiving prostanoids or receiving doublet background therapy
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; n = number of events; N = number of patients; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor RR = relative risk; WHO = World Health Organization

4.4.3.2 ERA in addition to prostanoid

Two RCTs reported on the effectiveness of an ERA in addition to prostanoid in treating PAH compared with placebo plus a prostanoid.

The BREATHE-2[35] double-blind, placebo-controlled trial enrolled 33 patients with New York Heart Association (NYHA) FC III/IV (generally equivalent to WHO FC III/IV) PAH who were scheduled to begin epoprostenol therapy within 2 weeks of screening. Patients were randomised at 2:1 ratio to receive additional treatment with either bosentan or placebo for 16 weeks. Baseline demographic and haemodynamic factors were evenly distributed between the two randomised groups, except that there were 20% more men in the monotherapy group and 10% more patients with PAH-CTD in the combination therapy group. The trial had a low-to-moderate risk of bias, mostly due to attrition bias; treatment discontinuation occurred more frequently in the combination therapy arm than in the monotherapy arm.

In the Han 2017[38] RCT, 27 treatment-naïve patients with WHO FC III/IV PAH were randomised into three groups to receive combination therapy with bosentan and iloprost or monotherapy with either bosentan or iloprost for 12 weeks. Of the 14 patients randomised to combination therapy or iloprost monotherapy, all had IPAH except one patient randomised to combination therapy who had chronic thromboembolic pulmonary hypertension. The patients in the iloprost groups were older (41.8 ± 5.3 years) compared to those receiving combination therapy (30.1 ± 7.4 years), and half (4/8) of those in the combination therapy arm required oxygen compared with only one out of seven patients in the monotherapy group. Additionally, more patients in the combination therapy group had WHO FC IV disease (3/8; 38%) compared with patients in the monotherapy group (1/6; 17%). Baseline haemodynamic factors were evenly distributed between the two randomised groups. This study had a high risk of bias, mostly due to the open-label study design.

As, both studies only enrolled patients with FC III/IV PAH, all reported outcomes are relevant to this patient subgroup.

a. Study-defined clinical worsening

Neither RCT reported on the proportion of patients who had clinical worsening during the study period.

b. All-cause mortality

b.ii PAH patients with FC III or IV

During a study period of 16 weeks, 3 patients in the ERA plus prostanoid combination therapy group from the BREATHE-2 trial died, but no patients in the prostanoid monotherapy group died (Table 4.55). The clinical investigators from the BREATHE-2 trial considered these deaths to reflect the severity and progressive nature of PAH rather than being related to the study treatment. The ARD (13.6%; 95% CI −0.70, 28.0; p = 0.20) did not reach statistical significance. The wide CI suggests this study was statistically underpowered for this outcome. The NNT (inverse of the ARD) indicates that for every eight patients treated with prostanoid monotherapy one additional death was prevented compared with ERA plus prostanoid combination therapy.

Table 4.55 Mortality rates for an ERA in addition to a prostanoid compared with prostanoid monotherapy in all PAH patients

Study ID	Follow-up period ERA/prostanoid	n/N (%)		RR (95% CI)
		ERA + prostanoid	Prostanoid	
BREATHE-2[35]	16 weeks Bosentan/epoprostenol	3/22 (14%)	0/11 (0%)	Not calculable

CI = confidence interval; ERA = endothelin receptor antagonist; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk

c. Hospitalisation due to worsening PAH

Neither RCT reported on the proportion of patients who were hospitalised during the study period.

d. Change in WHO FC from baseline

d.ii PAH patients with FC III or IV

Han 2017[38] reported on WHO FC at baseline and at 12 weeks, and found that all patients in the combination therapy group had improved their WHO FC from III/IV to I/II (Table 4.56). However, the data for the prostanoid monotherapy group could not be extracted because the authors did not specify how many patients with WHO FC II/IV at 12 weeks had improved or worsened. In the BREATHE-2 trial, patients receiving ERA plus prostanoid combination therapy were more likely to improve their WHO FC than those on prostanoid monotherapy (ARD = 13.6%; 95% CI −22.3, 49.5; p = 0.46), but the difference was not statistically significant, most likely due to the small sample

size. Thus, for every eight patients treated with ERA plus prostanoid combination therapy one additional patient improved their WHO FC compared with prostanoid monotherapy.

Table 4.56 The effectiveness of an ERA in addition to a prostanoid compared with prostanoid monotherapy in improving WHO FC in all PAH patients

Study ID Follow-up period ERA/prostanoid	Change in WHO FC	n/N (%)		RR (95% CI)
		ERA + prostanoid	Prostanoid	
BREATHE-2[35] 16 weeks Bosentan/ epoprostenol	Improved	13/22 (59%)	5/11 (46%)	1.30 (0.62, 2.71)

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

e. Change in 6MWD from baseline

e.ii PAH patients with FC III or IV

Both RCTs reported on the change in 6MWD for patients receiving combination therapy compared to those on monotherapy (Table 4.57). For patients in the BREATHE-2 trial, the mean (95% CI) 6MWD at baseline for patients in the combination therapy and monotherapy groups was depicted as shown in Figure 4.14. After 16 weeks, patients in the ERA plus prostanoid treatment arm improved their 6MWD from baseline by a median of 68 m compared with a median of 74 m in the placebo plus prostanoid group. This improvement was clinically important in both groups (see Section 4.3.5), but the difference between groups was not statistically significant. The 6MWD performance in the combination therapy group was adversely affected by two patients who were assigned a 6MWD of 0 m.

Han 2017[38] reported a large clinically important improvement in the combination therapy group (134 m), and a very small improvement in the monotherapy group (10 m). Thus, there was a clinically important and statistically significant improvement in 6MWD in the ERA plus prostanoid combination therapy group compared with the prostanoid monotherapy group.

Table 4.57 The effectiveness of an ERA in addition to a prostanoid compared with prostanoid monotherapy in improving 6MWD in all patients with WHO FC III/IV PAH

Study ID ERA/ prostanoid	N Time point	Mean ± SD baseline 6MWD, metres		Median/mean ± SD change from baseline, metres		Median/mean difference, metres
		ERA + prostanoid	Prostanoid	ERA + prostanoid	Prostanoid	
BREATHE-2[35] Bosentan/epoprostenol	N=33 16 weeks	NR	NR	Median = 68	Median = 74	Median = −6, NS
Han 2017[38] [a] Bosentan/iloprost	N=14 12 weeks	300.3 ± 36.2	330.8 ± 37.1	133.8 ± 25.6	10.2 ± 20.0	123.6, p<0.001

[a] 1 patient (12.5%) in the ERA + prostanoid group had CTEPH.
6MWD = 6-minute walk distance; CTEPH = chronic thromboembolic pulmonary hypertension; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; NR = not reported; NS = not significant; PAH = pulmonary arterial hypertension; SD = standard deviation; WHO = World Health Organization

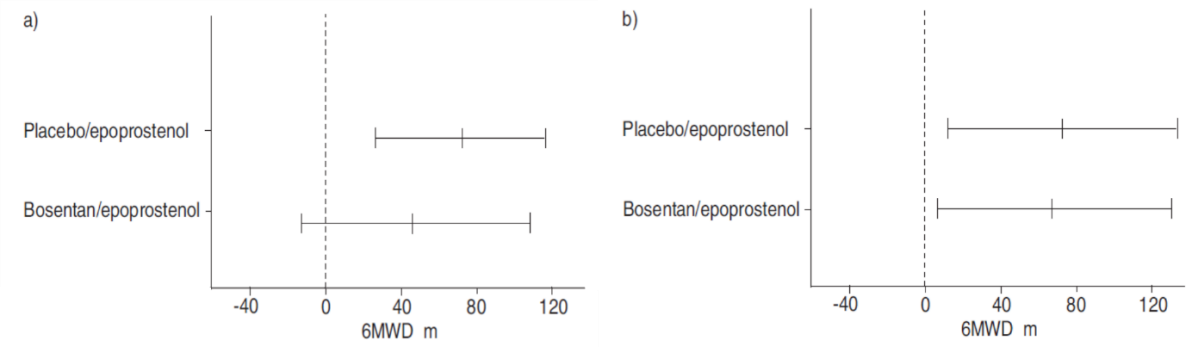


Figure 4.14 The mean (95% CI) 6MWD at baseline (a) and median (95% CI) at 16 weeks (b) in the BREATHE-2 trial

a) Baseline; b) Change from baseline at Week 16
6MWD = 6-minute walk distance; m = metres
Source: Humbert et al (2004)[35]

f. Change in QoL from baseline

f.ii PAH patients with FC III or IV

Han et al (2017)[38] reported on the change in QoL in patients treated with combination therapy compared to those on monotherapy using the MLHF questionnaire (Table 4.58). This questionnaire is widely used to evaluate QoL in heart failure patients. It contains 21 questions with a total score ranging from 0 to 105, with an increasing score representing a poorer QoL. Behlouli et al (2009)[84] estimated that a score of <24 represented a good QoL for heart failure patients, a score between 24 and 45 represents a moderate QoL, and a score >45 represents a poor QoL.

At baseline, the mean scores indicate that patients in both the combination therapy and monotherapy groups had a poor QoL. After 12 weeks the patients in the ERA plus prostanoid group had improved sufficiently to now have a mean score representing a good QoL. The mean score for patients receiving prostanoid monotherapy hardly changed from baseline, and patients still considered themselves to have a poor QoL. This suggests a significant and clinically important difference in the change in QoL between the two groups.

Table 4.58 The effectiveness of an ERA in addition to a prostanoid compared with prostanoid monotherapy in improving QoL in patients with WHO FC III/IV PAH

Study ID ERA/prostanoid Time point	Mean ± SD baseline QoL		Mean ± SD change from baseline		Mean difference, points
	ERA + prostanoid	Prostanoid	ERA + prostanoid	Prostanoid	
Han 2017[38] [a] Bosentan/iloprost 12 weeks	MLHF[b] 56.8 ± 7.5	65.5 ± 3.7	–37.0 ± 7.3	–1.7 ± 5.9	–35.3, p<0.002

[a] 1 patient (12.5%) in the ERA + prostanoid group had CTEPH.
[b] MLHF questionnaire total scores range from 0 to 105. A higher score indicates poorer QoL.
CTEPH = chronic thromboembolic pulmonary hypertension; ERA = endothelin receptor antagonist; FC = functional class; MLHF = Minnesota living with heart failure questionnaire; PAH = pulmonary arterial hypertension; QoL = quality of life; SD = standard deviation; WHO = World Health Organization

g. Change in haemodynamic parameters from baseline

g.ii PAH patients with FC III or IV

Both the BREATHE-2 and Han 2017 studies reported the change in several haemodynamic parameters from baseline to the end of the study period (Table 4.59). Although all of the reported parameters in the BREATHE-2 study showed greater improvement in the combination therapy group compared to the monotherapy group, none of the monotherapy-adjusted changes from baseline were statistically significant. Although the improvement in the cardiac index, PVR and total pulmonary resistance in the combination therapy group were large and likely to be clinically important, there was also a reasonably large improvement in the monotherapy group. Thus, the improvement gained from the addition of an ERA to prostanoid therapy was not clinically important.

In the Han 2017 study the monotherapy group changed little from baseline whereas the combination therapy group showed improvement. There was statistically significant improvement in the mPAP (p = 0.002) and cardiac index (p = 0.041) in the combination therapy group compared to the monotherapy group. The mean baseline value for the cardiac index was within the normal range for the combination therapy group and improved further with treatment. However, as the cardiac index can be normal in patients with PAH, the clinical significance of this change is uncertain. The 26% decrease in mean pulmonary arterial pressure and 22% decrease PVR in the combination therapy group compared with the monotherapy group is likely to be clinically important.

Table 4.59 The effectiveness of an ERA in addition to a prostanoid compared with prostanoid monotherapy in improving haemodynamic parameters in all PAH patients

Study ID ERA/ prostanoid Study period N	Haemo-dynamic parameter[a]	Mean ± SEM or SD baseline haemodynamic parameters		Mean ± SEM or SD % change from baseline		Mean % difference
		ERA + prostanoid	Prostanoid	ERA + prostanoid	Prostanoid	
BREATHE-2[35] Bosentan/ epoprostenol 16 weeks N=33	CAI (L/min/m^2) PVR (dyn*sec*cm^{-5}) TPR (dyn*sec/cm^{-5}) mPAP (mmHg) mRAP (mmHg)	1.7 ± 0.1 1,511 ± 129 1,697 ± 142 59.2 ± 4.0 11.9 ± 1.1	1.7 ± 0.2 1.426 ± 140 1,628 ± 154 60.9 ± 2.9 11.9 ± 2.2	48.7 ± 11.0% −35.2 ± 5.4% −36.3 ± 4.3% −9.0 ± 6.0% −1.9 mmHg ± 1.4	37.9 ± 13.3% −25.7 ± 7.2% −22.6 ± 6.2% −2.2 ± 3.6% 0.3 mmHg ± 1.3	10.8%, p=0.6 −9.5%, p=0.3 −13.7%, p=0.08 −6.8%, p=0.3 −2.2 mmHg, p=0.7
Han 2017[38 b] Bosentan/iloprost 12 weeks N=14	CAI (L/min/m^2) PVR (dyn*sec*cm^{-5}) mPAP (mmHg)	2.61 ± 0.31 1,038 ± 176 56.5 ± 5.5	2.20 ± 0.35 1,157 ± 165 55.7 ± 1.7	0.55 ± 0.20 (21.1%) −187 ± 174 (−18.0%) −18.9 ± 2.8 (−33.5%)	−0.09 ± 0.15 (−4.1%) 40 ± 161 (3.5%) −4.0 ± 3.5 (−7.2%)	17%, p=0.041 −21.5%, p=0.62 −26.3%, p=0.002

[a] An increase in CAI indicates improvement in haemodynamic parameters. A decrease in PVR, TPR, mPAP or mRAP indicates improvement in haemodynamic parameters.
[b] 1 patient (12.5%) in the ERA + prostanoid group had CTEPH.
CAI = cardiac index; CTEPH = chronic thromboembolic pulmonary hypertension; ERA = endothelin receptor antagonist; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; SD = standard deviation; SEM = standard error of the mean; TPR = total pulmonary resistance

h. Comparative safety

h.ii PAH patients with FC III or IV

In the BREATHE-2 trial, there was no significant difference in the proportion of patients from receiving bosentan/epoprostenol combination therapy compared with those receiving monotherapy who reported a serious AE, an AE leading to treatment discontinuation or worsening of PAH (Table 4.60). Additionally, no significant difference in the proportion of patients who had increased levels of transaminases was observed in either group; this had been previously associated with bosentan treatment.

Han et al (2017)[38] also reported no significant differences in the proportion of patients receiving combination therapy compared with monotherapy who had an AE, or a serious AE leading to treatment discontinuation (Table 4.60).

Table 4.60 The comparative safety of an ERA in addition to a prostanoid compared with prostanoid monotherapy in all patients with PAH

Study ID ERA/prostanoid Follow-up period	AEs	n/N (%)		RR (95% CI)
		ERA + prostanoid	Prostanoid	
BREATHE-2[35] Bosentan/epoprostenol 12 weeks	Serious AEs AEs leading to discontinuation Worsening of PAH Increased level of transaminases (bosentan)	3/22 (14%) 1/22 (5%) 1/22 (5%) 2/22 (9%)	2/11 (18%) 1/11 (9%) 2/9 (18%) 2/11 (18%)	0.75 (0.15, 3.85) 0.50 (0.03, 7.26) 0.25 (0.03, 2.47) 0.05 (0.08, 3.09)
Han 2017[38] [a] Bosentan/iloprost 12 weeks	Any AE Serious AEs leading to discontinuation	7/8 (88%) 0/8 (0%)	5/6 (83%) 0/6 (0%)	1.05 (0.67, 1.64) Not calculable

[a] 1 patient (12.5%) in the ERA + prostanoid group had CTEPH.
AE = adverse event; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; ERA = endothelin receptor antagonist; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk

4.4.3.3 PDE-5 inhibitor in addition to ERA

Five RCTs reported on the effectiveness of a PDE-5 inhibitor in addition to ERA in treating PAH compared with placebo plus ERA.

The AMBITION[30] double-blind trial randomised patients with WHO FC II/III PAH to receive combination therapy with ambrisentan plus tadalafil, or monotherapy with ambrisentan plus placebo, or tadalafil plus placebo. The mean duration of use of the randomly assigned study medication from the start of therapy to the final assessment visit was 74 weeks (79 weeks in the combination therapy group and 69 weeks in the monotherapy groups). The mean follow-up time

from randomisation to the end of the study was 87 weeks (89 weeks in the combination therapy group and 85 weeks in the monotherapy groups). Patients were diagnosed with IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-HIV or drug/toxin-induced PAH, and were stratified according to PAH aetiology and WHO FC. Coghlan et al (2016)[31] conducted a post hoc analysis of clinical worsening and safety in patients with PAH-CTD.

The Zhuang 2014[50] double-blind controlled study randomised patients with symptomatic PAH receiving ambrisentan for 4 months or more, to additional treatment with tadalafil or placebo for 16 weeks. The randomization was stratified for baseline 6MWD and PAH aetiology (IPAH/HPAH and anorexigen use versus other types). There were no significant differences between the tadalafil and placebo groups in any demographic or baseline characteristics, but the placebo group did have approximately twice as many patients with PAH caused by anorexigen use (7/64; 11% versus 4/60; 7%) or PAH-CHD (5/64; 8% versus 2/60; 3%). Pre-defined subgroup analysis was performed for 6MWD for patients with WHO FC III/IV.

The PHIRST[12] double-blind trial randomised PAH patients of any WHO FC to receive 20 mg or 40 mg tadalafil or placebo for 16 weeks. Background use of bosentan was permitted for patients taking a stable dose for a minimum of 12 weeks before screening. The results for those on background bosentan and randomised to either 40 mg tadalafil or placebo are included in this section. The randomisation was stratified for baseline walk distance (<325 m or >325 m), PAH aetiology (IPAH, HPAH and anorexigen use versus other types of PAH) and for bosentan use. The baseline characteristics were similar in the two treatment groups except that the placebo plus bosentan group had more patients with WHO FC III/IV PAH compared with the combination therapy groups (71% versus 58%). Pre-specified exploratory analysis for PAH patients receiving background bosentan was undertaken[45]. A post hoc subgroup analysis for 6MWD of patients with WHO FC III/IV PAH and patients with different PAH aetiologies who were receiving background bosentan was also conducted by Barst et al. (2011)[45].

The Vizza 2017[49] RCT was a 12-week, multicentre, multinational, double-blind study in which patients with IPAH or PAH-CTD who were taking bosentan at a stable dose for ≥3 months were randomised to sildenafil or placebo. Randomisation was intended to be stratified by baseline 6MWD and PAH aetiology, but after blinding was broken, it was realized that only baseline 6MWD stratification had occurred. Thus, there were some imbalances in the proportion of patients in each of the strata: fewer PAH-CTD patients with a 6MWD <325 m were assigned to the sildenafil treatment group (n=5) than to the placebo group (n=10). Additionally, more patients with WHO FC III were assigned to the placebo group (72%) compared with the sildenafil treatment groups (58%). Pre-specified analysis of the primary endpoint of 6MWD in patients with IPAH/HPAH or PAH-CTD was also conducted.

The Mainguy 2013[39] double-blind crossover trial randomised stable PAH patients already on PAH monotherapy to sildenafil or placebo for 28 days. This was followed by a 28-day washout period before patients were crossed over to placebo or sildenafil for a further 28-day period. Most patients had IPAH or PAH-CTD and were in WHO FC II. They were mostly being treated with ERAs

(n= 15 with bosentan and n=3 with ambrisentan), but 2 patients were being treated with epoprostenol.

The AMBITION trial had a low risk of bias, and the PHIRST, Zhuang 2014, Vizza 2017 and Mainguy 2013 trials had a low-to-moderate risk of bias. The increased risk was mainly due to lack of clarity in describing the randomisation allocations and blinding of assessments. There was also a large variation in the duration of the trials; varying from 4 weeks in the cross-over trial to a mean 74 weeks in the AMBITION trial, as described above.

a. Study-defined clinical worsening

Four RCTs reported on the effectiveness of PDE-5 inhibitor plus an ERA compared with placebo plus ERA in preventing clinical worsening in PAH patients of any WHO FC and disease aetiology. The AMBITION trial also reported clinical worsening in the PAH-CTD patient subgroup. The definition of clinical worsening included death, hospitalisation due to PAH, lung transplantation and start of new therapy in all trials that reported this outcome (see Section 4.3.5 for further details).

a.i PAH patients, irrespective of disease severity or aetiology

Only the AMBITION trial reported the HR for all PAH patients experiencing clinical worsening while receiving PDE-5 inhibitor plus ERA treatment compared with treatment with an ERA alone (Table 4.61). In this trial, patients receiving combination therapy were 2-times less likely to have clinical worsening than patients who received monotherapy over the 74-week study period. The Zhuang 2014 RCT reported a statistically significant reduction in the proportion of patients having a clinical worsening event in the combination therapy group compared with the monotherapy group.

Table 4.61 The effectiveness of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in preventing clinical worsening in all PAH patients

Study ID	PDE-5i/ERA Follow-up period	n/N (%)		HR (95% CI)
		PDE-5i + ERA	ERA	
AMBITION[30]	Tadalafil/ambrisentan FAV: mean 74 weeks EOS: mean 87 weeks	46/253 (18%) 52/253 (21%)	43/126 (34%) 47/126 (37%)	0.48 (0.31, 0.72), p<0.001 0.48 (0.32, 0.71), p<0.001
PHIRST Barst et al (2011)[45]	Tadalafil/bosentan 16 weeks	2/42 (5%)	5/45 (11%)	NR
Zhuang 2014[50]	Tadalafil/ambrisentan 16 weeks	5/60 (8%)	14/64 (22%)	NR, p=0.046
Vizza 2017[49]	Sildenafil/bosentan 12 weeks	3/51 (6%)	2/53 (6%)	NR

CI = confidence interval EOS = end of study; ERA = endothelin receptor antagonist; FAV = final assessment visit; HR = hazard ratio; n = number of patients with events; N = number of patients; NR = not reported; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor

A meta-analysis of the RR of having clinical worsening when being treated with a PDE-5 inhibitor plus an ERA compared with an ERA alone was performed (Figure 4.15). All except the Vizza 2017 study had a clinically significant point estimate favouring treatment with an ERA over placebo, but only the tadalafil plus ambrisentan studies reached statistical significance; they were also the two largest studies. The wide CIs of the other two studies suggest they were underpowered to detect a significant difference for this outcome. Overall, patients receiving combination therapy had a 2-fold lower risk of having a clinical worsening event compared with those receiving ERA monotherapy.

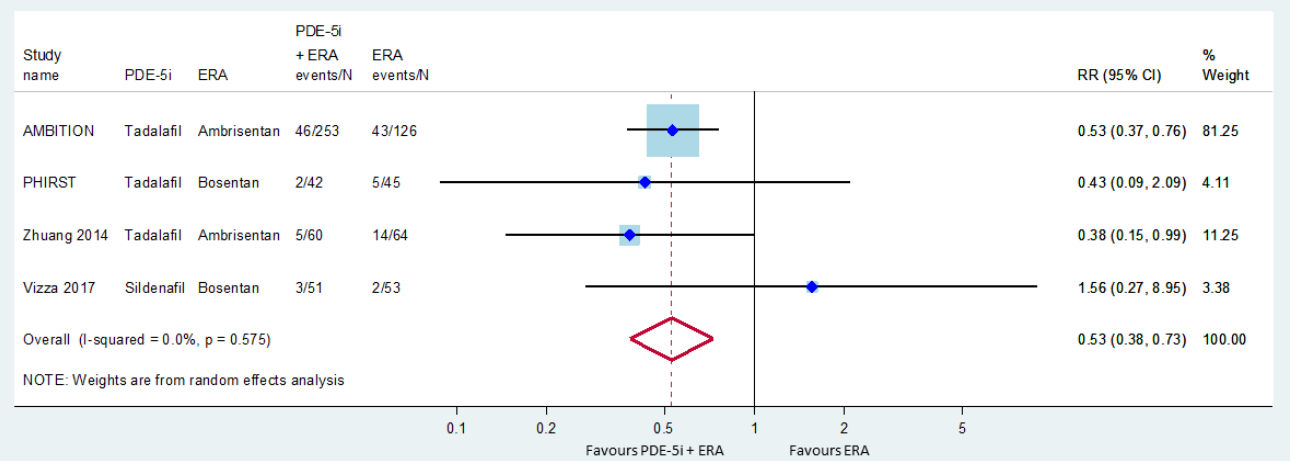


Figure 4.15 Forest plot showing the RR of having a clinical worsening event while being treated with a PDE-5 inhibitor and an ERA compared with an ERA alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonist; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

a.iii PAH patients with different disease aetiologies

Coghlan et al (2016)[31] reported on the proportion of patients with PAH-CTD who had clinical worsening while receiving combination therapy compared to those receiving monotherapy from the AMBITION trial (Table 4.62). Combination therapy was just as effective for patients with PAH-CTD as it was for patients with any PAH aetiology. PAH-CTD patients receiving combination therapy were also 2-times less likely to have clinical worsening than patients who received monotherapy over the 74-week study period.

Table 4.62 The effectiveness of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in preventing clinical worsening in patients with PAH-CTD

Study ID PAH aetiology	PDE-5i/ERA Follow-up period	n/N (%)		HR (95% CI)
		PDE-5i + ERA	ERA	
AMBITION Coghlan et al (2016)[31]	Tadalafil/ambrisentan FAV: mean 74 weeks	2/103 (19%)	NR/44	0.51 (0.25, 1.01)

CI = confidence interval; ERA = endothelin receptor antagonist; FAV = final assessment visit; HR = hazard ratio; n = number of patients with events; N = number of patients; NR = not reported; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor

b. All-cause mortality

b.i PAH patients, irrespective of disease severity or aetiology

Three RCTs reported on mortality rates for patients receiving PDE-5 inhibitor plus ERA combination therapy compared with ERA monotherapy in PAH patients of any WHO FC and disease aetiology (Table 4.63). The forest plots and pooled estimate in Figure 4.16 show that although the point estimate favoured combination therapy, there was no statistically significant difference in the risk of dying while receiving combination therapy does not differ significantly to that for patients those receiving monotherapy.

Table 4.63 Mortality rates for a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in all PAH patients

Study ID	PDE-5i/ERA Follow-up period	n/N (%)		RR (95% CI)
		PDE-5i + ERA	ERA	
AMBITION Hoeper et al (2016)[32]	Tadalafil/ambrisentan FAV: mean 74 weeks EOS: mean 87 weeks	3/302 (1%) 29/302 (10%)	3/152 (2%) 19/152 (13%)	0.46 (0.09, 1.08) 0.74 (0.41, 1.32)
Zhuang 2014[50]	Tadalafil/ambrisentan 16 weeks	0/60 (0%)	1/64 (2%)	0 (not calculable), p=1.00
Vizza 2017[49]	Sildenafil/bosentan 12 weeks	1/51 (2%)	0/53 (0%)	Not calculable

CI = confidence interval; EOS = end of study; ERA = endothelin receptor antagonist; FAV = final assessment visit; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

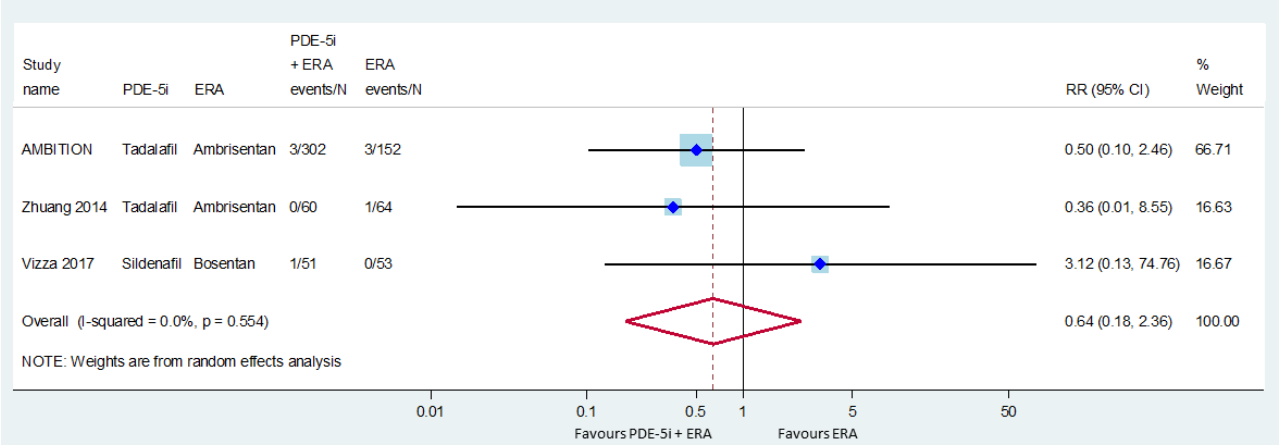


Figure 4.16 Forest plot showing the RR of dying while being treated with a PDE-5 inhibitor and an ERA compared with an ERA alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonist; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

c. Hospitalisation due to worsening PAH

c.i PAH patients, irrespective of disease severity or aetiology

Three RCTs reported on hospitalisations due to worsening PAH for patients receiving PDE-5 inhibitor plus ERA combination therapy compared with ERA monotherapy in PAH patients of any WHO FC and disease aetiology (Table 4.64). The forest plot shows that two of the studies had very wide CIs and were underpowered for this outcome (Figure 4.17). Nevertheless, the pooled RR significantly favoured combination therapy over monotherapy.

Table 4.64 Hospitalisation due to PAH for a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in all patients with PAH

Study ID	PDE-5i/ERA Follow-up period	n/N (%)		HR (95% CI)
		PDE-5i + ERA	ERA	
AMBITION[30]	Tadalafil/ambrisentan FAV: mean 74 weeks	19/253 (8%)	27/126 (21%)	0.32 (0.18, 0.58)
Zhuang 2014[50]	Tadalafil/ambrisentan 16 weeks	0/60 (0%)	2/64 (3%)	NR
Vizza 2017[49]	Sildenafil/bosentan 12 weeks	2/51 (4%)	2/53 (4%)	NR

CI = confidence interval; ERA = endothelin receptor antagonist; FAV = final assessment visit; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

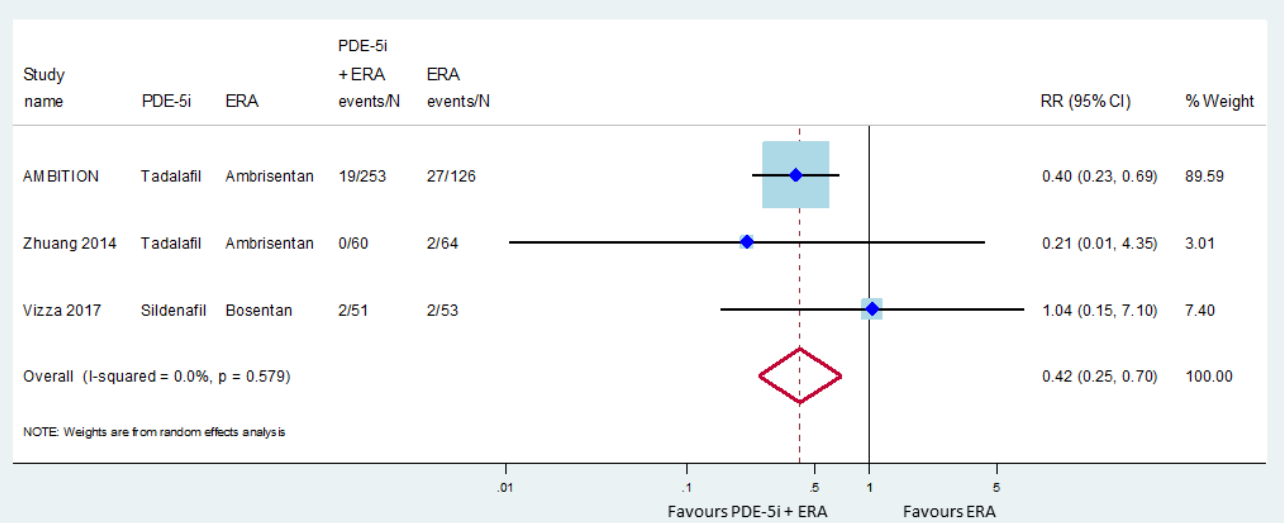


Figure 4.17 Forest plot showing the RR of being hospitalised due to worsening PAH while being treated with a PDE-5 inhibitor and an ERA compared with an ERA alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonist; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

d. Change in WHO FC from baseline

Four RCTs reported on the effectiveness of a PDE-5 inhibitor and an ERA compared with an ERA alone in improving WHO FC in PAH patients of any WHO FC and disease aetiology. The PHIRST trial also reported clinical worsening in IPAH/HPAH and PAH-CTD patient subgroups.

d.i PAH patients, irrespective of disease severity or aetiology

In three RCTs a greater proportion of patients receiving combination therapy improved their WHO FC over the study period compared with patients receiving monotherapy. However, in the PHIRST trial more patients in the monotherapy group improved compared to those in the combination therapy group (Table 4.65). More patients in the monotherapy group worsened compared with the combination therapy group in all four studies. Meta-analysis of the RR of improving the WHO FC when being treated with a PDE-5 inhibitor plus an ERA compared with an ERA alone showed no significant difference between the two treatment groups (Figure 4.18). However, the pooled RR for worsening of WHO FC favoured combination therapy over monotherapy with a 40% reduction in risk but did not quite reach statistical significance.

Table 4.65 The effectiveness of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in improving WHO FC in all patients with PAH

Study ID Follow-up period PDE-5i/ERA	Change in WHO FC	n/N (%)		RR (95% CI)
		PDE-5i + ERA	ERA	
AMBITION[30] 24 weeks Tadalafil/ambrisentan	Improved	94/252 (37%)	42/124 (34%)	1.10 (0.82, 1.48)
	Worsened	12/252 (5%)	9/124 (7%)	0.66 (0.28, 1.52)
PHIRST Barst et al (2011)[45] 16 weeks Tadalafil/bosentan	Improved	4/42 (10%)	11/45 (24%)	0.39 (0.13, 1.13)
	Worsened	4/42 (10%)	5/45 (11%)	0.86 (0.25, 2.98)
Zhuang 2014[50] 16 weeks Tadalafil/ambrisentan	Improved	26/60 (43%)	20/64 (31%)	1.39 (0.87, 2.21)
	Worsened	5/60 (8%)	12/64 (19%)	0.44 (0.17, 1.19)
Vizza 2017[49] 12 weeks Sildenafil/bosentan	Improved	10/51 (20%)	7/53 (13%)	1.48 (0.61, 3.60)
	Worsened	0/51 (0%)	1/53 (2%)	0 (not calculable)

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk; WHO = World Health Organization

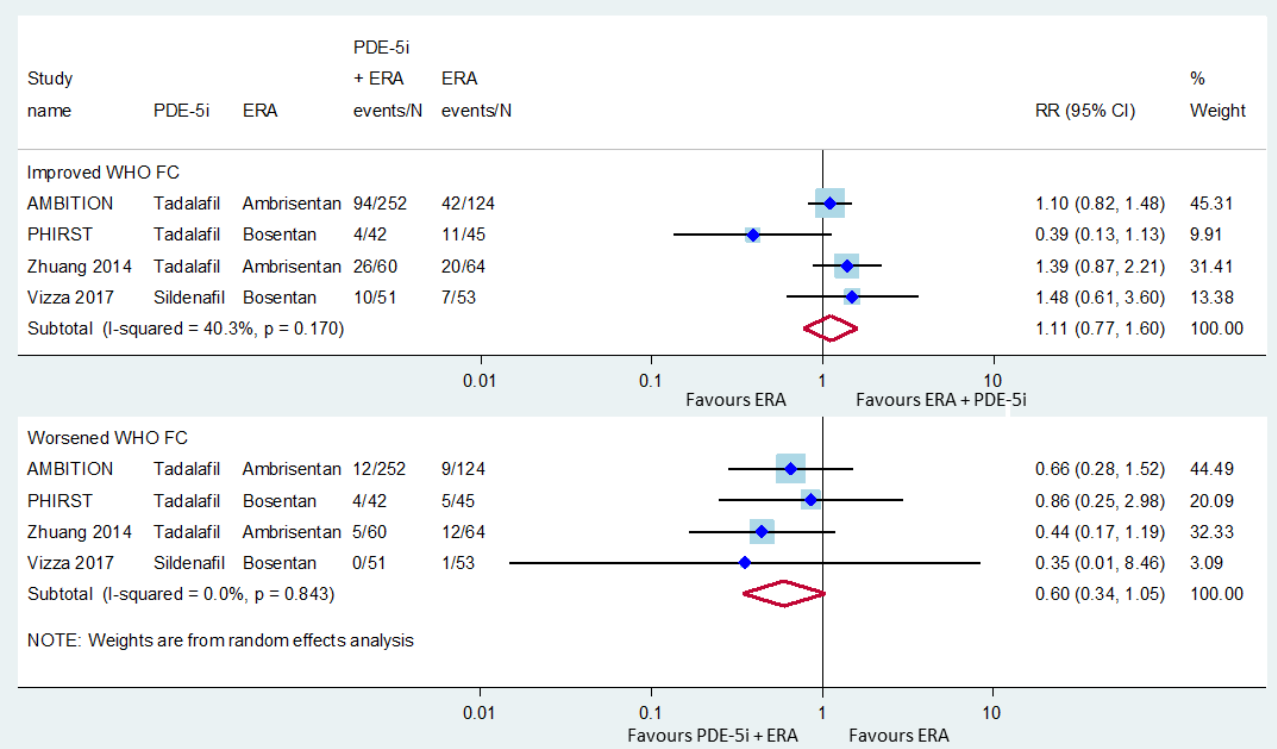


Figure 4.18 Forest plot showing the RR of improving or worsening the PAH WHO FC while being treated with a PDE-5 inhibitor and an ERA compared with an ERA alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk; WHO = World Health Organization

e. Change in 6MWD from baseline

Five RCTs reported on the effectiveness of PDE-5 inhibitor plus an ERA compared with placebo plus ERA in improving 6MWD in PAH patients of any WHO FC and disease aetiology. Two RCTs reported on the change in 6MWD for the WHO FC III/IV subgroup and two RCTs reported on the change in 6MWD in the IPAH/HPAH and PAH-CTD patient subgroups.

e.i PAH patients, irrespective of disease severity or aetiology

Three RCTs reported the mean or median change from baseline in 6MWD. All three of these studies showed a clinically significant improvement in the combination therapy group (over 40 m; Table 4.66) but not in the monotherapy group (18–27 m improvement). The mean difference between the combination therapy and monotherapy groups was statistically significant in two studies but only clinically significant in the Zhuang 2014 RCT.

The remaining two studies only reported the mean difference in 6MWD between the combination therapy and monotherapy groups. Only the Mainguy 2013 RCT showed a statistically significant difference in 6MWD favouring combination therapy over monotherapy but the distance was not clinically significant. The other study showed no difference in change in 6MWD for combination therapy compared with monotherapy over the 12-week study period.

Table 4.66 The effectiveness of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in improving 6MWD in all PAH patients

Study ID PDE-5i/ERA	N Follow-up period	Mean ± SD or median [IQR] baseline 6MWD, metres		Mean ± SD (95% CI) or median [IQR] change from baseline, metres		Mean difference (95% CI), metres
		PDE-5i + ERA	ERA	PDE-5i + ERA	ERA	
AMBITION[30] Tadalafil/ambrisentan	N=379 24 weeks	357.0 [292.0, 425.3]	368.5 [310.0, 427.5]	49.0 [4.6, 85.8]	27.0 [-14.0, 63.3]	22.0, p<0.001
PHIRST[12] Tadalafil/ bosentan	N=87 16 weeks	348.5 ± 84.9	360.9 ± 75.3	40.2 (23.1, 57.2)	18.8 (0.5, 37.2)	22.7 (–2.4, 47.8), p=0.076
Zhuang 2014[50] Tadalafil/ambrisentan	N=124 16 weeks	NR	NR	54.4 [30.2, 90.1]	18.3 [4.3, 34.8]	36.1, p<0.05
Mainguy 2013[39] [a] Sildenafil/ERA	N=20 4 weeks	NR	NR	NR	NR	18 (1, 24), p=0.02
Vizza 2017[49] Sildenafil/bosentan	N=104 12 weeks	NR	445 ± 97	NR	440 ± 98	–2.4, p=0.6 (90% CI –21.8, 17.1)

[a] 2 patients in the cross-over study had epoprostenol background therapy
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; IQR = interquartile range; N = number of patients; NR = not reported; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; SD = standard deviation

e.ii PAH patients with FC III or IV

Two studies reported on the change in 6MWD for patients with WHO FC III/IV PAH from baseline (Table 4.67). In both studies patients receiving either combination therapy or monotherapy showed an improvement in 6MWD, and although the median improvement was larger for those receiving combination therapy, the distance did not quite reach clinically importance (35 m, see Section 4.3.5).

Table 4.67 The effectiveness of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in improving 6MWD in patients with FC III/IV PAH

Study ID PDE-5i/ERA	N Follow-up period	Median baseline 6MWD, metres		Median change from baseline (95% CI), metres		Mean difference (95% CI), metres
		PDE-5i + ERA	ERA	PDE-5i + ERA	ERA	
PHIRST Barst et al (2011)[45] Tadalafil/bosentan	N=54 16 weeks	NR	NR	30.0 (12.7, 68.5)	16.5 (–5.6, 43.0)	13.5
Zhuang 2014[50] Tadalafil/ambrisentan	N=53 16 weeks	NR	NR	33.8 (10.9, 57.5)	13.7 (–8.7, 47.3)	20.1, p=0.136

6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; NR = not reported; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; SD = standard deviation; WHO = World Health Organization

e.iii PAH patients with different disease aetiologies

Two studies reported on the change in 6MWD for patients with either IPAH/HPAH or PAH-CTD from baseline (Table 4.68), but Vizza 2017 only depicted the change in 6MWD in a graph (Figure 4.19). Patients with IPAH/HPAH receiving combination therapy had a greater improvement in 6MWD than those receiving monotherapy in both studies, but the difference was not clinically important. In the PHIRST trial. Patients with PAH-CTD receiving combination therapy also improved their 6MWD by more than those receiving monotherapy. However, in the Vizza 2017 study, patients with PAH-CTD receiving combination therapy performed poorly, with a decreased 6MWD, compared to an increase in those receiving monotherapy (Figure 4.19).

