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Clinical evidence review of selexipag for treating pulmonary arterial hypertension (PAH) in adults

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About this clinical evidence review

Clinical evidence reviews provide a summary of the best available evidence for a single technology within a licensed indication for which the responsible commissioner is NHS England. The clinical evidence review supports NHS England in producing clinical policies but are **not NICE guidance or advice**.

Summary

This evidence review considers selexipag for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with World Health Organisation (WHO) functional class (FC) II to III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase-type 5 inhibitor (PDE-5), or as monotherapy in patients who are not candidates for these therapies.

Evidence review

A literature search was undertaken, which identified 249 references (see appendix 1 for search strategy). The company also provided a submission of evidence. Four published studies were included in the review.

Results

Evidence of the efficacy of selexipag comes from one randomised controlled trial (RCT) of 1,156 people with WHO FC I to IV compared with placebo, (Sitbon et al. 2015 – GRIPHON study), together with 2 additional studies and 2 post-hoc analyses of the GRIPHON study with smaller sample sizes (Simonneau et al. 2012, an RCT of 43 people with WHO FC II to III in comparison with placebo; Tanabe et al. 2017, an open label, non-comparative trial of 37 people from Japan with FC I to III, and post-hoc subgroup analysis of the RCT by Sitbon et al. (Gaine et al. 2017 and Coghlan et al. (2018)) containing FC II to III patients in comparison with placebo.

Effectiveness

Primary Outcomes

The primary outcome in the main trial, Sitbon et al. (2015) (n=1,156), showed that selexipag statistically significantly reduced the risk of a composite of either first morbidity event (that is, a complication related to PAH), or death from any cause when compared with placebo. Gaine et al. (2017) also indicated that selexipag statistically significantly reduced the risk of a

composite of death event occurring for a subgroup of people with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) when compared with placebo. Coghlan et al. (2018) also reported a reduction in risk in people with functional class FC III PAH, although this was not statistically significant.

Sitbon et al. (2015), Simonneau et al. (2012) and Tanabe et al. (2017) all indicated that selexipag statistically significantly reduced patient pulmonary vascular resistance (PVR) when compared with placebo or against no comparator.

Secondary Outcomes

Secondary outcome evidence from Sitbon et al. (2015), measuring "death due to PAH, or hospitalisation for worsening of PAH from baseline to the end of the treatment period" showed statistically significantly fewer occurrences in the selexipag group compared with placebo. There was no statistically significant difference in the risk of death from any cause by the end of the study compared with placebo. Three studies measured 6 minute walking distance (6MWD) as a secondary outcome. Sitbon et al. (2015) reported that people receiving selexipag had a statistically significant increase in median distance walked. Both Simonneau et al. (2012) and Tanabe et al. (2017) also reported a mean increase in walking distance although these results were not statistically significant.

Another secondary outcome measured in these three studies was change in the functional class of people receiving selexipag. None of the studies reported statistically significant results.

Sitbon et al. (2015) reported that selexipag statistically significantly reduced plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels and statistically significant improvements in the selexipag group were reported for Cardiac Index (CI) and mean right atrial pressure (mRAP). Tanabe et al.

(2017) reported statistically significant improvements from baseline in people receiving selexipag for mean pulmonary arterial pressure (mPAP) and cardiac index (CI) but no significant difference was found for mixed venous oxygen saturation (SvO_2) or mRAP. Simonneau et al. (2012) reported no difference between selexipag and placebo for Borg dyspnoea index, plasma NT-proBNP, mPAP, and (SvO_2).

Safety and tolerability

Sitbon et al. (2015) and Tanabe et al. (2017) studies were designed to titrate up the dose of selexipag until unmanageable adverse effects associated with prostacyclin use, such as headache or jaw pain were reported. A statistically significantly higher proportion of people discontinued selexipag in the Sitbon et al. (2015) study because of adverse events when compared with placebo with the most frequent of these being headache, diarrhoea and nausea. Death up to the end of the study due to PAH was also greater in the selexipag group although this was not statistically significant. The most common adverse events, measured over 26 weeks (Tanabe et al. 2017) which did not lead to discontinuation consisted of headache, diarrhoea, jaw pain, nausea and flushing.

A more detailed presentation of the effectiveness, safety and tolerability evidence can be found in the key outcomes section.

Evidence gaps

Studies either had no comparator (Tanabe et al. 2017) or were compared with placebo (Sitbon et al. 2015, Simonneau et al. 2012, Gaine et al. 2017 and Coghlan et al. 2018)). Patients were either not on any treatment or were on varying, locally determined background therapies ranging from monotherapy of an ERA or PDE-5 to dual therapy with an ERA plus a PDE-5 before starting additional treatment with either selexipag or placebo. Therefore there is no direct evidence of the addition of selexipag compared with the addition of

another active treatment. The main Sitbon et al. (2015) study population was WHO FC I to IV which is broader than that specified in the licence (FC II to III).