Table 4.68 The effectiveness of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in improving 6MWD in patients with different PAH aetiologies

Study ID PDE-5i/ERA	N Follow-up period	Mean baseline 6MWD, metres		Median change from baseline (95% CI), metres		Mean difference, metres
		PDE-5i + ERA	ERA	PDE-5i + ERA	ERA	
PHIRST Barst et al (2011)[45] Tadalafil/ bosentan	16 weeks IPAH/HPAH (N=53) PAH-CTD (N=17)	NR NR	NR NR	32.1 (7.4, 56.0) 22.0 (−8.0, 70.9)	23.5 (−1.6, 46.1) 1.3 (−49.6, 40.0)	8.6 20.7
Vizza 2017[49] Sildenafil/ bosentan	12 weeks IPAH/HPAH (n=67) PAH-CTD (n=35)	NR NR	NR NR	NR NR	NR NR	13.6 (90% CI −10.0, 37.1) −34.1 (90% CI −67.4, −0.8)

6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; HPAH = heritable PAH; IPAH = idiopathic PAH; NR = not reported; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor

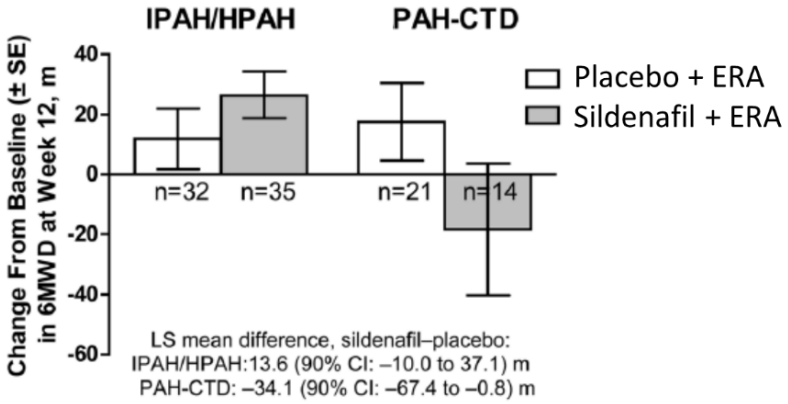


Figure 4.19 Mean (±SE) change from baseline to week 12 in 6MWD by PAH aetiology

6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; HPAH = heritable PAH; IPAH = idiopathic PAH; LS = least square; n = number of patients; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; SE = standard error
Source: Vizza et al (2017)[49]

f. Change in QoL from baseline

None of the RCTs reported on the change in QoL for patients treated with a PDE-5 inhibitor and an ERA compared with those treated with an ERA alone.

g. Change in haemodynamic parameters from baseline

g.i PAH patients, irrespective of disease severity or aetiology

The Zhuang 2014 study reported the change in PVR and mPAP over the 16-week study period (Table 4.69). In this study, patients receiving combination therapy showed twice the improvement compared to those in the monotherapy group, but this difference was not statistical significance and is unlikely to be clinically important.

Table 4.69 The effectiveness of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in improving haemodynamic parameters in all PAH patients

Study ID PDE-5 inhibitor/ERA Study period N	Haemodynamic parameter[a]	Mean ± SD baseline haemodynamic parameters		Mean ± SD value at 16 weeks (% change from baseline)		Mean % difference
		PDE-5i + ERA	ERA	PDE-5i + ERA	ERA	
Zhuang 2014[50] Tadalafil/ambrisentan 16 weeks N=124	PVR (dyn*sec*cm^{-5})	837 ± 389	843 ± 423	623 ± 365 (−26.7%)	735 ± 375 (−12.8%)	−13.9%
	mPAP (mmHg)	50 ± 12	53 ± 9	43 ± 8 (−14.2%)	50 ± 10 (−5.7%)	−8.5%

[a] A decrease in PVR or mPAP indicates improvement in haemodynamic parameters
ERA = endothelin receptor antagonist; mPAP = mean pulmonary artery pressure; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; PVR = pulmonary vascular resistance; SD = standard deviation

h. Comparative safety

Four RCTs reported on the comparative safety of PDE-5 inhibitor plus an ERA combination therapy compared with ERA monotherapy in PAH patients of any WHO FC and disease aetiology. The AMBITION trial also reported on the comparative safety of dual and mono therapy in the PAH-CTD patient subgroup.

h.i PAH patients, irrespective of disease severity or aetiology

Four studies reported on the proportion of any AE, serious AEs, AEs leading to discontinuation of study treatment and/or treatment-related AEs occurring in patients receiving combination therapy with compared with those on monotherapy (Table 4.70). There were no statistically significant differences between the two treatment arms in any study (Figure 4.20). All AEs reported by these studies have been previously noted to occur among patients taking either a PDE-5 inhibitor or an ERA.

Table 4.70 The comparative safety of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in all patients with PAH

Study ID Follow-up period PDE-5i/ERA	AE	n/N (%)		RR (95% CI)
		PDE-5i + ERA	ERA	
AMBITION[30] FAV: mean 74 weeks Tadalafil/ambrisentan	Serious AEs Discontinuation due to AEs	92/253 (36%) 31/253 (12%)	45/126 (36%) 14/126 (11%)	1.02 (0.77, 1.35) 1.10 (0.61, 2.00)
PHIRST Barst et al (2011)[45] 16 weeks Tadalafil/bosentan	Any AEs	39/42 (93%)	38/45 (84%)	1.10 (0.95, 1.28)
Zhuang 2014[50] 16 weeks Tadalafil/ambrisentan	Discontinuation due to AEs	3/60 (5%)	0/64 (0%)	Not calculable
Vizza 2017[49] 12 weeks Sildenafil/bosentan	Any AE Treatment-related AEs Serious AEs Treatment-related serious AEs	34/50 (68%) 17/50 (34%) 9/50 (18%) 1/50 (2%)	41/53 (77%) 13/53 (25%) 12/53 (23%) 0/53 (0%)	0.88 (0.69, 1.12) 1.39 (0.75, 2.55) 0.80 (0.37, 1.72) Not calculable

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FAV = final assessment visit; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

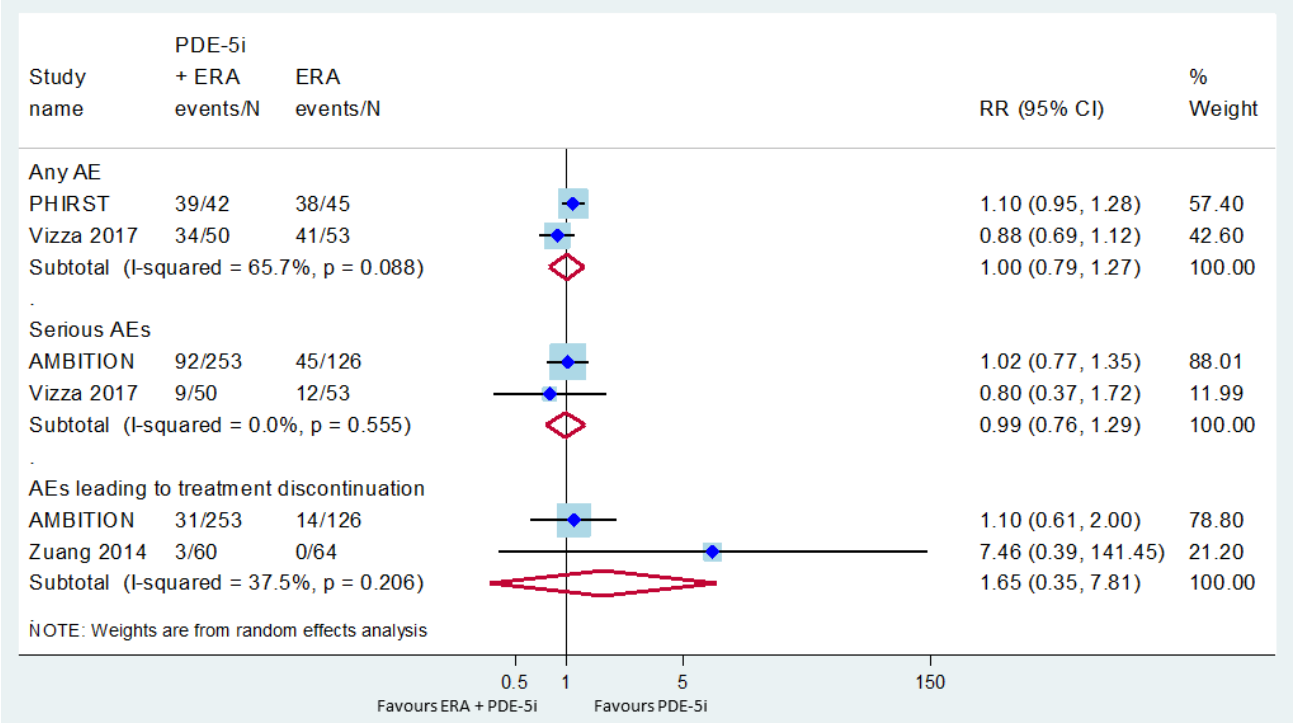


Figure 4.20 Forest plot showing the RR of having an AE, serious AE or an AE leading to treatment discontinuation while being treated with a PDE-5 inhibitor and an ERA compared with ERA alone in all PAH patients

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonists; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

h.iii PAH patients with different disease aetiologies

The AMBITION trial reported no statistically significant difference in the proportion of patients with PAH-CTD receiving combination therapy who had an AE, serious AE or an AE leading to discontinuation of study treatment compared with those on monotherapy, although the point estimate of RR for serious AEs (1.28; 95% CI 0.80, 2.04) suggests possible safety concerns in the use of combination therapy in patients with PAH-CTD (Table 4.71).

Table 4.71 The comparative safety of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy in patients with different PAH aetiologies

Study ID Follow-up period PDE-5i/ERA	AE	n/N (%)		RR (95% CI)
		PDE-5i + ERA	ERA	
AMBITION Coghlan et al (2016)[31] FAV: mean 74 weeks Tadalafil/ambrisentan	PAH-CTD Any AE Serious AEs Discontinuation due to AE	 102/103 (99%) 45/103 (44%) 14/103 (14%)	 42/44 (95%) 15/44 (34%) 8/44 (18%)	 1.04 (0.97, 1.11) 1.28 (0.80, 2.04) 0.75 (0.34, 1.65)

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FAV = final assessment visit; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

4.4.3.4 PDE-5 inhibitor in addition to prostanoid

The PACES-1[41] double-blind trial reported on the effectiveness of a PDE-5 inhibitor in addition to a prostanoid in treating PAH compared with placebo plus a prostanoid. Patients with IPAH, PAH-CTD, PAH-CHD or PAH associated with anorexigen use who were receiving long-term intravenous epoprostenol therapy were randomised to receive combination therapy with sildenafil plus epoprostenol, or monotherapy with placebo plus epoprostenol for 16 weeks. Randomisation was stratified by the baseline 6MWD (<325 m or ≥325 m) and aetiology of PAH (IPAH or other causes). The baseline characteristics for the two treatment groups were similar for demographic, WHO FC and haemodynamic assessments. The trial had a low risk of bias.

a. Study-defined clinical worsening

In the PACES-1 trial, clinical worsening was defined as death, lung transplantation, hospitalisation due to PAH, initiation of bosentan therapy, or change in epoprostenol dose of >10% due to clinical deterioration.

a.i PAH patients, irrespective of disease severity or aetiology

Patients receiving epoprostenol monotherapy had a statistically significant 3-fold greater risk of experiencing a clinical worsening event than those receiving sildenafil plus epoprostenol combination therapy (Table 4.72; ARD = −12.4%; 95% CI −20.1, −4.6; p = 0.002). The NNT indicates that for every nine patients treated with PDE-5 inhibitor plus prostanoid combination therapy one additional clinical worsening event was prevented compared with prostanoid monotherapy.

Table 4.72 The effectiveness of a PDE-5 inhibitor in addition to a prostanoid compared with prostanoid monotherapy in preventing clinical worsening in all PAH patients

Study ID	Follow-up period PDE-5i/prostanoid	n/N (%)		RR (95% CI)
		PDE-5i + prostanoid	Prostanoid	
PACES-1[41]	16 weeks Sildenafil/epoprostenol	8/134 (6%)	24/131 (18%)	0.33 (0.15, 0.70)

CI = confidence interval; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

b. All-cause mortality

b.i PAH patients, irrespective of disease severity or aetiology

The patients in the combination therapy group were less likely to die than those receiving monotherapy but the RR was not calculable (Table 4.73; ARD = −5.3%; 95% CI −9.2, −1.5; p = 0.007). The NNT indicates that for every 19 patients treated with ERA plus prostanoid combination therapy one additional death was prevented compared with prostanoid monotherapy.

Table 4.73 Mortality rates for a PDE-5 inhibitor in addition to a prostanoid compared with prostanoid monotherapy in all PAH patients

Study ID	Follow-up period PDE-5i/prostanoid	n/N (%)		RR (95% CI)
		PDE-5i + prostanoid	Prostanoid	
PACES-1[41]	16 weeks Sildenafil/epoprostenol	0/134 (0%)	7/131 (5%)	0 (not calculable)

CI = confidence interval; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

c. Hospitalisation due to worsening PAH

c.i PAH patients, irrespective of disease severity or aetiology

There was no significant difference in hospitalisation rates due to PAH between patients receiving combination therapy and those receiving monotherapy, although the point estimate favoured combination therapy (Table 4.74; ARD = −2.4%; 95% CI −8.6, −3.8; p = 0.44). The NNT indicates that 42 patients would need to be treated with combination therapy to prevent one additional death compared to monotherapy.

Table 4.74 Hospitalisation due to PAH for a PDE-5 inhibitor in addition to a prostanoid compared with prostanoid monotherapy in all patients with PAH

Study ID	PDE-5i/prostanoid Follow-up period	n/N (%)		RR (95% CI)
		PDE-5i + prostanoid	Prostanoid	
PACES-1[41]	Sildenafil/epoprostenol 16 weeks	8/134 (6%)	11/131 (8%)	0.71 (0.30, 1.71)

CI = confidence interval; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk

d. Change in WHO FC from baseline

The number of patients who had a change in their WHO FC after combination treatment compared with monotherapy was not reported for the PACES-1 trial.

e. Change in 6MWD from baseline

e.i PAH patients, irrespective of disease severity or aetiology

Patients receiving combination therapy improved their 6MWD by 30 m compared to a 1 m improvement in the monotherapy group. However, the improvement in 6MWD was not clinically important (Table 4.75).

Table 4.75 The effectiveness of a PDE-5 inhibitor in addition to a prostanoid compared with prostanoid monotherapy in improving 6MWD in all PAH patients

Study ID PDE-5i/prostanoid	N Follow-up period	Mean ± SD baseline 6MWD, metres		Mean change from baseline (95% CI), metres		Mean difference (95% CI), metres
		PDE-5i + prostanoid	Prostanoid	PDE-5i + prostanoid	Prostanoid	
PACES-1[41] Sildenafil/epoprostenol	N=267 16 weeks	348.9 ± 71.4	341.6 ± 77.3	29.8 (18.5, 41.2)	1 (−10.9, 12.9)	28.8 (13.9, 43.8), p<0.001

6MWD = 6-minute walk distance; CI = confidence interval; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; SD = standard deviation

f. Change in QoL from baseline

The number of patients whose QoL changed after combination treatment compared with monotherapy was not reported for the PACES-1 trial.

g. Change in haemodynamic parameters from baseline

g.i PAH patients, irrespective of disease severity or aetiology

The PACES-1 trial reported the change in PVR, mPAP and mRAP over the 6-month study period (Table 4.76). Patients receiving combination therapy showed improvement in all three parameters compared with no improvement or worsening in those receiving monotherapy. The difference was statistically significant (non-overlapping 95% CIs) for all three parameters and may be clinically important for PVR and mRAP.

Table 4.76 The effectiveness of a PDE-5 inhibitor in addition to a prostanoid compared with prostanoid monotherapy in improving haemodynamic parameters in all PAH patients

Study ID PDE-5i/ prostanoid Study period/N	Haemodynamic parameter[a]	Mean baseline haemodynamic parameters (95% CI)		Mean change from baseline (95% CI) [% change from baseline]		Mean % difference (95% CI)
		PDE-5i + prostanoid	Prostanoid	PDE-5i + prostanoid	Prostanoid	
PACES-1[41] Sildenafil/ epoprostenol 16 weeks/N=265	PVR (dyn*sec*cm^{-5})	850 (778, 922)	712 (635, 790)	−151 (−208, −93) [−17.8%]	22 (−37, 81) [3.1%]	−20.8%
	mPAP (mmHg)	52.5 (50.5, 54.4)	50.4 (48.0, 52.9)	−2.8 (−4.2, −1.4) [−5.3%]	1.1 (−0.4, 2.6) [2.2%]	−7.5%
	mRAP (mmHg)	8.9 (7.9, 9.9)	7.9 (7.0, 8.8)	−0.8 (−1.8, 0.1)	1.2 (0.2, 2.2)	−2.1 mmHg (−3.3, −0.9)

[a] A decrease in PVR, mPAP or mRAP indicates improvement in haemodynamic parameters.
CI = confidence interval; CSR = clinical study report; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; PVR = pulmonary vascular resistance; SD = standard deviation

h. Comparative safety

h.i PAH patients, irrespective of disease severity or aetiology

The proportion of patients who has an AE, a serious AE or an AE leading to discontinuation of study treatment did not differ between the combination therapy and monotherapy groups (Table 4.77). Although 3-times more patients receiving sildenafil as part of the combination therapy had blurred vision compared to patients in the epoprostenol monotherapy group, the difference did not reach statistical significance.

Table 4.77 The comparative safety of a PDE-5 inhibitor in addition to a prostanoid compared with prostanoid monotherapy in all patients with PAH

Study ID Follow-up period PDE-5i/prostanoid	AE	n/N (%)		RR (95% CI)
		PDE-5i + prostanoid	Prostanoid	
PACES-1[41] 16 weeks Sildenafil/ epoprostenol	Any AE	124/134 (93%)	128/131 (98%)	0.95 (0.90, 1.00)
	Serious AEs	29/134 (22%)	39/131 (30%)	0.73 (0.48, 1.10)
	Discontinuation due to AE	7/134 (5%)	14/131 (11%)	0.49 (0.20, 1.17)
	Relate to sildenafil: blurred vision	6/134 (5%)	2/131 (2%)	2.93 (0.60, 14.27)

AE = adverse event; CI = confidence interval; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RR = relative risk; SD = standard deviation; WHO = World Health Organization

4.4.3.5 Prostanoid in addition to ERA

Two RCTs reported on the effectiveness of a prostanoid in addition to an ERA in treating PAH compared with placebo plus an ERA.

The COMBI[36] open-label, RCT was performed to assess the safety and efficacy of inhaled iloprost in patients with WHO FC III IPAH who were already being treated with bosentan for a 12-week period. The trial was terminated early after a futility analysis predicted failure with respect to the pre-determined sample size. The baseline characteristics for the two treatment groups were similar for demographic and haemodynamic parameters. This study had a high risk of bias, mainly due to the lack of blinding.

The STEP[48] double-blind trial randomised patients with PAH already receiving treatment with bosentan to either iloprost inhalation or placebo for a 12-week period. Randomisation was stratified according to PAH aetiology (IPAH or PAH associated with CTD, CHD, HIV or anorexigen use). Nearly all included patients had NYHA FC III/IV (generally equivalent to WHO FC III/IV) PAH; one patient randomised to monotherapy had NYHA FC II (generally equivalent to WHO FC II) PAH. The baseline characteristics for the two treatment groups were similar for demographic, FC and haemodynamic assessments. However, the monotherapy group had more patients with IPAH (61% versus 50%) and fewer patients with PAH associated with CTD, CHD, HIV or anorexigen use (39% versus 50%). The trial had a low risk of bias.

As, both studies only enrolled patients with FC III/IV PAH, all reported outcomes are relevant to this patient subgroup.

a. Study-defined clinical worsening

Although the composite endpoint of clinical worsening in both RCTs included death, hospitalisation and symptomatic progression of PAH, the definition of these components differed (eg all-cause mortality vs PAH-related mortality and hospitalisation due to right-heart failure vs any hospitalisation) (see Section 4.3.5 for further details).

a.ii PAH patients with WHO FC III or IV

In the COMBI trial, the proportion of patients receiving combination therapy who experienced clinical worsening did not differ significantly from those receiving monotherapy (Table 4.78; ARD = −3.3%; 95% CI −26.7, 20.2; p = 0.79). More patients in the monotherapy group experienced clinical worsening in the monotherapy group compared to the combination therapy group in the STEP trial but the RR could not be calculated (ARD = −15.2%; 95% CI −27.4, −2.9; p = 0.02). Thus, between seven (STEP) and 31 (COMBI) patients with WHO FC III/IV PAH need to be treated with prostanoid plus ERA combination therapy to prevent clinical worsening in one additional patient compared with ERA monotherapy. The pooled RR point estimate favoured combination therapy over monotherapy, with a 60% reduction in clinical worsening events, but the 95% CI indicated that there could also be the opposite effect (Figure 4.21).

Table 4.78 The effectiveness of a prostanoid in addition to an ERA compared with ERA monotherapy in preventing clinical worsening in patients with WHO FC III/IV PAH

Study ID	Follow-up period Prostanoid/ERA	n/N (%)		RR (95% CI)
		Prostanoid + ERA	ERA	
COMBI[36] (WHO FC III)	Iloprost/bosentan 16 weeks	3/19 (16%)	4/21 (19%)	0.83 (0.21, 3.24)
STEP[48] (WHO FC III/IV)	Iloprost/bosentan 12 weeks	0/32 (0%)	5/33 (15%)[a]	0 (not calculable)

[a] One patient in the monotherapy group had WHO FC II PAH
CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organisation

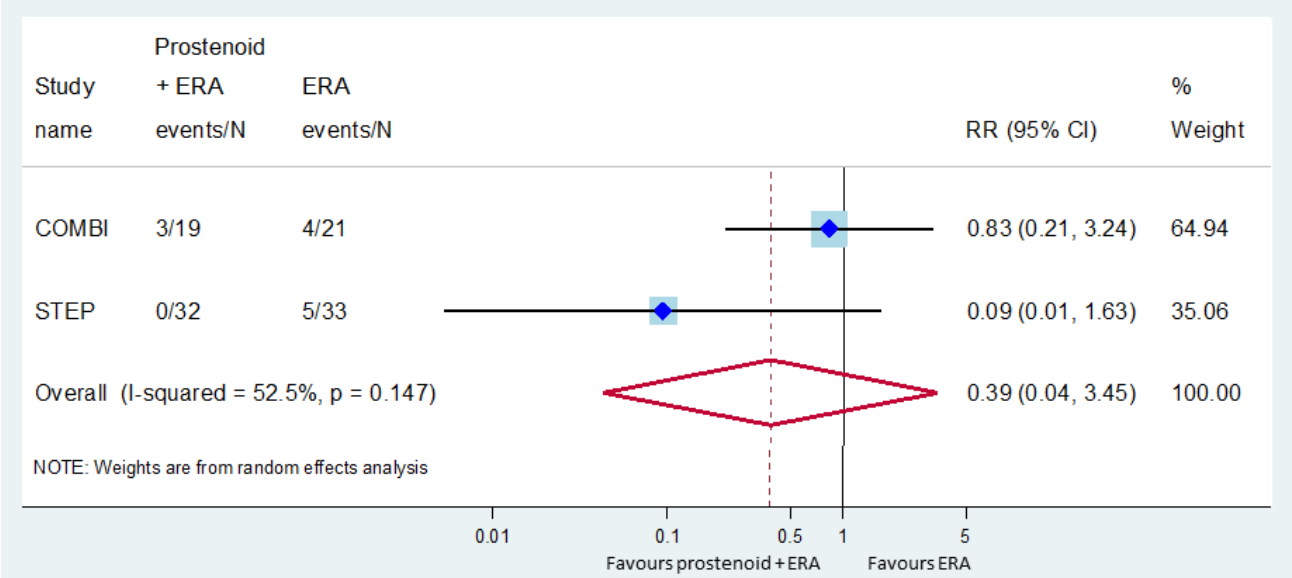


Figure 4.21 Forest plot showing the RR of having a clinical worsening event while being treated with a prostanoid and an ERA compared with an ERA alone in all PAH patients

CI = confidence interval; ERA = endothelin receptor antagonist; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk

b. All-cause mortality

b.ii PAH patients with FC III or IV

In both COMBI and STEP, no patients died during the study period (Table 4.79). Thus, the effect of prostanoid plus ERA combination therapy compared with ERA monotherapy on mortality rates cannot be determined.

Table 4.79 Mortality rates for a prostanoid in addition to an ERA compared with ERA monotherapy in patients with WHO FC III/IV PAH

Study ID	Follow-up period Prostanoid/ERA	n/N (%)		RR (95% CI)
		Prostanoid + ERA	ERA	
COMBI[36] (WHO FC III)	Iloprost/bosentan 16 weeks	0/19 (0%)	0/21 (0%)	Not calculable
STEP[48] [a] (WHO FC III/IV)	Iloprost/bosentan 12 weeks	0/32 (0%)	0/33 (0%)	Not calculable

[a] One patient in the monotherapy group had WHO FC II PAH
CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

c. Hospitalisation due to worsening PAH

c.ii PAH patients with FC III or IV

The COMBI trial reported that no patients were hospitalised for worsening PAH during the study period and the STEP study reported that four patients in the monotherapy group were hospitalised for worsening PAH (Table 4.80). As no patients in the combination therapy group died, the RR could not be calculated (pooled ARD = −5.5%; 95% CI −18.9, 7.8; p = 0.08). Thus, 19 patients with WHO FC III/IV PAH need to be treated with prostanoid plus ERA combination therapy to avoid hospitalisation in one additional patient compared with ERA monotherapy.

Table 4.80 Hospitalisation due to PAH for a prostanoid in addition to an ERA compared with ERA monotherapy in patients with WHO FC III/IV PAH

Study ID	Follow-up period Prostanoid/ERA	n/N (%)		RR (95% CI)
		Prostanoid + ERA	ERA	
COMBI[36] (WHO FC III)	Iloprost/bosentan 16 weeks	0/19 (0%)	0/21 (0%)	Not calculable
STEP[48] (WHO FC III/IV)	Iloprost/bosentan 12 weeks	0/32 (0%)	4/33 (12%)[a]	0 (not calculable)

[a] One patient in the monotherapy group had WHO FC II PAH
CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

d. Change in WHO FC from baseline

d.ii PAH patients with FC III or IV

The results from the STEP trial indicate that patients receiving prostanoid plus ERA combination therapy are almost 6 times more likely to improve in WHO FC than those receiving ERA monotherapy (Table 4.81; ARD = 28.3%; 95% CI 1.0, 46.7; p = 0.004). Only one patient, who was in the monotherapy group, worsened in WHO FC during the study period. Thus, the RR of clinical worsening could not be calculated (ARD = −3.0%; 95% CI −8.9, 2.8; p = 0.32). Overall, four patients with WHO FC III/IV PAH need to be treated with prostanoid plus ERA combination therapy for one additional patient to improve their WHO FC compared with ERA monotherapy, and 34 need to be treated to prevent worsening of WHO FC in one additional patient.

Table 4.81 The effectiveness of a prostanoid in addition to an ERA compared with ERA monotherapy in improving WHO FC in patients with WHO FC III/IV PAH

Study ID Follow-up period Prostanoid/ERA	Change in WHO FC	n/N (%)		RR (95% CI)
		Prostanoid + ERA	ERA	
STEP[48] [a] 12 weeks Iloprost/bosentan	Improved Worsened	11/32 (34%) 0/32 (0%)	2/33 (6%) 1/33 (3%)	5.67 (1.36, 23.61) 0 (not calculable)

[a] One patient in the monotherapy group had WHO FC II PAH
CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

e. Change in 6MWD from baseline

e.ii PAH patients with FC III or IV

There was a mean improvement in the 6MWD for patients receiving combination therapy in both studies, whereas the 6MWD for patients receiving monotherapy did not change (Table 4.82). However, the improvement was not clinically important.

Table 4.82 The effectiveness of a prostanoid in addition to an ERA compared with ERA monotherapy in improving 6MWD in patients with WHO FC III/IV PAH

Study ID Prostanoid/ ERA	N Follow-up period	Mean ± SD baseline 6MWD, metres		Mean ± SD change from baseline, metres		Mean difference, metres
		Prostanoid + ERA	ERA	Prostanoid + ERA	ERA	
COMBI[36] Iloprost/bosentan	N=40 WHO FC III 16 weeks	317 ± 74	296 ± 79	9 ± 100	−1 ± 27	10, p=0.49
STEP[48] [a] Iloprost/bosentan	N=65 WHO FC III/IV 12 weeks	336 ± 61	340 ± 73	30 ± 60	4 ± 61	26, p=0.051

[a] One patient in the monotherapy group had WHO FC II PAH
6MWD = 6-minute walk distance; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; SD = standard deviation; WHO = World Health Organization

f. Change in QoL from baseline

f.ii PAH patients with FC III or IV

The COMBI trial investigated the QoL of all included patients using EuroQoL visual analogue scale (EQ-VAS) (Table 4.83). The visual analogue scale measures a patients perceived health state on a 20 cm vertical scale, where 0 represents the "worst health you can imagine" and 100 represents "the best health you can imagine". Two studies investigating the use of the EQ-VAS for assessing changes in QoL for patients with COPD reported a minimum important difference of 6.5−8.0 points[85, 86]. In the COMBI trial, patients receiving combination therapy improved their QoL by 7 points compared to those receiving monotherapy, whose QoL decreased by 3 points. The mean improvement in QoL for patients receiving combination therapy compared with those on monotherapy was 10 points, which is a clinically important difference.

Table 4.83 The effectiveness of a prostanoid in addition to an ERA compared with ERA monotherapy in improving QoL in patients with WHO FC III/IV PAH

Study ID Prostanoid/ ERA	Questionnaire Follow-up period	Mean ± SD baseline QoL		Mean ± SD change from baseline		Mean difference, points
		Prostanoid + ERA	ERA	Prostanoid + ERA	ERA	
COMBI[36] Iloprost/bosentan	EQ-VAS [a] 16 weeks WHO FC III	n=19 40 ± 17	n=21 48 ± 16	+7 ± 19	–3 ± 11	10

[a] EQ-VAS scores range from 0 to 100. A higher score represents better QoL.
CI = confidence interval; ERA = endothelin receptor antagonist; EQ-VAS = EuroQoL visual analogue scale; FC = functional class; PAH = pulmonary arterial hypertension; QoL = quality of life; SD = standard deviation; WHO = World Health Organization

g. Change in haemodynamic parameters from baseline

g.ii PAH patients with FC III or IV

The STEP trial reported the change in PVR and mPAP over the 12-week study period (Table 4.84). In this study, patients receiving combination therapy showed improvement compared with no improvement or worsening in those receiving monotherapy. The difference was statistically significant and may be clinically important.

Table 4.84 The effectiveness of a prostanoid in addition to an ERA compared with ERA monotherapy in improving haemodynamic parameters in WHO FC III/IV PAH

Study ID Prostanoid/ ERA Study period N	Haemodynamic parameter[a]	Mean ± SD baseline haemodynamic parameter		Mean change from baseline (% change from baseline)		Mean % difference
		Prostanoid + ERA	ERA	Prostanoid + ERA	ERA	
STEP[48] [b] Iloprost/bosentan 12 weeks N=65	PVR (dyn*sec*cm^{-5}) mPAP (mmHg)	815 ±381 51 ± 11	783 ± 378 52 ± 13	−164 (−20.1%) −6 (−11.8%)	81 (10.3%) 2 (3.8%)	−30.4%, p=0.007 −15.6%, p=0.001

[a] A decrease in PVR or mPAP indicates improvement in haemodynamic parameters.
[b] One patient in the monotherapy group had WHO FC II PAH
CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; mPAP = mean pulmonary artery pressure; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; SD = standard deviation; WHO = World Health Organization

h. Comparative safety

h.ii PAH patients with FC III or IV

The proportion of patients who has an AE, a serious AE or an AE leading to discontinuation of study treatment did not differ significantly between the combination therapy and monotherapy groups (Table 4.85). However, in the COMBI trial 6-times as many patients in the combination therapy group had an AE compared to the monotherapy group (ARD = 26.8%; 95% CI 4.0, 49.6; p = 0.026). The pooled RR point estimate favoured ERA monotherapy over combination therapy but the 95% CIs were very wide and indicated that there could also be the opposite effect (Figure

4.22). The RR for AEs leading to discontinuation of treatment could not be calculated (ARD = 5.2%; 95% CI −4.8, 15.3; p = 0.29).

Table 4.85 The comparative safety of a prostanoid in addition to an ERA compared with ERA monotherapy in patients with WHO FC III/IV PAH

Study ID Follow-up period Prostanoid/ERA	AE	n/N (%)		RR (95% CI)
		Prostanoid + ERA	ERA	
COMBI[36] 16 weeks Iloprost/bosentan	Any AE Discontinuation due to intractable coughing	6/19 (32%) 1/19 (5%)	1/21 (5%) 0/21 (0%)	6.63 (0.88, 50.19) Not calculable
STEP[48 a] 12 weeks Iloprost/bosentan	Any AE Serious AEs Related to study drug	35/35 (100%) 5/35 (14%) 2/35 (6%)	29/32 (91%) 7/32 (22%) 1/32 (3%)	1.10 (0.97, 1.25) 0.65 (0.23, 1.85) 1.83 (0.17, 19.21)

[a] One patient in the monotherapy group had WHO FC II PAH
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; WHO = World Health Organization

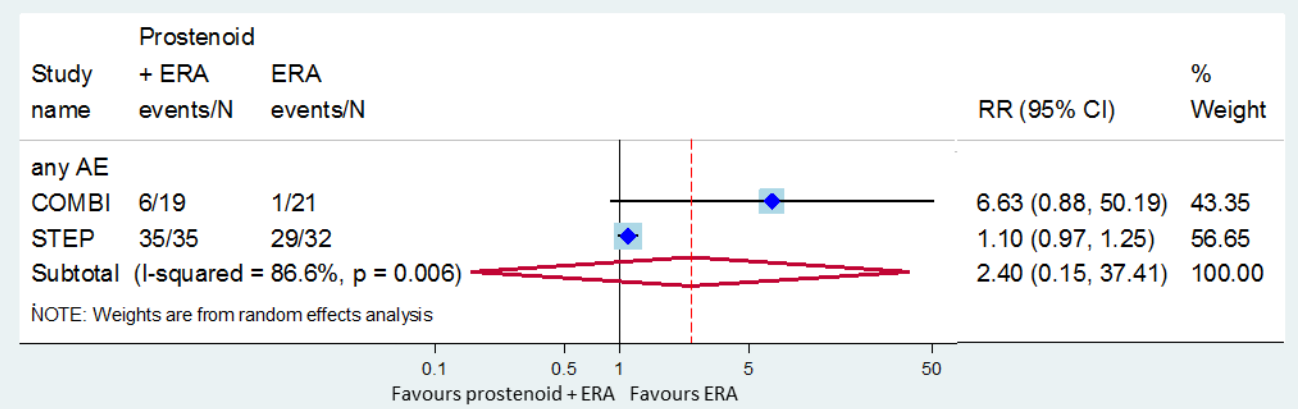


Figure 4.22 Forest plot showing the RR of having an AE while being treated with a prostanoid and an ERA compared with ERA alone in patients with WHO FC III/IV PAH

AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonists; FC = functional class; N = number of patients; RR = relative risk; WHO = World Health Organization

4.4.3.6 sGC stimulator in addition to ERA

Only one RCT was identified that reported on the effectiveness of a sGC stimulator plus an ERA in treating PAH compared with placebo plus ERA in patients with PAH. The PATENT-1[23] double-blind trial, with a low-to-moderate risk of bias, randomised PAH patients of any WHO FC, with or without background ERA or prostanoid therapy, to receive riociguat or placebo for 12 weeks. Approximately 44% of included patients were using an ERA drug (primarily bosentan) at baseline. The baseline characteristics for the riociguat plus ERA and placebo plus ERA subgroups were well balanced with respect to age and gender, but the combination therapy group had a larger proportion of patients with WHO FC III PAH (65% versus 55%) and the monotherapy group had more patient with WHO FC II PAH (43% versus 33%). The baseline haemodynamic parameters and the proportion of patients having different PAH aetiologies was not reported for this subgroup. Data was reported for all PAH patients and patients with WHO FC III/IV PAH who had background

ERA treatment, in the CSR (highlighted in green below). For the WHO FC III/IV PAH subgroup, 12/87 (14%) patients were treated with a prostanoid instead of an ERA.

a. Study-defined clinical worsening

In the PATENT-1 study, clinical worsening was defined as all-cause mortality, heart/lung transplantation, atrial septostomy, start of new PAH treatment (ERA, prostanoid or PDE-5 inhibitor), modification of a pre-existing prostanoid treatment, hospitalisation due to PAH, persistent decrease in 6MWD, or persistent worsening of WHO FC due to worsening of PAH.

a.i PAH patients, irrespective of disease severity or aetiology

Patients who received combination therapy were [redacted] to experience a clinical worsening event than those on monotherapy (Table 4.86), but this difference was not statistically [redacted] ARD = [redacted] The NNT indicates that [redacted] patients need to be treated with [redacted] to prevent clinical worsening in one additional patient compared with [redacted].

Table 4.86 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in preventing clinical worsening in all PAH patients

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + ERA	ERA	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase stimulator

a.ii PAH patients with FC III or IV

Patients with WHO FC III/IV PAH who received combination therapy were [redacted] to experience a clinical worsening event than those on monotherapy (Table 4.87), [redacted] ARD = [redacted] Among patients with WHO FC III/IV PAH, [redacted] need to be treated with [redacted] to prevent clinical worsening in one additional patient compared with [redacted].

Table 4.87 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in preventing clinical worsening in patients with WHO FC III/IV PAH

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + ERA	ERA	
PATENT-1[a] CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

[a] 14% of patients had background prostanoid therapy
CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

b. All-cause mortality

b.i PAH patients, irrespective of disease severity or aetiology

Patients who received combination therapy were [redacted] to die than those on monotherapy (Table 4.88), [redacted] ARD = [redacted]; [redacted] Thus, [redacted] patients need to be treated with [redacted] to prevent one additional death compared with [redacted].

Table 4.88 Mortality rates for a sGC stimulator in addition to an ERA compared with ERA monotherapy in all PAH patients

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + ERA	ERA	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase stimulator

b.ii PAH patients with FC III or IV

Patients with WHO FC III/IV PAH who received combination therapy were [redacted] to die than those on monotherapy (Table 4.89; ARD = [redacted] Among patients with WHO FC III/IV PAH, [redacted] need to be treated with [redacted] to prevent one additional death compared with [redacted].

Table 4.89 Mortality rates for a sGC stimulator in addition to an ERA compared with ERA monotherapy in patients with WHO FC III/IV PAH

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + ERA	ERA	
PATENT-1[a] CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

[a] 14% of patients had background prostanoid therapy
CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

c. Hospitalisation due to worsening PAH

c.i PAH patients, irrespective of disease severity or aetiology

Patients who received combination therapy were [redacted] to be hospitalised due to PAH than those on monotherapy (Table 4.90), [redacted] (ARD = [redacted] Thus, [redacted] patients need to be treated with sGC stimulator plus ERA combination therapy to avoid hospitalisation of one additional patient compared with ERA monotherapy.

Table 4.90 Hospitalisation due to PAH for a sGC stimulator in addition to an ERA compared with ERA monotherapy in all PAH patients

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + ERA	ERA	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase stimulator

c.ii PAH patients with FC III or IV

Patients with WHO FC III/IV PAH who received combination therapy were [redacted] to be hospitalised due to PAH than those on monotherapy (Table 4.91), [redacted] (ARD = [redacted] Among patients with WHO FC III/IV PAH, [redacted] need to be treated with [redacted] to avoid hospitalisation of one additional patient compared with [redacted].

Table 4.91 Hospitalisation due to PAH for a sGC stimulator in addition to an ERA compared with ERA monotherapy in patients with WHO FC III/IV PAH

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + ERA	ERA	
PATENT-1[a] CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

[a] 14% of patients had background prostanoid therapy
CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

d. Change in WHO FC from baseline

d.i PAH patients, irrespective of disease severity or aetiology

Patients who received combination therapy were [redacted] to improve their WHO FC and [redacted] to experience a worsening of WHO FC than those on monotherapy (ARD = [redacted] and [redacted], [redacted] for either outcome (Table 4.92). The NNT indicates that [redacted] patients need to be treated with [redacted]

[redacted] for one additional patient to improve their WHO FC compared with [redacted], and [redacted] to prevent worsening of WHO FC in one additional patient.

Table 4.92 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in improving WHO FC in all PAH patients

Study ID sGC stimulator	Change in WHO FC	n/N (%)		RR (95% CI)
		sGC stimulator + ERA	ERA	
PATENT-1 CSR Riociguat	Improved	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

d.ii PAH patients with FC III or IV

Patients with WHO FC III/IV PAH who received combination therapy were [redacted] to improve their WHO FC than those on monotherapy (Table 4.93), [redacted] (ARD = [redacted] patients in the monotherapy group experienced worsening of their WHO FC [redacted] (ARD = [redacted]. Among patients with WHO FC III/IV PAH, [redacted] need to be treated with [redacted] for one additional patient to improve in WHO FC compared with [redacted], and [redacted] to prevent worsening of WHO FC in one additional patient.

Table 4.93 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in improving WHO FC in patients with WHO FC III/IV PAH

Study ID sGC stimulator	Change in WHO FC	n/N (%)		RR (95% CI)
		sGC stimulator + ERA	ERA	
PATENT-1[a] CSR Riociguat	Improved	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]

[a] 14% of patients had background prostanoid therapy
CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

e. Change in 6MWD from baseline

e.i PAH patients, irrespective of disease severity or aetiology

There was [redacted] in the 6MWD for patients receiving combination therapy (Table 4.94), whereas the 6MWD for patients receiving monotherapy [redacted]. However, the improvement was [redacted], see Section 4.3.5).

Table 4.94 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in improving 6MWD in all PAH patients

Study ID sGC stimulator	N Time point	Mean ± SD baseline 6MWD, metres		Mean ± SD change from baseline, metres		Mean difference (95% CI), metres
		sGC stimulator + ERA	ERA	sGC stimulator + ERA	ERA	
PATENT-1 CSR Riociguat	N=167 Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6MWD = 6-minute walk distance; CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; N = number of patients; PAH = pulmonary arterial hypertension; sGC = soluble guanylate cyclase stimulator

e.ii PAH patients with FC III or IV

There was [redacted] in the 6MWD for patients with WHO FC III/IV PAH receiving combination therapy (Table 4.95), and [redacted] for patients receiving monotherapy. Thus, [redacted] improvement in 6MWD for patients receiving combination therapy compared to those on monotherapy [redacted].

Table 4.95 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in improving 6MWD in patients with WHO FC III/IV PAH

Study ID sGC stimulator	N Time point	Mean ± SD baseline 6MWD, metres		Mean ± SD change from baseline, metres		Mean difference (95% CI), metres
		sGC stimulator + ERA	ERA	sGC stimulator + ERA	ERA	
PATENT-1[a] CSR Riociguat	N=120 Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] 14% of patients had background prostanoid therapy
6MWD = 6-minute walk distance; CI = confidence interval; CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; SD = standard deviation; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

f. Change in QoL from baseline

f.i PAH patients, irrespective of disease severity or aetiology

The self-reported change in health-related QoL of patients receiving combination therapy compared with monotherapy was measured using the EQ-5D and LPH questionnaires. Scores for the EQ-5D questionnaire indicated that QoL [redacted] in the combination therapy group and [redacted] in the monotherapy group (a positive change from baseline denotes improvement; Table 4.96). The mean difference [redacted] according to previous studies investigating the minimal clinically important change in EQ-5D score in patients with COPD[85]. The scores for the LPH questionnaire showed an approximate [redacted] in QoL in the combination therapy group and a [redacted] in the monotherapy group (a higher score indicates that patients are more affected by their medical condition; Table 4.96). The minimally important difference for the LPH scale has been previously determined to be 7 points for the total score[83]. Thus, although there was [redacted] in QoL for the combination therapy group, the difference between the combination therapy group and monotherapy group [redacted].

Table 4.96 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in improving QoL in all PAH patients

Study ID sGC stimulator	N Time point	Mean ± SD baseline QoL		Mean ± SD change from baseline		Mean difference, points
		sGC stimulator + ERA	ERA	sGC stimulator + ERA	ERA	
PATENT-1 CSR Riociguat	N=167 Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] An increase in EQ-5D indicates better QoL. A decrease in LPH indicates better QoL.
CI = confidence interval; CSR = clinical study report; EQ-5D = EuroQol 5 dimension; ERA = endothelin receptor antagonist; LPH = living with pulmonary hypertension; N = number of patients; PAH = pulmonary arterial hypertension; QoL = quality of life; SD = standard deviation; sGC = soluble guanylate cyclase stimulator

f.ii PAH patients with FC III or IV

Scores for the EQ-5D questionnaire indicated that QoL [redacted] for patients with WHO FC III/IV PAH receiving combination therapy and [redacted] for patients receiving monotherapy (Table 4.97). The mean difference [redacted] suggests that [redacted]. Similarly, to the LPH scores for all PAH patients, there was [redacted] in QoL for the combination therapy group, [redacted] the monotherapy group and the difference between them [redacted].

Table 4.97 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in improving QoL in patients with WHO FC III/IV PAH

Study ID sGC stimulator	N Time point	Mean ± SD baseline QoL		Mean ± SD change from baseline		Mean difference, points (95% CI)
		sGC stimulator + ERA	ERA	sGC stimulator + ERA	ERA	
PATENT-1[a] CSR Riociguat	N=120 Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] An increase in EQ-5D indicates better QoL. A decrease in LPH indicates better QoL.
[a] 14% of patients had background prostanoid therapy
CI = confidence interval; CSR = clinical study report; EQ-5D = EuroQol 5 dimension; ERA = endothelin receptor antagonist; FC = functional class; LPH = living with pulmonary hypertension; N = number of patients; PAH = pulmonary arterial hypertension; QoL = quality of life; SD = standard deviation; sGC = soluble guanylate cyclase; WHO = World Health Organization

g. Change in haemodynamic parameters from baseline

g.i PAH patients, irrespective of disease severity or aetiology

In the PATENT-1 trial, patients who were receiving background therapy with an ERA and were randomised to riociguat treatment had a mean baseline PVR [redacted] than those who were randomised to placebo, but both groups are well above the normal laboratory PVR in adults of <250 dyn*sec*cm^{-5}. Any confounding of the treatment effect would favour [redacted] The treatment-naïve patients with WHO FC I/II PAH had a mean placebo-adjusted [redacted] in PVR of [redacted] after 12 weeks of riociguat treatment (Table 4.98). [redacted]

Table 4.98 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in improving PVR in all PAH patients

Study ID sGC stimulator	N Follow-up period	Mean ± SD baseline PVR[a], dyn*sec*cm^{-5}		Mean ± SD change from baseline, dyn*sec*cm^{-5} (% change from baseline)		Mean difference, dyn*sec*cm^{-5} (% change)
		sGC stimulator + ERA	ERA	sGC stimulator + ERA	ERA	
PATENT-1 CSR Riociguat	N=148 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] A decrease in PVR indicates improvement in haemodynamic parameters.
CSR = clinical study report; ERA = endothelin receptor antagonist; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; SD = standard deviation; sGC = soluble guanylate cyclase

g.ii PAH patients with FC III or IV

In the PATENT-1 trial, patients with WHO FC III/IV PAH receiving background therapy with an ERA who were randomised to riociguat treatment had a mean baseline PVR [redacted] than those who were randomised to placebo. Hence, any confounding of the treatment effect would favour [redacted]. These patients had a mean placebo-adjusted [redacted] in PVR of [redacted] after 12 weeks of riociguat treatment (Table 4.99). [redacted]

Table 4.99 The effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy in improving PVR in patients with WHO FC III/IV PAH

Study ID sGC stimulator	N Follow-up period	Mean ± SD baseline PVR[a], dyn*sec*cm^{-5}		Mean ± SD change from baseline, dyn*sec*cm^{-5} (% change from baseline)		Mean difference, dyn*sec*cm^{-5} (% change)
		sGC stimulator + ERA	ERA	sGC stimulator + ERA	ERA	
PATENT-1[b] CSR Riociguat	N=103 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] A decrease in PVR indicates improvement in haemodynamic parameters.
[b] 14% of patients had background prostanoid therapy
CSR = clinical study report; ERA = endothelin receptor antagonist; FC = functional class; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; SD = standard deviation; sGC = soluble guanylate cyclase; WHO = World Health Organization

h. Comparative safety

PATENT-1 did not report on the comparative safety of treatment with a sGC stimulator plus an ERA compared with treatment with an ERA alone.

4.4.3.7 sGC stimulator in addition to PDE-5 inhibitor

Only one RCT was identified that reported on the effectiveness of a sGC stimulator in addition to a PDE-5 inhibitor in treating PAH compared with placebo and a PDE-5 inhibitor in patients with PAH. The PATENT-PLUS[44] double-blind trial, with a low risk of bias, randomised PAH patients with symptomatic PAH receiving stable sildenafil therapy to receive riociguat or placebo for 12 weeks. After 12 weeks, patients were eligible for an open-label long-term extension study to assess the

long-term safety and tolerability of the riociguat/sildenafil combination. The combination therapy group had a greater proportion of patients with PAH-CTD (5/12, 42% versus 1/6, 17%), and a smaller proportion of patients with WHO FC II (6/12, 50% versus 4/6, 67%) and baseline 6MWD ≥ 320 m (7/12, 58% versus 6/6, 100%). Additionally, the baseline PVR dyn·s·cm^{-5} was lower in the combination therapy group (573 ± 241 versus 683 ± 195). These imbalances are not surprising considering the small sample size of the study.

a. Study-defined clinical worsening

The number of patients receiving sGC stimulator plus PDE-5 inhibitor combination treatment who had clinical worsening compared with those receiving PDE-5 inhibitor monotherapy was not reported for the PATENT-PLUS trial.

b. All-cause mortality

b.i PAH patients, irrespective of disease severity or aetiology

No patients died during the 12-week randomisation period of PATENT-PLUS study (Table 4.100). Thus, the effect of a sGC stimulator in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy on mortality rates cannot be determined.

Table 4.100 Mortality rates for a sGC stimulator in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in all PAH patients

Study ID sGC stimulator	Study period PDE-5 inhibitor	n/N (%)		RR (95% CI)
		sGC stimulator + PDE-5 inhibitor	PDE-5 inhibitor	
PATENT-PLUS[44] Riociguat	12 weeks Sildenafil	0/12 (0%)	0/6 (0%)	Not calculable

CI = confidence interval; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; sGC = soluble guanylate cyclase

c. Hospitalisation due to worsening PAH

The number of patients receiving sGC stimulator plus PDE-5 inhibitor combination treatment who were hospitalised compared with those receiving PDE-5 inhibitor monotherapy was not reported for the PATENT-PLUS trial.

d. Change in WHO FC from baseline

d.i PAH patients, irrespective of disease severity or aetiology

Patients who received combination therapy were approximately 2-times less likely to improve their WHO FC than those on monotherapy (Table 4.101), but this difference was not statistically significant (ARD = −16.7%; 95% CI −59.9, −26.5; p = 0.43). No patients in either group experienced worsening of their WHO FC during the randomisation period.

Table 4.101 The effectiveness of a sGC stimulator in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in improving WHO FC in all PAH patients

Study ID sGC stimulator/ PDE-5 inhibitor	Change in WHO FC	n/N (%)		RR (95% CI)
		sGC stimulator + PDE-5 inhibitor	PDE-5 inhibitor	
PATENT-PLUS[44] Riociguat/sildenafil	Improved	2/12 (17%)	2/6 (29%)	0.50 (0.09, 2.73)
	Worsened	0/12 (0%)	0/6 (0%)	Not calculable

CI = confidence interval; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

e. Change in 6MWD from baseline

e.i PAH patients, irrespective of disease severity or aetiology

Patients in the monotherapy group had a larger mean improvement in 6MWD than the combination therapy group, but both the distance of improvement and the mean difference between the two treatment groups were not clinically important (Table 4.102).

Table 4.102 The effectiveness of a sGC stimulator in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in improving 6MWD in all PAH patients

Study ID sGC stimulator/ PDE-5 inhibitor	N Time point	Mean ± SD baseline 6MWD, metres		Mean ± SD change from baseline, metres		Mean difference, metres
		sGC stimulator + PDE-5 inhibitor	PDE-5 inhibitor	sGC stimulator + PDE-5 inhibitor	PDE-5 inhibitor	
PATENT-PLUS[44] Riociguat/sildenafil	N=20 Week 12	359 ± 122	426 ± 66	7 ± 48	30 ± 56	–23

6MWD = 6-minute walk distance; CI = confidence interval; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; SD = standard deviation; sGC = soluble guanylate cyclase

f. Change in QoL from baseline

The change in QoL for patients receiving a sGC stimulator plus a PDE-5 inhibitor combination treatment compared with those receiving PDE-5 inhibitor monotherapy was not reported for the PATENT-PLUS trial.

g. Change in haemodynamic parameters from baseline

The PATENT-PLUS trial did not report on any haemodynamic outcomes.

h. Comparative safety

h.i PAH patients, irrespective of disease severity or aetiology

During the 12-week randomised phase of the PATENT-PLUS study, 1.5-times more patients receiving combination therapy had an AE compared with those on monotherapy, but this was not statistically significant (Table 4.103). Two patients in the combination therapy group had serious

AEs compared with no patients in the monotherapy group (ARD = 16.7%; 95% CI −4.4, 37.8; p = 0.29). Only one patient in the PATENT-PLUS study, who had been randomised to combination therapy, withdrew from treatment due to an AE (blurred vision) (ARD = 8.3%; 95% CI −7.3, 24.0; p = 0.47).

Table 4.103 The comparative safety of a sGC stimulator in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy in all PAH patients

Study ID sGC stimulator/ PDE-5 inhibitor	AE	n/N (%)		RR (95% CI)
		sGC stimulator + PDE-5 inhibitor	PDE-5 inhibitor	
PATENT-PLUS[44] Riociguat/sildenafil	Any AE Serious AEs AEs leading to discontinuation	12/12 (100%) 2/12 (17%) 1/12 (8%)	4/6 (67%) 0/6 (0%) 0/6 (0%)	1.50 (0.85, 2.64) Not calculable Not calculable

AE = adverse event; CI = confidence interval; n = number of events; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RR = relative risk; sGC = soluble guanylate cyclase

4.4.3.8 sGC stimulator in addition to prostanoid

The PATENT-1[23] double-blind trial, with a low-to-moderate risk of bias, reported on the effectiveness of a sGC stimulator plus a prostanoid in treating PAH compared with placebo plus prostanoid in patients with PAH. PAH patients of any WHO FC with or without background ERA or prostanoid therapy were randomised to receive riociguat or placebo for 12 weeks. However, only 6% of enrolled patients were receiving background prostanoid therapy (primarily inhaled iloprost) at baseline. Thus this subgroup was very small, involving only 27 patients. There were some imbalances in the baseline characteristics, which is not surprising considering the small sample size of the study. The combination therapy group had a greater proportion of female patients (5/12, 42% versus 1/6, 17%) and patients with WHO FC I (2/20, 10% versus 0/7, 0%), and a smaller proportion of patients with WHO FC III (12/20, 60% versus 5/7, 71%). Outcome data was reported for all PAH patients who had background prostanoid treatment in the CSR (highlighted in green below).

a. Study-defined clinical worsening

In the PATENT-1 study, clinical worsening was defined as all-cause mortality, heart/lung transplantation, atrial septostomy, modification of a pre-existing PAH treatment (ERA, prostanoid or PDE-5 inhibitor), or hospitalisation persistent decrease in 6MWD or persistent worsening of WHO FC due to worsening of PAH.

a.i PAH patients, irrespective of disease severity or aetiology

[redacted] receiving prostanoid monotherapy experienced a clinical worsening event, [redacted] (Table 4.104; ARD [redacted] The NNT (inverse of ARD) indicates that [redacted] patients need to be treated with sGC stimulator plus

prostanoid combination therapy to prevent one additional patient experiencing clinical worsening compared with prostanoid monotherapy.

Table 4.104 The effectiveness of a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy in preventing clinical worsening in all PAH patients

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + prostanoid	Prostanoid	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted])

CI = confidence interval; CSR = clinical study report; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase

b. All-cause mortality

b.i PAH patients, irrespective of disease severity or aetiology

[redacted] receiving prostanoid monotherapy died during the study period, [redacted] [redacted] (Table 4.105; ARD [redacted] As for clinical worsening [redacted] patients need to be treated with sGC stimulator plus prostanoid combination therapy to prevent one additional patient experiencing clinical worsening compared with prostanoid monotherapy.

Table 4.105 Mortality rates for a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy in all PAH patients

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + prostanoid	Prostanoid	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted])

CI = confidence interval; CSR = clinical study report; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase

c. Hospitalisation due to worsening PAH

c.i PAH patients, irrespective of disease severity or aetiology

[redacted] were hospitalised for worsening PAH during the 12-week study period (Table 4.106). Thus, the effect of a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy on mortality rates [redacted].

Table 4.106 Hospitalisation due to PAH for a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy in all PAH patients

Study ID sGC stimulator	Study period	n/N (%)		RR (95% CI)
		sGC stimulator + prostanoid	Prostanoid	
PATENT-1 CSR Riociguat	12 weeks	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase

d. Change in WHO FC from baseline

d.i PAH patients, irrespective of disease severity or aetiology

Patients receiving sGC stimulator plus prostanoid combination therapy were [redacted] than those receiving monotherapy, [redacted] (Table 4.107; ARD = [redacted]. The inverse of the ARD (NNT) indicated that [redacted] patients need to be treated with sGC stimulator plus prostanoid combination therapy for one additional patient to improve their WHO FC compared with prostanoid monotherapy. As [redacted] patients need to be treated with [redacted] to prevent worsening of WHO FC in one additional patient compared with [redacted].

Table 4.107 The effectiveness of a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy in improving WHO FC in all PAH patients

Study ID sGC stimulator	Change in WHO FC	n/N (%)		RR (95% CI)
		sGC stimulator + prostanoid	Prostanoid	
PATENT-1 CSR Riociguat	Improved	[redacted]	[redacted]	[redacted]
	Worsened	[redacted]	[redacted]	[redacted]

CI = confidence interval; CSR = clinical study report; FC = functional class; n = number of patients with events; N = number of patients; PAH = pulmonary arterial hypertension; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

e. Change in 6MWD from baseline

e.i PAH patients, irrespective of disease severity or aetiology

There was [redacted] in 6MWD for patients receiving combination therapy (Table 4.108). [redacted] in 6MWD for the monotherapy group. The mean difference between the combination therapy and monotherapy groups was [redacted]

Table 4.108 The effectiveness of a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy in improving 6MWD in all PAH patients

Study ID sGC stimulator	N Time point	Mean ± SD baseline 6MWD, metres		Mean ± SD change from baseline, metres		Mean difference (95% CI), metres
		sGC stimulator + prostanoid	Prostanoid	sGC stimulator + prostanoid	Prostanoid	
PATENT-1 CSR Riociguat	N=167 Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6MWD = 6-minute walk distance; CI = confidence interval; CSR = clinical study report; N = number of patients; PAH = pulmonary arterial hypertension; SD = standard deviation; sGC = soluble guanylate cyclase

f. Change in QoL from baseline

f.i PAH patients, irrespective of disease severity or aetiology

The mean scores for the EQ-5D questionnaire indicated that QoL [redacted] for patients receiving combination therapy and [redacted] for patients receiving monotherapy (Table 4.109). The mean difference [redacted] suggests that [redacted] for patients receiving [redacted]. According to the LPH scores, there was [redacted] in QoL for the combination therapy group, [redacted] the monotherapy group and the difference between them [redacted]

Table 4.109 The effectiveness of a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy in improving QoL in all PAH patients

Study ID sGC stimulator	N Time point	Mean ± SD baseline QoL		Mean ± SD change from baseline		Mean difference, points (95% CI)
		sGC stimulator + prostanoid	Prostanoid	sGC stimulator + prostanoid	Prostanoid	
PATENT-1 CSR Riociguat	N=167 Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[b] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
CI = confidence interval; CSR = clinical study report; EQ-5D = EuroQol 5 dimension; LPH = living with pulmonary hypertension; N = number of patients; PAH = pulmonary arterial hypertension; QoL = quality of Life; SD = standard deviation; sGC = soluble guanylate cyclase

g. Change in haemodynamic parameters from baseline

g.i PAH patients, irrespective of disease severity or aetiology

In the PATENT-1 trial, patients who were receiving background therapy with a prostanoid and were randomised to riociguat treatment [redacted] baseline PVR compared with than those who were randomised to placebo, [redacted] normal laboratory PVR in adults of <250 dyn*sec*cm^{-5}. The treatment-naïve patients with WHO FC I/II PAH had a mean placebo-adjusted [redacted] in PVR of [redacted] after 12 weeks of riociguat treatment (Table 4.110). This difference is [redacted].

Table 4.110 The effectiveness of a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy in improving PVR in all PAH patients

Study ID sGC stimulator	N Follow-up period	Mean ± SD baseline PVR[a], dyn*sec*cm^{-5}		Mean ± SD change from baseline, dyn*sec*cm^{-5} (% change from baseline)		Mean difference, dyn*sec*cm^{-5} (% change)
		sGC stimulator + prostanoid	Prostanoid	sGC stimulator + prostanoid	Prostanoid	
PATENT-1 CSR Riociguat	N=24 12 weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] A decrease in PVR indicates improvement in haemodynamic parameters.
CSR = clinical study report; N = number of patients; PVR = pulmonary vascular resistance; SD = standard deviation; sGC = soluble guanylate cyclase

h. Comparative safety

The PATENT-1 trial did not report on the comparative safety of the subgroup of patients with PAH receiving background therapy with a prostanoid in addition to the sGC stimulator compared with a placebo plus prostanoid in the treatment.

4.4.4 Research question 4

What is the effectiveness and safety of triple combination therapy involving any combination of an ERA, a PDE-5 inhibitor, a prostanoid, or a sGC stimulator, compared to dual combination therapy, in: i) PAH patients, irrespective of disease severity or aetiology; ii) PAH patients with FC III or IV; and iii) PAH patients with different disease aetiologies?

There was no evidence concerning the effectiveness and safety of triple combination therapy with PBS-listed PAH medicines, compared to dual combination therapy, in any patients with PAH.

4.4.5 Extended assessment of safety of PAH medicines

4.4.5.1 Results from clinical evidence included for extended safety assessment

No studies have been identified to be included in this section for extended assessment of safety concerning macitentan and iloprost. Safety results from clinical studies for other PAH medicines are summarised below.

ERA

Bosentan

A total of five single-arm observational studies were identified for extended safety assessment of bosentan. The follow-up period varied between 2 years to 4.3 years across studies. Among the included studies, Keogh 2011 was the largest study (N=528) which was a prospective, multicentre, Australian registry funded by the sponsor of bosentan (Actelion Pharmaceuticals). The registry was established subsequent to the listing of bosentan on the PBS, as part of a risk-sharing agreement.

Limited safety data were provided by published papers on the five included studies (Table 4.111). The safety profile of bosentan reported in the paediatric PAH patients in Study Hislop 2011[58] appeared comparable to that in the other four studies whose subjects were all or predominantly adults [57, 60, 66, 72]. None of the studies reported the incidence of any AEs during the study period. Serious AEs were either not observed (in Hislop 2011) or not reported (in the other four studies). Deaths judged to be related to bosentan were reported in two (1%) patients in the EARLY extension study: convulsion/vasculitis/worsening PAH in one patient and antiphospholipid syndrome/sudden death/systemic lupus erythematosus in the other patient[57]. AEs leading to treatment withdrawal occurred in a higher proportion of patients in the EARLY extension study than in the other four studies (20% vs 0%-6%). Similar trend was observed for AE of abnormal liver function (17% vs 2%-4%). In the EARLY extension study, a haemoglobin concentration of ≤100 g/L was found in 26 (15%) patients, only one of whom had a pre-treatment baseline value of ≤100 g/L.

Peripheral oedema was reported to occur in the EARLY extension study, but the incidence rate was not provided. Information on the occurrence of anaemia and fluid retention in other studies is lacking.

Table 4.111 AEs reported in bosentan studies included for extended assessment of safety

AEs	EARLY extension study (N=173)	Hislop 2011 (N=101)	Keogh 2011 (N=528)	Provencher 2006 (N=103)	Vis 2013 (N=64)
Serious AEs	NR	0 (0%)	NR	NR	NR
AEs leading to treatment withdrawal	35 (20%)	2 (2%)	31 (6%)	3[a] (3%)	0 (0%)
Death due to study drug	2 (1%)	NR	NR	NR	NR
AEs of interest					
Hepatic enzyme elevation[b]	29 (17%)	3 (3%)	NR	4 (4%)	1 (2%)
Decreased haemoglobin[c]	26 (15%)	NR	NR	NR	NR

[a] 3 patients permanently stopped bosentan therapy due to elevated liver enzymes. It is unclear whether there were more patients withdrew due to other AEs
[b] Defined as alanine aminotransferase or aspartate aminotransferase concentrations >3 x the upper limit of normal
[c] Defined as haemoglobin ≤100g/L
AE = adverse event, N = number of patients
Source: Simonneau et al 2014[57]; Hislop et al 2011[58]; Keogh 2011[60]; Provencher et al 2006[66]; Vis et al 2013[72]

Overall, no clear safety signals were detected by the five included observational studies. Abnormal liver function, haemoglobin decrease and peripheral oedema are three well-recognised AEs associated with ERAs. No conclusion can be drawn from the two so-called bosentan-related deaths reported in the EARLY extension study, given the absence of detailed information on these cases and the lack of a placebo-control arm. Some of the fatal AEs reported in the EARLY extension study can either be the primary condition of PAH (eg systemic lupus erythematosus), co-exist with or implicated in development of PAH or its primary conditions (eg vasculitis and antiphospholipid syndrome hypertension)[87-89].

Ambrisentan

Two observational studies (Vachiéry 2017 and ARIES extension study) were included for extended assessment of safety of ambrisentan. Results from these two studies are summarised in Table 4.112. Of note, the safety outcomes reported in the two studies slightly differed: treatment-emergent AEs (defined as undesirable events not present prior to medical treatment or an already present event that worsens either in intensity or frequency following the treatment) in Vachiéry 2017 and any AEs in ARIES extension study.

Vachiéry et al[70] analysed data from a large post-marketing registry program which enrolled 999 patients from 15 countries who were prescribed ambrisentan for the treatment of PAH. The mean exposure to ambrisentan for the safety population (N=998, excluding patient who did not receive ambrisentan) was 2.2 years. At baseline, 322 (32%) patients were treated with other PAH-specific therapies in addition to ambrisentan. In total, 83% (n=827) of patients reported ≥1 treatment-

emergent AEs during the study period, which were considered by the investigator to be mild to moderate (43%) or severe (38%). The most common AEs were peripheral oedema (23%), dyspnoea (15%), anaemia (14%) and heart failure (13%). Adverse events leading to discontinuation of ambrisentan occurred in 167 (17%) patients. A total of 514 (51%) experienced treatment-emergent AEs of interest. Treatment-emergent non-fatal serious AEs were observed in 395 (40%) patients.

In the ARIES extension study, patients who completed Trials ARIES-1 and ARIES-2 were treated with ambrisentan 2.5 mg, 5 mg or 10 mg od, with dose adjustments permitted per investigator discretion after the first 24 weeks of the extension study[55]. The ambrisentan PI recommended a dose regimen of 5 mg od and stated that additional benefit may be obtained by increasing the dose to 10 mg. The most common AEs during the 2-year treatment period included peripheral oedema (38%), headache, upper respiratory tract infection, and dizziness. A total of 22 (6%) patients discontinued study due to AEs. The most common AEs that led to ambrisentan withdrawal or death during the study were right ventricular failure and pulmonary hypertension (both 4%).

Table 4.112 AEs reported in Vachiéry 2017 and ARIES extension study

AEs	Vachiéry 2017 (N=999)	ARIES extension study (N=383)
Any AEs[a]	827 (83%)	NR
Severe AEs[a]	429 (43%)	NR
Non-fatal serious AEs[a]	395 (40%)	NR
AEs leading discontinuation of ambrisentan[a]	176 (17%)	22 (6%)
AEs of special interest[a, b]	514 (52%)	NR
Oedema/fluid retention	249 (25%)	NR (38%)
Hepatic enzyme elevation[c]	61 (6%)	12 (3%)
Anaemia	143 (14%)	NR
Heart failure	127 (13%)	NR
Hypersensitivity	77 (8%)	NR
Hypotension	67 (7%)	NR
Renal disorders	56 (6%)	NR

[a] Adverse drug reactions reported in Vachiéry 2017 were treatment-emergent adverse events, not any adverse events.
[b] Specified in Study Vachiéry 2017
[c] Defined as alanine aminotransferase or aspartate aminotransferase concentrations >3 x the upper limit of normal.
AE = adverse events; N = number of patients; NR = not reported
Source: Vachiéry et al 2017[70] and Qudiz et al 2009[55]

The safety results reported in Vachiéry 2017 and the ARIES extension study were generally in line with the known safety profile of ambrisentan. The AEs observed in these two single-arm studies were also reported in shorter-term RCTs and noted by the TAG-approved PI, except for renal disorders which occurred in 56 (6%) patients in Study Vachiéry 2017. The ambrisentan PI stated that the magnitude of the decrease in oral clearance is modest and unlikely to be of any clinical relevance in patients with moderate renal impairment. However, caution should be used in patients with severe renal impairment. Renal disorders are not included as AEs in the ambrisentan

PI, neither in the other ERA PI documents. Nickel et al (2017)[90] indicated that kidney dysfunction is a frequent co-morbidity in PAH. Potential mechanisms of PAH affecting the kidneys include increased venous congestion, decreased cardiac output, and neurohormonal activation. On a molecular level, increased transforming growth factor-β signalling and increased levels of circulating cytokines could have the potential to worsen kidney function. As vasoactive substances, most PAH-targeted therapy was shown to have nephroprotective potential in a pre-clinical or clinical setting[90]. Large, long-term, placebo-controlled trials are warranted to investigate the impact of PAH-targeted therapy, including ambrisentan, on kidney function.

PDE-5 inhibitor

Sildenafil

A total two RCTs (SUPER-1 and STARTS-1) and two observational studies (Sastry 2017 and STARTS extension study) were included for extended safety assessment of sildenafil.

When the PBAC recommended the listing of sildenafil at the November 2006 meeting, the safety results from the key trial SUPER-1 were reviewed. There was one article by Wirostko et al (2012) [53] published after the listing of sildenafil which reported the ocular safety of sildenafil in SUPER-1. In SUPER-1, patients were randomised to receive sildenafil 20 mg, 40 mg, or 80 mg or placebo tid. Among the different sildenafil doses, only 20 mg tid is the dosage regimen recommended by the PI for the treatment of PAH. During the 12-week trial, daily dosing up to 80 mg tid in the trial population was not associated with visual change and had no detrimental effect on best corrected visual acuity, contrast sensitivity, colour vision, or visual field, or on slit lamp examinations, funduscopy, or intraocular pressure. The incidence of observed and reported ocular AEs was low and comparable between placebo and sildenafil 20 mg groups. A modest, dose-related increase in the incidence of chromatopsia, cyanopsia, photophobia, visual brightness, and visual disturbance was observed, with the incidence of each of these effects being ≤7% with sildenafil 80 mg, <5% with sildenafil 40 mg and <2% for sildenafil 20 mg and placebo groups. Four cases of retinal haemorrhage were observed in participants receiving warfarin, one each in the sildenafil 20 mg and 80 mg groups (incidence rate of 1%), two in the sildenafil 40 mg group (incidence rate of 3%) and none in the placebo arm. Although Wirostko et al[53] also reported ocular safety in the SUPER extension study in the same paper, these data were not included in the literature review for assessment of the safety profile of sildenafil, given that a vast majority (>90%) of patients titrated up to 80 mg tid during the extension study, with only ≤3% of patients remaining or titrated down to the PI-recommended dose of 20 mg tid.

Table 4.113 Eye disorder AEs[a] reported in SUPER-1

AE (MedDRA preferred term)	Placebo (n=70)	Sildenafil		
		20 mg (n=69)	40 mg (n=67)	80 mg (n=71)
Abnormal sensation in eye	0 (0%)	2 (2.9%)	1 (1.5%)	0 (0%)
Chromatopsia	1 (1.4%)	1 (1.4%)	1 (1.5%)	3 (4.2%)
Cyanopsia	0 (0%)	0 (0%)	1 (1.5%)	3 (4.2%)
Eye haemorrhage NOS	1 (1.4%)	1 (1.4%)	1 (1.5%)	1 (1.4%)
Eye irritation	0 (0%)	2 (2.9%)	0 (0%)	2 (2.8%)
Eye pain	1 (1.4%)	1 (1.4%)	0 (0%)	3 (4.2%)
Halo vision	1 (1.4%)	0 (0%)	0 (0%)	2 (2.8%)
Photophobia	0 (0%)	0 (0%)	0 (0%)	4 (5.6%)
Photophobia aggravated	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)
Retinal haemorrhage	0 (0%)	1 (1.4%)	2 (3.0%)	1 (1.4%)
Vision blurred	4 (5.7%)	3 (4.3%)	2 (3.0%)	4 (5.6%)
Visual acuity reduced	0 (0%)	0 (0%)	2 (3.0%)	1 (1.4%)
Visual brightness	0 (0%)	0 (0%)	0 (0%)	2 (2.8%)
Visual disturbance NOS	0 (0%)	0 (0%)	3 (4.5%)	5 (7.0%)

[a] With incidence rate of ≥2% in any of the sildenafil arm
AE = adverse event; n = number of patients; NOS = not otherwise specified
Source: Wirostko et al 2012[53]

In Study Sastry 2007[52], a total of 139 patients receiving sildenafil for treatment of IPAH were followed up to 5 years. The authors reported that all patients tolerated sildenafil well without any major AEs or treatment discontinuation due to intolerance or adverse. Adverse events observed in this study included dyspepsia, headache and rash. None of the patients reported any visual problems.

The safety of sildenafil treatment in paediatric patients were investigated in Trial STARTS-1 and its extension study. In STARTS-1, children (aged 1-17 years) weighing ≥8 kg with IPAH, HPAH, PAH-CTD or PAH-CHD were randomised to low- (10 mg in patients >20 kg; no patients ≤ 20 kg received the low dose), medium- (10 mg in patients 8-20 kg; 20 mg in patients 20-45 kg; 40 mg in patients >45 kg) or high- (20 mg in patients 8-20 kg; 40 mg in patients 20-45 kg; 80 mg in patients >45 kg) dose sildenafil or placebo for 16 weeks. A summary of AEs reported in STARTS-1 is presented in Table 4.114. The majority of AEs were of mild or moderate intensity. Four (2%) patients in the sildenafil arms discontinued the study, two of which withdrew as a result of AEs; meanwhile, AEs leading to study discontinuation did not occur in placebo-treated patients. A total of 11 patients reported serious AEs, with two considered treatment related (both in the high-dose sildenafil group): stridor and arrhythmia in one patient each. Two patients died before randomisation (1 during and 1 before cardiac catheterisation); no additional deaths occurred during STARTS-1 treatment. Among AEs reported in this trial, pyrexia, increased erection, and upper respiratory tract infection occurred in >5% more patients in the sildenafil combined group versus placebo. Pyrexia, vomiting, and nausea appeared to be dose-related[54].

Table 4.114 AEs reported in STARTS-1

AEs	Placebo (n=60)	Sildenafil			
		Low dose (n=42)	Medium dose (n=55)	High dose (n=77)	Combined (n=174)
AEs leading to treatment discontinuation	0 (0%)	N	NR	NR	2 (1%)
Treatment-related serious AEs	0 (0%)	0 (0%)	0 (0%)	2 (3%)	2 (1%)
Fatal AEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AEs occurred in ≥5% of patients in the sildenafil combined group					
Headache	8 (13%)	5 (12%)	6 (11%)	12 (16%)	23 (13%)
Pyrexia	1 (2%)	3 (7%)	8 (15%)	9 (12%)	20 (12%)
Upper respiratory tract infection	4 (7%)	5 (12%)	9 (16%)	7 (9%)	21 (12%)
Vomiting	4 (7%)	3 (7%)	5 (9%)	11 (14%)	19 (11%)
Erection increased[a]	0 (0%)	0 (0%)	3 (13)	3 (12)	6 (9%)
Diarrhoea	5 (8%)	2 (5%)	3 (6%)	7 (9%)	12 (7%)
Bronchitis	1 (2%)	2 (5%)	5 (9%)	3 (4%)	10 (6%)
Cough	3 (5%)	2 (5%)	4 (7%)	2 (3%)	8 (5%)
Nasopharyngitis	4 (7%)	3 (7%)	3 (6%)	2 (3%)	8 (5%)
Nausea	0 (0%)	0 (0%)	4 (7%)	4 (5%)	8 (5%)

[a] Also included the term spontaneous penile erection. Percentage shown is for boys only: n=22, 17, 24, and 26 for placebo, sildenafil low-, medium-, and high-dose groups, respectively.
AE = adverse event; n = number of patients; NR = not reported
Source: Barst et al 2012[54]

Following completion of the 16-week Trial STARTS-1, subjects entered a long-term extension study. Patients who received sildenafil in STARTS-1 were maintained on the same sildenafil dose; whereas placebo-treated patients were randomised to receive low-, medium-, or high-dose sildenafil. Throughout the STARTS extension study, dose adjustment according to disease progression and tolerability was permitted. Over a median treatment exposure of 4.1 years, most (96%) patients reported ≥1 AE, with the majority of mild or moderate intensity. The most common treatment-related AEs were headache (15%) and vomiting (6%). Serious AEs were reported for 41% of patients (n=97), most commonly infections (28%, including pneumonia (7%) and upper respiratory tract infection (3%)), respiratory disorders (14%, including worsening of PH (5%) and worsening of PAH (3%)), and cardiac disorders (11%, most commonly cardiac failure (5%)). Five (2%) patients had serious AEs that were assessed as treatment-related, including enterocolitis, convulsion, hypoxia, hypersensitivity and stridor, and ventricular arrhythmia. Seventeen (7%) patients permanently discontinued because of AEs; most were considered to be related to the disease under study. The five (2%) discontinuations attributable to AEs that were assessed as treatment-related were decreased weight, convulsion, stridor, dyspnoea and hypoxia, and macular rash[69].

Eye disorders have been observed in temporal association with sildenafil for treatment of PAH and male erectile dysfunction. Results from SUPER-1 showed low (0%-4.3%) incidence of ocular AEs in patients receiving the recommended dose of 20 mg tid. Some eye disorders were reported to occur in sildenafil-treated patients but not in the placebo arm, eg retinal haemorrhage, abnormal sensation in eye and eye irritation. No new safety signal were identified by the clinical evidence included in the literature review. The safety profile seen in the paediatric studies, i.e. STARTS-1 and its extension study, was generally consistent with that in adults.

Tadalafil

The safety of tadalafil as monotherapy in treating PAH patients, regardless of WHO FC, were reported by two short-term RCTs: Mukhopadhyay 2011 and PHIRST. In the double-blind crossover trial by Mukhopadhyay et al (2011)[40], tadalafil was well tolerated by all patients during a treatment period of 6 weeks, with no treatment withdrawal due to major adverse effects. Two (7.1%) patients complained of nasal stuffiness and two (7.1%) of headache while on tadalafil therapy. Two (7.1%) placebo-treated patients experienced fatigue and lethargy. No other information on the safety outcomes was provided.

When the PBAC recommended the listing of tadalafil at the November 2011 meeting, the comparative safety of tadalafil versus placebo was assessed in a mixed population of patients with or without bosentan background therapy in PHIRST. The published paper by Barst et al (2011)[45] which reported safety results according to background therapy has not been reviewed by the PBAC and, therefore, was included in the literature review: the safety results of the subgroup of with background therapy were presented in Section 4.4.3 (research question 3: dual therapy versus monotherapy); whereas the safety results of patients with no background therapy, regardless of PAH FC, were not applicable to either research question 1 (monotherapy in WHO FC I-II PAH) or research question 2 (monotherapy in WHO FC III-IV PAH) and, therefore, were presented below for extended assessment of safety.

In PHIRST, PAH patients were randomised to receive placebo or tadalafil 2.5 mg, 10 mg, 20 mg or 40 mg od, with or without bosentan as background therapy, for 16 weeks. The TGA-recommended dose for tadalafil is 40 mg od. Results of AEs in the subgroup of treatment-naïve patients (i.e. without background therapy)[45] are presented in Table 4.115. Overall, higher proportion of patients receiving tadalafil 40 mg experienced treatment-emergent AEs than in the placebo group (97% vs 73%; risk difference: 24% (95% CI: 9%, 40%)). Headache was the most common AE, occurring in >30% of patients receiving tadalafil monotherapy compared with 8% in the placebo-treated patients. Other AEs with a notable higher incidence (difference of >5%) in the tadalafil 40 mg group included diarrhoea, nausea, nasopharyngitis, upper respiratory tract infection, myalgia, flushing, dyspepsia and pain in the extremities.

Table 4.115 TEAEs reported in PHIRST

TEAEs	Placebo (n=37)	Tadalafil		
		Tadalafil 40 mg (n=37)	Tadalafil 20 mg (n=37)	Combined[a] (n=152)
Patients with ≥1 TEAE	27 (73%)	36 (97%)	32 (86%)	138 (91%)
TEAEs occurred in ≥5% of patients in the tadalafil combined group				
Headache	3 (8%)	14 (38%)	12 (32%)	47 (31%)
Diarrhoea	1 (3%)	5 (14%)	4 (11%)	19 (12%)
Peripheral oedema	3 (8%)	3 (8%)	6 (16%)	18 (12%)
Pulmonary hypertension	4 (11%)	4 (11%)	6 (16%)	18 (12%)
Back pain	2 (5%)	3 (8%)	5 (14%)	16 (10%)
Nausea	2 (5%)	5 (14%)	6 (16%)	16 (10%)
Nasopharyngitis	1 (3%)	6 (16%)	1 (3%)	14 (9%)
Dyspnoea	2 (5%)	3 (8%)	2 (5%)	11 (7%)
Muscle spasm	1 (3%)	1 (3%)	4 (11%)	11 (7%)
Upper respiratory tract infection	2 (5%)	4 (11%)	2 (5%)	11 (7%)
Myalgia	1 (3%)	6 (16%)	2 (5%)	10 (7%)
Dizziness	4 (11%)	4 (11%)	0 (0%)	9 (6%)
Epistaxis	2 (5%)	1 (3%)	4 (11%)	9 (6%)
Flushing	1 (3%)	4 (11%)	2 (5%)	9 (6%)
Dyspepsia	0 (0%)	3 (8%)	2 (5%)	8 (5%)
Pain in the extremities	0 (0%)	4 (11%)	1 (3%)	8 (5%)

[a] In addition to those patients receiving tadalafil 20 mg and 40 mg, the combined total includes all treat-native patients who received tadalafil, including those receiving 2.5 mg and 10 mg (data not shown)
n = number of patients; TEAE = treatment-emergent adverse event.
Source: Barst et al 2011[45]

Results from PHIRST support the conclusion of inferior safety of tadalafil monotherapy versus placebo for treatment of patients with PAH. The AEs reported in Trials PHIRST and Mukhopadhyay 2011 are consistent with the known safety profile of tadalafil, with no new safety signal identified.