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Abbreviations

Term	Definition
PAH	Pulmonary arterial hypertension
PVR	Pulmonary vascular resistance
PDE-5	Phosphodiesterase-type 5 inhibitor
ERA	Endothelin receptor antagonist
WHO FC	World Health Organisation Functional Class
IP	Prostaglandin I_2 receptor
NTpro-BNP	N-terminal prohormone of brain natriuretic peptide
EMA	European Medicines Agency

Medical definitions

Term	Definition
Balloon atrial septostomy	A procedure that is used to create an opening in the wall between the upper chambers of the heart (atria). This is performed in certain cases to improve blood oxygenation, particularly for congenital heart defects.
Borg dyspnoea index	A numerical scale for assessing shortness of breath, from 0 representing no dyspnoea to 10 as maximal dyspnoea.
Dyspnoea	Sudden shortness of breath or breathing difficulty
Flushing	A redness of the skin, typically over the cheeks or neck.
Pulmonary arterial pressure (PAP)	A measure of the blood pressure found in the pulmonary artery.
N-terminal prohormone of brain natriuretic peptide (NTpro-BNP)	NT-proBNP levels in the blood are used for screening, diagnosis of acute congestive heart failure (CHF) and may be useful to establish prognosis in heart failure.
Cardiac Index (CI)	A system used to measure cardiac output, or the amount of blood pumped out of the left ventricle each minute. The cardiac index is the amount of blood pumped per minute in litres divided by the body surface area of the patient.
Right atrial pressure	The blood pressure in the right atrium of the heart.
Mixed venous oxygen saturation (SvO_2)	The percentage of oxygen bound to haemoglobin in blood returning to the right side of the heart. This reflects the amount of oxygen "left over" after the tissues remove what they need.

Introduction

Focus of review

Pulmonary arterial hypertension (PAH) is a rare, severe, progressive and usually fatal disease caused by changes in the smaller branches of the pulmonary arteries. The walls of the arteries that carry blood from the heart to the lungs become thick and stiff, narrowing the space for blood to pass through and increasing blood pressure. As the pulmonary arteries are less able to stretch, the heart has to work harder to pump blood to the lungs. People with PAH experience increasingly debilitating symptoms (including dyspnoea during exercise, fatigue, weakness and chest pain), increased morbidity, frequent hospitalisations, and ultimately, right heart failure leading to premature death. The increasingly debilitating symptoms for people with PAH have a significantly detrimental impact on their quality of life; a survey of 563 people (PHAUK 2017) with pulmonary hypertension found 60% of people stated the disease has a "major impact" on their quality of life. There is no cure for PAH. It is a life limiting condition with poor prognosis and a post-diagnosis cumulative survival at 4 years of 48% (National Audit of Pulmonary Hypertension 8th Annual Report).

PAH is typically scored on the basis of the severity of PAH-related symptoms into 4 different World Health Organisation (WHO) functional classes (FC I to IV) that reflect clinical outcomes, with Class IV PAH being the most severe. In addition, people are also stratified according to risk based on the use of risk variables as recommended in the 2015 European Society of Cardiology and the European Respiratory Society (ESC/ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension. In the early stages (FC I / low risk) some symptoms are experienced during exercise but as the disease progresses symptoms are experienced during rest (FC IV / high risk).

Epidemiology

The estimated UK and Ireland annual incidence of diagnosed PAH in the general population ranges from 1.1 to 7.6 cases per million persons, whilst the prevalence of diagnosed PAH in the general population is between 6.6 and 26 cases per million persons (Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. 2015). Data from previous National Audits of Pulmonary Hypertension estimated that PAH has a diagnosed prevalence of 2,657 patients within an active specialist centre in England (The 6th Annual National Audit of Pulmonary Hypertension (PH) 2015) and a diagnosed incidence of 491 patients following a first referral to a specialised centre in England (National Audit of Pulmonary Hypertension 2014).

Product overview.

Mode of action

The active substance in selexipag, an oral tablet treatment, is a prostaglandin I_2 receptor agonist. This means it works in a similar way to prostacyclin, a naturally occurring substance that regulates blood pressure by attaching to receptors in the muscles of blood vessel walls, causing the vessels to relax and widen. By attaching to prostacyclin receptors, selexipag also widens the blood vessels and so lowers the pressure inside them, improving symptoms of the disease.

Regulatory status

Selexipag was granted a licence by the European Medicines Agency (EMA) in May 2016 and is indicated for the long-term treatment of PAH in adult patients with WHO FC II to III, either as combination therapy in patients insufficiently controlled with an ERA and/or a PDE-5 inhibitor, or as monotherapy in patients who are not candidates for these therapies.

Dosing information

Formulation

Oral film coated tablets given twice daily.

Strengths

200, 400, 600, 800, 1,000, 1,200, 1,400 and 1,600 micrograms.

The recommended starting dose is 200 micrograms twice daily. Each patient should be up-titrated to the highest individually tolerated dose, which can range from 200 to 1,600 micrograms (µg) twice daily.

The Summary of Product Characteristics (SPC) notes that selexipag should only be initiated and monitored by a physician experienced in the treatment of PAH. Please see SPC for further details of the dosing recommendations.

Treatment pathway and current practice

As PAH is a progressive and ultimately terminal disease, the overall goal of treatment is to reduce the risk of disease progression and achieve a low risk status. Current PAH-specific treatments include the following, given either alone or in combination:

- Calcium channel blockers (CCBs) such as nifedipine: CCBs restrict how much calcium can enter cells. Reducing the amount of calcium entering the muscle cells in the blood vessels causes them to relax which allows the arteries to widen and help to lower blood pressure.
- Phosphodiesterase-type 5 inhibitors (PDE-5) such as sildenafil and tadalafil: PDE-5 is a type of enzyme found in blood vessel walls that helps control blood flow to the pulmonary arteries. PDE-5 inhibitors stop these enzymes from working properly which helps the blood vessels to relax, increasing blood flow to the lungs, and lowering blood pressure.
- Endothelin receptor antagonists (ERAs) such as bosentan, macitentan and ambrisentan: Endothelin is made in the layer of

cells that line the heart and blood vessels. It causes the blood vessels to constrict (become narrower), which can increase blood pressure. In people with PH the body produces too much endothelin. ERAs reduce the amount of endothelin in the blood, therefore limiting the harm that an excess of endothelin can cause.