Prostacyclin analogue

A total of seven single-arm observational studies were included for extended assessment of safety concerning IV use of epoprostenol. The follow-up period ranged from 2 years to 4 years across these studies. Of these, results of general AEs were reported by the VA1A4001 extension study[71]. During this 3-year study, all 97 patients enrolled experienced ≥1 AE. The most common AEs were diarrhoea, jaw pain, nausea, headache, pain, rash, flushing, depression, right-heart failure, and infection. Serious AEs occurred in 66 (68%) patients. Two (2%) patients withdrew from the study due to AEs: one patient experienced respiratory distress on the first day of epoprostenol infusion necessitating permanent discontinuation of the medication and died 5 days later; the other patient had AE of hypotension, which was not alleviated after dose decrease, and permanently withdrew from the study. A total of 44 (45%) deaths were subsequent to various AEs, with about half deaths following right-heart failure. None of the deaths occurred during the study were judged by the investigators to be related to epoprostenol or the drug delivery system.

The other six studies focused mainly on the AEs attributable to the IV delivery system, particularly bloodstream infection. The incidence of overall adverse effects/complications associated with the

drug delivery system (including bloodstream infection, local port site infection, cutaneous complications, functional port complications and implantation procedure related complications) was provided by Dickinson et al (2009)[56], which reported that 73 (66%) patients had a total of 175 complications during a cumulative follow-up period of 104,992 days, resulting in an overall complication rate of 0.61 per patient-year (ppy). In Dickinson 2009, there were a total of 45 bloodstream infections including seven cases of sepsis, corresponding to a rate of 0.15 ppy for bloodstream infections and 0.02 ppy for sepsis. The remaining five observational studies either reported results of bloodstream infections or sepsis, but not both. The rates of bloodstream infections ranged from 0.04 ppy to 0.15 ppy across Studies Kallen 2008[59], Kitterman 2012[61] and Oudiz 2004[63]; and the sepsis rates were 0.14 ppy in McLaughlin 2002[62] and 0.19 ppy in Sitbon 2002[67]. The rate of local port site infection was 0.11 ppy and 0.24 ppy in studies Dickinson 2009 and McLaughlin 2002, respectively. Catheter replacement or removal occurred at a rate of 0.15 ppy in McLaughlin 2002 and 0.31 ppy in Oudiz 2004. The incidence of death related to IV catheter was low, between 0% and 3% across studies, with vast majority (12 out of 13) of fatal cases as a result of catheter infection and the other death due to a peri-operative complication[56, 63, 67, 71].

Table 4.116 AEs reported in epoprostenol studies included for extended assessment of safety

AEs	Dickinson 2009 (N=111)	Kallen 2008 (N=195)	Kitterman 2012 (N=NR)	McLaughlin 2002 (N=162)	Oudiz 2004 (N=192)	Sitbon 2002 (N=178)	VA1A4001 extension study (N=97)
Any AEs	NR	NR	NR	NR	NR	NR	97 (100%)
Serious AEs	NR	NR	NR	NR	NR	NR	66 (68%)
AEs leading to study withdrawal	NR	NR	NR	NR	NR	NR	2 (2%)
Death due to drug-related AEs	NR	NR	NR	NR	NR	NR	0 (0%)
Any AEs related to drug delivery system	73 (66%)	NR	NR	NR	NR	NR	NR
Local port site infection	0.11 ppy	NR	NR	0.24 ppy	NR	NR	NR
Bloodstream infection[a]	0.15 ppy	0.15 ppy	0.04 ppy	NR	0.06 ppy	NR	NR
Sepsis[a]	0.02 ppy	NR	NR	0.14 ppy	NR	0.19 ppy	NR
Catheter replacement or removal required	NR	NR	NR	0.15 ppy	0.31 ppy	NR	NR
Death related to drug delivery system	3 (3%)	NR	NR	4 (2%)	2 (1%)	4 (2%)	0 (0%)

[a] Bloodstream infection was defined as a positive blood culture. If a positive blood culture was associated with clinical signs of a systemic infection (eg temperature >38°C, tachycardia, tachypnoea, chills, general malaise, low blood pressure), the infection was defined as sepsis.
AE = adverse event; N = number of patients; NR = not reported; ppy = per patient year
Source: Dickinson et al 2009[56]; Kallen et al 2008[59]; Kitterman et al 2012[61]; McLaughlin et al 2002[62]; Oudiz et al 2004[63]; Sitbon et al 2002[67]; Badesch et al 2009[71]

Overall, the seven studies included for extended safety assessment of epoprostenol did not detect any new safety signals. The IV administration route of epoprostenol pose additional safety concerns compared with other oral PAH medications.

sCG stimulator

The PATENT extension study[65] was a multicentre, open-label, long-term study where all patients received riociguat individually adjusted to a maximum dose of 2.5 mg tid, with or without background therapy. During a median treatment duration of 2.7 years, almost all patients (98%) treated with riociguat experienced AEs. Both drug-related AEs and serious AEs occurred in around 60% of the overall population, with AEs more frequent in the pre-treated group (receiving background therapy with ERA and/or prostanoid) than the treatment-naïve group (without background therapy) (Table 4.117). The most common serious AEs were syncope (in 10% patients, with 3% considered drug-related), worsening PAH (10% patients, 1% drug-related), and right ventricular failure (8% patients, 0% drug-related). Serious AEs of haemoptysis and pulmonary haemorrhage occurred in 13 patients (3%). Of these 13 patients, the cases were considered study-drug related by the investigators in four (1%) patients, including two (0.5%) fatal cases. There were 45 (11%) patients in the PATENT extension study discontinued riociguat treatment as a result of AEs.

The safety profile section of the riociguat PI was based on two short-term (12-16 weeks) placebo-controlled RCTs in patients with PAH (PATENT-1) and in patients with chronic thromboembolic pulmonary hypertension (CHEST-1). The AEs observed in the PATENT extension study were also reported in these two RCTs, but generally with a higher incidence rate due to its longer follow-up (2.7 years). Serious haemoptysis and pulmonary haemorrhage, including cases with fatal outcome have been included in the riociguat PI.

Table 4.117 AEs reported in the PATENT extension study

AEs	Riociguat (n=197)	Riociguat ± ERA and/or prostanoid (n=199)
Any AEs	190 (96%)	198 (99%)
Drug-related AEs	104 (53%)	128 (64%)
Serious AEs	103 (52%)	135 (68%)
Discontinuation due to AEs	14 (7%)	31 (16%)
AEs of special interest in >5% of overall population		
Hypotension	21 (11%)	30 (15%)
Syncope	11 (6%)	27 (14%)
Haemoptysis or pulmonary haemorrhage	18 (9%)	12 (6%)

AE = adverse event; ERA = endothelin receptor antagonist; n = number of patients
Source: Ghofrani et al 2016[65]

ERA in combination with PDE-5 inhibitor

Sitbon et al[68] conducted a retrospective analysis of real-world clinical data in 97 patients with newly diagnosed WHO FC III-IV PAH who were treated with upfront combination therapy of bosentan + sildenafil (63%), bosentan + tadalafil (18%), ambrisentan + tadalafil (11%) or ambrisentan + sildenafil (8%). The authors concluded that ERA in combination with PDE-5 inhibitor

were generally well tolerated with AEs consistent with the drugs' known side effect profiles. Over a median follow-up period of 2.5 years, treatment discontinuation or switching due to AEs occurred in five (5%) patients: one patient stopped sildenafil due to blurred vision; two patients were switched from bosentan to ambrisentan due to elevated liver enzyme > 5 ULN; and the other two were switched from ambrisentan to bosentan due to leg oedema. All switches between ERAs led to resolution of the AE. No other safety results were provided by the published paper.

Visual disturbance in patients receiving sildenafil has been noted by sildenafil PI. ERAs are known to be associated with increased risk of abnormal liver function and peripheral oedema. In summary, the safety data from Sitbon 2016 do not reveal any new safety concerns.

PDE-5 inhibitor in combination with prostacyclin analogue

Long-term safety results of combination therapy with sildenafil and epoprostenol were reported by the PACES extension study which recruited patients with IPAH or PAH-CTD who completed the randomised placebo-controlled Trial PACES-1[64]. Over median sildenafil exposure of 3.2 years, all patients experienced ≥1 AEs. Most AEs were mild or moderate in severity. The most common treatment-related AEs included headache (49%), flushing (22%), and nausea (17%). Serious AEs occurred in 77% of patients; however, only 7% of patients had a serious AE which was considered to be treatment-related. Adverse events leading to premature discontinuation were reported in 19% of patients. Treatment-related serious AEs that resulted in discontinuation included, in one(0.4%) patient each, cardiac failure, cardiac arrest, thrombolic thrombocytopenic purpura, rectal haemorrhage, skin reaction and suicide attempt. There were no discontinuations because of laboratory test abnormalities during the study. The investigator considered two (0.8%) deaths, both from cardiac arrest, to be related to sildenafil treatment.

One (0.4%) patient in the PACES extension study withdrew due to suicide attempt judged by the investigator to be treatment-related. This AE has not been noted in the sildenafil PI, neither in the epoprostenol PI. Given its low incidence and the absence of control group in the PACES extension study, the temporal association between this AE and combination therapy with sildenafil and epoprostenol cannot be established. Other AEs reported in PACES extension study have been identified by clinical trials or post-marketing data and are noted by sildenafil and/or epoprostenol PI document(s): for example, cardia arrest in the sildenafil PI; thrombocytopenia and increased risk of haemorrhage in the epoprostenol PI; headache, flushing, nausea, and skin reaction for both PI documents.

4.4.5.2 Safety information from regulatory agency

Safety signals from variations to the EMA PI

As stated in the Methodology section 4.3.4, among the three regulatory agencies of TGA, EMA and FDA, the EMA is the only one which provides the systematic information on variations and updates to the PI (also called SmPC) on its website for products that are centrally authorised. Changes arose due to new clinical trial data, extensions to indications or amendments triggered by periodic safety update reports. In order to identify any safety signals that has not been identified by the

TGA, the safety-related changes to the EMA SmPC were compared against the current Australian PI approved by the TGA and FDA product label. The key differences are summarised in Table 4.118.

Table 4.118 Comparison of changes to EMA SmPC with FDA PL and TGA PI

EC approval date Variations to EMA SmPC (safety-related only)	FDA PL	TGA PI
Bosentan		
26/09/2017 Pharmacokinetic interaction between tadalafil and bosentan to be mentioned in the bosentan SmPC per Srinivas et al (2016), i.e. the exposure of tadalafil was reduced by bosentan; whilst tadalafil did not affect the exposure of bosentan or its metabolites.	The drug interaction between tadalafil has been noted in the tadalafil PL, but not in the bosentan PL.	The drug interaction between tadalafil has been noted in the tadalafil PI, but not in the bosentan PI.
22/04/2010 A new warning statement against use of bosentan in COPD based on results of an exploratory safety study, and a note that "an increase in minute ventilation and a decrease in oxygen saturation were observed and the most frequent adverse event was dyspnoea, which resolved with discontinuation of bosentan".	Such warning is not included in the FDA PL	Such warning is not included in the TGA PI
Ambrisentan		
23/03/2010 Based on results of a drug-drug interaction study with rifampicin, Sections 4.5 (Interaction with other medicinal products) and 5.2 (Pharmacokinetic properties) updated to include a transient (approximately 2-fold) increase in ambrisentan exposure (not clinically relevant) in patients receiving rifampicin. A warning statement is added in section 4.4 (Special warnings and precautions for use) that patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin.	Drug interaction between ambrisentan and rifampicin is not included in the FDA PL	Although the TGA PI included information on drug interaction between ambrisentan and rifampicin, no warning statement is included regarding the requirement of close monitoring in patients on ambrisentan therapy when starting treatment with rifampicin
Sildenafil		
Pending There are no adequate and well controlled studies in lactating women. Based on data from one lactating woman, it has been concluded that sildenafil and its active metabolite N-desmethylsildenafil are excreted into breast milk at very low levels.	The FDA PL states that it is not known if sildenafil or its metabolites are excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when sildenafil is administered to a nursing woman.	The TGA PI states that no information is available on its secretion into breast milk. Sildenafil should not be administered to breast-feeding mothers.
13/12/2013 The assessment of the data concerning background incidence, literature, clinical trials, post-marketing experience, and data mining leads to inclusion of the terms 'penile haemorrhage', 'haematospermia', and 'haematuria' to Section 4.8	AEs of 'penile haemorrhage', 'haematospermia', and 'haematuria' are not included in the FDA PL	AEs of 'penile haemorrhage', 'haematospermia', and 'haematuria' are not included in the TGA PI

EC approval date Variations to EMA SmPC (safety-related only)	FDA PL	TGA PI
(Undesirable effects) with a frequency of uncommon. This was the outcome of a safety review initiated by the EMA that concluded these genitourinary bleeding events were a class effect of PDE-5 inhibitors and should be reflected in product information for both PAH and erectile dysfunction indications.		
13/04/2012 Update of Section 4.4 (Special warnings and precautions for use) of the SmPC following CHMP request in order to add a section regarding the potential for vaso-occlusive crises occurring in patients being treated for pulmonary hypertension secondary to sickle cell anaemia.	Such waring has been included in the FDA PL.	Such waring is not included in the TGA PI.
24/10/2011 Following deaths related to an ongoing paediatric study (the STARTS extension study) and corresponding Data Monitoring Board recommendations, update to Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use) and 5.1 (Pharmacodynamic properties), to highlight that in paediatric patients, doses higher than the recommended doses (10 mg tid in children weighing <20 kg and 20 mg tid in those >20 kg) should not be used. ps: the Sections 4.8 (Undesirable effects) and 5.1 (Pharmacodynamic properties) of the SmPC were revised following submission of the final study report of the STARTS extension study in the paediatric population (EC approved date: 17/11/2014).	Use of sildenafil, particularly chronic use, is not recommended in children.	Sildenafil is not indicated for use in children under 18 years of age.
Tadalafil		
24/01/2013 The EMA requested the manufacturers of all PDE-5 inhibitors to compile a cumulative review of all penile haemorrhage, haematospermia, haematuria and penile hematoma adverse events with a view to considering whether genitourinary bleeding may be a class effect. As a result, haematuria, haematospermia and penile haemorrhage have been added to section 4.8 (Undesirable effects) of the tadalafil SmPC with a frequency of uncommon.	AEs of haematuria, haematospermia and penile haemorrhage are not included in the FDA PL	AEs of haematuria, haematospermia and penile haemorrhage are not included in the TGA PI
26/03/2010 Following the assessment of PSUR 10 (reports from 16 October 2007 - 15 October 2008) section 4.8 (Undesirable effects) of the SmPC was modified to add text [underlined] “stroke <u>including haemorrhagic events</u>”	Although stroke is included as an AE, the text ‘including haemorrhagic events’ is not.	Although stroke is included as an AE, the text ‘including haemorrhagic events’ is not.

EC approval date Variations to EMA SmPC (safety-related only)	FDA PL	TGA PI
Riociguat		
02/05/2017 Results of an interaction study indicated that ethinyl estradiol and levonorgestrel exposure was not affected when administered on top of a treatment with riociguat. Text added, including "Based on this study and as riociguat is not an inducer of any of the relevant metabolic enzymes, also no pharmacokinetic interaction is expected with other hormonal contraceptives"	Information on the drug interaction between riociguat and hormonal contraceptives is not included in the FDA PL	Information on the drug interaction between riociguat and hormonal contraceptives is not included in the TGA PI

AE= adverse event; CHMP = Committee for Medicinal Products for Human Use; COPD = chronic obstructive pulmonary disease; EC = European Commission; EMA = European Medicines Agency; FDA = Food and Drug Administration; PDE-5 = phosphodiesterase type 5; PI = Product Information; PL = Product Label; PSUR = Periodic Safety Update Report; SmPC = Summary of Product Characteristics; TGA = Therapeutic Goods Administration
Source: www.ema.europa.eu

Apart from the five PAH medicines listed in the table above, no key differences were identified for macitentan and iloprost between the PI documents from the three regulatory agencies. The other PAH medicine, i.e. epoprostenol, is not centrally authorised (authorised on a country-by-country basis instead). Thus the same type of SmPC changes to safety information is not available for epoprostenol brands. However, the PI for epoprostenol was 'harmonised' in 2012 to ensure currency and consistency across the 14 countries, including the UK. This process was coordinated by the EMA and, based on a comprehensive review of efficacy and safety data, resulted in a single consistent SmPC text for all 14 countries. A comparison of the current UK SmPC with the 2012 document from the EMA process indicates there have been minimal changes in terms of safety data.

Potential important safety signals identified via reviewing the safety-related variations to the EMA SmPC include: use of bosentan in patients with chronic obstructive pulmonary disease; AEs of penile haemorrhage and haematospermia in patients receiving PDE-5 inhibitors (both sildenafil and tadalafil); potential for vaso-occlusive crises in patients receiving sildenafil for PH secondary to sickle cell anaemia; and intracerebral haemorrhage in tadalafil-treated patients.

The EMA SmPC states that sildenafil is indicated for treatment of paediatric patients aged 1 year to 17 years old with PAH. The SmPC also indicates that efficacy of sildenafil in terms of improvement of exercise capacity or pulmonary haemodynamic parameters has been shown in children with primary pulmonary hypertension and PAH-CHD, which was supported by clinical data from short-term RCT STARTS-1. In the long-term STARTS extension study, however, an increase in deaths was observed in patients administered higher doses of sildenafil. During a median follow-up of 4.6 years, there were a total of 42 deaths reported. Thirty-seven deaths occurred prior to a decision taken by the Data Monitoring Committee to down titrate subjects to a lower dosage, based on an observed mortality imbalance with increasing sildenafil doses. Among these 37 deaths, the number (%) of deaths was 5/55 (9.1%), 10/74 (13.5%), and 22/100 (22%) in the sildenafil low, medium, and high dose groups, respectively, with causes of deaths being related to PAH. to PAH. Based on this result, the EMA SmPC highlights that doses higher than the

recommended doses (i.e. 10 mg tid in children weighing <20 kg and 20 mg tid in those >20 kg) should not be used in paediatric patients with PAH.

Based on the observation of increasing mortality with increasing sildenafil doses in the STARTS extension study, the FDA revised the Revatio (sildenafil) drug label in August 2012, adding a warning stating that "use of Revatio, particularly chronic use, is not recommended in children." This recommendation was FDA also issued a Drug Safety Communication at that time. In Marh 2014, The FDA clarified its previous recommendation related to prescribing sildenafil for children with PAH: sildenafil is FDA-approved only to treat PAH in adults, not in children; however, health care professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient.

The results from the short-term Trial STARTS-1 and its long-term extension study have been included in the TGA-approved PI. The Australian PI clearly states that sildenafil is not indicated for use in children under 18 years of age. The use of sildenafil in paediatric patients was also discussed in ToR 1 section (guideline review).

Other safety signal detection

In addition to safety signals brought forward within the routine periodic safety update reports and variations procedures, the EMA maintains a list of all safety signals that have triggered further investigation outside (or in addition to) those procedures by the Pharmacovigilance Risk Assessment Committee since September 2012[§]. A summary for PAH medicines is presented in Table 4.119. Safety signals can arise from any source including pharmacovigilance reporting, but also ongoing clinical trials, literature reports and so on.

§ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp

Table 4.119 PAH safety signals considered by PRAC since September 2012

Type of Safety Signal	PRAC Meeting	Update to SmPC Recommended?	FDA PL	TGA PI
Sildenafil				
Increased risk of incident melanoma	July 2014 November 2014	No	Not included in the FDA PL	Not included in the TGA PI
NAION	April 2015	No	When used to treat erectile dysfunction, NAION, a cause of decreased vision including permanent loss of vision, has been reported post-marketing in temporal association with the use of PDE-5 inhibitors, including sildenafil.	Physicians should advise patients to stop use of all PDE-5 inhibitors, including sildenafil, and seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of NAION, a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE-5 inhibitors when used in the treatment of male-erectile dysfunction.
Pulmonary haemorrhage in off label paediatric use	January 2015 May 2015	No	Not included in the FDA PL. Use of sildenafil, particularly chronic use, is not recommended in children.	Not included in the TGA PI. Sildenafil is not indicated for use in children under 18 years of age.
Iloprost				
Bradycardia	September 2017	No	–	Bradycardia is a frequently observed symptom following overdose of iloprost.
Riociguat				
Increased mortality and SAEs in patients with PH-IIP in a single clinical trial	June 2016 October 2016	Yes No	–	Riociguat is contraindicated in patients with PH-IIP. No further information provided.

NAION = non-arteritic anterior ischaemic optic neuropathy; FDA = Food and Drug Administration; PDE=5 = phosphodiesterase type 5; PH-IIP = pulmonary hypertension associated with idiopathic interstitial pneumonias; PI = Product Information; PL = Product Label; PRAC = Pharmacovigilance Risk Assessment Committee; SAE = serious adverse event; SmPC = Summary of Product Characteristics; TGA = Therapeutic Goods Administration
Source: www.ema.europa.eu

A trend to increased mortality was observed in a Phase II clinical trial of patients with idiopathic interstitial pneumonia and who received riociguat (the RISE-IIP study). The trial was terminated early as a result. The Pharmacovigilance Risk Assessment Committee initially recommended a contraindication for idiopathic interstitial pneumonia patients and in June 2016, the EMA published an advisory that riociguat is not indicated for treatment of patients with idiopathic interstitial pneumonia and furthermore should not be used in such patients in light of the trial

results in idiopathic interstitial pneumonia patients. After a second Pharmacovigilance Risk Assessment Committee consideration in October 2016, the Committee revised its view on receiving further information from the sponsor. The Committee considered that "no definitive underlying mechanisms or subgroups at risk could be identified" and imposed a suite of follow-up measures relating to the potential link between mortality, riociguat and both idiopathic interstitial pneumonia and also combined pulmonary fibrosis and emphysema. No change has been made to the SmPC regarding interstitial pneumonia. Both TGA PI and FDA product label contraindicate use of riociguat in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias. No further safety information regarding the use of riociguat (i.e. results from Trial RISE-IIP) has been included.

4.5 Conclusions

4.5.1 Effectiveness and safety of monotherapy in WHO FC I or II PAH

4.5.1.1 ERA versus placebo

Clinical effectiveness

The detailed GRADE[1] assessments of the outcomes when comparing an ERA with placebo are reported in Table 4.146 in Appendix 4C. A summary of these results is provided in Table 4.120. The evidence base for the outcomes ranked as critical and not important were considered to be of high quality (GRADE ⊕⊕⊕⊕) and the evidence base for the outcomes ranked as important was considered to be of moderate (GRADE ⊕⊕⊕⊙) or low (GRADE ⊕⊕⊙⊙) quality.

When taking the whole body of evidence into account, there were [redacted] patients experiencing clinical worsening when taking an ERA medication compared with placebo. There was also a clinically important placebo-adjusted difference from baseline in PVR in the ERA group. All other outcomes also favoured the use of an ERA over a placebo, but the range of point estimates included in the 95% CI indicates that a lack of effect cannot be ruled out.

Thus, the use of an ERA medication to treat patients with WHO FC I/II PAH is likely to be beneficial.

Table 4.120 Balance of clinical benefits and harms of an ERA, relative to placebo

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=357 k=4 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +2	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
All-cause mortality	N=256 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
Improved WHO FC	N=101 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	ARD = 14.0% (95% CI 4.4, 23.6)	Significantly more patients treated with an ERA improved their WHO FC compared with placebo (p = 0.0056)	Moderate ⊕⊕⊕⊙ Important
Worsened WHO FC	N=101 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	RR = 0.25 (95% CI 0.03, 2.20)	Fewer patients had WHO FC worsening when treated with an ERA compared with placebo, but the 95% CI indicates that there could also be the opposite effect	Low ⊕⊕⊙⊙ Important
Change in 6MWD from baseline	N=154 k=3 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0	Range 25.7−40.0 m further	Patients treated with an ERA had a larger mean improvement in their 6MWD compared with those on placebo, and the difference could be clinically important in 2 out of 3 studies	Moderate ⊕⊕⊕⊙ Important
Change in haemodynamic parameters from baseline	N=156 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: 0 Publication bias: 0 Association: 0	PVR MD = 23.1% improvement (95% CI 8.9, 35.1)	Patients treated with an ERA had a larger mean improvement in their haemodynamic parameters compared with those on placebo	Low ⊕⊕⊙⊙ Not important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; MD = mean difference; N = number of patients; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Safety

No conclusions about the comparative safety of an ERA medication versus placebo in patients with WHO FC I/II PAH could be made due to a lack of evidence.

4.5.1.2 PDE-5 inhibitor versus placebo

Clinical effectiveness

The detailed GRADE[1] assessments of the outcomes when comparing a PDE-5 inhibitor with placebo are reported in Table 4.147 in Appendix 4C. A summary of these results is provided in Table 4.121. The evidence base for the critical outcome of all-cause mortality is derived from two observational cohort studies and is of very low quality (GRADE ⊕⊙⊙⊙). Thus, although the RR favours PDE-5 inhibitor over conventional therapy, the true effect is uncertain as the 95% CI indicates that there may also be no or the opposite effect.

The evidence base presented for important outcomes of improved or worsened WHO FC was considered to be of low quality (GRADE ⊕⊕⊙⊙). Thus, the true effect of treating WHO FC I/II PAH with a PDE-5 inhibitor compared with a placebo is uncertain. The estimates suggested there was no difference in the proportion of patients whose WHO FC either improved or worsened, indicating that PDE-5 inhibitor may be equally as effective as placebo with respect to changing the WHO FC of patients with WHO FC I/II PAH. However, the wide 95% CIs and small study size indicate the study was likely underpowered to detect a difference.

Thus, there is considerable uncertainty as to whether the use of a PDE-5 inhibitor medication to treat patients with WHO FC I/II PAH would be beneficial.

Table 4.121 Balance of clinical benefits and harms of a PDE-5 inhibitor, relative to placebo or conventional therapy

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
All-cause mortality	N=76 k=2 cohort	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: +1	RR = 0.32 (95% CI 0.05, 1.90)	Fewer patients died from any cause when treated with a PDE-5 inhibitor compared with placebo, but the 95% CI indicates that there may also be no or the opposite effect.	Very low ⊕⊙⊙⊙ Critical
Improved WHO FC	N=22 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	RR = 1.00 (95% CI 0.07, 15.00)	The same proportion of patients improved their WHO FC taking a PDE-5 inhibitor compared with placebo, but the wide 95% CI indicates that the study was underpowered for this outcome	Low ⊕⊕⊙⊙ Important
Worsened WHO FC	N=22 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association:	Not estimable	The WHO FC did not worsen for any patient during the study period	Low ⊕⊕⊙⊙ Important
Change in 6MWD from baseline	N=73 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0	Range 10.8−50.2 m further	Patients treated with a PDE-5 inhibitor had a larger improvement in 6MWD compared with those on placebo, and the difference was clinically important in 1 study	Low ⊕⊕⊙⊙ Important

[a] GRADE Working Group grades of evidence[1]
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PDE-5 = phosphodiesterase type 5; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Safety

No conclusions about the comparative safety of a PDE-5 inhibitor versus placebo in patients with WHO FC I/II PAH could be made due to a lack of evidence.

4.5.1.3 Prostanoid versus placebo

There was no evidence to inform on the safety and effectiveness of prostanoids in treating patients with WHO FC I/II PAH.

4.5.1.4 sGC stimulator versus placebo

Clinical effectiveness

The evidence for the sGC stimulators comes from a single RCT[23]. The GRADE[1] assessments of the outcomes when comparing a sGC stimulator with placebo are reported in [redacted] in Appendix 4C. A summary of these results is provided in Table 4.122. The evidence base for all outcomes was considered to be of high quality (GRADE ⊕⊕⊕⊕). Thus, the true effect of treating WHO FC I/II PAH with an sGC stimulator compared with placebo is likely to be close to the reported point estimate.

When taking GRADE into account, the evidence favouring the use of a sGC stimulator over placebo [redacted]. There was also [redacted] placebo-adjusted mean difference [redacted] of the haemodynamic parameter, PVR. There was [redacted] to determine whether treatment with an sGC stimulator prevents hospitalisation. This was also true for preventing mortality [redacted] over the 12-week study period. There was [redacted] for the remaining outcomes. Given the short study period of 12 weeks, the study was [redacted].

Thus, there is [redacted] as to whether the use of a sGC stimulator medication to treat patients with WHO FC I/II PAH [redacted].

Table 4.122 Balance of clinical benefits and harms of a sGC stimulator, relative to placebo

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=107 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	[redacted]	[redacted]	Low ⊕⊕⊙⊙ Critical
All-cause mortality	N=107 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
Hospitalisation due to worsening PAH	N=107 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important
Improved WHO FC	N=107 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Important
Worsened WHO FC	N=107 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +2	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important
Change in 6MWD from baseline	N=107 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Important
Change in QoL from baseline	N=107 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important
Change in haemodynamic parameters from baseline	N=107 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: 0 Publication bias: 0 Association: +1	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Not important

[a] GRADE Working Group grades of evidence[1]
[b] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[c] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQol 5 dimension; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; LPH = living with pulmonary hypertension; MD = mean difference; N = number of patients; PVR = pulmonary vascular resistance; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; sGC stimulator = soluble guanylate cyclase; WHO = World Health Organization

Safety

No conclusions about the comparative safety of a sGC stimulator versus placebo in patients with WHO FC I/II PAH could be made due to a lack of evidence.

4.5.2 New evidence of effectiveness and safety of monotherapy in WHO FC III and IV

No new evidence was identified.

4.5.3 Effectiveness and safety of dual combination therapy

4.5.3.1 ERA in addition to PDE-5 inhibitor

Clinical effectiveness

Of the four trials that provided the evidence base for comparing the effectiveness of an ERA in addition to PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy, three trials enrolled patients on stable PDE-5 inhibitor monotherapy (sequential combination therapy) and one trial (AMBITION) enrolled treatment naïve patients (initial combination therapy). There were no statistically significant differences between the outcomes for patients receiving initial combination therapy versus monotherapy for the AMBITION trial compared with the other three trials with patients receiving sequential combination therapy versus monotherapy. Two RCTs also included subgroup analyses for patients with WHO FC III/IV PAH, and two RCTs included subgroup analyses for patients with different PAH aetiologies.

The detailed GRADE[1] assessments of effectiveness outcomes when comparing an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy are reported in Table 4.149 to Table 4.151 in Appendix 4C. The evidence for the effectiveness outcomes for all PAH patients is summarised in Table 4.123.

All outcomes were considered to be of high quality (GRADE ⊕⊕⊕⊕), except for all-cause mortality (moderate GRADE ⊕⊕⊕⊙) and change in 6MWD (low GRADE ⊕⊕⊙⊙). Thus, the true effect of treating WHO FC I/II PAH with an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy is likely to be close to the reported point estimate. However, the possibility of the true estimate being close to the 95% CIs cannot be ruled out.

When taking the whole body of evidence into account, [redacted] patients experienced [redacted] and PHA-related hospitalisation when taking combination therapy compared with monotherapy. The differences between combination therapy and monotherapy [redacted]

[redacted], and there was little difference in improved or worsened WHO FC between treatment arms. However, the range of values in the 95% CIs included clinically relevant values favouring combination therapy over monotherapy, except for worsened WHO FC, which also had values favouring monotherapy. Thus, the true effect could not be determined for these outcomes. The mean differences in [redacted] and QoL [redacted], but [redacted].

Thus, there is some evidence to suggest that the use of an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy to treat PAH patients is likely to be beneficial.

Table 4.123 Balance of clinical benefits of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy in all PAH patients

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=1,124 k=4 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
All-cause mortality	N=1124 k=4 RCTs	Risk of bias: 0 Inconsistency: −1 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Critical
Hospitalisation due to worsening PAH	N=761 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	Pooled RR = 0.67 (95% CI 0.45, 0.98)	Significantly fewer patients on combination therapy were hospitalised compared with monotherapy	High ⊕⊕⊕⊕ Important
Improved WHO FC	N=706 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	Pooled RR = 1.10 (95% CI 0.85, 1.42)	There was little difference in the proportion of patients receiving combination therapy or monotherapy who improved their WHO FC	High ⊕⊕⊕⊕ Important
Worsened WHO FC	N=706 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 1.00 (95% CI 0.58, 1.73)	There was no difference in the proportion of patients receiving combination therapy or monotherapy who had worsening of their WHO FC	High ⊕⊕⊕⊕ Important

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Change in 6MWD from baseline	N=1,046 k=4 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: −1 Publication bias: 0 Association: 0	Range 17.3 m less to 26.3 m further	In 3 out of 4 studies, patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy [redacted]	Low ⨁⨁⊙⊙ Important
Change in QoL from baseline	N=299 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	SF-36 physical component [b] MD = 1.4 point improvement (95% CI 0, 2.9)	Patients on combination therapy had a larger mean improvement in their QoL than those on monotherapy	High ⨁⨁⨁⨁ Important

[a] GRADE Working Group grades of evidence [1]
[b] SF-36 physical component summary scores range from 0 to 100. A higher score indicates better QoL.
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; MD = mean difference; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; SF-36 = short form 36; WHO = World Health Organization

The evidence for the two outcomes reported for patients with WHO FC III/IV PAH is summarised in Table 4.124. Both critical outcomes were considered to be of high quality (GRADE ⨁⨁⨁⨁). Thus, the true effect of treating WHO FC III/IV PAH with an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy is likely to be close to the reported point estimate.

When taking the whole body of evidence into account, [redacted] patients experienced clinical worsening when taking combination therapy compared with monotherapy. This [redacted]. Although the point estimate for all-cause mortality was [redacted], it [redacted]. However [redacted] the true effect could not be determined.

Thus, there is some uncertainty as to whether the use of an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy to treat patients with WHO FC III/IV PAH is likely to be beneficial.

Table 4.124 Balance of clinical benefits of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy in patients with WHO FC III/IV PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=351 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
All-cause mortality	N=157 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

The evidence for clinical worsening for patients with different PAH aetiologies is summarised in Table 4.125. The evidence provided for this outcome was considered to be of high quality (GRADE ⊕⊕⊕⊕).

When taking the whole body of evidence into account, there was no statistically significant difference in the proportion of patients with different PAH aetiologies who experienced clinical worsening with combination therapy or monotherapy treatment. Thus, there is some uncertainty as to whether there is differential effectiveness in patients with different PAH aetiologies treated with an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy.

Table 4.125 Balance of clinical benefits of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy in patients with different PAH aetiologies

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening in IPAH/HPAH	N=226 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	HR = 0.82 (95% CI 0.55, 1.21)	Fewer patients with IPAH/HPAH on combination therapy experienced clinical worsening compared with monotherapy, but the 95% CI indicates that there could be no or the opposite effect	High ⊕⊕⊕⊕ Critical
Clinical worsening in PAH CTD	N=231 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	Pooled HR = 0.59 (range 0.12, 1.07)	Fewer patients with PAH-CTD on combination therapy experienced clinical worsening compared with monotherapy, but this did not quite reach statistical significance	High ⊕⊕⊕⊕ Critical
Clinical worsening in PAH-CHD	N=20 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	HR = 0.57 (95% CI 0.10, 3.17)	Fewer patients with PAH-CHD on combination therapy experienced clinical worsening compared with monotherapy, but the 95% CI indicates that the study was underpowered for this outcome	Low ⊕⊕⊙⊙ Critical

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
CHD = associated with congenital heart disease; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; HR = hazard ratio; HPAH = heritable PAH; IPAH = idiopathic PAH; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial

Safety

The detailed GRADE[1] assessments of safety outcomes when comparing an ERA in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy are reported in Table 4.152 and Table 4.153 in Appendix 4C. The evidence for the safety outcomes for all PAH patients are summarised in Table 4.126. There were no new safety signal identified.

All outcomes were considered to be of high quality (GRADE ⊕⊕⊕⊕). Patients were just as likely to experience an AE after starting combination therapy as they were on monotherapy. Patients on combination therapy were significantly less likely to have a serious AE. The point estimate indicated that patients were more likely to have an AE leading to treatment discontinuation compared with those on monotherapy, but the 95% CI indicates that there could also be no effect. The comparative safety of ERA plus PDE-5 inhibitor relative to PDE-5 inhibitor monotherapy with

regard to AEs of interest of abnormal liver function and decreased haemoglobin was in different directions.

Thus, use of an ERA in addition to a PDE-5 inhibitor could be non-inferior to PDE-5 inhibitor monotherapy in terms of safety when treating PAH patients.

Table 4.126 Balance of clinical harms of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy in all patients with PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Any AE	N=333 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 0.99 (95% CI 0.93, 1.06)	The proportion of patients that experience an AE with combination therapy will be similar to the proportion on monotherapy	High ⊕⊕⊕⊕ Important
Serious AEs	N=705 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	Pooled RR = 0.82 (95% CI 0.69, 0.96)	Significantly fewer patients experienced a serious AE with combination therapy compared with monotherapy	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation	N=705 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	Pooled RR = 1.47 (95% CI 0.81, 2.66)	More patients needed to discontinue treatment due to an AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be no or the opposite effect	High ⊕⊕⊕⊕ Important
Abnormal liver function AEs	N=307 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: +1	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important
Haemoglobin decrease-related AEs	N=307 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: +1	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; RR = relative risk

The evidence for the safety outcomes for patients with different PAH aetiologies are summarised in Table 4.127. Any AE and serious AE outcomes were considered to be of high quality (GRADE ⊕⊕⊕⊕) and discontinuation of study medication due to an AE was of moderate quality (GRADE ⊕⊕⊕⊙).

Overall, the comparative safety of an ERA plus a PDE-5 inhibitor relative to PDE-5 inhibitor monotherapy in the subgroup of patients with IPAH/HPAH and in the subgroup of patients with PAH-CTD appeared to be largely consistent with the comparative safety in the overall PAH population.

Table 4.127 Balance of clinical harms of an ERA in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy in patients with different PAH aetiologies

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
IPAH/HPAH					
Any AE in IPAH/HPAH	N=204 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 1.04 (95% CI 0.97, 1.12)	The proportion of patients with IPAH/HPAH that experience an AE with combination therapy was similar to the proportion on monotherapy	High ⊕⊕⊕⊕ Important
Serious AEs in IPAH/HPAH	N=204 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 0.85 (95% CI 0.58, 1.25)	Fewer patients with IPAH/HPAH had a serious AE with combination therapy compared with monotherapy, but the study was likely underpowered for this outcome	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation in IPAH/HPAH	N=204 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	RR = 0.98 (95% CI 0.44, 2.20)	The proportion of patients who had an AE leading to treatment discontinuation was similar for both the combination therapy and monotherapy	Moderate ⊕⊕⊕⊙ Important
PAH-CTD					
Any AE in PAH-CTD	N=143 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 1.02 (95% CI 0.96, 1.07)	The proportion of patients with PAH-CTD who experienced an AE with combination therapy was similar to the proportion on monotherapy	High ⊕⊕⊕⊕ Important

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Serious AEs in PAH-CTD	N=143 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	RR = 0.87 (95% CI 0.60, 1.28)	Fewer patients with PAH-CTD had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be no or the opposite effect.	High ⨁⨁⨁⨁ Important
AEs leading to treatment discontinuation in PAH-CTD	N=143 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	RR = 0.91 (95% CI 0.37, 2.19)	Fewer patients had an AE leading to treatment discontinuation with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be no or the opposite effect.	Moderate ⨁⨁⨁⊙ Important

[a] GRADE Working Group grades of evidence [1]
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; HPAH = heritable PAH; IPAH = idiopathic PAH; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; RR = relative risk

4.5.3.2 ERA in addition to a prostanoid

Clinical effectiveness

Both of the trials that provided the evidence base for comparing the effectiveness of an ERA in addition to prostanoid compared with prostanoid monotherapy enrolled treatment naïve patients who received either initial combination therapy or initial monotherapy. Additionally, both studies only enrolled patients with WHO FC III/IV.

The detailed GRADE[1] assessments of effectiveness outcomes when comparing an ERA in addition to prostanoid, relative to prostanoid tor monotherapy are reported in Table 4.154 and Table 4.155 in Appendix 4C. The evidence for the effectiveness outcomes for all PAH patients are summarised in Table 4.128. All outcomes were considered to be of very low (GRADE ⨁⊙⊙⊙), except all-cause mortality, which was of low quality (GRADE ⨁⨁⊙⊙). Thus, the true effect may be substantially different from the point estimate.

When taking the whole body of evidence into account, more patients died from any cause whilst more patients improved their WHO FC when taking combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was not statistically powered to detect a true difference. The mean difference in the haemodynamic parameters all favoured combination therapy but were not large enough to be clinically important. The mean differences in 6MWD and QoL favouring combination therapy over monotherapy were clinically important.

Thus, there is uncertainty as to whether an ERA in addition to prostanoid, relative to prostanoid monotherapy, is beneficial in patients with WHO FC III/IV PAH.

Table 4.128 Balance of clinical benefits of an ERA in addition to a prostanoid, relative to prostanoid monotherapy in patients with WHO FC III/IV PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
All-cause mortality	N=33 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	ARD = 13.6% (95% CI −0.70, 28.0)	More patients died from any cause with combination therapy compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome (p = 0.20)	Low ⊕⊕⊙⊙ Critical
Improved WHO FC	N=33 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	RR = 1.30 (95% CI 0.62, 2.71)	More patients on combination therapy improved their WHO FC compared with those on monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome	Very low ⊕⊙⊙⊙ Important
Change in 6MWD from baseline	N=47 k=2 RCTs	Risk of bias: −1 Inconsistency: −1 Indirectness: −1 Imprecision: −2 Publication bias: 0 Association: 0	Range 6.0 m less to 123.6 m further	Patients on combination therapy had either a smaller or a large improvement in their 6MWD than those on monotherapy	Very Low ⊕⊙⊙⊙ Important
Change in QoL from baseline	N=14 k=1 RCT	Risk of bias: −2 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	MLHF[b] MD = 35.34 point improvement	Patients on combination therapy had a larger, clinically important mean improvement in their QoL compared with monotherapy	Very low ⊕⊙⊙⊙ Important
Change in haemodynamic parameters from baseline	N=47 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: −2 Imprecision: −2 Publication bias: 0 Association: 0	CAI Range 10.8−17% improvement PVR Range 9.5−21.5% improvement mPAP Range 6.8−26.3% improvement	Patients on combination therapy had larger mean improvements in their haemodynamic parameters compared with monotherapy and were likely to be clinically important in 1 out of 2 studies	Very low ⊕⊙⊙⊙ Not important

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Change in haemodynamic parameters from baseline	N=33 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: −2 Publication bias: 0 Association: 0	mRAP MD = 2.2 mmHg improvement TPR MD 13.7% improvement	Patients on combination therapy had larger mean improvements in their haemodynamic parameters compared with monotherapy	Very low ⨁⊙⊙⊙ Not important

[a] GRADE Working Group grades of evidence [1]
[b] MLHF questionnaire total scores range from 0 to 105. A higher score indicates poorer QoL.
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CAI = cardiac index; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; MD = mean difference; MLHF = Minnesota living with heart failure; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; MD = mean difference; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; TPR = total pulmonary pressure; WHO = World Health Organization

Safety

The detailed GRADE[1] assessments of safety outcomes when comparing an ERA in addition to prostanoid, relative to prostanoid monotherapy are reported in Table 4.155 in Appendix 4C. The evidence for the safety outcomes for all PAH patients are summarised in Table 4.129. There were no new safety signal identified.

The evidence for all the safety outcomes were considered to be of low (GRADE ⨁⨁⊙⊙) or very low quality (GRADE ⨁⊙⊙⊙). Thus, the true effect may be substantially different from the point estimate. Patients were just as likely to experience an AE after starting combination therapy as they were on monotherapy. Patients on combination therapy were less likely to have either a serious AE or an AE that would lead to treatment discontinuation compared with those on monotherapy, but the wide 95% CI indicates that the study was statistically underpowered.

Thus, although there is uncertainty, use of an ERA in addition to a prostanoid may be non-inferior to prostanoid monotherapy when treating patients with WHO FC III/IV PAH.

Table 4.129 Balance of clinical harms of an ERA in addition to a prostanoid, relative to prostanoid monotherapy in patients with WHO FC III/IV PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Any AE	N=14 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	RR = 1.05 (95% CI 0.67, 1.64)	The proportion of patients who experience an AE with combination therapy was similar to the proportion on monotherapy.	Low ⊕⊕⊙⊙ Important
Serious AEs	N=33 k=1 RCT	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	Pooled RR = 0.75 (95% CI 0.15, 3.85)	Fewer patients experienced a serious AE with combination therapy compared with monotherapy, but the wide 95% CI indicates the study was likely underpowered for this outcome.	Very low ⊕⊙⊙⊙ Important
AEs leading to treatment discontinuation	N=33 k=1 RCT	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	Pooled RR = 0.50 (95% CI 0.03, 7.26)	Fewer patients needed to discontinue treatment due to an AE with combination therapy compared with monotherapy, but the wide 95% CI indicates the study was likely underpowered for this outcome.	Very low ⊕⊙⊙⊙ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

4.5.3.3 PDE-5 inhibitor in addition to ERA

Clinical effectiveness

Of the five RCTs that provided the evidence base for comparing the effectiveness of a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy, four trials enrolled patients on stable ERA monotherapy (sequential combination therapy) and one trial (AMBITION) enrolled treatment naïve patients (initial combination therapy). There were no statistically significant differences between the outcomes for patients receiving initial combination therapy versus monotherapy for the AMBITION trial compared with the other four trials with patients receiving sequential combination therapy versus monotherapy. Additionally, two RCTs also included subgroup analysis for patients with WHO FC III/IV PAH, and three RCTs included subgroup analysis for patients with different PAH aetiologies.

The detailed GRADE[1] assessments of the outcomes when comparing a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy are reported in Table 4.156 to Table 4.158 in Appendix 4C. A summary of these results for all PAH patients with is provided in Table 4.130.

The evidence for all outcomes was considered to be of high quality (GRADE ⊕⊕⊕⊕), except for all-cause mortality (moderate GRADE ⊕⊕⊕⊙) and change in haemodynamic parameters (low GRADE ⊕⊕⊙⊙).

When taking the whole body of evidence into account, the number of patients experiencing clinical worsening and hospitalisation due to PAH would be significantly reduced when taking a PDE-5 inhibitor in addition to an ERA compared with ERA monotherapy. All other outcomes also favoured the use of combination therapy over monotherapy, but the range of point estimates included in the 95% CI indicates that a lack of effect or an opposite effect cannot be ruled out. The mean difference in haemodynamic parameters and 6MWD favoured combination therapy over monotherapy but the size of the differences were not clinically important, except in one out of five studies reporting the change in 6MWD.

Thus, there is some evidence to suggest that the use of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy to treat PAH patients is likely to be beneficial.

Table 4.130 Balance of clinical benefits of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy in all PAH patients

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=694 k=4 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	Pooled RR = 0.53 (95% CI 0.38, 0.73)	Significantly fewer patients on combination therapy experienced clinical worsening compared with monotherapy	High ⊕⊕⊕⊕ Critical
All-cause mortality	N=682 k=3 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: +1	Pooled RR = 0.64 (95% CI 0.18, 2.36)	Fewer patients died from any cause with combination therapy compared with monotherapy, but the 95% CI indicates that there may also be no or the opposite effect.	Moderate ⊕⊕⊕⊙ Critical
Hospitalisation due to worsening PAH	N=607 k=3 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	Pooled RR = 0.42 (95% CI 0.25, 0.70)	Significantly fewer patients died from any cause with combination therapy compared with monotherapy and the difference was clinically important in 1 study	High ⊕⊕⊕⊕ Important
Improved WHO FC	N=691 k=4 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	Pooled RR = 1.11 (95% CI 0.77, 1.60)	The proportion of patients who improved their WHO FC with combination therapy will be similar to the proportion on monotherapy.	High ⊕⊕⊕⊕ Important

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Worsened WHO FC	N=691 k=4 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: +1	Pooled RR = 0.60 (95% CI 0.34, 1.05)	Fewer patients on combination therapy had WHO FC worsening than those on monotherapy, but the result did not quite reach statistical significance.	High ⊕⊕⊕⊕ Important
Change in 6MWD from baseline	N=726 k=5 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0	Range 2.4 m less to 36.1 m further	In 4 out of 5 studies, patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, and the difference was clinically important in 1 study	Moderate ⊕⊕⊕⊙ Important
Change in haemodynamic parameters from baseline	N=124 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: 0 Publication bias: 0 Association: 0	PVR MD = 13.9% improvement mPAP MD = 8.5% improvement	Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy	Low ⊕⊕⊙⊙ Not important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; mPAP = mean pulmonary artery pressure; MD = mean difference; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

The moderate quality (GRADE ⊕⊕⊕⊙) evidence for the change in 6MWD reported for patients with WHO FC III/IV PAH is summarised in Table 4.131. The mean difference in 6MWD favoured combination therapy over monotherapy but the size of the difference was not clinically important in either study.

Thus, there is limited evidence to determine whether the use of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy to treat patients with WHO FC III/IV PAH is likely to be beneficial.

Table 4.131 Balance of clinical benefits of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy in patients with WHO FC III/IV PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Change in 6MWD from baseline	N=109 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0	Range 13.5−20.1 m further	Patients with WHO FC III/IV PAH on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important	Moderate ⊕⊕⊕⊙ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
6MWD = 6-minute walk distance; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; WHO = World Health Organization

The evidence for effectiveness outcomes for patients with different PAH aetiologies is summarised in Table 4.132. The evidence provided for clinical worsening in patients with PAH-CTD was considered to be of high quality (GRADE ⊕⊕⊕⊕), and for change in 6MWD it was of moderate quality (GRADE ⊕⊕⊕⊙) in patients with IPAH/HPAH and very low quality (GRADE ⊕⊙⊙⊙) in patients with PAH-CTD.

Clinical worsening in patients with PAH-CTD favoured combination therapy, and just failed to reach statistical significance (upper 95% CI = 1.01). There was an improvement of 6MWD in patients with IPAH/HPAH and in those with PAH-CTD receiving combination therapy compared with monotherapy, but the distance was not clinically importance.

Thus, there is limited evidence as to whether there is differential effectiveness in patients with different PAH aetiologies treated with a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy.

Table 4.132 Balance of clinical benefits of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy in patients with different PAH aetiologies

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
IPAH/HAPH					
Change in 6MWD from baseline in IPAH/HPAH	N=120 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0	Range 8.6−13.6 m further	Patients with IPAH/ HPAH on combination therapy had a larger mean improvement in their 6MWD compared with monotherapy, but the difference was not clinically important.	Moderate ⊕⊕⊕⊙ Important
PAH-CTD					
Clinical worsening in PAH CTD	N=147 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	HR = 0.51 (95% CI 0.25, 1.01)	Fewer patients with PAH-CTD experienced clinical worsening with combination therapy compared with monotherapy, but the difference failed to reach statistical significance	High ⊕⊕⊕⊕ Critical
Change in 6MWD from baseline in PAH-CTD	N=55 k=2 RCTs	Risk of bias: 0 Inconsistency: −1 Indirectness: −1 Imprecision: −2 Publication bias: 0 Association: 0	Range 34.1 m less to 20.7 m further	Patients on combination therapy had either a smaller or a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important	Very low ⊕⊙⊙⊙ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; k = number of studies; MD = mean difference; N = number of patients; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; WHO = World Health Organization

Safety

The detailed GRADE[1] assessments of safety outcomes when comparing a PDE-5 inhibitor in addition to ERA, relative to ERA monotherapy are reported in Table 4.159 and Table 4.160 in Appendix 4C. The evidence for the safety outcomes for all PAH patients is summarised in Table 4.133. There were no new safety signal identified by any of the included trials.

Any AE and serious AE outcomes were considered to be of high quality (GRADE ⊕⊕⊕⊕) and discontinuation of study medication due to an AE was of moderate quality (GRADE ⊕⊕⊕⊙).

Patients were just as likely to experience either any AE or a serious AE after starting combination therapy as they were on monotherapy. Patients on combination therapy were more likely to have

an AE that would lead to treatment discontinuation compared with those on monotherapy, but the 95% CI indicates that there could also be no or the opposite effect.

Thus, the use of a PDE-5 inhibitor in addition to ERA may be non-inferior to ERA monotherapy when treating PAH patients.

Table 4.133 Balance of clinical harms of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy in all PAH patients

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Any AE	N=190 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	Pooled RR = 1.00 (95% CI 0.79, 1.27)	The proportion of patients who experienced an AE with combination therapy was similar to the proportion on monotherapy	High ⊕⊕⊕⊕ Important
Serious AEs	N=482 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	Pooled RR = 0.99 (95% CI 0.76, 1.29)	The proportion of patients who had a serious AE with combination therapy was similar to the proportion on monotherapy	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation	N=503 k=2 RCTs	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	Pooled RR = 1.65 (95% CI 0.35, 7.81)	More patients needed to discontinue treatment due to an AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be no or the opposite effect.	Moderate ⊕⊕⊕⊙ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; RR = relative risk

The evidence for the safety outcomes for patients with PAH-CTD is summarised in Table 4.134. There were no new safety signal identified.

All outcomes were considered to be of high quality (GRADE ⊕⊕⊕⊕). Patients were just as likely to have an AE and less likely to experience AE-related treatment discontinuation after starting combination therapy as they were on monotherapy. However, patients on combination therapy were more likely to have a serious AE compared with those on monotherapy, but the 95% CI did not reach statistical significance.

Thus, there is potential safety concern associated with the use of a PDE-5 inhibitor in addition to an ERA when treating patients with PAH-CTD.

Table 4.134 Balance of clinical harms of a PDE-5 inhibitor in addition to an ERA, relative to ERA monotherapy in patients with PAH-CTD

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Any AE in PAH-CTD	N=146 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 1.04 (95% CI 0.97, 1.11)	The proportion of patients with PAH-CTD who experienced an AE with combination therapy was similar to the proportion on monotherapy	High ⊕⊕⊕⊕ Important
Serious AEs in PAH-CTD	N=146 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 1.28 (95% CI 0.80, 2.04)	More patients with PAH-CTD experienced a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be no or the opposite effect.	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation in PAH-CTD	N=146 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 0.75 (95% CI 0.34, 1.65)	Fewer patients with PAH-CTD needed to discontinue treatment due to an AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be no or the opposite effect.	High ⊕⊕⊕⊕ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; RR = relative risk

4.5.3.4 PDE-5 inhibitor in addition to prostanoid

Clinical effectiveness

Only one RCT provided evidence for comparing the effectiveness of a PDE-5 inhibitor in addition to a prostanoid compared with prostanoid monotherapy, and enrolled patients were on stable epoprostenol monotherapy (sequential combination therapy). No WHO FC or PAH aetiology subgroup analysis was undertaken. The detailed GRADE[1] assessments of effectiveness outcomes when comparing a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy are reported in Table 4.161 in Appendix 4C. The evidence for the effectiveness outcomes for all PAH patients is summarised in Table 4.135.

Both critical outcomes were considered to be of high quality (GRADE ⊕⊕⊕⊕), the important outcomes were of moderate quality (GRADE ⊕⊕⊕⊙), and the surrogate outcome of change in haemodynamic parameters was of low quality (GRADE ⊕⊕⊙⊙).

When taking the whole body of evidence into account, significantly fewer patients experienced clinical worsening or died when taking combination therapy compared with monotherapy. However, although the point estimate for hospitalisation favoured combination therapy over monotherapy, the 95% CIs indicated that there may also be the opposite effect. The mean difference in 6MWD for combination therapy versus monotherapy was not clinically important. The mean difference for two of the three parameters reported may be clinically important.

Thus, the use of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy to treat PAH patients is likely to be beneficial.

Table 4.135 Balance of clinical benefits of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy in all PAH patients

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=265 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: +1	RR = 0.33 (95% CI 0.15, 0.70)	Significantly fewer patients experienced clinical worsening with combination therapy compared with monotherapy	High ⊕⊕⊕⊕ Critical
All-cause mortality	N=265 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	ARD = −5.3%; 95% CI −9.2, −1.5)	Significantly fewer patients died from any cause with combination therapy compared with monotherapy (p = 0.007)	High ⊕⊕⊕⊕ Critical
Hospitalisation due to worsening PAH	N=265 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	RR = 0.71 (95% CI 0.30, 1.71)	Fewer patients were hospitalised with combination therapy compared with monotherapy, but the 95% CI indicates that there may also be the opposite effect.	Moderate ⊕⊕⊕⊙ Important
Change in 6MWD from baseline	N=265 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0	MD = 28.8 m further (95% CI 13.9, 43.8)	Patients on combination therapy had a larger mean improvement in their 6MWD compared with those on monotherapy, but the difference was not clinically important	Moderate ⊕⊕⊕⊙ Important
Change in haemodynamic parameters from baseline	N=265 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: 0 Publication bias: 0 Association: 0 to +1	PVR MD = 20.8% improvement mPAP MD = 7.5% improvement mRAP 2.1 mmHg improvement	Patients on combination therapy had a larger mean improvement in their haemodynamic parameters compared with those on monotherapy and this improvement may be clinically important for PVR and mRAP	Low ⊕⊕⊙⊙ Not important

[a] GRADE Working Group grades of evidence [1]

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; MD = mean difference; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; RR = relative risk

Safety

The detailed GRADE[1] assessments of safety outcomes when comparing a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy are reported in Table 4.162 in Appendix 4C. The evidence for the safety outcomes for all PAH patients is summarised in Table 4.136. There were no new safety signal identified.

All outcomes were considered to be of high quality (GRADE ⊕⊕⊕⊕). Patients were just as likely to experience any AE after starting combination therapy as they were on monotherapy. Patients on combination therapy were less likely to have a serious AE and more likely to have an AE that would lead to treatment discontinuation compared with those on monotherapy, but the 95% CI indicates that there could also be no or the opposite effect.

Thus, the use of a PDE-5 inhibitor in addition to a prostanoid is likely to be non-inferior to prostanoid monotherapy in term of safety when treating PAH patients.

Table 4.136 Balance of clinical harms of a PDE-5 inhibitor in addition to a prostanoid, relative to prostanoid monotherapy in all patients with PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Any AE	N=265 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 0.95 (95% CI 0.90, 1.00)	The proportion of patients who experienced an AE with combination therapy was similar to the proportion on monotherapy	High ⊕⊕⊕⊕ Important
Serious AEs	N=265 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 0.73 (95% CI 0.48, 1.10)	Fewer patients experienced a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be no or the opposite effect.	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation	N=265 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	RR = 0.49 (95% CI 0.20, 1.17)	Fewer patients needed to discontinue treatment due to an AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be the opposite effect.	High ⊕⊕⊕⊕ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
AE = adverse event; CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; RR = relative risk

4.5.3.5 Prostanoid in addition to an ERA

Clinical effectiveness

Both of the RCTs that provided the evidence base for comparing the effectiveness of a prostanoid in addition to an ERA compared with ERA monotherapy enrolled patients on stable ERA monotherapy (sequential combination therapy). One trial enrolled patients with WHO FC III IPAH and the other patients with WHO FC III/IV PAH.

The detailed GRADE[1] assessments of the outcomes when comparing a prostanoid in addition to an ERA, relative to ERA monotherapy in patients with WHO FC III/IV PAH are reported in Table 4.163 in Appendix 4C. A summary of these results is provided in Table 4.137. The evidence base for the critical outcomes was considered to be of very low quality (GRADE ⊕⊕⊙⊙) for clinical worsening and moderate quality (GRADE ⊕⊕⊕⊙) for the mortality rate. Other outcomes were considered to be of moderate to very low quality.

When taking the whole body of evidence into account, significantly more patients improved their WHO FC on combination therapy compared with monotherapy, but this was a low quality (GRADE ⊕⊕⊙⊙) outcome. Less patients experienced clinical worsening on combination therapy

compared with monotherapy but the 95% CI indicates that there could also be the opposite effect. No patients died during the study periods of the two included RCTs, so the effect of combination therapy compared with monotherapy on all-cause mortality could not be determined. There was some evidence to suggest that fewer patients were hospitalised or had worsening of their WHO FC with combination therapy compared with monotherapy, but the ARD was small (3−7%). Patients on combination therapy had a larger mean improvement in their 6MWD, haemodynamic parameters and QoL than those on monotherapy, but only the mean differences in PVR and QoL improvement were large enough to be clinically important.

Thus, the use of a prostanoid in addition to an ERA, relative to ERA monotherapy to treat patients with WHO FC III/IV PAH may be beneficial.

Table 4.137 Balance of clinical benefits of a prostanoid in addition to an ERA, relative to ERA monotherapy in patients with WHO FC III/IV PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=105 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	Pooled RR = 0.39 (95% CI 0.04, 3.45)	Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be the opposite effect.	Very low ⨁⊙⊙⊙ Critical
All-cause mortality	N=105 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	Not estimable	There were no deaths during the study period	Moderate ⨁⨁⨁⊙ Critical
Hospitalisation due to worsening PAH	N=105 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	Pooled ARD = −5.5% (95% CI −18.9, 7.8)	Fewer patients were hospitalised with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be the opposite effect.	Moderate ⨁⨁⨁⊙ Important
Improved WHO FC	N=65 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	RR = 5.67 (95% CI 1.36, 23.61)	Significantly more patients on combination therapy improved their WHO FC than those on monotherapy	Low ⨁⨁⊙⊙ Important

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Worsened WHO FC	N=65 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	ARD = −3.0% (95% CI −8.9, 2.8)	Fewer patients experienced clinical worsening with combination therapy compared with monotherapy, but the difference was not statistically significant (p = 0.32)	Moderate ⊕⊕⊕⊙ Important
Change in 6MWD from baseline	N=105 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0	Range 10−26 m further	Patients on combination therapy had a larger mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important	Low ⊕⊕⊙⊙ Important
Change in QoL from baseline	N=40 k=1 RCT	Risk of bias: −2 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: +1	EQ-VAS[b] MD = 10 point improvement	Patients on combination therapy had a larger clinically important mean improvement in their QoL than those on monotherapy	Very low ⊕⊙⊙⊙ Important
Change in haemodynamic parameters from baseline	N=65 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: −1 Publication bias: 0 Association: +1	PVR MD = 30.4% improvement mPAP MD = 15.6% improvement	Patients on combination therapy had a larger mean improvement in their haemodynamic parameters than those on monotherapy. The differences were likely to be clinically important	Low ⊕⊕⊙⊙ Not important

[a] GRADE Working Group grades of evidence [1]
[b] EQ-VAS scores range from 0 to 100. A higher score represents better QoL.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-VAS = EuroQoL visual analogue scale; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; MD = mean difference; mPAP = mean pulmonary artery pressure; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Safety

The detailed GRADE[1] assessments of safety outcomes when comparing a prostanoid in addition to ERA, relative to ERA monotherapy in patients with WHO FC III/IV PAH are reported in Table 4.164 in Appendix 4C. The evidence for the safety outcomes for all PAH patients is summarised in Table 4.138. There were no new safety signal identified by any of the included trials.

Two outcomes were of very low quality (GRADE ⊕⊙⊙⊙) and one outcome was of low quality (GRADE ⊕⊕⊙⊙). Patients on combination therapy were more likely to have an AE and less likely to have a serious AE compared with those on monotherapy, but the wide 95% CI indicates that

there could also be the opposite effect. There was little evidence to determine whether more patients with combination therapy compared with monotherapy as only one patient (in the combination therapy group) discontinued treatment due to an AE.

Thus, there is considerable uncertainty as to whether the use of a prostanoid in addition to ERA is likely to be as safe as ERA monotherapy in patients with WHO FC III/IV PAH.

Table 4.138 Balance of clinical harms of a prostanoid in addition to an ERA, relative to ERA monotherapy in patients with WHO FC III/IV PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Any AE	N=107 k=2 RCTs	Risk of bias: −1 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	Pooled RR = 2.40 (95% CI 0.15, 37.41)	More patients experienced an AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be the opposite effect.	Very low ⊕⊙⊙⊙ Important
Serious AEs	N=67 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	RR = 0.65 (95% CI 0.23, 1.85)	Fewer patients had a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that there could also be the opposite effect.	Low ⊕⊕⊙⊙ Important
AEs leading to treatment discontinuation	N=40 k=1 RCT	Risk of bias: −2 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	ARD = 5.2% (95% CI −4.8, 15.3)	More patients needed to discontinue treatment due to an AE with combination therapy compared with monotherapy, but the difference was not statistically significant (p = 0.29)	Very low ⊕⊙⊙⊙ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
AE = adverse event; ARD = absolute risk difference; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

4.5.3.6 sGC stimulator in addition to an ERA

Clinical effectiveness

The RCT that provided the evidence base for comparing the effectiveness of a sGC stimulator in addition to an ERA compared with ERA monotherapy enrolled a subgroup of patients with background ERA therapy (sequential combination therapy). Subgroup analysis for patients with WHO FC III/IV PAH was also included.

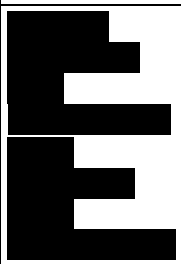
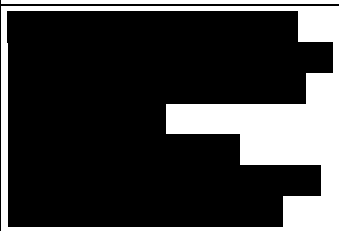
The detailed GRADE[1] assessments of the outcomes when comparing a sGC stimulator in addition to an ERA, relative to ERA monotherapy are reported in [redacted] and [redacted] in Appendix 4C. A summary of these results for all PAH patients is provided in Table 4.139.Table 4.139The evidence base for all outcomes was considered to be of high (GRADE ⊕⊕⊕⊕) or moderate (GRADE ⊕⊕⊕⊙) quality, except for change in haemodynamic parameters which is of low quality (GRADE ⊕⊕⊙⊙).

When taking the whole body of evidence into account, the point estimates indicate that the number of patients experiencing clinical worsening, dying from any cause or being hospitalised would be [redacted] when on combination therapy compared with monotherapy [redacted]. Similarly, [redacted] patients will have an improvement in their WHO FC and [redacted] a worsening of WHO FC, [redacted] Patients on combination therapy had [redacted] in their 6MWD, PVR and QoL than those on monotherapy, but only the mean difference for EQ-5D QoL [redacted].

Thus, there is limited evidence indicating that the use of a sGC stimulator in addition to an ERA, relative to ERA monotherapy to treat PAH patients may be beneficial.

Table 4.139 Balance of clinical benefits of a sGC stimulator in addition to an ERA, relative to ERA monotherapy in all PAH patients

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=167 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Critical
All-cause mortality	N=167 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
Hospitalisation due to worsening PAH	N=167 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Important

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Improved WHO FC	N=167 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0			Moderate ⨁⨁⨁⊙ Important
Worsened WHO FC	N=167 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0			Moderate ⨁⨁⨁⊙ Important
Change in 6MWD from baseline	N=167 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: 0			Moderate ⨁⨁⨁⊙ Important
Change in QoL from baseline	N=167 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0 to +1			High ⨁⨁⨁⨁ Important
Change in haemodynamic parameters from baseline	N=148 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: 0 Publication bias: 0 Association: 0			Low ⨁⨁⊙⊙ Not important

[a] GRADE Working Group grades of evidence [1]
[b] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[c] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; CI = confidence interval; EQ-5D = EuroQual 5 dimension; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; LPH = living with pulmonary hypertension; MD = mean difference; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

A summary of these results for patients with WHO FC III/IV PAH is provided in Table 4.140. The evidence base for all outcomes was considered to be of high (GRADE ⨁⨁⨁⨁) or moderate (GRADE ⨁⨁⨁⊙) quality.

When taking the whole body of evidence into account, significantly fewer patients dies or had worsening of their WHO FC when on combination therapy compared with monotherapy. The point estimates indicate that the number of patients experiencing clinical worsening or hospitalisation would [redacted] when on combination therapy compared with monotherapy, [redacted]. Similarly, [redacted] patients had an improvement in their WHO FC, [redacted]. Patients on combination therapy had [redacted] in their 6MWD, PVR and QoL than those on monotherapy, and the mean differences for 6MWD, PVR and EQ-5D QoL were [redacted].

Thus, there is [redacted] evidence indicating that the use of a sGC stimulator in addition to an ERA, relative to ERA monotherapy to treat patients with WHO FC III/IV PAH [redacted]

Table 4.140 Balance of clinical benefits of a sGC stimulator in addition to an ERA, relative to ERA monotherapy in patients with WHO FC III/IV PAH

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=120 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: 0	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Critical
All-cause mortality	N=120 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
Hospitalisation due to PAH	N=120 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: +2	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Important
Improved WHO FC	N=120 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −1 Publication bias: 0 Association: +1	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Important

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Worsened WHO FC	N=120 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important
Change in 6MWD from baseline	N=120 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: 0 Publication bias: 0 Association: +1	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important
Change in QoL from baseline	N=120 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: 0 Publication bias: 0 Association: 0 to +1	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important
Change in haemodynamic parameters from baseline	N=103 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: 0 Publication bias: 0 Association: +1	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Not important

[a] GRADE Working Group grades of evidence [1]
[b] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[c] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQual 5 dimension; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; MD = mean difference; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

Safety

No conclusions about the comparative safety of a sGC stimulator in addition to an ERA, relative to ERA monotherapy in PAH patients could be made due to a lack of evidence.

4.5.3.7 sGC stimulator in addition to PDE-5 inhibitor

Clinical effectiveness

The RCT that provided the evidence base for comparing the effectiveness of a sGC stimulator in addition to a PDE-5 inhibitor compared with PDE-5 inhibitor monotherapy enrolled patients

receiving stable PDE-5 inhibitor therapy (sequential combination therapy). No WHO FC or PAH aetiology subgroup analysis was undertaken.

The detailed GRADE[1] assessments of the outcomes when comparing a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy are reported in Table 4.167 in Appendix 4C. A summary of these results is provided in Table 4.120. The evidence base for all outcomes were considered to be of low quality (GRADE ⨁⨁⊙⊙), except for change in 6MWD, which was considered to be of very low quality (GRADE ⨁⊙⊙⊙). Thus, the true effect of treating PAH with a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy is likely to be substantially different from the estimate of the effect.

When taking the whole body of evidence into account, fewer patients on combination therapy improved their WHO FC compared with monotherapy. Patients on combination therapy also had a smaller mean improvement in their 6MWD than those on monotherapy. The difference in mortality and worsening of WHO FC between the two treatment arms could not be determined as no patients had these outcomes during the study period. Additionally, given the small study size, it is likely that the RCT were underpowered to detect a true difference for these outcomes.

Thus, there is insufficient evidence to determine whether use of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy to treat PAH patients is likely to be beneficial.

Table 4.141 Balance of clinical benefits of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy in all PAH patients

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
All-cause mortality	N=18 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	Not estimable	No patients died during the study period	Low ⊕⊕⊙⊙ Critical
Improved WHO FC	N=18 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	RR = 0.50 (95% CI 0.09, 2.73)	Fewer patients on combination therapy improved their WHO FC compared with monotherapy, but the wide 95% CI indicates that the study was underpowered for this outcome.	Low ⊕⊕⊙⊙ Important
Worsened WHO FC	N=18 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	Not estimable	No patients had worsening of their WHO FC	Low ⊕⊕⊙⊙ Important
Change in 6MWD from baseline	N=18 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: −2 Publication bias: 0 Association: 0	MD = 23 m less	Patients on combination therapy had a smaller mean improvement in their 6MWD than those on monotherapy, but the difference was not clinically important	Very low ⊕⊙⊙⊙ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; MD = mean difference; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

Safety

The detailed GRADE[1] assessments of safety outcomes when comparing a sGC stimulator in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy are reported in Table 4.168 in Appendix 4C. The evidence for the safety outcomes for all PAH patients is summarised in Table 4.142. There were no new safety signal identified.

All outcomes were considered to be of low quality (GRADE ⊕⊕⊙⊙). Patients on combination therapy were more likely to have an AE a compared with those on monotherapy, but the 95% CI indicates that there could also be no effect. There is some evidence to suggest that more patients would either experience a serious AE or need to discontinue treatment due to an AE with

combination therapy compared with monotherapy. However, the study was very small and likely to be underpowered to detect a true difference.

Thus, there is considerable uncertainty whether the use of a sGC stimulator in addition to PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy, would cause additional harm to PAH patients.

Table 4.142 Balance of clinical harms of a sGC stimulator in addition to a PDE-5 inhibitor, relative to PDE-5 inhibitor monotherapy in all PAH patients

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Any AE	N=18 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	RR = 1.50 (0.85, 2.64)	More patients experienced an AE with combination therapy compared with monotherapy, but the 95% CI indicates that the study was underpowered for this outcome.	Low ⊕⊕⊙⊙ Important
Serious AEs	N=18 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	ARD = 16.7% (−4.4, 37.8)	More patients experienced a serious AE with combination therapy compared with monotherapy, but the 95% CI indicates that the study was underpowered for this outcome	Low ⊕⊕⊙⊙ Important
AEs leading to treatment discontinuation	N=18 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0	ARD = 8.3% (−7.3, 24.0)	More patients needed to discontinue treatment due to an AE with combination therapy compared with monotherapy, but the 95% CI indicates that the study was underpowered for this outcome	Low ⊕⊕⊙⊙ Important

[a] GRADE Working Group grades of evidence [1]
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
AE = adverse event; ARD = absolute risk difference; CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; N = number of patients; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; RCT = randomised controlled trial; RR = relative risk; sGC = soluble guanylate cyclase

4.5.3.8 sGC stimulator in addition to a prostanoid

Clinical effectiveness

The RCT that provided the evidence base for comparing the effectiveness of a sGC stimulator in addition to a prostanoid compared with prostanoid monotherapy enrolled a subgroup of patients with background prostanoid therapy (sequential combination therapy). As this was a very small subgroup, no additional subgroup analysis based on WHO FC or PAH aetiology was undertaken.

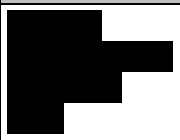
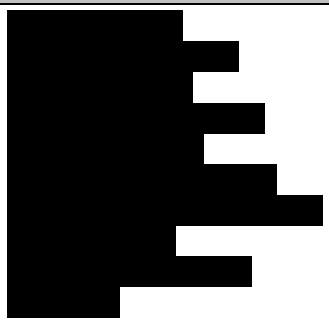
The detailed GRADE[1] assessments of the outcomes when comparing a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy are reported in [redacted] in Appendix 4C. A summary of these results is provided in Table 4.143. The evidence base for most outcomes

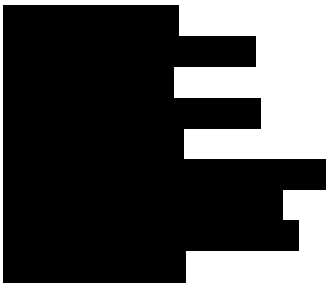
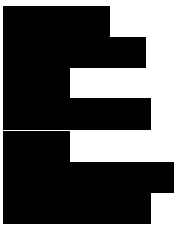
considered to be of low quality (GRADE ⊕⊕⊙⊙). However, the study was very small and is likely underpowered to detect a true difference in this patient subgroup.

When taking the whole body of evidence into account, patients on combination therapy had a larger mean improvement in their 6MWD, PVR and QoL than those taking a placebo; the large mean differences between the combination and monotherapy groups were clinically important. More patients improved their WHO FC on combination therapy compared with monotherapy, but the wide 95% CI indicates that there may also be the opposite effect. All other outcomes numerically favoured the use of combination therapy over monotherapy. The small sample size indicates that the study was statistically underpowered to detect a true difference.

Thus, there is considerable uncertainty as to whether the use of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy to treat PAH patients is likely to be beneficial.

Table 4.143 Balance of clinical benefits of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy in all PAH patients

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Clinical worsening	N=27 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0			Low ⊕⊕⊙⊙ Critical
All-cause mortality	N=27 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0			Low ⊕⊕⊙⊙ Critical
Hospitalisation due to PAH	N=27 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0			Low ⊕⊕⊙⊙ Critical
Improved WHO FC	N=27 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0			Very low ⊕⊕⊙⊙ Important

Outcomes	Participants (studies)	Quality of evidence	Results	Interpretation	GRADE[a] Importance
Worsened WHO FC	N=27 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0			Low ⨁⨁⊙⊙ Important
Change in 6MWD from baseline	N=27 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −1 Imprecision: −2 Publication bias: 0 Association: +1			Low ⨁⨁⊙⊙ Important
Change in QoL from baseline	N=27 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: 0 Imprecision: −2 Publication bias: 0 Association: 0 to +1			Moderate ⨁⨁⨁⊙ Important
Change in haemodynamic parameters from baseline	N=27 k=1 RCT	Risk of bias: 0 Inconsistency: 0 Indirectness: −2 Imprecision: −2 Publication bias: 0 Association: +1			Very low ⨁⊙⊙⊙ Not important

[a] GRADE Working Group grades of evidence [1]
[b] EQ-5D utility scores range from −0.59 to 1.00. A higher score represents better QoL.
[c] LPH total scores range from 0 to 105. A higher score indicates poorer QoL.
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-5D = EuroQual 5 dimension; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; k = number of studies; LPH = living with pulmonary hypertension; MD = mean difference; N = number of patients; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; sGC = soluble guanylate cyclase; WHO = World Health Organization

Safety

No conclusions about the comparative safety of a sGC stimulator in addition to a prostanoid, relative to prostanoid monotherapy in PAH patients could be made due to a lack of evidence.

4.5.4 Effectiveness and safety of triple combination therapy

No clinical evidence was identified.

4.5.5 Extended assessment of safety

The four RCTs included for the extended safety assessment of PAH medicines had a short-term study period of 6 to 16 weeks. Results from Trial STARTS-1 indicated that, in paediatric PAH patients, sildenafil had an inferior safety profile, with AEs of pyrexia, increased erection, and upper respiratory tract infection occurring more frequently in children treated with sildenafil than those receiving placebo. The incidence of pyrexia, vomiting, and nausea appeared to be sildenafil dose-related. The results of eye disorder AEs from SUPER-1 indicated that, in general, sildenafil dosing up to 80 mg tid was tolerated from an ocular perspective in patients with PAH. In this population, the incidence of ocular AEs was low and comparable between the 20 mg tid (PI-recommended dose) and placebo groups, but with some AEs occurred only in patients receiving sildenafil, eg retinal haemorrhage. PHIRST trial reported higher incidence of overall AEs, diarrhoea, nausea, nasopharyngitis, upper respiratory tract infection, myalgia, flushing, dyspepsia and pain in the extremities in patients receiving tadalafil at a recommended dose of 40 mg od, compared with patients in the placebo arm. Insufficient trial data was provided by Mukhopadhyay 2011 for evaluation of comparative safety of tadalafil versus placebo.

The study period in the observational studies included for extended assessment of safety varied between 2 years to up to 5 years. This reflects the typical prolonged use of PAH medicines in clinical practice. However, any interpretation of the safety results should considered the non-comparative nature of these observational studies for safety assessment, which could hinder the establishment of a temporal association between PAH medicines and AEs observed in these studies, especially when the incidence of AEs is low. Overall, observational study findings generally agreed with each other and with the safety results reported by clinical trials and post-marketing data included in respective PI documents. No clear safety signal has been detected on the basis of the included observational studies. The incidence of some known treatment-related AEs in the observational studies may be higher than that reported by clinical trials, given the long-term follow-up period of the included observational studies.

There was limited data from the included studies on the safety of PAH medicines for treatment of paediatric PAH patients: STARTS-1 and its extension study for sildenafil and Hiplop 2011 for bosentan. Study results suggested that the safety profile seen in the paediatric patients was generally consistent with that in adults for both drugs.

The following safety signals are noted by the EMA SmPC, but have not been included in the TGA-approved PI: use of bosentan in patients with chronic obstructive pulmonary disease (increase in minute ventilation, decrease in oxygen saturation and dyspnoea); AEs of penile haemorrhage and haematospermia in patients receiving PDE-5 inhibitors (both sildenafil and tadalafil); potential for vaso-occlusive crises in patients receiving sildenafil for PH secondary to sickle cell anaemia; intracerebral haemorrhage in tadalafil-treated patients; and increased mortality and serious AEs in patients receiving riociguat for treatment of PH associated with idiopathic interstitial pneumonias.

Higher risk of mortality with increasing sildenafil dose for treatment paediatric PAH was reported by a long-term observational study. Different decisions were made by regulatory agencies based on this finding: the TGA states that sildenafil is not indicated for use in paediatric patients; the FDA

does not recommend the use of sildenafil in paediatric patients (health care professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient); whilst the EMA recommends the use of sildenafil but only at a recommended low dose.