- Prostaglandins such as epoprostenol and iloprost: Prostaglandin is a substance produced in the body that causes the blood vessels in the lungs to dilate (become wider). Artificial prostaglandins can therefore help dilate the blood vessels in lungs, improving the amount of blood pumped around the body and oxygen in the blood, and can also help slow scarring and cell growth in the blood vessels of the lungs.
- Soluble guanylate cyclase stimulators (SGCS) such as riociguat: Soluble guanylate cyclase is an enzyme that acts as a receptor for nitric oxide. Stimulating this receptor causes blood vessels to relax and widen.

Eligibility criteria for some of these drugs are set out in NHS England clinical commissioning policies Targeted Therapies for Pulmonary Hypertension Functional Class II, Targeted Therapies for use in Pulmonary Hypertension in Adults (which covers people with FCIII and FCIV), and Riociguat for Pulmonary Arterial Hypertension. NHS England has also published service specifications (which define the standards of care expected from organisations funded by NHS England to provide specialised care) for people with PAH as follows: Pulmonary Hypertension Centres (Adult) and Pulmonary Hypertension Shared Care (Adult).

PAH is a rare subgroup of pulmonary hypertension (PH), which is much more common. The World Health Organisation (WHO) classifies PH into 5 groups depending on the underlying cause. Group 1 PH, the subtype covered in this review, is PAH, which consists of Idiopathic (IPAH) and Heritable (HPAH)

such as bone morphogenetic protein receptor type 2 (BMPR2), activin receptor-like kinase 1 gene (ALK1), endoglin (with or without haemorrhagic telangiectasia) type or unknown cause. It also includes those with drug and toxin-induced PAH and people with Associated (APAH) including connective tissue diseases, Human immunodeficiency virus (HIV) infection, portal hypertension, congenital heart disease (CHD), schistosomiasis and chronic haemolytic anaemia. Groups 2 to 5 cover PH with various underlying causes (these groups are not considered further in this document).

Monotherapy with an oral PDE-5 is routinely commissioned as first line therapy. Where a PDE-5 is not clinically appropriate, an ERA may be used as an alternative. Monotherapy with a prostanoid is routinely commissioned for people at WHO FC IV status with Group 1 clinical classification.

Second line therapy can be given to people with the disease that has failed to respond to therapy of adequate dose and duration (typically 8-12 weeks treatment), or people who cannot tolerate one of the oral therapies. In this case they should be switched to an alternative oral product as monotherapy. Second line therapy can also be given to people who initially responded to first-line therapy but then deteriorated despite dose escalation (if appropriate) and those who have had a suboptimal response to first-line therapy (with dose escalation where appropriate). In these circumstances they may be considered for dual therapy. A prostanoid is routinely commissioned and may be given to people with WHO FC III, (Group 1 clinical classification), who have failed to respond adequately or tolerate dual therapy with an oral PDE-5 and an oral ERA. In exceptional cases, where an acutely unwell patient requires in-patient treatment, monotherapy with a prostanoid may be given as an alternative to dual therapy. A prostanoid is not routinely commissioned for people who do not have a Group 1 clinical classification.

Dual therapy will only be funded in combinations involving a PDE-5 unless there are exceptional circumstances (a person switching from one mono-therapy to an alternative mono-therapy (up to a maximum of 12 weeks),

people who have been listed for a heart-lung transplantation, double lung transplantation or for people making the transition from children's services to adult services where it would be inappropriate to change treatments only to comply with the commissioning policy). Dual therapy will be commissioned for people with progressive disease who have failed to respond to 1st and 2nd-line monotherapy, who have initially responded to monotherapy but subsequently deteriorated despite dose escalation (if appropriate) or those who have had a suboptimal response to monotherapy (with dose escalation, where appropriate). In exceptional cases, where a person is acutely unwell and hospitalised, the progression to dual therapy may be accelerated.

Triple therapy will only be routinely commissioned for people who have been formally assessed by a transplant centre and accepted as a suitable candidate.

If people do not respond to these treatments, lung transplantation may be considered.

Selexipag is an orally available prostacyclin receptor agonist. It acts in the same way as other prostacyclin receptor agonists by provoking a biological response upon binding to a receptor. A prostacyclin receptor (or prostaglandin I_2 receptor) is a receptor for prostacyclin, a compound of the prostaglandin type which is produced in arterial walls. This functions as a vasodilator (causes the smooth muscle in blood vessels to relax) and in doing so widens them to reduce blood pressure.

Evidence base

Identification of studies

A literature search was undertaken, which identified 249 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 36 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the

identified studies and 5 studies were included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

Results

Overview of included studies

Two randomised controlled trials (RCTs) were identified from the search (Simonneau et al. 2012 and Sitbon et al. 2015) along with an open label non-comparative trial (Tanabe et al. 2017) and 2 post hoc subgroup analyses (Gaine et al. 2017 and Coghlan et al. (2018)) of the main trial by Sitbon et al. (2015). Within the trials, people were on a variety of background therapies before the addition of selexipag or a placebo ranging from no therapy to monotherapy with an ERA or PDE-5 and dual therapy of an ERA plus a PDE-5.