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Appendix 4.A Studies included in the literature review

Table 4.144 Studies included to address research questions

Study ID Author year Study period Location	Study design Level of evidence Duration of follow-up Risk of bias	Eligibility criteria	N[a] Population characteristics	Intervention[b] Comparator Background therapy (if any)	Outcomes assessed
Randomised controlled trials					
AMBITION[30-32] 2010-2014 US, Canada, Europe, Australia, Japan	RCT, DB Level II evidence Follow-up: 20 months Risk of bias: low	*Inclusion criteria* - Age of 18-75 years, weighted ≥40 kg - Patients with WHO FC II-III IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-DT, PAH-HIV - Patients who had had either not received previous treatment with an approved therapy for PAH or had received treatment <14 days and had not received any approved therapy for PAH within 7 days before enrolment *Exclusion criteria* - Patients who received ERA or PDE-5i at any time and discontinued	N=500 Ambrisentan + tadalafil (N=253) / Ambrisentan (N=126) / Tadalafil (N=121) Age, mean±SD (yrs): 55±14 / 54±15 / 55±15 Gender, female, n (%): 188 (74%) / 100 (79%) / 100 (83%) PAH aetiology, n (%) IPAH: 127 (50%) / 72 (57%) / 66 (55%) HPAH: 7 (3%) / 3 (2%) / 4 (3%) PAH-CTD: 103 (41%) / 44 (35%) / 40 (33%) PAH-CHD: 5 (2%) / 1 (1%) / 3 (2%) PAH-DT: 6 (2%) / 4 (3%) / 6 (5%) PAH-HIV: 5 (2%) / 2 (2%) / 2 (2%) WHO FC, n (%)	*Intervention* Ambrisentan + tadalafil Ambrisentan: initial dose of 5 mg for 8 weeks, then up-titrated to 10 mg Tadalafil: initial dose of 20 mg for 4 weeks, then up-titrated to 40 mg *Comparator* Ambrisentan + placebo Tadalafil + placebo Ambrisentan: initial dose of 5 mg for 8 weeks, then up-titrated to 10 mg Tadalafil: initial dose of 20 mg for 4 weeks, then up-titrated to 40 mg	*Effectiveness* Primary: - Time to clinical worsening[c] Secondary: - Change in 6MWD at Week 24[c] - Change in WHO FC at Week 24[c] - Hospitalisation[c] - Change in BDS at Week 24 - % of participants with a satisfactory clinical response within 24 weeks Others: - Mortality[c] *Safety* - Adverse event[c]

<table>
<tr>
<td></td>
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<td>due to tolerance issues other than those associated with liver function abnormalities
- Patients who had previously discontinued ambrisentan or tadalafil for safety or tolerability reasons</td>
<td>
<table>
<tr><td>II
III</td><td>76 (30%)
177 (70%)</td><td>38 (30%)
88 (70%)</td><td>41 (34%)
80 (66%)</td></tr>
<tr><td>No history of therapy specifically for PAH, n (%)</td><td>242 (96%)</td><td>120 (95%)</td><td>115 (95%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>48.1±12.4</td><td>50.4±12.5</td><td>48.1±12.6</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>824±467</td><td>852±395</td><td>789±409</td></tr>
</table>
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</tr>
<tr>
<td>ARIES-1[6, 33, 34]
2003-2006
US, Mexico, South America, Australia, Europe</td>
<td>RCT, DB
Level II evidence
Follow-up: 12 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Patients with IPAH, PAH-CTD, PAH-HIV or anorexigen-associated PAH

Inclusion criteria:
- Patients with 6MWD <150 m or >450 m
- Patients previous treated with bosentan, sitaxsentan, sildenafil, epoprostenol, iloprost, or treprostinil</td>
<td>N=134
<table>
<tr><td></td><td>Ambrisentan 5 mg (N=67)</td><td>Placebo (N=67)</td></tr>
<tr><td>Age, mean±SD (yrs)</td><td>53±14</td><td>48±16</td></tr>
<tr><td>Gender, female, n (%)</td><td>56 (84%)</td><td>59 (88%)</td></tr>
<tr><td>PAH aetiology, n (%)
IPAH
PAH-CTD
PAH-HIV
PAH-DT</td><td>
42 (63%)
19 (28%)
3 (5%)
2 (3%)</td><td>
43 (64%)
21 (31%)
2 (3%)
1 (2%)</td></tr>
<tr><td>WHO FC, n (%)
I
II
III
IV</td><td>
1 (2%)
20 (30%)
40 (60%)
6 (9%)</td><td>
2 (3%)
23 (34%
41 (61%)
1 (2%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>47±13</td><td>50±15</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>834±424</td><td>968±518</td></tr>
</table>
</td>
<td>Intervention:
Ambrisentan: 5 mg od

Intervention
Placebo od</td>
<td>Effectiveness:
Primary:
- Change in 6MWD at Week 12[c]
Secondary:
- Time to clinical worsening[c]
- Change in WHO FC at Week 12[c]
- Change in SF-36 Health Survey physical functioning scales at Week 12
- Change in BDS at Week 12

Safety
- Adverse events</td>
</tr>
</table>

<table>
<tr>
<td></td>
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<td></td>
<td>Data on the patient characteristics for the WHO FC I-II subgroup and WHO FC III-IV subgroup between the two treatment groups were not available. Randomisation was not stratified according to WHO FC.</td>
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</tr>
<tr>
<td>ARIES-2[33, 34]
2003-2006
Europe, Israel, South America</td>
<td>RCT, DB
Level II evidence
Follow-up: 12 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Patients with IPAH, PAH-CTD, PAH-HIV or anorexigen-associated PAH

Inclusion criteria:
- Patients with 6MWD <150 m or >450 m
- Patients previous treated with bosentan, sitaxsentan, sildenafil, epoprostenol, iloprost, or treprostinil</td>
<td>N=128
<table>
<tr><th></th><th>Ambrisentan 5 mg (N=63)</th><th>Placebo (N=65)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>50±16</td><td>51±14</td></tr>
<tr><td>Gender, female, n (%)</td><td>51 (81%)</td><td>44 (68%)</td></tr>
<tr><td>PAH aetiology, n (%)</td><td></td><td></td></tr>
<tr><td>IPAH</td><td>41 (65%)</td><td>42 (65%)</td></tr>
<tr><td>PAH-CTD</td><td>21 (33%)</td><td>22 (34%)</td></tr>
<tr><td>PAH-HIV</td><td>1 (2%)</td><td>1 (2%)</td></tr>
<tr><td>PAH-DT</td><td>0 (0%)</td><td>0 (0%)</td></tr>
<tr><td>WHO FC, n (%)</td><td></td><td></td></tr>
<tr><td>I</td><td>1 (2%)</td><td>2 (3%)</td></tr>
<tr><td>II</td><td>28 (44%)</td><td>24 (37%)</td></tr>
<tr><td>III</td><td>33 (52%)</td><td>37 (57%)</td></tr>
<tr><td>IV</td><td>1 (2%)</td><td>2 (3%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>48±14</td><td>51±3</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>931±672</td><td>971±579</td></tr>
</table>
Data on the patient characteristics for the WHO FC I-II subgroup and WHO FC III-IV subgroup between the two treatment groups were not available. Randomisation was not stratified according to WHO FC.</td>
<td>Intervention:
Ambrisentan: 5 mg od

Intervention
Placebo od</td>
<td>Effectiveness:
Primary:
- Change in 6MWD at Week 12[c]
Secondary:
- Time to clinical worsening[c]
- Change in WHO FC at Week 12[c]
- Change in SF-36 Health Survey physical functioning scales at Week 12
- Change in BDS at Week 12

Safety
- Adverse events</td>
</tr>
</table>

<table>
<tr>
<td>BREATHE-2[35]
No later than 2004[d]
US, Europe</td>
<td>RCT, DB
Level II evidence
Follow-up: 16 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Patients with WHO FC III/IV IPAH or PAH-CTD
- Scheduled for epoprostenol therapy within 2 weeks of screening.

Exclusion criteria
- Patients with moderate to severe interstitial lung disease
- Patients had started or stopped any PAH treatment within 1 month of screening</td>
<td>N=33
<table>
<tr><td></td><td>Bosentan (N=22)</td><td>Placebo (N=11)</td></tr>
<tr><td>Age, mean±SD (yrs)</td><td>45±17</td><td>47±19</td></tr>
<tr><td>Gender, female, n (%)</td><td>17 (77%)</td><td>6 (55%)</td></tr>
<tr><td>PAH aetiology, n (%)
IPAH
PAH-CTD</td><td>
17 (77%)
5 (23%)</td><td>
10 (91%)
1 (9%)</td></tr>
<tr><td>WHO FC, n (%)
III
IV</td><td>
17 (77%)
5 (23%)</td><td>
8 (73%)
3 (27%)</td></tr>
<tr><td>Time since diagnosis, mean±SD (months)</td><td>13±30</td><td>15±21</td></tr>
</table>
</td>
<td>Intervention:
Bosentan + epoprostenol
Bosentan: initial dose of 62.5 mg bid for 4 weeks, then 125 mg bid
Epoprostenol: initial dose of 2 ng/kg/min for 4 days, then 4 ng/kg/min, then dose increase of 2 ng/kg/min at 2-week intervals to a target dose of 12-16 ng/kg/min

Comparator:
Placebo + epoprostenol
Epoprostenol: initial dose of 2 ng/kg/min for 4 days, then 4 ng/kg/min, then dose increase of 2 ng/kg/min at 2-week intervals to a target dose of 12-16 ng/kg/min</td>
<td>Effectiveness
Primary:
- Change in TPR at Week 16[c]
Secondary:
- Change in 6MWD at Week 16[c]
- Change in WHO FC at Week 16[c]
- Change in dyspnoea fatigue rating[c]
- Change in CI, PVR, mPAP, CI, and mRAP at Week 16[c]
Others:
- Mortality[c]

Safety
- Adverse events[c]</td>
</tr>
<tr>
<td>COMBI[36]
2004
Germany</td>
<td>RCT, OL
Level II evidence
Follow-up: 12 weeks
Risk of bias: high</td>
<td>Inclusion criteria
- Age of 18-75 years
- Patients with IPAH
- Stable WHO FC III for >3 months
- Bosentan therapy for >3 months
- 6MWD of 150-425 m

Exclusion criteria
- Patients with severe lung disease
- Clinical instability (defined as right-heart failure within the last 3 months)</td>
<td>N=40
<table>
<tr><td></td><td>Iloprost + bosentan (N=19)</td><td>Bosentan (N=21)</td></tr>
<tr><td>Age, mean±SD (yrs)</td><td>48 ± 14</td><td>56 ± 13</td></tr>
<tr><td>Gender, female, n (%)</td><td>15 (79%)</td><td>16 (76%)</td></tr>
<tr><td>PAH aetiology, n (%)
IPAH</td><td>
19 (100%)</td><td>
21 (100%)</td></tr>
<tr><td>WHO FC, n (%)
III</td><td>NR
19 (100%)</td><td>
21 (100%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>54±12</td><td>59±19</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>839±531</td><td>805±369</td></tr>
</table>
</td>
<td>Intervention
Iloprost + bosentan
Bosentan: 125 mg bid
Iloprost: 5 µg inhaled 6 times daily

Comparator
Bosentan alone
Bosentan: 125 mg bid</td>
<td>Effectiveness:
Primary:
- Change in 6MWD at Week 12[c]
Secondary:
- Change in WHO FC
- Change in EQ-VAS[c]
- Clinical worsening[c]
Others:
- Mortality[c]
- Hospitalisation due to PAH

Safety
- Adverse events[c]</td>
</tr>
</table>

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<tr>
<td></td>
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<td>- SBP <85 mmHg
- Concomitant sildenafil therapy or treatment with prostanoids within 3 months</td>
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</tr>
<tr>
<td>COMPASS-2[37]
2006-2012
US, Europe, Brazil, Saudi Arabia</td>
<td>RCT, DB
Level II evidence
Follow-up: 38.9 months
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Age of ≥18 years
- Patients with symptomatic IPAH, HPAH, PAH-CTD, PAH-CHD, or PAH-DT
- 6MWD of 150-480m
- Receiving a stable dose of sildenafil ≥20 mg tid for ≥3 months prior to randomisation

Exclusion criteria
- Receiving PAH medicines other than sildenafil within 3 months prior to randomisation</td>
<td>N=334
<table><tr><th></th><th>Bosentan + sildenafil (n=159)</th><th>Placebo + sildenafil (n=175)</th></tr><tr><td>Age, mean±SD (yrs)</td><td>53±15</td><td>55±16</td></tr><tr><td>Gender, female, n (%)</td><td>125 (79%)</td><td>128 (73%)</td></tr><tr><td>PAH aetiology, n (%)</td><td></td><td></td></tr><tr><td>IPAH</td><td>99 (62%)</td><td>114 (65%)</td></tr><tr><td>PAH-CTD</td><td>43 (27%)</td><td>45 (26%)</td></tr><tr><td>PAH-CHD</td><td>9 (6%)</td><td>11 (6%)</td></tr><tr><td>PAH-DT</td><td>5 (3%)</td><td>3 (2%)</td></tr><tr><td>HPAH</td><td>3 (2%)</td><td>2 (1%)</td></tr><tr><td>WHO FC, n (%)</td><td></td><td></td></tr><tr><td>II</td><td>71 (45%)</td><td>69 (39%)</td></tr><tr><td>III</td><td>88 (55%)</td><td>104 (59%)</td></tr><tr><td>IV</td><td>0 (0%)</td><td>2 (1%)</td></tr><tr><td>Time from diagnosis, mean±SD (mths)</td><td>25±47</td><td>26±51</td></tr><tr><td>Sildenafil dose, median (interquartile range) (mg)</td><td>60 (60-60)</td><td>60 (60-75)</td></tr></table></td>
<td>Intervention
Bosentan: initial dose of 62.5 mg bid for 4 weeks, then 125 mg bid

Comparator
Placebo

Background therapy
Sildenafil (100%): ≥20 mg tid</td>
<td>Effectiveness
Primary:
- Time to first mortality/morbidity event[c]
Secondary:
- Change in 6MWD at Week 16[c]
- Change in WHO FC at Week 16[c]
- Time to the first occurrence of death, hospitalisation for PAH or start of IV prostanoid therapy, atrial septostomy, or lung transplant
- All-cause morality[c]

Safety
- Adverse events[c]</td>
</tr>
<tr>
<td>EARLY[9]
2004-2006
US, Europe, Brazil</td>
<td>RCT
Level II evidence
Follow-up: 6 months
Risk of bias: low</td>
<td>Inclusion criteria
- Age of ≥12 years
- Patients with WHO FC II IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-HIV or anorexigen-associated PAH</td>
<td>N=185
<table><tr><th></th><th>Bosentan (N=93)</th><th>Placebo (N=92)</th></tr><tr><td>Age, mean±SD (yrs)</td><td>45±17</td><td>44±17</td></tr><tr><td>Gender, female, n (%)</td><td>71 (76%)</td><td>58 (63%)</td></tr><tr><td>PAH aetiology, n (%)</td><td></td><td></td></tr><tr><td>IPAH</td><td>54 (58%)</td><td>58 (63%)</td></tr></table></td>
<td>Intervention
Bosentan: initial dose of 62.5 mg bid, up-titrated to 125 mg bid after 4 weeks if body weight ≥40 kg

Comparator</td>
<td>Effectiveness:
Primary:
- PVR at Months 6[c]
- Change in 6MWD at Month 6[c]
Secondary:</td>
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<td>- 6MWD <80% of the normal predicted value or <500 m
- BDS ≥2
- PVR≥320 cyn/s*cm[5]

Exclusion criteria
- Patients who had been treated for PAH within 4 weeks of randomisation</td>
<td>
<table>
<tr><td>PAH-CTD</td><td>18 (19%)</td><td>15 (16%)</td></tr>
<tr><td>PAH-CHD</td><td>16 (17%)</td><td>16 (17%)</td></tr>
<tr><td>PAH-HIV</td><td>5 (5%)</td><td>2 (2%)</td></tr>
<tr><td>Other</td><td>0 (0%)</td><td>1 (1%)</td></tr>
<tr><td>WHO FC, n (%)
II</td><td>93 (100%)</td><td>92 (100%)</td></tr>
<tr><td>Time from diagnosis, mean±SD (yrs)</td><td>2.9±5.5</td><td>3.7±6.5</td></tr>
<tr><td>Concomitant use of sildenafil</td><td>14 (15%)</td><td>15 (16%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>52.5±18.5</td><td>52.3±16.0</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>839±531</td><td>805±369</td></tr>
</table>
Data on the patient characteristics for the no background therapy subgroup and with background therapy subgroup between the two treatment groups were not available. However, randomisation was stratified according to sildenafil use at enrolment.
</td>
<td>Placebo bid

Background therapy
Sildenafil: 15% in the bosentan arm vs 16% in the placebo arm</td>
<td>- Time to clinical worsening[c]
- Change in WHO FC at Month 6
- Change in BDS at Month 6
- Change in mRAP, mPAP and CI at Month 6
Others:
- Mortality[c]

Safety:
- Adverse events[c]</td>
</tr>
<tr>
<td>Han 2017[38]
2012-2015
China</td>
<td>RCT, OL
Level II evidence
Follow-up: 13 weeks
Risk of bias: high</td>
<td>Inclusion criteria
- Age of 15-80 years
- Patients with WHO FC III-IV IPAH or CTEPH[e]
- Patients with no previous treatment with an approved therapy for PAH before enrolment

Exclusion criteria
- Patients with acute pulmonary thrombo-embolism, left-sided</td>
<td>N=14[e]
<table>
<tr><td></td><td>Bosentan + iloprost (N=8)</td><td>Iloprost (N=6)</td></tr>
<tr><td>Age, mean±SD (yrs)</td><td>30±7</td><td>42±5</td></tr>
<tr><td>Gender, female, n (%)</td><td></td><td></td></tr>
<tr><td>Pulmonary hypertension aetiology, n (%)
IPAH
CTEPH</td><td>
7 (88%)
1 (13%)</td><td>
6 (100%)
0 (0%)</td></tr>
<tr><td>WHO FC, n (%)
III</td><td>5 (63%)</td><td>5 (83%)</td></tr>
</table>
</td>
<td>Intervention
Bosentan + iloprost
Bosentan: initial dose of 62.5 mg bid for 1 month, then 125 mg bid
Iloprost: increasing dose to a target of 10 µg 4-6 times/day

Comparator
Iloprost: increasing dose to a target of 10 µg 4-6 times/day</td>
<td>Effectiveness
Primary:
- Change in 6MWD at Week 6 and Month 3[c]
Secondary:
- Change in WHO FC at Week 6 and Month 3
- Change in MLHF questionnaire score at Week 6 and Month 3[c]
- Change in CI, mPAP and PVR at Month 3[c]</td>
</tr>
</table>

		heart disease, severe pulmonary disease, or portal hypertension	IV: 3 (38%); 1 (17%) mPAP, mean±SD (mmHg): 65.5±5.5; 55.7±1.7 PVR, mean±SD (dyn*s*cm^{-5}): 1038±176; 1157±165		*Safety*: - Adverse events[c]
Mainguy 2013[39] 2009-2011 Canada	RCT, DB, cross-over Level II evidence Follow-up: 4 weeks Risk of bias: low-to-moderate	*Inclusion criteria* - PAH patients with stable clinical condition who were on monotherapy over the last 4 months but naïve to PDE-5i *Exclusion criteria* - Unstable PAH (defined as recent syncope) or WHO FC IV - LVEF <40% - Significant restrictive or obstructive lung disease - SBP <100/60 mmHg	N=20 Age, mean±SD (yrs): 29±12 Gender, female, n (%): 15 (54%) PAH aetiology, n (%) IPAH: 9 (45%) PAH-CTD: 8 (40%) PAH-CHD: 2 (10%) HPAH: 1 (5%) WHO FC, n (%) II: 15 (75%) III: 5 (25%) mPAP, mean±SD (mmHg): 44±16 PVR index, mean±SD (Wood units/m^2): 6.6±3.1 Data on the patient characteristics for the two treatment arms were not available.	*Intervention:* Sildenafil: 20 mg tid *Comparator* Placebo *Background therapy* ERA (90%) EPO (10%)	*Effectiveness* Primary: - Change in 6MWD[c] - Change in the endurance shuttle walk test - Change in the cycle endurance test
Mukhopadhyay 2011[40] No later than 2011[d] India	RCT, DB, cross-over Level II evidence Follow-up: 6 weeks Risk of bias: low-to-moderate	*Inclusion criteria* - Age of ≥18 years - Patients with WHO FC II-III PAH-CHD (Eisenmenger syndrome) - Stable medical therapy and clinical condition for 3 months prior to screening. - 6 MWD of 150-450 m	N=28 Age, mean±SD (yrs): 53±15 Gender, female, n (%): 16 (80%) PAH aetiology, n (%) PAH-CHD: 28 (100%) WHO FC, n (%) II: 22 (79%) III: 6 (21%) mPAP, mean±SD (mmHg): 75±17 PVR, mean±SD (Wood units): 33.8±12.2 Data on the patient characteristics for the two treatment arms were not available.	*Intervention* Tadalafil 40 mg for 6 weeks followed by crossover to placebo after a washout period of 2 weeks *Comparator* Placebo for 6 weeks followed by crossover to tadalafil 40 mg after a washout period of 2 weeks	*Effectiveness* Primary: - Change in 6MWD 6 weeks after treatment Secondary: - Change in WHO FC[c] - Change in PVR *Safety*: - Adverse events[c]

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<tr>
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<td>- A systemic pulse oximetry of 70%-90% at rest in room air

Exclusion criteria
- Patients on treatment with prostanoid, ERA, PDE-5i, or any other vasodilator within 1 month prior to screening
- Congestive heart failure or with PCWP >15 mmHg
- Atrial fibrillation
- Patent ductus arteriosus
- Complex congenital heart defects
- LVEF <40%
- Restrictive or obstructive lung disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACES-1[41]
2003-2006
US, Canada, Europe, Israel</td>
<td>RCT, DB
Level II evidence
Follow-up: 16 weeks
Risk of bias: low</td>
<td>Inclusion criteria
- Age of ≥16 years
- Patients with IPAH, PAH-DT, PAH-CTD or PAH-CHD
- Patients who had received epoprostenol for ≥3 months, received the “optimal” dose with no change for ≥4 weeks, and been</td>
<td>N=267
<table>
<tr><th></th><th>Sildenafil (N=134)</th><th>Placebo (N=133)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>48±13</td><td>48±13</td></tr>
<tr><td>Gender, female, n (%)</td><td>110 (82%)</td><td>103 (77%)</td></tr>
<tr><td>PAH aetiology, n (%)
IPAH
PAH-CTD</td><td>
107 (80%)
27 (20%)</td><td>
105 (79%)
28 (21%)</td></tr>
<tr><td>WHO FC, n (%)
I</td><td>
1 (1%)</td><td>
2 (2%)</td></tr>
</table></td>
<td>Intervention
Sildenafil: 20 mg tid for 4 weeks, then up-titrated to 40 mg tid for a further 4 weeks, then up-titrated to 80 mg tid for the last 8 weeks.

Comparator
Placebo

Background therapy</td>
<td>Effectiveness
Primary:
- Change in 6MWD at Week 16[c]
Secondary:
- Change in PVR, mPAP and mRAP[c]
- Time to clinical worsening[c]
- Change in BDS[c]
- Change in SF-36 score
Other:</td>
</tr>
</table>

<table>
<tr>
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<td>stable for right heart catheterisation
Exclusion criteria
- Patients who had a change in epoprostenol dose within 4 weeks before receiving the randomly assigned drug
- Patients who were receiving bosentan, nitrates, or nitric oxide donor drugs
- Patients with cardiovascular disease, retinopathy or chronic obstructive pulmonary disease</td>
<td>
<table>
<tr><td>II</td><td>34 (25%)</td><td>34 (26%)</td></tr>
<tr><td>III</td><td>88 (66%)</td><td>87 (65%)</td></tr>
<tr><td>IV</td><td>10 (7%)</td><td>6 (5%)</td></tr>
<tr><td>Missing</td><td>1 (1%)</td><td>4 (3%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td colspan="2">52±11</td><td>51±13</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td colspan="2">857±363</td><td>755±368</td></tr>
<tr><td>Epoprostenol dose, median (range) (ng/kg/min)</td><td colspan="2">28 (3-179)</td><td>29 (4-181)</td></tr>
</table>
</td>
<td>Epoprostenol (100%): 3-181 ng/kg/min</td>
<td>- Mortality[c]
- Hospitalisation due to PAH[c]

Safety:
- Adverse events[c]</td>
</tr>
<tr>
<td>PATENT-1[23, 42, 43]
2008-2012
US, Canada, Mexico, Asia, Europe, South America, Australia</td>
<td>RCT, DB
Level II evidence
Follow-up: 12 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Patients with symptomatic IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-PH or PAH-DT
- mPAP of ≥25 mmHg
- PVR > 300 dyn*sec*cm^{-5}
- 6MWD of 150-450 m
- Patients who were receiving no other treatment for PAH or were receiving treatment with ERA or prostanoid (excluding IV prostanoids) at</td>
<td>N=380
Treatment-naïve
<table>
<tr><td></td><td>Riociguat 2.5 mg (N=123)</td><td>Placebo (N=66)</td></tr>
<tr><td>Age, mean±SD (yrs)</td><td>48±17</td><td>48±18</td></tr>
<tr><td>Gender, female, n (%)</td><td>94 (76%)</td><td>52 (79%)</td></tr>
<tr><td>WHO FC, n (%)</td><td></td><td></td></tr>
<tr><td>I</td><td>3 (2%)</td><td>4 (6%)</td></tr>
<tr><td>II</td><td>65 (53%)</td><td>35 (53%)</td></tr>
<tr><td>III</td><td>55 (45%)</td><td>25 (38%)</td></tr>
<tr><td>IV</td><td>0 (0%)</td><td>2 (3%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>49.3±15</td><td>48.9±16</td></tr>
</table>
</td>
<td>Intervention
Riociguat: dose adjusted up to 2.5 mg tid

Comparator
Placebo

Background therapy:
ERA: 44% in the riociguat arm vs 43% in the placebo arm
Prostanoid (8% in the riociguat arm vs 6% in the placebo arm)</td>
<td>Effectiveness
Primary:
- Change in 6MWD at Week 16[c]
Secondary:
- Change in WHO FC at Week 16[c]
- Time to clinical worsening[c]
- Change in EQ-5D score[c]
- Change in LPH questionnaire score[c]
- Change in PVR[c]
Others
- Mortality[c]</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>doses that had been stable for ≥3 months

Exclusion criteria
- Patients who were receiving PDE-5i at enrolment</td>
<td>
<table>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>888±505</td><td>855±477</td></tr>
</table>
Data on the patient characteristics for the WHO FC I-II, treatment-naïve subgroup and WHO FC III-IV, treatment-naïve subgroup between the two treatment groups were not available.
Randomisation was not stratified according to WHO FC.
</td>
<td></td>
<td>- Hospitalisation due to PAH[c]

Safety
- Adverse events[c]</td>
</tr>
<tr>
<td>PATENT-1[23, 42, 43]
2008-2012
US, Canada, Mexico, Asia, Europe, South America, Australia

Continued</td>
<td></td>
<td></td>
<td>
Pre-treated with ERA
<table>
<tr><th></th><th>Riociguat 2.5 mg (N=113)</th><th>Placebo (N=54)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>55±15</td><td>53±15</td></tr>
<tr><td>Gender, female, n (%)</td><td>96 (85%)</td><td>42 (78%)</td></tr>
<tr><td>WHO FC, n (%)
I
II
III
IV</td><td>
1 (1%)
37 (33%)
74 (65%)
1 (1%)</td><td>
0 (0%)
23 (43%)
29 (55%)
1 (2%)</td></tr>
</table>
Pre-treated with prostanoid
<table>
<tr><th></th><th>Riociguat 2.5 mg (N=20)</th><th>Placebo (N=7)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>50±17</td><td>52±17</td></tr>
<tr><td>Gender, female, n (%)</td><td>15 (75%)</td><td>4 (57%)</td></tr>
<tr><td>WHO FC, n (%)
I
II
III
IV</td><td>
2 (10%)
6 (30%)
12 (60%)
0 (0%)</td><td>
0 (0%)
2 (29%)
5 (71%)
0 (0%)</td></tr>
</table>
</td>
<td></td>
<td></td>
</tr>
</table>

<table>
<tr>
<td>PATENT-PLUS[44]
2010-2013
Europe</td>
<td>RCT, DB
Level II evidence
Follow-up: 12 weeks
Risk of bias: low</td>
<td>Inclusion criteria
- Age of 18-75 years
- Patients with symptomatic PAH receiving stable ≥3 months) sildenafil therapy (approved dose: 20 mg tid
- 6MWD >150 m
- PVR >300 dyn*s*cm^{-5}, mPAP≥25 mgHg, SBP ≥95 mmHg and heart rate ≤105 beats/min in the first 2 hours after taking sildenafil

Exclusion criteria
- Patients receiving treatment with other PDE-5is, unspecific PDE inhibitors, ERAs, prostanoids or nitric oxide donors</td>
<td>N=18
<table>
<tr><th></th><th>Riociguat (N=12)</th><th>Placebo (N=6)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>58±11</td><td>61±10</td></tr>
<tr><td>Gender, female, n (%)</td><td>8 (67%)</td><td>4 (67%)</td></tr>
<tr><td>PAH aetiology, n (%)</td><td></td><td></td></tr>
<tr><td>IPAH</td><td>5 (42%)</td><td>4 (67%)</td></tr>
<tr><td>PAH-CTD</td><td>5 (42%)</td><td>1 (17%)</td></tr>
<tr><td>PAH-CHD</td><td>1 (8%)</td><td>0 (0%)</td></tr>
<tr><td>PAH-PH</td><td>1 (8%)</td><td>1 (17%)</td></tr>
<tr><td>WHO FC, n (%)</td><td></td><td></td></tr>
<tr><td>I</td><td>1 (8%)</td><td>0 (0%)</td></tr>
<tr><td>II</td><td>6 (50%)</td><td>4 (67%)</td></tr>
<tr><td>III</td><td>4 (33%)</td><td>2 (33%)</td></tr>
<tr><td>IV</td><td>1 (8%)</td><td>0 (0%)</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>573±241</td><td>683±195</td></tr>
</table>
</td>
<td>Intervention
Riociguat: up to 2.5 mg tid

Comparator
Placebo

Background therapy
Sildenafil (100%): 20 mg tid</td>
<td>Effectiveness
Primary
- Maximum change in supine SBP from baseline within 4 hours of dosing
Secondary:
- Maximum change in standing SBP, supine and standing DBP, and supine and standing heart rate from baseline within 4 hours of study medication
- Area under effect curve for change from baseline in standing and supine SBP, DBP and heart rate within 4 hours of study
- Changes in 6MWD at Week 12[c]
- Change in WHO FC at Week 12[c]
- Time to clinical worsening[c]
-
- Change in PVR, mPAP and CI at Week 12
Others:
- Mortality[c]
- Hospitalisation due to PAH
Safety
- Adverse events[c]</td>
</tr>
</table>

<table>
<tr>
<td>PHIRST[12, 13, 45]
2005-2007
US, Canada, Europe, Japan</td>
<td>RCT, DB
Level II evidence
Follow-up: 16 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Age of ≥12 years
- Patients with symptomatic IPAH, HPAH, PAD-DT, PAH-CTD, PAH-CHD or PAH-HIV

Exclusion criteria
- 6MWD <150 m or >450 m
- Treatment with IV epoprostenol, IV or inhaled iloprost, or subcutaneous treprostinil</td>
<td>N=161
<table>
<tr><th></th><th>Tadalafil 40 mg (N=79)</th><th>Placebo (N=82)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>53±15</td><td>55±15</td></tr>
<tr><td>Gender, female, n (%)</td><td>59 (75%)</td><td>65 (79%)</td></tr>
<tr><td>PAH aetiology, n (%)</td><td></td><td></td></tr>
<tr><td>IPAH/HPAH</td><td>46 (58%)</td><td>54 (66%)</td></tr>
<tr><td>PAH-CTD</td><td>19 (24%)</td><td>16 (20%)</td></tr>
<tr><td>PAH-CHD</td><td>10 (13%)</td><td>10 (12%)</td></tr>
<tr><td>PAH-DT</td><td>4 (5%)</td><td>2 (2%)</td></tr>
<tr><td>WHO FC, n (%)</td><td></td><td></td></tr>
<tr><td>I</td><td>2 (3%)</td><td>1 (1%)</td></tr>
<tr><td>II</td><td>26 (33%)</td><td>23 (28%)</td></tr>
<tr><td>III</td><td>51 (65%)</td><td>56 (68%)</td></tr>
<tr><td>IV</td><td>0 (%)</td><td>2 (2%)</td></tr>
<tr><td>Concomitant use of bosentan</td><td>42 (53%)</td><td>45 (55%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>54±8</td><td>49±12</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>901±488</td><td>827±399</td></tr>
</table>
Data on the patient characteristics for the WHO FC I-II, no background therapy subgroup, the WHO FC III-IV, no background therapy subgroup, and the with background therapy were not available. Randomisation was stratified according to background therapy; but WHO FC was not a stratification factor.</td>
<td>Intervention
Tadalafil: 40 mg od

Comparator
Placebo

Background therapy
Bosentan (53% in the tadalafil arm vs 55% in the placebo arm): maximal dose of 125 mg bid</td>
<td>Effectiveness
Primary:
- Change in 6MWD at Week 16[c]
Secondary:
- Change in WHO FC[c]
- Time to clinical worsening[c]
- Change in BDS
- Change in SF-36 score
- Change in EQ-5D score
- Change in PVR, mPAP and CI

Safety
- Adverse events[c]</td>
</tr>
</table>

<table>
<tr>
<td>SERAPHIN[7, 46, 47]
2008-2012
US, Canada, Europe, Asia, South America, Australia</td>
<td>RCT, DB
Level II evidence
Follow-up: 129 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion
- Age of ≥12 years
- Patients with WHO FC II-IV IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-HIV, or PAH-DT
- 6MWD ≥50 m
- Allow for concomitant treatment with oral PDE-5i, oral or prostanoid, provided that the patient had been receiving a stable dose for ≥3 months before randomisation

Exclusion criteria
- Patients receiving IV or subcutaneous prostanoid</td>
<td>N=492
<table>
<tr><th></th><th>Macitentan 10 mg (n=242)</th><th>Placebo (n=250)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>46±15</td><td>47±17</td></tr>
<tr><td>Gender, female, n (%)</td><td>194 (80%)</td><td>184 (74%)</td></tr>
<tr><td>Aetiology</td><td></td><td></td></tr>
<tr><td>IPAH</td><td>134 (56%)</td><td>126 (51%)</td></tr>
<tr><td>PAH-CTD</td><td>73 (30%)</td><td>81 (33%)</td></tr>
<tr><td>PAH-CHD</td><td>21 (9%)</td><td>26 (10%)</td></tr>
<tr><td>PAH-DT</td><td>5 (2%)</td><td>8 (3%)</td></tr>
<tr><td>HPAH</td><td>2 (1%)</td><td>3 (1%)</td></tr>
<tr><td>PAH-HIV</td><td>6 (2%)</td><td>3 (1%)</td></tr>
<tr><td>WHO FC</td><td></td><td></td></tr>
<tr><td>I</td><td>1 (0.4%)</td><td>0 (0%)</td></tr>
<tr><td>II</td><td>120 (50%)</td><td>129 (52%)</td></tr>
<tr><td>III</td><td>116 (48%)</td><td>116 (47%)</td></tr>
<tr><td>IV</td><td>5 (2%)</td><td>4 (2%)</td></tr>
<tr><td>Time from diagnosis, mean±SD (yrs)</td><td>2.6±3.6</td><td>2.6±3.7</td></tr>
<tr><td>With background therapy, n (%)</td><td>154 (64%)</td><td>150 (62%)</td></tr>
<tr><td>PDE-5i</td><td>150 (62%)</td><td>150 (60%)</td></tr>
<tr><td>Prostanoid</td><td>15 (6%)</td><td>7 (3%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>53.5±17.6</td><td>53.1±18.1</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>1040±673</td><td>996±784</td></tr>
</table>
Data on the patient characteristics for the WHO FC I-II, no background therapy subgroup, the WHO FC III-IV, no background therapy subgroup, and the with background therapy were not available. Randomisation was not stratified according to background therapy or WHO FC.</td>
<td>Intervention
Macitentan 10 mg od

Comparator
Placebo

Background therapy
PDE-5i (62% in the macitentan arm vs 60% in the placebo arm)
Prostanoid (6% in the macitentan arm vs 3% in the placebo arm)</td>
<td>Effectiveness:
Primary:
- Time to first PAH-related event up to the EOT[c]
Secondary:
- Change in 6MWD at Month 6[c]
- Change in WHO FC at Month 6
- PAH-related death or hospitalisation up to the EOT
- All-cause mortality up to the EOT and up to the EOS[c]
- Change in SF-36 score[c]
- Time to all-cause hospitalisation[c]
- Time to PAH-related hospitalisation

Safety
- Adverse events[c]</td>
</tr>
</table>

<table>
<tr>
<td>STEP[48]
2004
USA</td>
<td>RCT, DB
Level II evidence
Follow-up: 12 weeks
Risk of bias: low</td>
<td>Inclusion criteria
- Age of 10-80 years
- Patients with symptomatic PAH receiving bosentan for ≥4 months
- 6MWD 100-425 m

Exclusion criteria
- Patients with thromboembolic disease, untreated obstructive sleep apnoea, portal hypertension, left-sided or unrepaired CHD, or substantial obstructive or restrictive lung disease
- Patients who were taking PDE-5i or other prostanoid</td>
<td>N=67
<table>
<tr><td></td><td>Iloprost (n=34)</td><td>Placebo (n=33)</td></tr>
<tr><td>Age, mean±SD (yrs)</td><td>51±14</td><td>49±15</td></tr>
<tr><td>Gender, female, n (%)</td><td>27 (79%)</td><td>26 (79%)</td></tr>
<tr><td>Aetiology</td><td></td><td></td></tr>
<tr><td>IPAH</td><td>16 (50%)</td><td>20 (61%)</td></tr>
<tr><td>Associated PAH</td><td>17 (50%)</td><td>13 (39%)</td></tr>
<tr><td>WHO FC</td><td></td><td></td></tr>
<tr><td>II</td><td>0 (0%)</td><td>1 (3%)</td></tr>
<tr><td>III</td><td>35 (97%)</td><td>30 (91%)</td></tr>
<tr><td>IV</td><td>1 (3%)</td><td>2 (6%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>51±11</td><td>52±13</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>815±381</td><td>783±378</td></tr>
</table>
</td>
<td>Intervention
Iloprost: 5 µg inhaled 6-9 times daily

Comparator
Placebo

Background therapy
Bosentan (100%): 125 mg bid</td>
<td>Effectiveness:
- Change in 6MWD[c]
- Change in wHO FC[c]
- Time to clinical worsening[c]
- Change in BDS[c]
- Change in mPAP and PVR[c]
Others:
- Mortality[c]
- Hospitalisation due to PAH

Safety
- Adverse events[c]</td>
</tr>
<tr>
<td>SUPER-1[11, 53]
2002-2003
US, Mexico, South America, Europe, Asia, South Africa, Australia</td>
<td>RCT, DB
Level II evidence
Follow-up: 12 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Patients with IPAH, PAH-CTD or PAH-CHD

Exclusion criteria
- Patients treated with IV epoprostenol, oral bosentan, IV or inhaled iloprost, or subcutaneous treprostinil
- 6MWD <100 m or >450 m</td>
<td>N=139
<table>
<tr><td></td><td>Sildenafil 20 mg (N=69)</td><td>Placebo (N=70)</td></tr>
<tr><td>Age, mean±SD (yrs)</td><td>47±14</td><td>49±17</td></tr>
<tr><td>Gender, female, n (%)</td><td>49 (71%)</td><td>57 (81%)</td></tr>
<tr><td>Aetiology</td><td></td><td></td></tr>
<tr><td>IPAH</td><td>44 (64%)</td><td>42 (60%)</td></tr>
<tr><td>PAH-CTD</td><td>20 (29%)</td><td>22 (31%)</td></tr>
<tr><td>PAH-CHD</td><td>4 (6%)</td><td>6 (9%)</td></tr>
<tr><td>WHO FC</td><td></td><td></td></tr>
<tr><td>I</td><td>0 (0%)</td><td>1 (1%)</td></tr>
</table>
</td>
<td>Intervention
Sildenafil: 20 mg tid

Comparator
Placebo</td>
<td>Effectiveness
Primary:
- Change in 6MWD at Week 12[c]
Secondary:
- Time to clinical worsening
- Change in WHO FC
- Change in BDS
- Change in mPAP, PVR and CI

Safety
- Adverse events[c]</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>II</td><td>24 (35%)</td><td>32 (46%)</td></tr>
<tr><td>III</td><td>40 (58%)</td><td>34 (49%)</td></tr>
<tr><td>IV</td><td>5 (7%)</td><td>3 (4%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>54±13</td><td>56±16</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>987±464</td><td>1051±512</td></tr>
</table>
Data on the patient characteristics for the WHO FC I-II subgroup and the WHO FC III-IV subgroup were not available. Randomisation was not stratified according to WHO FC.
</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vizza 2017[49]
2006-2012
US, Europe, Australia, Israel, China</td>
<td>RCT, DB
Level II evidence
Follow-up: 12 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Age of ≥18 years
- Patients with IPAH, HPAH, PAH-CTD or PAH-CHD
- Patients who were receiving treatment with bosentan at a stable dose for ≥3 months
- 6MWD 100-450 m

Exclusion criteria
- Change of dose/class of standard background PAH therapy within 30 days
- Current use of chronic PAH-specific therapy (e.g. prostacyclin, PDE5i, ERA other than bosentan)</td>
<td>N=103
<table>
<tr><td></td><td>Sildenafil (N=50)</td><td>Placebo (N=53)</td></tr>
<tr><td>Age, mean±SD (yrs)</td><td>55±15</td><td>57±14</td></tr>
<tr><td>Gender, female, n (%)</td><td>37 (74%)</td><td>41 (77%)</td></tr>
<tr><td>Aetiology</td><td></td><td></td></tr>
<tr><td>IPAH/HPAH</td><td>35 (70%)</td><td>32 (60%)</td></tr>
<tr><td>PAH-CTD</td><td>15 (30%)</td><td>21 (40%)</td></tr>
<tr><td>WHO FC</td><td></td><td></td></tr>
<tr><td>II</td><td>20 (40%)</td><td>15 (28%)</td></tr>
<tr><td>III</td><td>29 (58%)</td><td>38 (72%)</td></tr>
<tr><td>IV</td><td>1 (2%)</td><td>0 (0%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>47±13</td><td>50±13</td></tr>
</table>
</td>
<td>Intervention
Sildenafil: 20 mg tid

Comparator
Placebo

Background therapy
Bosentan (100%): 62.5-125 mg bid</td>
<td>Effectiveness
Primary:
- Change in 6MWD at Week 12[c]
Secondary:
- Change in WHO FC[c]
- Time to clinical worsening[c]
Others:
- Mortality[c]
- Hospitalisation due to PAH[c]

Safety
- Adverse events[c]</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>- Acutely decompensated heart failure within 30 days
- LVEF <45%
- History of chronic restrictive lung disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhuang 2014[50]
2011-2013
China</td>
<td>RCT, DB
Level II evidence
Follow-up: 16 weeks
Risk of bias: low-to-moderate</td>
<td>Inclusion criteria
- Age of 18-70 years
- Patients with symptomatic IPAH, HPAH, PAH-CTD, PAH-CHD (repaired) or PAH-DT
- Patients with a stable WHO FC for ≥1 month
- Patients who had received ambrisentan for ≥4 months
- 6MWD 150-400 m

Exclusion criteria
- Patients with portal hypertension, left-sided or unrepaired CHD, or substantial obstructive or restrictive lung disease</td>
<td>N=124
<table>
<tr><th></th><th>Tadalafil (N=60)</th><th>Placebo (N=64)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>52±12</td><td>51±14</td></tr>
<tr><td>Gender, female, n (%)</td><td>46 (77%)</td><td>52 (81%)</td></tr>
<tr><td>Aetiology</td><td></td><td></td></tr>
<tr><td>IPAH/HPAH</td><td>41 (68%)</td><td>37 (58%)</td></tr>
<tr><td>PAH-CTD</td><td>13 (22%)</td><td>15 (23%)</td></tr>
<tr><td>PAH-CHD</td><td>2 (3%)</td><td>5 (8%)</td></tr>
<tr><td>PAH-DT</td><td>4 (7%)</td><td>7 (11%)</td></tr>
<tr><td>WHO FC</td><td></td><td></td></tr>
<tr><td>II</td><td>36 (60%)</td><td>35 (55%)</td></tr>
<tr><td>III</td><td>21 (35%)</td><td>27 (42%)</td></tr>
<tr><td>IV</td><td>3 (5%)</td><td>2 (3%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>50±12</td><td>53±9</td></tr>
<tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>837±389</td><td>843±423</td></tr>
</table>
</td>
<td>Intervention
Tadalafil 40 mg od

Comparator
Placebo

Background therapy
Ambrisentan (100%): 10 mg od</td>
<td>Effectiveness
- Change in 6MWD[c]
- Change in WHO FC[c]
- Clinical worsening[c]
- Change in mPAP and PVR[c]
- Mortality[c]
- Hospitalisation due to PAH[c]

Safety
- Adverse events[c]</td>
</tr>
</table>

<table>
<tr><th colspan="6">Observational studies</th></tr>
<tr>
<td>Sun 2013[51]
2005-2011
China</td>
<td>Retrospective and prospective cohort
Level III-2 evidence
Follow-up: 35.8 months
Risk of bias: moderate</td>
<td>Inclusion criteria
- Patients with PAH-CHD (Eisenmenger syndrome)
- Not amenable to receive corrective cardiac surgery for the irreversible PAH
-
Exclusion criteria
- Patients with small septal defects (atrial septal defect <2 cm effective diameter, ventricular septal defect <1 cm effective diameter and/or aortopulmonary communication <0.4 cm)</td>
<td>N=121
<table><tr><th></th><th>Sildenafil (N=68)</th><th>Conventional therapy (N=53)</th></tr><tr><td>Age, mean±SD (yrs)</td><td>31±10</td><td>29±10</td></tr><tr><td>Gender, female, n (%)</td><td>48 (71%)</td><td>39 (74%)</td></tr><tr><td>Aetiology</td><td></td><td></td></tr><tr><td>PAH-CHD</td><td>68 (100%)</td><td>53 (100%)</td></tr><tr><td>WHO FC</td><td></td><td></td></tr><tr><td>I</td><td>0 (0%)</td><td>4 (7.7%)</td></tr><tr><td>II</td><td>40 (59%)</td><td>32 (60%)</td></tr><tr><td>III</td><td>27 (40%)</td><td>17 (32%)</td></tr><tr><td>IV</td><td>1 (1%)</td><td>0 (0%)</td></tr><tr><td>mPAP, mean±SD (mmHg)</td><td>78±19</td><td>80±18</td></tr><tr><td>PVR, mean±SD (dyn*s*cm^{-5})</td><td>2664±1446</td><td>2696±1405</td></tr></table></td>
<td>Intervention
Sildenafil: 60-100 mg daily

Comparator
Conventional therapy</td>
<td>Effectiveness
- Change in 6MWD
- Change in WHO FC
- Mortality[c]
- Change in mPAP and PVR</td>
</tr>
<tr>
<td>Sastry 2007[52]
1999-2006
India</td>
<td>Historical control study
Level III-3 evidence
Follow-up: up to 5 years
Risk of bias: moderate-to-high</td>
<td>Inclusion criteria
- Patients with IPAH
- Systolic PAP ≥60 mgHg

Exclusion criteria
- Patients with significant left heart disease or shunt lesions</td>
<td>N=178
<table><tr><th></th><th>Sildenafil (n=139)</th><th>Conventional therapy (n=39)</th></tr><tr><td>Age, mean±SD (yrs)</td><td>28±13</td><td>29±12</td></tr><tr><td>Gender, female, n (%)</td><td>87 (63%)</td><td>22 (56%)</td></tr><tr><td>Aetiology</td><td></td><td></td></tr><tr><td>IPAH</td><td>139 (100%)</td><td>39 (100%)</td></tr><tr><td>WHO FC</td><td></td><td></td></tr></table></td>
<td>Intervention
Sildenafil: 25-50 mg tid

Comparator
Conventional therapy</td>
<td>Effectiveness
- Mortality[c]
- Change in WHO FC

Safety
- Adverse events</td>
</tr>
</table>

			II	60 (43%)	19 (49%)		
			III	64 (46%)	18 (46%)		
			IV	15 (11%)	2 (5%)		
			Systolic PAP, mean±SD (mmHg)	102±27	95±25		

[a] Number of patients in the control arm and those in the active treatment arm where a PAH medicine was given at the recommended dose regimen.
[b] Only including the active treatment arm where a PAH medicine was given at the recommended dose regimen.
[c] Outcomes reported in the literature review
[d] Publication year. Information on the study period was not available.
[e] The bosentan monotherapy arm was excluded from the review, given that a non-trivial proportion of patients (28.6% (2 out of 7)) in this treatment group had CTEPH, not PAH.
6MWD = 6-minute walk distance; BDS = Borg dyspnoea scale; bid = twice daily; CTEPH = chronic thromboembolic pulmonary hypertension; DB = double-blinded; DBP = diastolic blood pressure; EOT = end of treatment; EOS = end of study; EQ-5D = EuroQoL 5 dimensions; EQ-VAS = EuroQoL visual analogue scale; ERA = endothelin receptor antagonist; FC = functional class; IV = intravenous; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; LPH = Living with pulmonary hypertension; LVEF = left ventricular ejection fraction; MLHF = Minnesota living with heart failure; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; od = once daily; PDE-5i = phosphodiesterase type 5 inhibitor; OL = open-label; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PAH-DT = drug/toxin-induced pulmonary arterial hypertension; PAH-HIV = pulmonary arterial hypertension associated with human immunodeficiency virus infection; PAH-PH = pulmonary arterial hypertension associated with portal hypertension; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; SBP = systolic blood pressure; SD = standard deviation; SF-36 = 36-Item Short Form Survey; tid = three times a day; TPR = total pulmonary resistance; WHO = World Health Organization

Table 4.145 Additional[a] studies included for extended assessment of safety

<table>
<tr><th>Study ID
Author year
Study period
Location</th><th>Study design
Level of evidence
Duration of follow-up</th><th>Eligibility criteria</th><th>N[b]
Population characteristics</th><th>Intervention[c]
Comparator (if any)
Combination therapy (if any)</th></tr>
<tr><td colspan="5">Randomised controlled trials</td></tr>
<tr>
<td>STARTS-1[54]
2003-2008
North, South, and Central America, Asia, Europe</td>
<td>RCT, DB
Level II evidence
Follow-up: 16 weeks</td>
<td>Inclusion criteria
- Age of 1-17 years, weighing ≥8 kg
- Patients with IPAH, HPAH, PAH-CTD, or PAH-CHD (children with unrepaired shunts were enrolled only if their condition was considered inoperable because of their pulmonary vascular obstructive disease)

Exclusion criteria
- Patients receiving prostanoid, ERA, or PDE-5i</td>
<td>N=234
<table>
<tr><th></th><th>Sildenafil low dose (n=42)</th><th>Sildenafil median dose (n=55)</th><th>Sildenafil high dose (n=77)</th><th>Placebo (n=60)</th></tr>
<tr><td>Age, n (%)
1-4 years
4-12 years
13-17 years</td><td>
0 (0%)
25 (60%)
17 (40%)</td><td>
9 (16%)
28 (51%)
18 (33%)</td><td>
19 (25%)
36 (47%)
22 (29%)</td><td>
7 (12%)
37 (62%)
16 (27%)</td></tr>
<tr><td>Gender, female, n (%)</td><td>188 (74%)</td><td></td><td>100 (79%)</td><td>100 (83%)</td></tr>
<tr><td>PAH aetiology, n (%)
IPAH/HPAH
PAH-CHD</td><td>
12 (29%)
30 (71%)</td><td>
19 (35%)
36 (65%)</td><td>
26 (34%)
51 (66%)</td><td>
21 (35%)
39 (65%)</td></tr>
<tr><td>WHO FC, n (%)
I
II</td><td>
9 (21%)
23 (55%)</td><td>
20 (36%)
25 (45%)</td><td>
21 (27%)
43 (56%)</td><td>
25 (42%)
29 (48%)</td></tr>
</table>
</td>
<td>Intervention
Sildenafil: at low, median or high doses
<table>
<tr><th rowspan="2">Body weight (kg)</th><th colspan="3">Sildenafil dose, mg*</th></tr>
<tr><th>Low</th><th>Med</th><th>High</th></tr>
<tr><td>≥8-20</td><td>NA</td><td>10</td><td>20</td></tr>
<tr><td>>20-45</td><td>10</td><td>20</td><td>40</td></tr>
<tr><td>>45</td><td>10</td><td>40</td><td>80</td></tr>
</table>
NA = not applicable
*Sildenafil tid dose to achieve target sildenafil steady state maximum concentrations of 47, 140, and 373 ng/mL

Comparator
Placebo</td>
</tr>
</table>

			III	9 (21%)	8 (15%)	12 (16%)	6 (10%)
			IV	0 (0%)	1 (2%)	0 (0%)	0 (0%)
			Missing	1 (2%)	1 (2%)	1 (1%)	0 (0%)
			mPAP, mean±SD (mmHg)	66±23	62±18	62±24	59±22
Observational studies							
ARIES extension study[55] No later than 2009[d] US, Mexico, South America, Australia, Europe, Israel	Prospective case series Level IV evidence Follow-up: 2 years	*Inclusion criteria* - Patients with IPAH or PAH-CTD, PAH-HIV or anorexigen-associated-PAH who completed Trials ARIES-1 and ARIES-2	N=383 Age, mean±SD (yrs): 51±15 Gender, female, n (%): 302 (79%) PAH aetiology, n (%): IPAH: 241 (63%); PAH-CTD: 124 (32%); PAH-HIV: 11 (3%); PAH-DT: 6 (2%) WHO FC, n (%): I: 12 (3%); II: 163 (43%); III: 178 (46%); IV: 30 (8%) mPAP, mean±SD (mmHg): 49±14 PVR, mean±SD (mmHg/L/min): 11.0±6.5				*Intervention* Ambrisentan: 2.5 mg, 5 mg or 10 mg od Combination therapy Sildenafil and/or prostanoid (18%)
Dickinson 2009[56] 1998-2006 Netherlands	Retrospective case series Level IV evidence Follow-up: 2.6 years	*Inclusion criteria* - Patients with pulmonary hypertension who were treated with epoprostenol through a totally implantable access port	N=111 Age, mean (range) (yrs): 44 (2-74) Gender, female, n (%): 86 (77%) PAH aetiology, n (%): IPAH: 45 (41%); HPAH: 11 (10%); PAH-CTD: 16 (14%); PAH-CHD: 11 (10%); PAH-PH: 7 (6%); PAH-HIV: 1 (1%); PAH-DT: 1 (1%); PAH-Gaucher disease Type 1: 1(1%); CTEPH: 18 (16%) WHO FC, n (%): II: 42 (4%); III: 53 (48%); IV: 54 (49%)				*Intervention* Epoprostenol (dose not stated)
EARLY extension study[57] 2004-2011 US, Europe, Brazil	Prospective case series Level IV evidence Follow-up: 51.4 months	*Inclusion criteria* - Patients with WHO FC II IPAH, HPAH, PAH-CTD, PAH-CHD, PAH-HIV or anorexigen-associated PAH patients who entered the double-blinded phase of Trial EARLY,	N=111 Age, mean±SD (yrs): 45±18 Gender, female, n (%): 120 (69%) PAH aetiology, n (%): IPAH: 106 (61%); PAH-CHD: 31 (18%); PAH-CTD: 29 (17%); PAH-HIV: 7 (4%) WHO FC, n (%):				*Intervention* Bosentan: 125 mg bid *Combination therapy* Sildenafil and/or prostanoid (17%-46%)

		completed the trial and tolerated treatment	I: 6 (3%); II: 160 (92%); III: 7 (4%) Time from diagnosis, mean±SD (yrs): 3.4±5.9 Concomitant use of sildenafil, n (%): 19 (17%) mPAP, mean±SD (mmHg): 53±8 PVR, mean±SD (dyn*s*cm^{-5}): 853±505	
Hislop 2011[58] 2002-2008 UK	Retrospective case series Level IV evidence Follow-up: 2.6 years	*Inclusion criteria:* - Children with IPAH or PAH-CHD (either post-repair or with Eisenmenger syndrome) who were treated with bosentan	N=101 Age, mean±SD (yrs): 8.9±5.3 Gender, female, n (%): 58 (57%) PAH aetiology, n (%): IPAH: 42 (42%); PAH-CHD: 59 (58%) Bosentan monotherapy, n (%): 67 (66%) mPAP, mean±SD (mmHg): 56±21 PVR, mean±SD (units*m^2): 21±14	*Intervention* Bosentan: 15-125 mg bid, according to body weight: <10 kg: 15 mg bid 10-20 kg: 31.5 mg bid 20-40 kg: 62.5 mg bid >40 mg: 125 mg bid *Combination therapy* Sildenafil and/or EPO (34%-63%)
Kallen 2008[59] 2004-2006 US	Retrospective case series Level IV evidence Follow-up: 4 years	*Inclusion criteria* - Patients given treatment with IV prostanoid for PAH	N=195 (data on baseline characteristics only available for 158 patients) Age, median (yrs): 47 Gender, female, n (%): 124 (78%) Duration of IV prostanoid treatment, median (yrs): 4	*Intervention* Epoprostenol (dose not stated)
Keogh 2011[60] 2004-2007 Australia	Prospective case series Level IV evidence Follow-up: 2.1 years	*Inclusion criteria* - Patients with IPAH or PAH-CTD who were already on bosentan or newly started bosentan therapy	N=528 Age, mean±SD (yrs): 59±17 Gender, female, n (%): 406 (77%) PAH aetiology, n (%): IPAH: 306 (58%); PAH-CTD: 220 (42%) WHO FC, n (%): II: 32 (6%); III: 370 (70%); IV 102 (19%)	*Intervention* Bosentan (dose not stated) *Combination therapy* Sildenafil or prostanoid (11%)
Kitterman 2012[61] 2006-2010 US	Prospective case series Level IV evidence Follow-up: 2 years	*Inclusion criteria* - PAH patients who either had already received or initiated IV prostanoid (epoprostenol or treprostinil)	N=1,146 Age, mean±SD (yrs): 48±16 Gender, female, n (%):905 (79%) PAH aetiology, n (%): IPAH: 585 (51%); HPAH: 50 (4%); PAH-CTD: 258 (23%); PAH-CHD: 89 (8%); PAH-PH: 67 (6%); PAH-DT:	*Intervention* Epoprostenol or treprostinil (dose not stated)

<table>
<tr><td></td><td></td><td></td><td>61 (5%); PAH-HIV: 23 (2%); Other associated PAH: 2 (1%); Pulmonary veno-occlusive disease: 2 (0.2%)
WHO FC, n (%):
I: 65 (6%); II: 318 (30%); III: 542 (52%); IV: 123 (12%)
Time from diagnosis to enrolment, mean±SD (mths): 38±42</td><td></td></tr>
<tr><td>McLaughlin 2002[62]
1991-2001
US</td><td>Case series (unclear if retrospective or prospective)
Level IV evidence
Follow-up: 31 months</td><td>Inclusion criteria
- Patients with primary PAH who were treated with epoprostenol</td><td>N=162
Age, mean (yrs): 42
Gender, female:male ratio: 3:1
PAH aetiology, n (%):
IPAH: 127 (78%); HPAH: 22 (14%); PAH-DT: 13 (8%)
WHO FC, n (%):
III: 75 (46%); IV: 87 (54%)</td><td>Intervention
Epoprostenol: initial dose of 2 ng/kg/min, gradually increased to a maximum tolerated dose, depending on the symptoms of pulmonary hypertension and side effects of epoprostenol</td></tr>
<tr><td>Oudiz 2004[63]
1987-2000
US</td><td>Retrospective and prospective case series
Level IV evidence
Follow-up: 3.6 years</td><td>Inclusion criteria
- Patients with IPAH, PAH-CTD, PAH-CHD, PAH-HIV or PAH-PH who were treated with infusion of epoprostenol via a peripheral vein, with a right heart catheter in place</td><td>N=192
Age, mean±SD (yrs): 40±22
Gender, female, %: 79%
PAH aetiology, %:
IPAH: 65%; PAH-CHD: 19%; PAH-CTD: 12%; PAH-PH: 2%; PAH-HIV: 2%</td><td>Intervention
Epoprostenol (dose not stated)</td></tr>
<tr><td>PACES extension study[64]
2003-2009
US, Canada, Europe, Israel</td><td>Prospective case series
Level IV evidence
Follow-up: 3.2 years</td><td>Inclusion criteria
- Patients with IPAH, HPAH, PAH-CTD, PAH-CHD who completed Trial PACES-1

Exclusion criteria
- Use of nitrates or nitric oxide donors, protease inhibitors, or α-blockers</td><td>N=265*
<table><tr><th></th><th>Sildenafil (N=134)</th><th>Placebo (N=131**)</th></tr><tr><td>Age, mean±SD (yrs)</td><td>48±13</td><td>48±13</td></tr><tr><td>Gender, female, n (%)</td><td>110 (82%)</td><td>102 (78%)</td></tr><tr><td>PAH aetiology, n (%)</td><td></td><td></td></tr><tr><td>IPAH</td><td>107 (80%)</td><td>104 (79%)</td></tr><tr><td>PAH-CTD</td><td>27 (20%)</td><td>27 (21%)</td></tr><tr><td>WHO FC, n (%)</td><td></td><td></td></tr><tr><td>I</td><td>1 (1%)</td><td>2 (2%)</td></tr><tr><td>II</td><td>34 (25%)</td><td>35 (27%)</td></tr><tr><td>III</td><td>89 (66%)</td><td>88 (67%)</td></tr><tr><td>IV</td><td>10 (7%)</td><td>6 (5%)</td></tr></table></td><td>Intervention
Sildenafil: initial dose of 20 mg tid, then titrated to 40 mg tid, and then to 80 mg tid, as tolerated. Patients could reduce the dose of sildenafil to a minimum of 20 mg tid

Combination therapy
Epoprostenol (100%)</td></tr>
</table>

			Epoprostenol dose, mean±SD (ng/kg/min): 32.9±22.1 / 32.0±22.4 Epoprostenol treatment duration, mean (range) (yrs): 2.8 (0.2-10.5) / 2.9 (0.3-11.7) * Data on demographic and disease characteristics when patients started the PACES extension study were not available. Instead, the published paper presented the baseline characteristics for the Trial PACES-1 ** Two patients who did not receive placebo were excluded.	
PATENT extension study[65] 2009-2014 North America, South America, Asia, Europe, Australia	Prospective case series Level IV evidence Follow-up: 139 weeks	*Inclusion criteria:* - Patients with symptomatic PAH who completed Trial PATENT-1 without ongoing study drug-related serious adverse events *Exclusion criteria:* - Patients who withdrew from PATENT-1, due to pulmonary hypertension-related clinical worsening	N=396 Age, mean±SD (yrs): 50±16 Gender, female, n (%): 317 (80%) PAH aetiology, n (%): IPAH: 245 (62%); HPAH: 9 (2%); PAH-CTD: 94 (24%); PAH-CHD: 33 (8%); PAH-DT: 3 (1%); PAH-PH: 12 (3%) WHO FC, n (%): I: 12 (3%); II: 169 (43%); III: 212 (54%); IV: 2 (1%)	*Intervention* Riociguat: up to 2.5 mg tid *Combination therapy* ERA and/or prostanoid (50%-55%)
Provencher 2006[66] 1999-2004 France	Retrospective case series Level IV evidence Follow-up: 24 months	*Inclusion criteria* - Age of >15 years - Patients with WHO FC III or IV IPAH who were treated with first-line bosentan *Exclusion criteria* - PAH related with an associated condition - Patients with an acute response during acute vasoreactivity testing	N=103 Age, mean±SD (yrs): 54±16 Gender, female, n (%): 75 (73%) PAH aetiology, n (%): IPAH: 103 (100%) WHO FC, n (%): III: 91 (88%); IV: 12 (12%) Time from diagnosis, median (range) (mths): 4 (1-22) Concomitant use of sildenafil, n (%): 19 (17%) mPAP, mean±SD (mmHg): 58±12	*Intervention* Bosentan: initial dose of 62.5 mg bid for 4 weeks, then 125 mg bid *Combination therapy* Prostanoid (44%)
Sitbon 2002[67] 1992-2001 France	Retrospective case series Level IV evidence	*Inclusion criteria* - Age of > 15 years - Patients with severe primary pulmonary hypertension who	N=178 Age, mean±SD (yrs): 43±13 Gender, female, n (%): 135 (76%) PAH aetiology, n (%):	*Intervention* Epoprostenol: initial dose of 1 ng/kg/min, then increased by 1 ng/kg/min every 12 hours up to 10 ng/kg/min, then adjusted

	Follow-up: 26 months	were treated with long-term epoprostenol *Exclusion criteria* - Patients with PAH-CTD, PAH-CHD, PAH-PH, PAH-HIV, or distal CTEPH - Chronic pulmonary disease - Patients with an acute pulmonary vasodilator response that predicted a clinical response to oral calcium channel blockers	IPAH/HPAH/PAH-DT: 178 (100%) WHO FC, n (%): III: 120 (67%); IV: 58 (33%) Time since onset of symptoms, mean±SD (mths): 34±34 mPAP, mean±SD (mmHg): 67±14	systematically to reach a mean level of 14±4 ng/kg/min at 3 months. Thereafter, dose adjustments were based on clinical symptoms consistent with clinical deterioration or the occurrence of adverse events, distance walked during exercise testing, and hemodynamic measurements
Sitbon 2016[68] 2007-2013 France	Retrospective case series Level IV evidence Follow-up: 30 months	*Inclusion criteria* - Age of >18 years - Patients with newly diagnosed PAH of any aetiology and in WHO FC II-IV who were initiated on first-line dual oral combination treatment with ERA (bosentan or ambrisentan) and PDE-5i (sildenafil or tadalafil) *Inclusion criteria* - Patients with non-group 1 pulmonary hypertension and pulmonary veno-occlusive disease - Unstable patients in need of parenteral prostacyclin and those for whom ERAs were contraindicated	N=97 Age, mean±SD (yrs): 54±17 Gender, female, n (%): 63 (65%) PAH aetiology, n (%): IPAH: 52 (54%); HPAH: 15 (15%); PAH-CTD: 12 (12%); PAH-DT: 7 (7%); PAH-PH: 9 (9%); PAH-CHD: 1 (1%); PAH-HIV: 1 (1%) WHO FC, n (%): II: 15 (15%); III: 70 (72%); IV: 12 (12%) Time since onset of symptoms, mean±SD (mths): 34±34 mPAP, mean±SD (mmHg): 54±10 PVR, mean±SD (dyn*s*m^{-5}): 1021±357	*Intervention* Bosentan or ambrisentan + sildenafil or tadalafil Bosentan: initial dose of 62.5 mg bid, then increased to 125 mg bid after 4 weeks Ambrisentan: initial dose of 5 mg od, then increased to 10 mg od if needed Sildenafil: initial dose of 20 mg tid, then increased to 40 mg tid if needed Tadalafil: initial dose of 20 mg od, then up-titrated to 40 mg od after 3-7 days, according to tolerability *Combination therapy* Prostanoid or selexipag (29%)
STARTS extension study [69] 2004-2011	Prospective case series Level IV evidence	*Inclusion criteria* - Children weighing ≥8 kg - Patients with IPAH, HPAH, PAH-CTD, or PAH-CHD who completed Trial STARTS	N=220*	*Intervention* Sildenafil: both upward and downward dose titrations of sildenafil permitted. Doses received after dose titrations

<table>
<tr>
<td>North, South, and Central America, Asia and Europe</td>
<td>Follow-up: 4.1 years</td>
<td></td>
<td>
<table>
<tr><th></th><th>Sildenafil low dose (n=42)</th><th>Sildenafil median dose (n=55)</th><th>Sildenafil high dose (n=77)</th><th>Placebo (n=60)</th></tr>
<tr><td>Weight, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>≤20 kg</td><td>0 (0%)</td><td>15 (27%)</td><td>35 (46%)</td><td>18 (30%)</td></tr>
<tr><td>>20 kg</td><td>42 (100%)</td><td>40 (73%)</td><td>42 (55%)</td><td>42 (70%)</td></tr>
<tr><td>PAH aetiology, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>IPAH/HPAH</td><td>12 (29%)</td><td>19 (35%)</td><td>26 (34%)</td><td>21 (35%)</td></tr>
<tr><td>PAH-CHD</td><td>30 (71%)</td><td>36 (65%)</td><td>51 (66%)</td><td>39 (65%)</td></tr>
<tr><td>WHO FC, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>9 (21%)</td><td>20 (36%)</td><td>21 (27%)</td><td>25 (42%)</td></tr>
<tr><td>II</td><td>23 (55%)</td><td>25 (45%)</td><td>43 (56%)</td><td>29 (48%)</td></tr>
<tr><td>III/IV</td><td>9 (21%)</td><td>9 (16%)</td><td>12 (16%)</td><td>6 (10%)</td></tr>
<tr><td>Missing</td><td>1 (2%)</td><td>1 (2%)</td><td>1 (1%)</td><td>0 (0%)</td></tr>
<tr><td>mPAP, mean±SD (mmHg)</td><td>66±23</td><td>62±18</td><td>62±24</td><td>59±22</td></tr>
</table>
* Data on demographic and disease characteristics when patients started the STARTS extension study were not available. Instead, the published paper presented the baseline characteristics for the Trial STARTS-1
</td>
<td>were equivalent to those in other dose groups
<table>
<tr><th rowspan="2">Body weight (kg)</th><th colspan="3">Sildenafil dose, mg*</th></tr>
<tr><th>Low</th><th>Med</th><th>High</th></tr>
<tr><td>≥8-20</td><td>NA</td><td>10</td><td>20</td></tr>
<tr><td>>20-45</td><td>10</td><td>20</td><td>40</td></tr>
<tr><td>>45</td><td>10</td><td>40</td><td>80</td></tr>
</table>
NA = not applicable
*Sildenafil tid dose to achieve target sildenafil steady state maximum concentrations of 47, 140, and 373 ng/mL</td>
</tr>
<tr>
<td>Vachiéry 2017 [70]
2008-2013</td>
<td>Prospective case series</td>
<td>Inclusion criteria</td>
<td>N=998
Age, mean±SD (yrs): 30±15
Gender, female, n (%): 667 (67%)</td>
<td>Intervention
Ambrisentan: 5 mg or 10 mg od</td>
</tr>
</table>

<table>
<tr>
<td>Europe, Canada, Australia</td>
<td>Level IV evidence
Follow-up: 2.2 years</td>
<td>- PAH patients who were prescribed ambrisentan for medically appropriate use</td>
<td>PAH aetiology, n (%):
IPAH: 446 (45%); HPAH: 8 (<1%); Associated PAH: 418 (42%); missing data: 126 (13%)
WHO FC, n (%):
I: 22 (2%); II: 258 (26%); III: 642 (65%); IV: 68 (7%); missing data: 8 (1%)
mPAP, mean±SD (mmHg): 48±14 (n=789)
PVR, mean±SD (dyn*s*m^{-5}): 805±759 (n=717)</td>
<td>Combination therapy
Other PAH medicines (32% at baseline)</td>
</tr>
<tr>
<td>VA1A4001 extension study[71]
No later than 2009[d]
North America</td>
<td>Prospective case series
Level IV evidence
Follow-up: up to 3 year</td>
<td>Inclusion criteria
- Patients with WHO FC III or IV PAH associated with scleroderma who completed Trial VA1A4001</td>
<td>N=97
Age, median (range) (yrs): 57 (23-78)
Gender, female, n (%): 87 (90%)
PAH aetiology, n (%):
PAH-CTD: 97 (100%)
WHO FC, n (%):
II: 5 (5%); III: 77 (79%); IV: 15 (15%)</td>
<td>Intervention
Epoprostenol: initial dose of 2 ng/kg/min, then up-titrated based on tolerability</td>
</tr>
<tr>
<td>Vis 2013[72]
2005-2010
Netherlands</td>
<td>Case series (unclear if retrospective or prospective)
Level IV evidence
Follow-up: 3.9-4 years</td>
<td>Inclusion criteria
- Adult PAH patients with Eisenmenger syndrome and other CHDs or patients with persistent PAH after previous closure of their CHD defect
- Patients with WHO FC II-IV
- Receiving bosentan for treatment of PAH

Exclusion criteria
- Patients receiving prostanoid, PDE-5i, glibenclamide or cyclosporine before study inclusion
- Patients with obstruction of the right ventricular outflow tract, pulmonary valve, or pulmonary arteries</td>
<td>N=64
<table>
<tr><th></th><th>With Down syndrome (N=34)</th><th>Without Down syndrome (N=30)</th></tr>
<tr><td>Age, mean±SD (yrs)</td><td>46±14</td><td>36±10</td></tr>
<tr><td>Gender, female, n (%)</td><td>23 (68%)</td><td>11 (37%)</td></tr>
<tr><td>PAH aetiology, n (%)
PAH-CHD</td><td>
34 (100%)</td><td>
30 (100%)</td></tr>
<tr><td>WHO FC, n (%)
II
III
IV</td><td>
4 (12%)
28 (82%)
2 (6%)</td><td>
8 (27%)
20 (67%)
2 (7%)</td></tr>
<tr><td>Systolic PAP, mean±SD (mmHg)</td><td>83±23</td><td>93±11</td></tr>
</table>
</td>
<td>Intervention
Bosentan: 125 mg bid

Combination therapy
Sildenafil (2%)</td>
</tr>
</table>

[a] Three RCTs (Mukhopadhyay 2011, PHIRST and SUPER-1) and one observational study (Sastry 2007) were also included for extended assessment of safety of PAH medicines. For study profiles of these studies, see Table 4.144.

[b] Number of patients in the control arm and those in the active treatment arm where a PAH medicine was given at the recommended dose regimen.
[c] Only including the active treatment arm where a PAH medicine was given at the recommended dose regimen.
[d] Publication year. Information on the study period was not available
bid = twice daily; CTEPH = chronic thromboembolic pulmonary hypertension; DB = double-blinded; ERA = endothelin receptor antagonist; FC = functional class; IV = intravenous; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; od = once daily; PDE-5i = phosphodiesterase type 5 inhibitor; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PAH-CTD = pulmonary arterial hypertension associated with connective tissue disease; PAH-DT = drug/toxin-induced pulmonary arterial hypertension; PAH-HIV = pulmonary arterial hypertension associated with human immunodeficiency virus infection; PAH-PH = pulmonary arterial hypertension associated with portal hypertension; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; SBP = systolic blood pressure; SD = standard deviation; tid = three times a day; WHO = World Health Organization
.

Appendix 4.B Excluded studies

Those articles which had potentially relevant populations, interventions, comparators and outcomes, but which were not included in the systematic review (n=118), are listed below, by reason for exclusion.

EVIDENCE PREVIOUSLY REVIEWED BY PBAC (n=16)

Badesch DB, Bodin F, Channick RN, Frost A, Rainisio M, Robbins IM, et al. Complete results of the first randomized, placebo-controlled study of bosentan, a dual endothelin receptor antagonist, in pulmonary arterial hypertension. *Current Therapeutic Research - Clinical and Experimental*. 2002;63(4):227-46.

Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: A randomized, controlled trial. *Annals of Internal Medicine*. 2000;132(6):425-34.

Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, et al. Treatment of Pulmonary Arterial Hypertension With the Selective Endothelin-A Receptor Antagonist Sitaxsentan. *Journal of the American College of Cardiology*. 2006;47(10):2049-56.

Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *New England Journal of Medicine*. 1996;334(5):296-301.

Berger RMF, Beghetti M, Galiè N, Gatzoulis MA, Granton J, Lauer A, et al. Atrial septal defects versus ventricular septal defects in BREATHE-5, a placebo-controlled study of pulmonary arterial hypertension related to Eisenmenger's syndrome: A subgroup analysis. *International Journal of Cardiology*. 2010;144(3):373-8.

Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: A randomised placebo-controlled study. *Lancet*. 2001;358(9288):1119-23.

Denton CP, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: A subgroup analysis of the pivotal clinical trials and their open-label extensions. *Annals of the Rheumatic Diseases*. 2006;65(10):1336-40.

Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RMF, Lauer A, et al. Bosentan therapy in patients with Eisenmenger syndrome: A multicenter, double-blind, randomized, placebo-controlled study. *Circulation*. 2006;114(1):48-54.

Hinderliter AL, Willis IPW, Barst RJ, Rich S, Rubin LJ, Badesch DB, et al. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. *Circulation*. 1997;95(6):1479-86.

Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, et al. Inhaled iloprost for severe pulmonary hypertension. *New England Journal of Medicine*. 2002;347(5):322-9.

Raymond RJ, Hinderliter AL, Willis IPW, Ralph D, Caldwell EJ, Williams W, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *Journal of the American College of Cardiology*. 2002;39(7):1214-9.

Rubin LJ, Badesch DB, Barst RJ, Galiè N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. *New England Journal of Medicine*. 2002;346(12):896-903.

Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Annals of Internal Medicine*. 1990;112(7):485-91.

Saji T, Myoishi M, Sugimura K, Tahara N, Takeda Y, Fukuda K, et al. Efficacy and safety of inhaled iloprost in Japanese patients with pulmonary arterial hypertension - Insights from the IBUKI and AIR Studies. *Circulation Journal*. 2016;80(4):835-42.

Shapiro S, Pollock DM, Gillies H, Henig N, Allard M, Blair C, et al. Frequency of edema in patients with pulmonary arterial hypertension receiving ambrisentan. *American Journal of Cardiology*. 2012;110(9):1373-7.

Wilkins MR, Paul G, Strange J, Tunariu N, Gin-Sing W, Banya W, et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. *American Journal of Respiratory and Critical Care Medicine*. 2005;171(11):1292-7.

DUPLICATED STUDY DATA (n=3)

Croxtall JD, Lyseng-Williamson KA. Tadalafil: in pulmonary arterial hypertension. *Drugs*. 2010;70(4):479-88.

Gilbert C, Brown MCJ, Cappelleri JC, Carlsson M, McKenna SP. Estimating a minimally important difference in pulmonary arterial hypertension following treatment with sildenafil. *Chest*. 2009;135(1):137-42.

NCT01179334. An Interaction Study to Evaluate Changes in Blood Pressure Following 1, 1.5, 2, and 2.5 mg Riociguat Tid (Dose Titration) Compared to Placebo Treatment on the Background of Stable Sildenafil Pretreatment in Subjects With Symptomatic Pulmonary Arterial Hypertension. 2010: Available from: https://clinicaltrials.gov/ct2/show/NCT01179334.

INCORRECT/MIXED POPULATION (n=8)

Badesch DB, Hill NS, Burgess G, Rubin LJ, Barst RJ, Galiè N, et al. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. *Journal of Rheumatology*. 2007;34(12):2417-22.

Eskandar AM. Effect of sildenafil in the management of preoperative pulmonary hypertension. *Alexandria Journal of Medicine*. 2014;50(1):13-6.

Galiè N, Denton CP, Dardi F, Manes A, Mazzanti G, Li B, et al. Tadalafil in idiopathic or heritable pulmonary arterial hypertension (PAH) compared to PAH associated with connective tissue disease. *International Journal of Cardiology*. 2017;235:67-72.

Higenbottam TW, Spiegelhalter D, Scott PJ, Fuster V, Dinh-Xuan AT, Caine N, et al. Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hypertension. *British Heart Journal*. 1993;70(4):366-70.

Humbert M, Coghlan J, Ghofrani H, Grimminger F, He J, Riemekasten G, et al. Riociguat for the treatment of pulmonary arterial hypertension associated with connective tissue disease: results from PATENT-1 and PATENT-2. 2016: Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/500/CN-01402500/frame.html.

Maxey DM, Ivy DD, Ogawa MT, Feinstein JA. Food and drug administration (FDA) postmarket reported side effects and adverse events associated with pulmonary hypertension therapy in pediatric patients. *Pediatric Cardiology*. 2013;34(7):1628-36.

Olschewski H, Hoeper MM, Behr J, Ewert R, Meyer A, Borst MM, et al. Long-term therapy with inhaled iloprost in patients with pulmonary hypertension. *Respiratory Medicine*. 2010;104(5):731-40.

Pepke-Zaba J, Gilbert C, Collings L, Brown MCJ. Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. *Chest*. 2008;133(1):183-9.

INCORRECT/MIXED INTERVENTION OR COMPARATOR (n=22)

Angalakuditi M, Edgell E, Beardsworth A, Buysman E, Bancroft T. Treatment patterns and resource utilization and costs among patients with pulmonary arterial hypertension in the United States. *Journal of Medical Economics*. 2010;13(3):393-402.

Beghetti M, Rudzinski A, Zhang M. Efficacy and safety of oral sildenafil in children with Down syndrome and pulmonary hypertension. *BMC Cardiovascular Disorders*. 2017;17(1).

Bharani A, Patel A, Saraf J, Jain A, Mehrotra S, Lunia B. Efficacy and safety of PDE-5 inhibitor tadalafil in pulmonary arterial hypertension. *Indian Heart Journal*. 2007;59(4):323-8.

Bhasin S, Gogia P, Nair R, Sahoo TK. Perioperative sildenafil therapy for children with ventricular septal defects and associated pulmonary hypertension undergoing corrective surgery: A randomised clinical trial. *Indian Journal of Anaesthesia*. 2017;61(10):798-802.

Diller GP, Alonso-Gonzalez R, Dimopoulos K, Alvarez-Barredo M, Koo C, Kempny A, et al. Disease targeting therapies in patients with Eisenmenger syndrome: Response to treatment and long-term efficiency. *International Journal of Cardiology*. 2013;167(3):840-7.

Diller GP, Körten MA, Bauer UMM, Miera O, Tutarel O, Kaemmerer H, et al. Current therapy and outcome of Eisenmenger syndrome: Data of the German National Register for congenital heart defects. *European Heart Journal*. 2016;37(18):1449-55.

Fraisse A, Butrous G, Taylor MB, Oakes M, Dilleen M, Wessel DL. Intravenous sildenafil for postoperative pulmonary hypertension in children with congenital heart disease. *Intensive Care Medicine*. 2011;37(3):502-9.

Fritz JS, Blair C, Oudiz RJ, Dufton C, Olschewski H, Despain D, et al. Baseline and follow-up 6-min walk distance and brain natriuretic peptide predict 2-year mortality in pulmonary arterial hypertension. *Chest*. 2013;143(2):315-23.

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Hoeper MM, Seyfarth HJ, Hoeffken G, Wirtz H, Spiekerkoetter E, Pletz MW, et al. Experience with inhaled iloprost and bosentan in portopulmonary hypertension. *European Respiratory Journal*. 2007;30(6):1096-102.

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Jacobs W, Boonstra A, Brand M, Rosenberg DM, Schaaf B, et al. Long-term outcomes in pulmonary arterial hypertension in the first-line epoprostenol or first-line Bosentan era. *Journal of Heart and Lung Transplantation*. 2010;29(10):1150-8.

Kemp K, Savale L, O'Callaghan DS, Jaís X, Montani D, Humbert M, et al. Usefulness of first-line combination therapy with epoprostenol and bosentan in pulmonary arterial hypertension: An observational study. *Journal of Heart and Lung Transplantation*. 2012;31(2):150-8.

Lammi MR, Mathai SC, Saketkoo LA, Domsic RT, Bojanowski C, Furst DE, et al. Association between Initial Oral Therapy and Outcomes in Systemic Sclerosis-Related Pulmonary Arterial Hypertension. *Arthritis and Rheumatology*. 2016;68(3):740-8.

Reichenberger F, Mainwood A, Morrell NW, Parameshwar J, Pepke-Zaba J. Intravenous epoprostenol versus high dose inhaled iloprost for long-term treatment of pulmonary hypertension. *Pulmonary Pharmacology and Therapeutics*. 2011;24(1):169-73.

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Sakao S, Tanabe N, Kasahara Y, Tatsumi K. Survival of Japanese patients with pulmonary arterial hypertension after the introduction of endothelin receptor antagonists and/or phosphodiesterase type-5 inhibitors. *Internal Medicine*. 2012;51(19):2721-6.

Sastry BKS, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of sildenafil in primary pulmonary hypertension: A randomized, placebo-controlled, double-blind, crossover study. *Journal of the American College of Cardiology*. 2004;43(7):1149-53.

Shirai Y, Yasuoka H, Takeuchi T, Satoh T, Kuwana M. Intravenous epoprostenol treatment of patients with connective tissue disease and pulmonary arterial hypertension at a single center. *Modern Rheumatology*. 2013;23(6):1211-20.

Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. *American Heart Journal*. 2006;151(4):851.e1-.e5.

Sitbon O, McLaughlin VV, Badesch DB, Barst RJ, Black C, Galiè N, et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. *Thorax*. 2005;60(12):1025-30.