A summary of the characteristics of the studies can be found in Table 1. More detailed evidence and results can be found in appendices 3 and 4.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Sitbon et al. 2015 RCT	Adults (18-75) with symptomatic PAH (WHO functional class I – IV). (n=1156)	Selexipag 200µg twice daily and titrated up to a maximum dose of 1,600µg twice daily by increments of 200µg vs placebo	Composite of death from any cause or a complication related to PAH.
Coghlan et al. 2018 Post hoc subgroup analysis of an RCT – (Sitbon et al. 2015)	Adults with PAH associated with CTD (WHO functional class II – III). (n=376)	Selexipag 200µg twice daily and titrated up to a maximum dose of 1,600µg twice daily by increments of 200µg vs placebo	Composite of death from any cause or a complication related to PAH.
Gaine et al. 2017	Adults with PAH	Selexipag 200µg	Composite of death

Post hoc subgroup analysis of an RCT – (Sitbon et al. 2015)	associated with CTD (WHO functional class II – III). (n=334)	twice daily and titrated up to a maximum dose of 1,600µg twice daily by increments of 200µg vs placebo	from any cause or a complication related to PAH.
Simonneau et al. 2012 RCT	Adults with symptomatic PAH (WHO functional class II – III). (n=43)	Selexipag 200µg twice daily and titrated up to a maximum dose of 1,600µg twice daily by increments of 200µg vs placebo	Change in pulmonary vascular resistance (PVR).
Tanabe et al. 2017 Open label, non-comparative trial	Adult patients with PAH (WHO functional class I – III). (n=37)	Selexipag 200µg twice daily and titrated up to 1,600µg by increments of 200µg. No comparator	Change in pulmonary vascular resistance (PVR).

Key outcomes

The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 2 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study can be found in appendices 3 and 4.

Effectiveness

The primary outcome in the main trial by Sitbon et al. (2015) (n=1156) was a composite outcome measuring either first morbidity event (that is, a complication related to PAH), or death from any cause. The composite morbidity and mortality primary outcome reflects the regulatory suggestion in the EMA "Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension" which states that "the investigation of a composite primary endpoint that reflects, in addition to mortality, time to clinical worsening is encouraged in PAH". Also the European

Public Assessment Report (EPAR) states that the primary outcome in this study is clinically relevant. This showed that selexipag statistically significantly reduced this outcome when compared with placebo, with a rate of 27.0% compared with 41.6% [HR 0.60 (99% CI: 0.46 to 0.78) p<0.001].

When interpreting this data, comments from the EPAR document (EMEA/H/C/003774/0000) and the study authors should be taken into account. The EPAR notes that the primary outcome is statistically significant and clinically relevant, but causes issues when assessing the true effect of selexipag on all-cause mortality. This is because of the composite nature of the primary outcome, the option to discontinue selexipag in patients after the first primary endpoint event, and the possibility to switch placebo patients to selexipag after the first event. The study authors stated that the use of this measure was a limitation of the study because it contains a number of subjective components. To address this limitation, the authors stated that the disease progression component was stringently defined and all events were adjudicated by a three-person critical-event committee. Secondary outcomes measured in the studies included death due to PAH or hospitalisation for worsening of PAH up to end of the treatment, death from any cause up to the end of study, 6 minute walking distance (6MWD), change in WHO FC, and various haemodynamic outcomes (that is outcomes relating to blood flow). Secondary outcome evidence within Sitbon et al. (2015), measuring death due to PAH or hospitalisation for worsening of PAH up to the end of the treatment period, showed statistically significantly fewer occurrences in the selexipag group when compared with placebo, 17.8% versus 23.5% respectively [HR 0.7 (95% CI: 0.54 to 0.91) p=0.003]. There was no statistically significant difference in the secondary outcome of death from any cause up to the end of study [HR 0.97 (95% CI: 0.74 to 1.28) p=0.42] when compared with placebo. The company submission noted that this outcome included people who may have received other treatments for PAH including open label selexipag. A total of 155 patients from the placebo group who discontinued treatment after the occurrence of a primary endpoint event and

63 patients from the selexipag group who discontinued selexipag after the occurrence of a primary endpoint event received open-label selexipag. The inclusion of patients treated with open-label selexipag in the placebo arm may affect the risk of death for people randomised to placebo, thus affecting the observed treatment effect of selexipag versus placebo on survival. In addition, these secondary outcome measures also formed part of the primary outcome measure. The EPAR also stated that the mortality data is complex to assess. At the primary analysis time point (end of study +7days), selexipag appeared to have a negative effect on mortality as the primary outcome component, whereas the analysis up to study closure suggested a neutral effect and mathematical models which take into account the cross-over even indicated a best case scenario of up to 25% reduction in mortality. They noted that these models should, however, be interpreted with caution because in any such model assumptions have to be made.

Simonneau et al. (2012) and Tanabe et al. (2017) measured pulmonary vascular resistance (PVR) as a primary outcome. The clinical benefit to patients of a reduction in PVR is an increase in the width of their pulmonary blood vessels which leads to a reduction in blood pressure and alleviation of symptoms associated with PAH. Both studies showed a statistically significant reduction in PVR for patients receiving selexipag. Simonneau et al. (2012) reported an average (calculated as a geometric mean expressed as a percentage of baseline value) reduction of -33% (95% CI: -47 to -15.2) p=0.0022 at week 17, and Tanabe et al. (2017) showed a mean change from baseline of -122.9 dyn.s/cm^5 ± 115.2 (95% CI: -402 to 90) p<0.0001.

Three studies measured 6 minute walking distance (6MWD) as a secondary outcome. Sitbon et al. (2015) reported a median increase in distance walked at 26 weeks (measured at drug trough, that is, when the amount of the drug in the blood is at its lowest therapeutic concentration. This usually occurs immediately before the next dose is taken) of 4 metres for patients receiving selexipag, and a median decrease of 9 metres for those receiving placebo.

This indicated a statistically significant treatment effect for selexipag of 12 metres (99% CI: 1 to 24), p=0.003, although it should be noted that missing values were imputed by the authors for 21.6% of the patients in this analysis, which adds uncertainty to the finding. Values were imputed based on the following rules:

1. For patients unable to walk at week 26, 0 metres was imputed.

2. If rule 1 did not apply, 10 metres was imputed. The 10 metre value was the second lowest observed 6-minute walking distance value at 26 weeks, irrespective of study treatment group.

Simonneau et al. (2012) also reported a mean increase in walking distance at week 17 for people receiving selexipag [24.7 metres (95% CI: -1.6 to 50.9)] but this was not statistically significant when compared with placebo [0.4m (95% CI: -19.7 to 20.5)]. Tanabe et al. (2017) also reported an increase in mean walking distance for people taking selexipag from 445 metres ± 102.2 at baseline to 459 metres ± 112.8 at 16 weeks, reporting this as statistically significant (p=0.0324). There was no comparator for this evidence. It should be noted that the 6MWD test is a short-term functional outcome and cannot be used to draw conclusions about longer-term outcomes in PAH.

Sitbon et al. (2015) reported no statistically significant difference in change of WHO functional class in patients (measured as an absence of worsening in functional class) with 77.8% in the selexipag group and 74.9% in the placebo group maintaining functional class from baseline to week 26 [OR 1.16 (99% CI: 0.81 to 1.66) p=0.28]. It should be noted that missing values were imputed by the authors for 18.3% of the patients in this analysis which again adds uncertainty to the finding. Tanabe et al. (2017) indicated an improvement in functional class for patients receiving selexipag [n=4 (12.1%) (95% CI: 3.4 to 28.1%)] with no patients experiencing a deterioration although this was not measured against a comparator. Simonneau et al. (2012) also reported no statistically significant change, with 5 (15.6%) patients receiving selexipag

experiencing an improvement in functional class compared with 1 (10%) in the placebo group. Two patients in each group experienced a worsening in functional class.

Simonneau et al. (2012), Tanabe et al. (2017) and Sitbon et al. (2015) reported haemodynamic outcomes (that is, outcomes relating to blood flow) as secondary outcomes including:

- Borg dyspnoea index (A numerical scale for assessing shortness of breath, from 0 representing no dyspnoea to 10 as maximal dyspnoea).
- plasma NT-proBNP (Levels in the blood are used for screening and diagnosis of acute congestive heart failure (CHF)).
- mean pulmonary arterial pressure (mPAP) (A measure of the blood pressure found in the pulmonary artery).
- mixed venous oxygen saturation (SvO_2) (The percentage of oxygen bound to haemoglobin in blood returning to the right side of the heart).
- Cardiac Index (CI) (A system used to measure cardiac output, or the amount of blood pumped out of the left ventricle each minute. The cardiac index is the amount of blood pumped per minute in litres divided by the body surface area of the patient), and
- mean right atrial pressure (mRAP) (The blood pressure in the right atrium of the heart).

Simonneau et al. (2012) reported no statistically significant difference between selexipag and placebo groups for Borg dyspnoea index [-0.1 units (95% CI: -1.4 to 1.1)], plasma NT-proBNP [-212.8 pg/ml (95% CI: -1,012.1 to 586.5)], mean pulmonary arterial pressure (mPAP) [-7.4 mmHg (95% CI: -15.9 to 1.1) p=0.1], and mixed venous oxygen saturation (SvO_2) [4.1% (95% CI: -3.8 to 11.9) p=0.3]. Statistically significant improvements in the selexipag group

were reported for Cardiac Index (CI) [0.5 L/min (95% CI: 0.13 to 0.83) p=0.01] and mean right arterial pressure (mRAP) [3.2 mmHg (0.8 to 5.7) p=0.02]. Tanabe et al. (2017) reported statistically significant changes from baseline in patients receiving selexipag for mPAP [-3.1 mmHg ± 6.0 (95% CI: -16 to 8) p=0.0091], and cardiac index [0.33 L/min ± 0.57 (95% CI: -0.6 to 1.7) p=0.0025]. No statistically significant difference was found for SvO_2 [-0.41% ± 5.38 (95% CI: -16.4 to 13.7) p=0.9771] and mRAP [0.2 mmHg ± 3.7 (95% CI: -8 to 6) p=0.7010]. Again, these outcomes were not measured against a comparator. Sitbon et al. (2015) reported a statistically significant reduction in NT-proBNP plasma levels of -123 pg/ml (p<0.001) when compared with placebo.