Williams MH, Das C, Handler CE, Akram MR, Davar J, Denton CP, et al. Systemic sclerosis associated pulmonary hypertension: Improved survival in the current era. *Heart*. 2006;92(7):926-32.

NO OUTCOME OF INTEREST (n=6)

Bigdelian H, Sedighi M. The role of preoperative sildenafil therapy in controlling of postoperative pulmonary hypertension in children with ventricular septal defects. *Journal of Cardiovascular and Thoracic Research*. 2017;9(3):179-82.

Galiè N, Hinderliter AL, Torbicki A, Fourme T, Simonneau G, Pulido T, et al. Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and Doppler measures in patients with pulmonary arterial hypertension. *Journal of the American College of Cardiology*. 2003;41(8):1380-6.

Galiè N, Jansa P, Pulido T, Channick RN, Delcroix M, Ghofrani HA, et al. SERAPHIN haemodynamic substudy: The effect of the dual endothelin receptor antagonist macitentan on haemodynamic parameters and NT-proBNP levels and their association with disease progression in patients with pulmonary arterial hypertension. *European Heart Journal*. 2017;38(15):1147-55.

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Reza Sabri M, Bigdelian H, Hosseinzadeh M, Ahmadi A, Ghaderian M, Shoja M. Comparison of the therapeutic effects and side effects of tadalafil and sildenafil after surgery in young infants with pulmonary arterial hypertension due to systemic-to-pulmonary shunts. *Cardiology in the Young*. 2017:1-8.

Webb DJ, Vachiery JL, Hwang LJ, Maurey JO. Sildenafil improves renal function in patients with pulmonary arterial hypertension. *British Journal of Clinical Pharmacology*. 2015;80(2):235-41.

SYSTEMATIC REVIEW WITH DIFFERENT SELECTION CRITERIA (n=32)

Avouac J, Wipff J, Kahan A, Allanore Y. Effects of oral treatments on exercise capacity in systemic sclerosis related pulmonary arterial hypertension: A meta-analysis of randomised controlled trials. *Annals of the Rheumatic Diseases*. 2008;67(6):808-14.

Badiani B, Messori A. Targeted Treatments for Pulmonary Arterial Hypertension: Interpreting Outcomes by Network Meta-analysis. *Heart Lung and Circulation*. 2016;25(1):46-52.

Chen YF, Jowett S, Barton P, Malottki K, Hyde C, Gibbs JSR, et al. Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: A systematic review and economic evaluation. *Health Technology Assessment*. 2009;13(49):ix-320.

Coeytaux RR, Schmit KM, Kraft BD, Kosinski AS, Mingo AM, Vann LM, et al. Comparative effectiveness and safety of drug therapy for pulmonary arterial hypertension. *Chest*. 2014;145(5):1055-63.

Duo-Ji MM, Long ZW. Comparative efficacy and acceptability of endothelin receptor antagonists for pulmonary arterial hypertension: A network meta-analysis. *International Journal of Cardiology*. 2017;234:90-8.

Fox BD, Shimony A, Langleben D. Meta-analysis of monotherapy versus combination therapy for pulmonary arterial hypertension. *American Journal of Cardiology*. 2011;108(8):1177-82.

Fox BD, Shtraichman O, Langleben D, Shimony A, Kramer MR. Combination Therapy for Pulmonary Arterial Hypertension: A Systematic Review and Meta-analysis. *Canadian Journal of Cardiology*. 2016;32(12):1520-30.

Gali N, Palazzini M, Manes A. Pulmonary arterial hypertension: From the kingdom of the near-dead to multiple clinical trial meta-analyses. *European Heart Journal*. 2010;31(17):2080-6.

Galie N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J*. 2009;30(4):394-403.

Gao XF, Zhang JJ, Jiang XM, Ge Z, Wang ZM, Li B, et al. Targeted drugs for pulmonary arterial hypertension: A network meta-analysis of 32 randomized clinical trials. *Patient Preference and Adherence*. 2017;11:871-85.

Giannetta E, Feola T, Gianfrilli D, Pofi R, Dall'Armi V, Badagliacca R, et al. Is chronic inhibition of phosphodiesterase type 5 cardioprotective and safe? A meta-analysis of randomized controlled trials. *BMC Medicine*. 2014;12(1).

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He B, Zhang F, Li X, Tang C, Lin G, Du J, et al. Meta-analysis of randomized controlled trials on treatment of pulmonary arterial hypertension. *Circulation Journal*. 2010;74(7):1458-64.

Igarashi A, Inoue S, Ishii T, Tsutani K, Watanabe H. Comparative Effectiveness of Oral Medications for Pulmonary Arterial Hypertension. *Int Heart J*. 2016;57(4):466-72.

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Li T, Chen Y, Zang W, Geng N, Ma S, Li X. Prostacyclin and its analogues in pulmonary artery hypertension: A meta-analysis. *Current Medical Research and Opinion*. 2013;29(8):889-99.

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Silva MA, Donovan JL, Durie R, Ventura D, Alspach RM, Kanaan AO, et al. A Mixed Treatment Comparison Meta-Analysis of Pharmacotherapeutic Monotherapy and Placebo for Pulmonary Artery Hypertension. *Clinical Pulmonary Medicine*. 2017;24(4):149-59.

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Zhang H, Li X, Huang J, Li H, Su Z, Wang J. Comparative efficacy and safety of prostacyclin analogs for pulmonary arterial hypertension: A network meta-Analysis. *Medicine (United States)*. 2016;95(4).

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Zheng Y, Yang T, Chen G, Hu E, Gu Q, Xiong C. Prostanoid therapy for pulmonary arterial hypertension: A meta-analysis of survival outcomes. *European Journal of Clinical Pharmacology*. 2014;70(1):13-21.

HIGHER LEVEL OF EVIDENCE AVAILABLE (n=7)

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Haworth SG, Hislop AA. Treatment and survival in Children with pulmonary arterial hypertension: The UK Pulmonary Hypertension Service for Children 2001 2006. *Heart*. 2009;95(4):312-7.

Oudiz RJ, Roveran G, Hansen JE, Sun XG, Wasserman K. Effect of sildenafil on ventilatory efficiency and exercise tolerance in pulmonary hypertension. *European Journal of Heart Failure*. 2007;9(9):917-21.

Sfikakis PP, Papamichael C, Stamatelopoulos KS, Tousoulis D, Fragiadaki KG, Katsichti P, et al. Improvement of vascular endothelial function using the oral endothelin receptor antagonist bosentan in patients with systemic sclerosis. *Arthritis and Rheumatism*. 2007;56(6):1985-93.

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LONG-TERM OBSERVATIONAL STUDY WITH <50 PATIENTS RECEIVING TREATMENT (n=24)

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Halank M, Hoeper MM, Ghofrani HA, Meyer FJ, Stähler G, Behr J, et al. Riociguat for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: Results from a phase II long-term extension study. *Respiratory Medicine*. 2017;128:50-6.

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Appendix 4.C Evidence Profile Tables

Question 1

Table 4.146 Evidence profile table for ERA compared with placebo for patients with WHO FC I/II PAH

Outcome (follow-up)	No. of studies and study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with ERA	Study event rates (%) with placebo	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Clinical worsening (12–115 weeks)	4 RCTs	Serious [c]	Not serious	Not serious	Not serious	Very strong association	[redacted]	[redacted]	[redacted]	[redacted]	High ⨁⨁⨁⨁ Critical
Mortality (26–129 weeks)	2 RCTs	Serious [c]	Not serious	Not serious	Not serious	Strong association	[redacted]	[redacted]	[redacted]	[redacted]	High ⨁⨁⨁⨁ Critical
Improved WHO FC (12 weeks)	2 RCTs	Serious [c]	Not serious	Not serious	Not serious	None	7/50 (14%)	0/51 (0%)	ARD = 14.0% (4.4, 23.6)	140 fewer per 1,000 (from 44 fewer to 236 fewer)	Moderate ⨁⨁⨁⊙ Important
Worsened WHO FC (12 weeks)	2 RCTs	Serious [c]	Not serious	Not serious	Serious [d]	None	1/50 (2%)	4/51 (8%)	RR = 0.25 (0.03, 2.20)	59 fewer per 1,000 (from 76 fewer to 94 more)	Low ⨁⨁⊙⊙ Important
Change in 6MWD (26 weeks)	3 RCTs	Not serious	Not serious	Serious [e]	Not serious	None	[redacted]	[redacted]	-	[redacted]	Moderate ⨁⨁⨁⊙ Important
Change in haemodynamic parameters (26 weeks)	1 RCT	Not serious	Not serious	Very serious [e]	Not serious	None	[redacted]	[redacted]	-	[redacted]	Low ⨁⨁⊙⊙ Not important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Randomisation was not stratified by subgroup of interest
[d] Wide 95% CIs that span 1
[e] Surrogate outcome
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Table 4.147 Evidence profile table for PDE-5 inhibitor compared to placebo for patients with WHO FC I/II PAH

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with PDE-5 inhibitor	Study event rates (%) with placebo	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
All-cause mortality (48 months)	2 cohort studies	Serious [c,d,e]	Not serious	Not serious	Serious [f]	Strong association	10/100 (10%)	11/55 (20%)	RR = 0.32 (0.05, 1.90)	136 fewer per 1,000 (from 180 more to 190 fewer)	Very low ⊕⊙⊙⊙ Critical
Improved WHO FC (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [f,g]	None	1/22 (5%)	1/22 (5%)	RR = 1.00 (0.07, 15.00)	0 fewer per 1,000 (from 42 fewer to 636 more)	Low ⊕⊕⊙⊙ Important
Worsened WHO FC (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [g]	None	0/22 (0%)	0/22 (0%)	Not estimable	Not estimable	Low ⊕⊕⊙⊙ Important
Change in 6MWD from baseline (12–16 weeks)	2 RCTs	Serious [h]	Not serious	Serious [i]	Not serious	None	40 patients tested	33 patients tested	-	Median MD 30.5 m further (range 10.8 further to 50.2 further)	Low ⊕⊕⊙⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Classification of intervention status subject to bias as patients made their own decisions
[d] No adjustments were made for potential confounding

[e] No baseline characteristics for subgroup of interest
[f] Wide 95% CIs that span 1
[g] Small study size
[h] Randomisation was not stratified by subgroup of interest
[i] Surrogate outcome
⨁⨁⨀⨀ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁⨀⨀⨀ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

[redacted]

Question 3

ERA in addition to PDE-5 inhibitor

Table 4.149 Evidence profile table for effectiveness of ERA plus PDE-5 inhibitor combination therapy compared to PDE-5 inhibitor monotherapy for all PAH patients

Outcome (follow-up)	No. of studies and study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other considerations[a]	Study event rates (%) with ERA + PDE-5i	Study event rates (%) with PDE-5i	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Clinical worsening (26–169 weeks)	4 RCTs	Not serious	Not serious	Not serious	Not serious	Strong association	[redacted]	[redacted]	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
Mortality (26–169 weeks)	4 RCTs	Not serious	Serious [c]	Not serious	Not serious	None	[redacted]	[redacted]	[redacted]	[redacted]	Moderate ⊕⊕⊕⊙ Critical
Hospitalisation due to PAH (74–104 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	Strong association	59/456 (12.9%)	71/305 (23.3%)	RR = 0.67 (0.45, 0.98)	77 fewer per 1,000 (from 5 fewer to 128 fewer)	High ⊕⊕⊕⊕ Important
Improved WHO FC (12 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	None	119/411 (29.0%)	67/295 (22.7%)	RR = 1.10 (0.85, 1.42)	23 more per 1,000 (from 34 fewer to 95 more)	High ⊕⊕⊕⊕ Important
Worsened WHO FC (12 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	None	25/411 (6.1%)	24/295 (8.1%)	RR = 1.00 (0.58, 1.73)	0 fewer per 1,000 (from 34 fewer to 55 more)	High ⊕⊕⊕⊕ Important
Change in 6MWD from baseline (26 weeks)	4 RCTs	Not serious	Not serious	Serious [d]	Serious [e]	None	581 patients tested	465 patients tested	-	Median MD 23.8 m further (range 17.3 m less to 26.3 m further)	Low ⊕⊕⊙⊙ Important

Outcome (follow-up)	No. of studies and study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other considerations[a]	Study event rates (%) with ERA + PDE-5i	Study event rates (%) with PDE-5i	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Change in QoL from baseline (26 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	150 patients tested	149 patients tested	-	SF-36 physical component[f] Median 1.4 points improvement (0 to 2.9 points)	High ⊕⊕⊕⊕ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Trials show results trending in opposite directions
[d] Surrogate outcome
[e] Wide range
[f] SF-36 physical component summary scores range from 0 to 100. A higher score indicates better QoL.
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; SF-36 = short form 36; WHO = World Health Organization

Table 4.150 Evidence profile table for effectiveness of ERA plus PDE-5 inhibitor combination therapy compared to PDE-5 inhibitor monotherapy for patients with WHO FC III/IV PAH

Outcome (follow-up)	No. of studies and study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with ERA + PDE-5i	Study event rates (%) with PDE-5i	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Clinical worsening (104–169 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	Strong association	[redacted]	[redacted]	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical
Mortality (129 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	[redacted]	[redacted]	[redacted]	[redacted]	High ⊕⊕⊕⊕ Critical

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; HR = hazard ratio; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Table 4.151 Evidence profile table for effectiveness of ERA plus PDE-5 inhibitor combination therapy compared to PDE-5 inhibitor monotherapy for patients with different PAH aetiologies

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with ERA + PDE-5i	Study event rates (%) with PDE-5i	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Clinical worsening in IPAH/HPAH (169 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	44/107 (41.1%)	60/119 (50.4%)	HR = 0.82 (0.55, 1.21)	67 fewer per 1,000 (from 68 more to 184 fewer)	High ⨁⨁⨁⨁ Critical
Clinical worsening in PAH CTD (74−169 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	Strong association	2/146 (28.8%)	-/85	HR = 0.59 (0.12, 1.07)	Not estimable	High ⨁⨁⨁⨁ Critical
Clinical worsening in PAH-CHD (169 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c]	None	2/9 (22.2%)	4/11 (36.4%)	HR = 0.57 (0.10, 3.17)	137 fewer per 1,000 (from 319 fewer to 398 more)	Low ⨁⨁⊙⊙ Critical

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Wide 95% CIs span 1
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PAH-CHD = PAH associated with congenital heart disease; PAH-CTD = PAH associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial

Table 4.152 Evidence profile table for comparative safety of ERA plus PDE-5 inhibitor combination therapy compared to PDE-5 inhibitor monotherapy for all PAH patients

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with ERA + PDE-5i	Study event rates (%) with PDE-5i	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Any AE (104 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	144/159 (90.6%)	159/174 (91.4%)	RR = 0.99 (0.93, 1.06)	9 fewer per 1,000 (from 55 more to 64 fewer)	High ⊕⊕⊕⊕ Important
Serious AEs (24−104 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	None	165/411 (40.1%)	152/294 (51.7%)	RR = 0.82 (0.69, 0.96)	93 fewer per 1,000 (from 21 fewer to 160 fewer)	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation (24−104 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	None	70/411 (17.0%)	36/294 (12.2%)	RR = 1.47 (0.81, 2.66)	58 more per 1,000 (from 23 fewer to 203 more)	High ⊕⊕⊕⊕ Important
Abnormal liver function AEs (12 weeks)	1 RCT	Not serious	Not serious	Serious[c]	Not serious	Strong association	[redacted]	[redacted]	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important
Haemoglobin decrease-related AEs (12 weeks)	1 RCT	Not serious	Not serious	Serious[c]	Not serious	Strong association	[redacted]	[redacted]	[redacted]	[redacted]	High ⊕⊕⊕⊕ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Surrogate outcome
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; RR = relative risk

Table 4.153 Evidence profile table for comparative safety of ERA + PDE-5 inhibitor combination therapy compared to PDE-5 inhibitor monotherapy for patients with different PAH aetiologies

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with ERA + PDE-5i	Study event rates (%) with PDE-5i	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Any AE in IPAH/HPAH (24 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	130/134 (97.0%)	65/70 (92.9%)	RR = 1.04 (0.97, 1.12)	37 more per 1,000 (from 28 fewer to 111 more)	High ⊕⊕⊕⊕ Important
Any AE in PAH-CTD (24 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	102/103 (99.0%)	39/40 (97.5%)	RR = 1.02 (0.96, 1.07)	20 more per 1,000 (from 39 fewer to 68 more)	High ⊕⊕⊕⊕ Important
Serious AEs in IPAH/HPAH (24 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	44/134 (32.8%)	27/70 (38.6%)	RR = 0.85 (0.58, 1.25)	58 fewer per 1,000 (from 96 more to 162 fewer)	High ⊕⊕⊕⊕ Important
Serious AEs in PAH-CTD (24 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	45/103 (43.7%)	20/40 (50.0%)	RR = 0.87 (0.60, 1.28)	65 fewer per 1,000 (from 140 more to 200 fewer)	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation in IPAH/HPAH (24 weeks)	1 RCT	Not serious	Not serious	Not serious	Serious[c]	None	15/134 (11.2%)	8/70 (11.4%)	RR = 0.98 (0.44, 2.20)	2 fewer per 1,000 (from 64 fewer to 137 more)	Moderate ⊕⊕⊕⊙ Important
AEs leading to treatment discontinuation in PAH-CTD (24 weeks)	1 RCT	Not serious	Not serious	Not serious	Serious[c]	None	14/103 (13.6%)	6/40 (15.0%)	RR = 0.91 (0.37, 2.19)	13 fewer per 1,000 (from 95 fewer to 179 more)	Moderate ⊕⊕⊕⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Wide 95% CIs

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; HPAH = heritable PAH; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; RR = relative risk

ERA in addition to prostanoid

Table 4.154 Evidence profile table for effectiveness of ERA plus prostanoid combination therapy compared to prostanoid monotherapy for patients with WHO FC III/IV PAH

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirectness	Imprecision	Other considerations [a]	Study event rates (%) with ERA + prostanoid	Study event rates (%) with prostanoid	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
All-cause mortality (16 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c]	None	3/22 (13.6%)	0/11 (0.0%)	ARD = 13.6% (−0.70, 28.0)	136 more per 1,000 (from 7 fewer to 280 more)	Low ⊕⊕⊙⊙ Critical
Improved WHO FC (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c,d]	None	13/22 (59.1%)	5/11 (45.5%)	RR = 1.30 (0.62, 2.71)	136 more per 1,000 (from 173 fewer to 777 more)	Very low ⊕⊙⊙⊙ Important
Change in 6MWD from baseline (12−16 weeks)	2 RCTs	Serious [e]	Serious [f]	Serious [f]	Very serious [c]	None	30 patients tested	17 patients tested	-	MD 64.8 m further (range 6.0 m less to 123.6 m further)	Very low ⊕⊙⊙⊙ Important
Change in QoL from baseline (12 weeks)	1 RCT	Very serious [e]	Not serious	Not serious	Very serious [c]	None	150 patients tested	149 patients tested	-	MLHF[g] MD 35.34 points improvement	Very low ⊕⊙⊙⊙ Important

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirectness	Imprecision	Other considerations [a]	Study event rates (%) with ERA + prostanoid	Study event rates (%) with prostanoid	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Change in haemodynamic parameters from baseline (12−16 weeks)	2 RCTs	Serious [e]	Not serious	Very serious [g]	Very serious [c]	None	30 patients tested	17 patients tested	-	CAI Median MD 13.9% improvement (range 10.8−17) PVR Median MD 12.5% improvement (range 9.5−21.5) mPAP Median MD 16.6% improvement (range 6.8−26.3)	Very low ⨁⊙⊙⊙ Not important
Change in haemodynamic parameters from baseline (16 weeks)	1 RCT	Not serious	Not serious	Very serious[g]	Very serious [c]	Strong association	22 patients tested	11 patients tested	-	mRAP MD 2.2 mmHg improvement TPR MD 13.7% improvement	Very low ⨁⊙⊙⊙ Not important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Small study size
[d] Wide 95% CIs
[e] One RCT had a high risk of bias
[f] Trials show results trending in opposite directions
[g] Surrogate outcome
[h] MLHF questionnaire total scores range from 0 to 105. A higher score indicates poorer QoL.
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

6MWD = 6-minute walk distance; ARD = absolute risk difference; CAI = cardiac index; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; MLHF = Minnesota living with heart failure; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; TPR = total pulmonary pressure; WHO = World Health Organization

Table 4.155 Evidence profile table for comparative safety of ERA + prostanoid combination therapy compared to prostanoid monotherapy for patients with WHO FC III/IV PAH

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with ERA + prostanoid	Study event rates (%) with prostanoid	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Any AE (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c]	None	7/8 (87.5%)	5/6 (83.3%)	RR = 1.05 (0.67, 1.64)	42 more per 1,000 (from 275 fewer to 533 more)	Low ⊕⊕⊙⊙ Important
Serious AEs (12 weeks)	1 RCT	Seriou s [d]	Not serious	Not serious	Very serious [c,e]	None	3/22 (13.6%)	2/11 (18.2%)	RR = 0.75 (0.15, 3.85)	45 fewer per 1,000 (from 155 fewer to 518 more)	Very low ⊕⊙⊙⊙ Important
AEs leading to treatment discontinuation (12 weeks)	1 RCT	Seriou s [d]	Not serious	Not serious	Very serious [c]	None	1/22 (4.5%)	1/11 (9.1%)	RR = 0.50 (0.03, 7.26)	45 fewer per 1,000 (from 88 fewer to 569 more)	Very low ⊕⊙⊙⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Small study size
[d] One RCT had a high risk of bias
[e] Wide 95% CIs
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

PDE-5 inhibitor in addition to ERA

Table 4.156 Evidence profile table for effectiveness of PDE-5 inhibitor plus ERA combination therapy compared to ERA monotherapy for all PAH patients

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with PDE-5i + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Clinical worsening (12–74 weeks)	4 RCTs	Not serious	Not serious	Not serious	Not serious	Strong association	56/406 (13.8%)	64/288 (22.2%)	RR = 0.53 (0.38, 0.73)	104 fewer per 1,000 (from 60 fewer to 138 fewer)	High ⊕⊕⊕⊕ Critical
Mortality (12–74 weeks)	3 RCTs	Not serious	Not serious	Not serious	Very serious [d]	Strong association	4/413 (1.0%)	4/269 (1.5%)	RR = 0.64 (0.18, 2.36)	5 fewer per 1,000 (from 12 fewer to 20 more)	Moderate ⊕⊕⊕⊙ Critical
Hospitalisation due to PAH (12–74 weeks)	3 RCTs	Not serious	Not serious	Not serious	Not serious	Strong association	96/364 (26.4%)	60/243 (24.7%)	RR = 0.42 (0.25, 0.70)	74 fewer per 1,000 (from 38 fewer to 96 fewer)	High ⊕⊕⊕⊕ Important
Improved WHO FC (12–74 weeks)	4 RCTs	Not serious	Not serious	Not serious	Not serious	None	134/405 (33.1%)	80/276 (29.0%)	RR = 1.11 (0.77, 1.60)	32 more per 1,000 (from 67 fewer to 174 more)	High ⊕⊕⊕⊕ Important
Worsened WHO FC (12–74 weeks)	4 RCTs	Not serious	Not serious	Not serious	Serious [d]	Strong association	21/405 (5.2%)	27/276 (9.8%)	RR = 0.60 (0.34, 1.05)	39 fewer per 1,000 (from 5 more to 65 fewer)	High ⊕⊕⊕⊕ Important
Change in 6MWD from baseline (26 weeks)	5 RCTs	Not serious	Not serious	Serious [e]	Not serious	None	425 patients tested	301 patients tested	-	Median MD 22.0 m further (range 2.4 m less to 36.1 m further)	Moderate ⊕⊕⊕⊙ Important

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with PDE-5i + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Change in haemodynamic parameters from baseline (16 weeks)	1 RCT	Not serious	Not serious	Very serious [e]	Not serious	None	60 patients tested	64 patients tested	-	PVR MD 13.9% improvement mPAP MD 8.5% improvement	Low ⨁⨁⊙⊙ Not important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Trials show results trending in opposite directions
[d] Wide 95% CIs span 1
[e] Surrogate outcome
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Table 4.157 Evidence profile table for effectiveness of PDE-5 inhibitor plus ERA combination therapy compared to ERA monotherapy for patients with WHO FC III/IV PAH

Outcome (follow-up)	No. of studies and study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with PDE-5i + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Change in 6MWD from baseline (26 weeks)	2 RCTs	Not serious	Not serious	Serious [c]	Not serious	None	48 patients tested	61 patients tested	-	Median MD 16.8 m further (range 13.5 m further to 20.1 m further)	Moderate ⨁⨁⨁⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Surrogate outcome
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; WHO = World Health Organization

Table 4.158 Evidence profile table for effectiveness of PDE-5 inhibitor plus ERA combination therapy compared to ERA monotherapy for patients with different PAH aetiologies

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other considera-tion [a]	Study event rates (%) with PDE-5i + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Clinical worsening in PAH CTD (74 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	Strong association	2/103 (1.9%)	-/44	HR = 0.51 (0.25, 1.01)	Not estimable	High ⨁⨁⨁⨁ Critical
Change in 6MWD from baseline in IPAH/HPAH (26 weeks)	2 RCTs	Not serious	Not serious	Serious [c]	Not serious	None	57 patients tested	63 patients tested	-	Median MD 11.1 m further (range 8.6 m further to 13.6 m further)	Moderate ⨁⨁⨁⊙ Important
Change in 6MWD from baseline in PAH-CTD (26 weeks)	2 RCTs	Not serious	Serious [d]	Serious [c]	Serious [e]	None	26 patients tested	29 patients tested	-	Median MD 6.7 m less (range 34.1 m less to 20.7 m further)	Very low ⨁⊙⊙⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] surrogate outcome
[d] Trials show results trending in opposite directions
[e] Wide range
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; HPAH = heritable PAH; HR = hazard ratio; IPAH = idiopathic PAH; MD = mean difference; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial

Table 4.159 Evidence profile table for comparative safety of PDE-5 inhibitor + ERA combination therapy compared to ERA monotherapy for all PAH patients

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with PDE-5i + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Any AE (12−16 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	None	73/92 (79.3%)	79/98 (80.6%)	RR = 1.00 (0.79, 1.27)	0 fewer per 1,000 (from 169 fewer to 218 more)	High ⊕⊕⊕⊕ Important
Serious AEs (12−16 weeks)	2 RCTs	Not serious	Not serious	Not serious	Not serious	None	101/303 (33.3%)	57/179 (31.8%)	RR = 0.99 (0.76, 1.29)	3 fewer per 1,000 (from 76 fewer to 92 more)	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation (12−16 weeks)	2 RCTs	Not serious	Not serious	Not serious	Serious [c]	None	34/313 (10.9%)	14/190 (7.4%)	RR = 1.65 (0.35, 7.81)	48 more per 1,000 (from 48 fewer to 502 more)	Moderate ⊕⊕⊕⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Wide 95% CIs span 1
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; RR = relative risk

Table 4.160 Evidence profile table for comparative safety of PDE-5 inhibitor plus ERA combination therapy compared to ERA monotherapy for patients with PAH-CTD

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre--cision	Other conside-rations[a]	Study event rates (%) with PDE-5i + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Any AE in PAH-CTD (74 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	102/103 (99.0%)	42/44 (95.5%)	RR = 1.04 (0.97, 1.11)	38 more per 1,000 (from 29 fewer to 105 more)	High ⊕⊕⊕⊕ Important
Serious AEs in PAH-CTD (74 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	45/103 (43.7%)	15/44 (34.1%)	RR = 1.28 (0.80, 2.04)	95 more per 1,000 (from 68 fewer to 355 more)	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation in PAH-CTD (74 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	14/103 (13.6%)	8/44 (18.2%)	RR = 0.75 (0.34, 1.65)	45 fewer per 1,000 (from 118 more to 120 fewer)	High ⊕⊕⊕⊕ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PAH-CTD = PAH associated with connective tissue disease; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; RR = relative risk

PDE-5 inhibitor in addition to a prostanoid

Table 4.161 Evidence profile table for effectiveness of PDE-5 inhibitor plus prostanoid combination therapy compared to prostanoid monotherapy for all PAH patients

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with PDE-5i + prostanoid	Study event rates (%) with prostanoid	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Clinical worsening (16 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	Strong association	8/134 (6.0%)	24/131 (18.3%)	RR = 0.33 (0.15, 0.70)	123 fewer per 1,000 (from 55 fewer to 156 fewer)	High ⊕⊕⊕⊕ Critical
Mortality (16 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	0/134 (0.0%)	7/131 (5.3%)	ARD = −5.3% (−9.2, −1.5)	53 fewer per 1,000 (from 15 fewer to 92 fewer)	High ⊕⊕⊕⊕ Critical
Hospitalisation due to PAH (16 weeks)	1 RCT	Not serious	Not serious	Not serious	Serious [c]	None	8/134 (6.0%)	11/131 (8.4%)	RR = 0.71 (0.30, 1.71)	24 fewer per 1,000 (from 59 fewer to 60 more)	Moderate ⊕⊕⊕⊙ Important
Change in 6MWD from baseline (16 weeks)	1 RCT	Not serious	Not serious	Serious [d]	Not serious	None	134 patients tested	131 patients tested	-	MD 28.8 m further (from 13.9 m further to 43.8 m further)	Moderate ⊕⊕⊕⊙ Important
Change in haemodynamic parameters from baseline (16 weeks)	1 RCT	Not serious	Not serious	Very serious [d]	Not serious	Strong association None Strong association	134 patients tested	131 patients tested	-	PVR MD 20.8% improvement mPAP MD 7.5% improvement mRAP MD 2.1 mmHg improvement	Low ⊕⊕⊙⊙ Not important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]

[c] Wide 95% CIs span 1
[d] Surrogate outcome
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; PVR = pulmonary vascular resistance; RCT = randomised controlled trial; RR = relative risk

Table 4.162 Evidence profile table for comparative safety of PDE-5 inhibitor plus prostanoid combination therapy compared to prostanoid monotherapy for all PAH patients

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with PDE-5i + prostanoid	Study event rates (%) with prostanoid	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Any AE (12−16 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	124/134 (92.5%)	128/131 (97.7%)	RR = 0.95 (0.90, 1.00)	49 fewer per 1,000 (from 0 fewer to 98 fewer)	High ⊕⊕⊕⊕ Important
Serious AEs (12−16 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	29/134 (21.6%)	39/131 (29.8%)	RR = 0.73 (0.48, 1.10)	80 fewer per 1,000 (from 30 more to 155 fewer)	High ⊕⊕⊕⊕ Important
AEs leading to treatment discontinuation (12−16 weeks)	1 RCT	Not serious	Not serious	Not serious	Not serious	None	7/134 (5.2%)	14/131 (10.7%)	RR = 0.49 (0.20, 1.17)	55 fewer per 1,000 (from 18 more to 85 fewer)	High ⊕⊕⊕⊕ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect
AE = adverse event; CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; RR = relative risk

Prostanoid in addition to an ERA

Table 4.163 Evidence profile table for effectiveness of prostanoid plus ERA combination therapy compared to ERA monotherapy for patients with WHO FC III/IV PAH

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with prostanoid + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Clinical worsening (12−16 weeks)	2 RCTs	Serious [c]	Not serious	Not serious	Very serious [d]	None	3/51 (5.9%)	9/54 (16.7%)	RR = 0.39 (0.04, 3.45)	102 fewer per 1,000 (from 160 fewer to 408 more)	Very low ⊕⊙⊙⊙ Critical
Mortality (12−16 weeks)	2 RCTs	Serious [c]	Not serious	Not serious	Not serious	None	0/51 (0.0%)	0/54 (0.0%)	No deaths	Not estimable	Moderate ⊕⊕⊕⊙ Critical
Hospitalisation due to PAH (12−16 weeks)	2 RCTs	Serious [c]	Not serious	Not serious	Not serious	None	0/51 (0.0%)	4/54 (0.0%)	ARD = −5.5% (−18.9, 7.8)	55 fewer per 1,000 (from 78 more to 189 fewer)	Moderate ⊕⊕⊕⊙ Important
Improved WHO FC (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [d]	Very strong association	11/32 (34.4%)	2/33 (6.1%)	RR = 5.67 (1.36, 23.61)	283 more per 1,000 (from 22 more to 1,000 more)	Low ⊕⊕⊙⊙ Important
Worsened WHO FC (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Serious [d]	None	0/32 (0.0%)	1/33 (3.0%)	ARD = −3.0% (−8.9, 2.8)	30 fewer per 1,000 (from 28 more to 89 fewer)	Moderate ⊕⊕⊕⊙ Important
Change in 6MWD from baseline (12−16 weeks)	2 RCTs	Serious [c]	Not serious	Serious [e]	Not serious	None	51 patients tested	54 patients tested	-	Median MD 18 m further (10 m further to 26 m further)	Low ⊕⊕⊙⊙ Important
Change in QoL from baseline (16 weeks)	1 RCT	Very serious [c]	Not serious	Not serious	Very serious [g]	Strong association	19 patients tested	21 patients tested	-	EQ-VAS[f] MD 10 point improvement	Very low ⊕⊙⊙⊙ Important

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with prostanoid + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Change in haemodynamic parameters from baseline (12 weeks)	1 RCT	Not serious	Not serious	Very serious[e]	Serious [g]	Strong association Strong association	32 patients tested	33 patients tested	-	PVR MD 30.4% improvement mPAP MD 15.6% improvement	Low ⨁⨁⊙⊙ Not important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] One RCT had a high risk of bias
[d] Wide 95% CIs span 1
[e] Surrogate outcome
[f] EQ-VAS scores range from 0 to 100. A higher score represents better QoL.
[g] small study size
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; ARD = absolute risk difference; CI = confidence interval; EQ-VAS = EuroQoL visual analogue scale; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; QoL = quality of life; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

Table 4.164 Evidence profile table for comparative safety of prostanoid plus ERA combination therapy compared to ERA monotherapy for patients with WHO FC III/IV PAH

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with prostanoid + ERA	Study event rates (%) with ERA	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Any AE (12−16 weeks)	2 RCTs	Seriou s [c]	Not serious	Not serious	Very serious[d]	None	41/54 (75.9%)	30/53 (56.6%)	RR = 2.40 (0.15, 37.41)	792 more per 1,000 (from 481 fewer to 1,000 more)	Very low ⨁⊙⊙⊙ Important
Serious AEs (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious[d, e]	None	5/35 (14.3%)	7/32 (21.9%)	RR = 0.65 (0.23, 1.85)	77 fewer per 1,000 (from 168 fewer to 186 more)	Low ⨁⨁⊙⊙ Important
AEs leading to treatment discontinuation (16 weeks)	1 RCT	Very serious [c]	Not serious	Not serious	Very serious [e]	None	1/19 (5.3%)	0/21 (0.0%)	ARD = 5.2% (−4.8, 15.3)	52 more per 1,000 (from 48 fewer to 153 more)	Very low ⨁⊙⊙⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] One RCT had a high risk of bias
[d] Wide 95% CIs
[e] Small study size
⨁⨁⨁⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
AE = adverse event; CI = confidence interval; ERA = endothelin receptor antagonist; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; RCT = randomised controlled trial; RR = relative risk; WHO = World Health Organization

sGC stimulator in addition to an ERA

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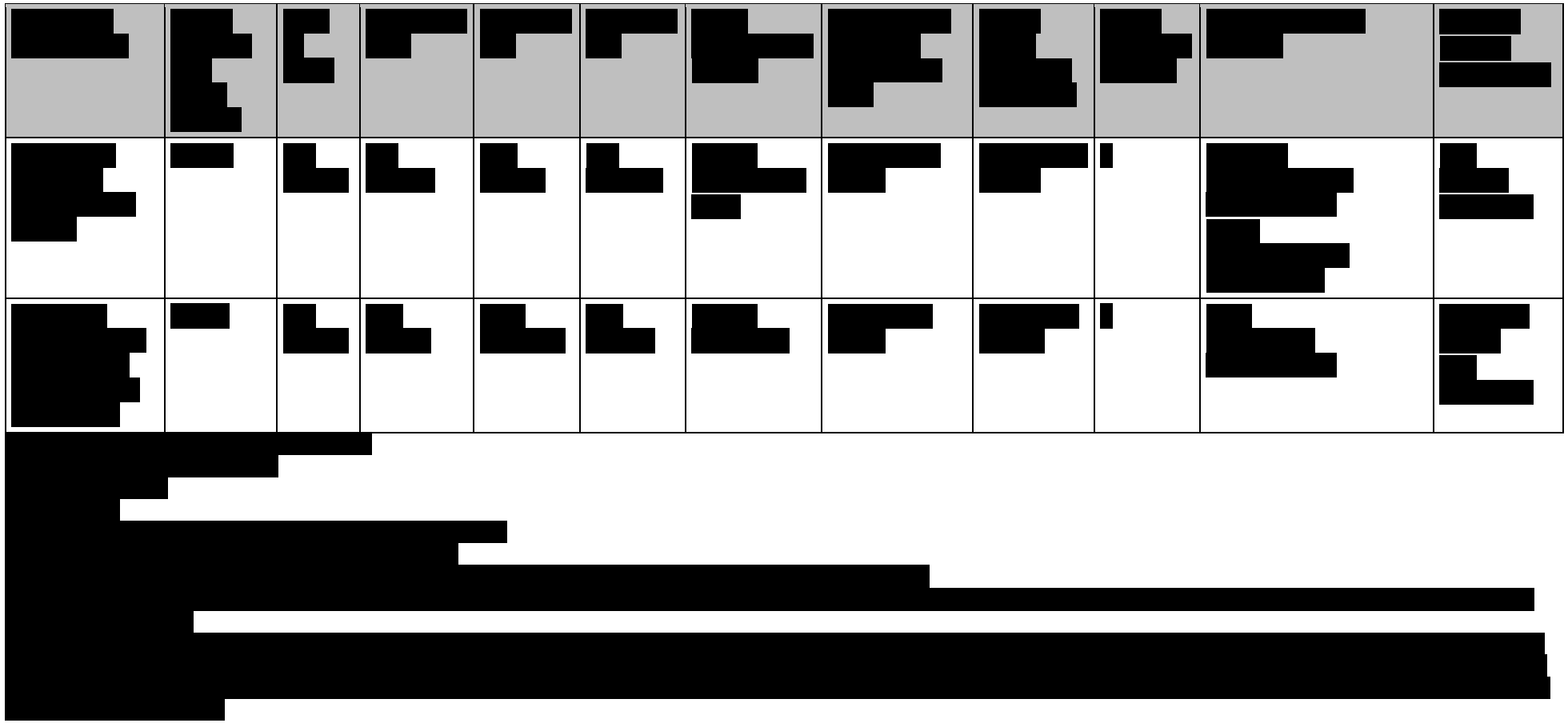

sGC stimulator in addition to PDE-5 inhibitor

Table 4.167 Evidence profile table for effectiveness of sGC stimulator + PDE-5 inhibitor combination therapy compared to PDE-5 inhibitor monotherapy for all PAH patients

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with sGC + PDE-5i	Study event rates (%) with PDE-5i	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Mortality (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c]	None	0/12 (0.0%)	0/6 (0.0%)	Not estimable	Not estimable	Low ⨁⨁⊙⊙ Critical
Improved WHO FC (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious[c, d]	None	2/12 (16.7%)	2/6 (33.3%)	RR = 0.50 (0.09, 2.73)	167 fewer per 1,000 (from 303 fewer to 577 more)	Low ⨁⨁⊙⊙ Important
Worsened WHO FC (12 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c]	None	0/12 (0.0%)	0/6 (0.0%)	Not estimable	Not estimable	Low ⨁⨁⊙⊙ Important
Change in 6MWD from baseline (12 weeks)	1 RCT	Not serious	Not serious	Serious [e]	Very serious [c]	None	12 patients tested	6 patients tested	-	MD 23 m less	Very low ⨁⊙⊙⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Small study size
[d] Wide 95% CIs that span 1
[e] Surrogate outcome
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
6MWD = 6-minute walk distance; CI = confidence interval; FC = functional class; GRADE = grading of recommendations assessment, development and evaluation[1]; MD = mean difference; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; RR = relative risk; sGC = soluble guanylate cyclase stimulator; WHO = World Health Organization

Table 4.168 Evidence profile table for comparative safety of sGC stimulator + PDE-5 inhibitor combination therapy compared to PDE-5 inhibitor monotherapy for all PAH patients

Outcome (follow-up)	No. of studies and study design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Other conside-rations[a]	Study event rates (%) with sGC + PDE-5i	Study event rates (%) with PDE-5i	Effect measure (95%CI)	Absolute effect (95%CI)	GRADE[b] Quality Importance
Any AE (104 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c]	None	12/12 (100%)	4/6 (66.7%)	RR = 1.50 (0.85, 2.64)	333 more per 1,000 (from 100 fewer to 1,000 more)	Low ⨁⨁⊙⊙ Important
Serious AEs (24−104 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c]	None	2/12 (16.7%)	0/6 (0.0%)	ARD = 16.7% (−4.4, 37.8)	167 more per 1,000 (from 44 fewer to 378 more)	Low ⨁⨁⊙⊙ Important
AEs leading to treatment discontinuation (24−104 weeks)	1 RCT	Not serious	Not serious	Not serious	Very serious [c]	None	1/12 (8.3%)	0/6 (0.0%)	ARD = 8.3% (−7.3, 24.0)	83 more per 1,000 (from 73 fewer to 240 more)	Low ⨁⨁⊙⊙ Important

[a] Other considerations such as publication bias and effect size
[b] GRADE Working Group grades of evidence[1]
[c] Small study size
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
AE = adverse event; ARD = absolute risk difference; CI = confidence interval; GRADE = grading of recommendations assessment, development and evaluation[1]; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; RCT = randomised controlled trial; RR = relative risk; sGC = soluble guanylate cyclase stimulator

sGC stimulator in addition to a prostanoid

[redacted]