Quality of life

Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)

The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is a disease specific patient-reported outcome measure (questionnaire) which assesses the symptoms, functioning and quality of life (QoL) of people with pulmonary hypertension. The EPAR document stated that there was no statistically significant difference when selexipag was compared with placebo for 'overall symptom score' in CAMPHOR within the Sitbon et al. (2015) study. Median absolute change from baseline to Week 26 was 0.0 (99% CI: −1.0 to 1.0) p=0.2185)]. For the sub-scale 'Breathlessness' the treatment effect of selexipag compared with placebo was also not statistically significant [0.0 (99% CI: −0.4 to 0.0) p=0.1700]. The EPAR document stated that this finding is not fully understood since the clear benefit for morbidity would be expected to translate into improved quality of life. It added that although the CAMPHOR questionnaire used in GRIPHON has been validated in mainly small populations with PAH in different regions, it is unclear at present whether it is sensitive to changes in quality of life as a possible explanation as to why no difference in quality of life between the two groups was observed.

Subgroup population evidence

Gaine et al. (2017) is a post-hoc subgroup analysis of the Sitbon et al. (2015) GRIPHON trial therefore the primary outcome was also a composite outcome measuring either first morbidity event (that is, a complication related to PAH), or death from any cause. The analysis showed that among people with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD), selexipag statistically significantly reduced the risk of this outcome by 41% [HR 0.59 (95% CI: 0.41 to 0.85)] when compared with placebo. This analysis was undertaken on participants with FC I (n=3), FC II (n=154), FC III (n=176) and FC IV (n=1).

Coghlan et al. (2018) is also a post hoc subgroup analysis of the Sitbon et al. (2015) GRIPHON trial with the same primary outcome looking at people with WHO FC II and III PAH that is insufficiently controlled with dual therapy with an ERA plus PDE-5 (n=376). The study indicated that treatment with selexipag for FC III patients, the sub population selexipag would be used in clinical practice as indicated by clinical feedback, resulted in a non-statistically significant 33% reduction in the risk of the primary outcome: a composite of either first morbidity event (that is, a complication related to PAH), or death from any cause [HR 0.67 (95% CI: 0.45 to 1.01)] up to the end of trial + 7 days after last dose, when compared with placebo (Kaplan-Meier plot). This result was post adjustment for 6MWD at baseline, a parameter with known prognostic relevance as stated in the study. The study also reported that treatment with selexipag (200 – 1600 µg twice daily) resulted in a non-statistically significant reduction, post adjustment for 6MWD at baseline [HR 0.63 (95% CI: 0.38 to 1.05)] for FC III patients, in the occurrence of Critical Event Committee (CEC) - confirmed death due to PAH or first CEC-confirmed hospitalisation due to PAH worsening up to 7 days after last dose when compared with placebo.

The EPAR document reported a non-significant reduction in the risk of time from randomisation to first CEC-confirmed morbidity/mortality event up to 7

days after last study day drug intake for people receiving selexipag in addition to ERAs and PDE-5 background therapy at baseline [HR 0.63 (99% CI: 0.39 to 1.01)]. This result incorporates all functional class patients within the Sitbon et al. (2015) study. The document also reported the same outcome for WHO FC I/II patients at baseline showing a non-significant reduction in risk for people receiving selexipag [HR 0.63 (99% CI: 0.40 to 1.00)] when compared with placebo, although there was a statistically significant reduction for WHO FC III/IV patients at baseline [HR 0.60 (99% CI: 0.43 to 0.83)].

It should be noted that the GRIPHON trial was not powered to show differences within subgroups and the purpose of the analyses was to evaluate the consistency of the treatment effect. Therefore the statistics associated with the subgroup analysis findings should therefore be interpreted with caution and treated as descriptive only.

Safety and tolerability

Sitbon et al. (2015) stated that 252 (43.8%) of the 574 patients receiving selexipag reported one or more serious adverse events and a statistically significant higher proportion of patients discontinued selexipag due to adverse events compared with placebo; 82 (14.3%) and 41 (7.1%) respectively ($p<0.001$). The most frequent adverse events leading to discontinuation were headache (3.3%), diarrhoea (2.3%) and nausea (1.7%). Death from any cause (measured as a first primary endpoint event) was 28 patients (4.9%) in the selexipag group and 18 patients (3.1%) in the placebo group. The most common adverse events determined from a long term study of 33 patients (Tanabe et al. 2017, n=136 weeks), were headache (73%), diarrhoea (45.9%), jaw pain (45.9%), nausea (37.8%) and flushing (32.4%). Simonneau et al. (2012) reported similar numbers of adverse events in patients receiving either selexipag or placebo with no deaths during the 17 week follow up period.

Evidence gaps

Studies either had no comparator (Tanabe et al. (2017)) or were compared with placebo (Sitbon et al. (2015), Simonneau et al. (2012), Gaine et al. (2017) and Coghlan et al. (2018)). Within the Sitbon et al. (2015) study some participants were not on any background treatments, others were on varying, locally determined background therapies (either monotherapy or dual therapy) before starting additional treatment with either selexipag or placebo. Therefore there is no direct evidence of the addition of selexipag compared with the addition of another active treatment. Selexipag is licenced for WHO FC II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies. However, the main trial (Sitbon et al. 2015) reported outcomes for a broader population (WHO FC I to IV) than that specified within the licence (FC II to III). The study participants received varying background therapies (monotherapy, dual therapy) or none at the start of the trial which may disguise the true treatment effect. In addition, the study population results do not distinguish between the 2 groups specified within the licence (selexipag monotherapy and selexipag as combination with ERA and/or PDE-5), although some post-hoc subgroup analyses was completed.

Key ongoing studies

The following study is ongoing:

Trial NCT02558231 The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension: A Multi-center, Double-blind, Placebo-controlled, Phase 3b Study. Status: currently recruiting. Estimated completion date: December 2019.

Table 2: Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
Composite of death or complication related to pulmonary arterial hypertension (PAH)	Sitbon et al. (2015)	8/10	Directly applicable	B	This composite outcome is a combination of clinical events that might happen including hospitalisation, disease progression, and death from any cause, where any one of those events would count as part of the composite endpoint. Due to the clinical conditions associated with PAH, patients have an increased risk of morbidity and mortality. Sitbon et al. (2015) showed that selexipag statistically significantly reduced the risk of the composite outcome of death from any cause, or a complication related to PAH occurring when compared with placebo at 26 weeks follow up, with a rate of 27.0% for selexipag compared with 41.6% for placebo, hazard ratio (HR) 0.60 (99% CI: 0.46 to 0.78) p<0.001. The evidence suggests that receiving selexipag results
	Gaine et al. (2017)	8/10	Directly applicable		

	Coghlan et al. (2018)	8/10	Directly applicable		in a lowering in the risk of a morbidity or mortality event occurring. This result was supported by a sub group analysis study; Gaine et al. (2017) for people with PAH associated with connective tissue disease and for people with FCIII PAH uncontrolled with dual therapy; Coghlan (2018). Results should be interpreted with caution because the study authors noted that the composite outcome contains a number of subjective components (although steps were taken to address this weakness including adjudication by a blinded 3-person panel). Also, although the use of a composite mortality/morbidity outcome is "encouraged" by the EMA in PAH, the EPAR stated that the outcome made it difficult to assess the true effect on all-cause mortality.
Pulmonary vascular resistance (PVR)	Simonneau et al. (2012)	7/10	Directly applicable	B	PAH causes the tiny arteries in the lungs to become narrow or blocked making it harder for blood to flow through them. PVR is the resistance that must be overcome to push blood through the pulmonary circulatory system and create flow. Simonneau et al. (2012) showed a statistically

	Tanabe et al. (2017)	5/10	Directly applicable		significant reduction in PVR at 17 weeks follow-up for patients receiving selexipag compared with placebo, with an average (geometric mean expressed as a percentage of baseline value) treatment effect of -33% (95% CI -47 to -15.2) p=0.0022. This result was supported by Tanabe et al. (2017). The evidence indicates that receiving selexipag reduces the resistance in these arteries by somewhere between 15.2 to 47%, which will allow increased blood flow, a reduction in lung blood pressure, alleviation of the symptoms of PAH, and a reduction in the risk of heart failure because the heart does not have to work as hard to pump blood through the arteries. Evidence should be interpreted with caution because the studies are not sufficiently powered due to the numbers involved. Therefore the statistics associated with the findings should therefore be treated as descriptive only.
6 minute walking distance (6MWD)	Simonneau et al. (2012)	7/10	Directly applicable	A	6MWD measures the distance an individual is able to walk over a total of 6 minutes on a hard, flat surface. Symptoms of people with PAH include shortness of breath when undertaking mild exercise and the 6MWD test is a measure of how well patients can cope with this. Sitbon et al. (2015) reported a statistically significant improvement for selexipag of 12 metres (99% CI: 1 to 24), p=0.003 in median walking distance when compared with placebo at 26 weeks follow up. This result was supported by 2 smaller studies; Simonneau et al. (2012) (although the result was not statistically
	Sitbon et al. (2015)	8/10	Directly applicable		
	Tanabe et al. (2017)	5/10	Directly applicable		

					significant) and Tanabe et al. (2017). The evidence suggests that receiving selexipag significantly improves the ability of patients to undertake mild exercise with improved functional capacity. Results should be interpreted with caution because values were assigned to patients who could not be measured by the authors for 21.6% of the patients within the study. This adds uncertainty to the finding because missing values were determined based on a criteria outlined within the study rather than on actual patient data.
Change in WHO functional class	Simonneau et al. 2012	7/10	Directly applicable	A	WHO functional class describes how severe a patient's pulmonary hypertension (PH) is. There are four different classes: I is the mildest and IV the most severe form of PH. Improvement in functional class indicates an improvement in the symptoms the patient is experiencing. Sitbon et al. (2015) reported no significant change in WHO functional class of patients (measured as an absence of worsening in functional class) when compared with placebo at 26 weeks follow up. Odds Ratio (OR) 1.16 (99% CI: 0.81 to 1.66) p=0.28. The evidence suggests that selexipag neither improves nor decreases the functional class of patients. This result was supported by 2 smaller studies; Simonneau et al. (2012) and Tanabe et al. (2017). Results should be interpreted with caution because values were assigned to patients who could not be
	Sitbon et al. 2015	8/10	Directly applicable		
	Tanabe et al. 2017	5/10	Directly applicable		

					measured by the authors for 18.3% of the patients within the study. This adds uncertainty to the finding because missing values were not based on actual patient data.

Relevance to guidelines and NHS England policies

NICE have not issued any guidelines or policies on managing pulmonary arterial hypertension with selexipag.

The following NHS England policies have published regarding PAH:

- Clinical Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. July 2015. NHS England Reference A11/P/c
- Clinical Commissioning Policy: Targeted Therapies for Pulmonary Hypertension Functional Class II. April 2013. NHS England Reference NHSCB/A11/P/a
- Clinical Commissioning Policy: Selexipag in the treatment of pulmonary arterial hypertension. July 2016. NHS England Reference 10617/P
- Clinical Commissioning Policy: Riociguat for pulmonary arterial hypertension. February 2017. NHS England Reference 16055/P

References

Pulmonary Hypertension UK (2017) 'What it means to live with PH today'.

Included studies

Coghlan G, Channick R, Chin K et al. Targeting the Prostacyclin Pathway with Selexipag in Patients with Pulmonary Arterial Hypertension Receiving Double Combination Therapy: Insights from the Randomized Controlled GRIPHON Study. American Journal of Cardiovascular Drugs. 2018; Jan 6. [Epub ahead of print].

Gaine S, Chin K, Coghlan G, Channick R et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. European Respiratory Journal. 2017; 50:1602493.

Simonneau G, Torbicki A, Hoeper M et al. Selexipag: an oral prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. European Respiratory Journal. 2012; 40(4):874-880.

Sitbon O, Channick R, Chin K, Frey A et al. Selexipag for the treatment of pulmonary arterial hypertension. New England Journal of Medicine 2015; 373:2522-2533.

Tanabe N, Ikeda S, Tahara N, et al. Efficacy and safety of an orally administered selective prostacyclin receptor agonist, selexipag, in Japanese patients with pulmonary arterial hypertension. Journal of Circulation. 2017; 81(9):1360-1367.

Appendix 1: Search strategy

Search strategies

Databases

Database: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
Platform: Ovid
Version: 1946 - date
Search date: 10/10/2017
Number of results retrieved: 59
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 exp Hypertension, Pulmonary/ (34285)
2 Pulmonary Artery/ (46333)
3 ((hyperten* or arter*) adj4 pulmonary).tw. (99260)
4 (FPAH or HPAH or IPAH or PAH or APAH).tw. (20495)
5 primary obliterative pulmonary vascular disease.tw. (0)
6 or/1-5 (134290)
7 (selexipag or uptravi or ACT-293987).tw. (77)
8 6 and 7 (62)
9 limit 8 to english language (62)
10 animals/ not humans/ (4641117)
11 9 not 10 (59)

Database: Embase
Platform: Ovid
Version: 1974 to 2017 October 09
Search date: 10/10/2017
Number of results retrieved: 257

Database: Embase <1974 to 2017 October 09>
Search Strategy:
---
1 exp Hypertension, Pulmonary/ (77534)
2 Pulmonary Artery/ (38169)
3 ((hyperten* or arter*) adj4 pulmonary).tw. (128513)
4 (FPAH or HPAH or IPAH or PAH or APAH).tw. (29398)
5 primary obliterative pulmonary vascular disease.tw. (0)
6 or/1-5 (178190)
7 Selexipag/ (285)
8 (selexipag or uptravi or ACT-293987).tw. (157)
9 7 or 8 (297)

10 6 and 9 (267)
11 nonhuman/ not human/ (4094882)
12 10 not 11 (260)
13 limit 12 to english language (257)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR –10 of 12,October 2017 DARE – 2 of 4, April 2015 (legacy database)
CENTRAL –9 of 12, October 2017
HTA –4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 10/10/2017
Number of results retrieved: CDSR 0; DARE 0 ; CENTRAL 39 ; HTA 0 ; NHS EED 0 .
Search strategy:

Search Name: selexipag
Date Run: 10/10/17 08:28:21.839
Description:

ID	Search	Hits
#1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	711
#2	MeSH descriptor: [Pulmonary Artery] this term only	462
#3	(hyperten* or arter*) near/4 pulmonary:ti,ab,kw (Word variations have been searched)	4845
#4	{or #1-#3}	4852
#5	selexipag or uptravi or ACT-293987:ti,ab,kw (Word variations have been searched)	45
#6	#4 and #5	39

Trials registries

Clinicaltrials.gov

Search date: 05/10/2017
Number of results retrieved: 8
Search strategy and link to results page: Pulmonary Arterial Hypertension | Selexipag | Phase 2, 3, 4

Clinicaltrialsregister.eu

Search date: 06/10/2017
Number of results retrieved: 6
Search strategy and link to results page:

Appendix 2: Study selection

The search strategy presented in Appendix 1 yielded 355 studies. Following de-duplication, 249 records were subsequently screened on titles and abstract in EPPI Reviewer according to the following inclusion/exclusion criteria.

Table 3: Sifting criteria

Sifting criteria	Inclusion	Exclusion
Population	• Adults with pulmonary arterial hypertension (including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease) with WHO functional class (FC) II III	• Non-humans • Healthy volunteers
Intervention	• Selexipag (Uptravi)	
Comparator	• Any	
Outcomes	Relevant patient orientated outcomes, such as: • Time to morbidity or mortality event after treatment period • Worsening of PAH (including hospitalisation because of PAH, and need for lung transplantation or balloon atrial septostomy) • Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH • Disease progression (including 6 minute walking test, hospitalisation for PAH, worsening echo and haemodynamic parameters, increasing functional class, and composites of these outcomes); • Mortality • Health related quality of life and safety	

	(including adverse effects)	
Other		• Abstracts • Non-English language • Duplicates • Opinion pieces • Commentaries • Editorials

Table 5: Studies excluded at full text.

Study reference	Reason for exclusion
Badiani B, and Messori A. Targeted Treatments for Pulmonary Arterial Hypertension: Interpreting Outcomes by Network Meta-analysis. Heart Lung and Circulation. 2016; 25 (1): 46-52	Review of studies covered within CER document
Baker W L, Darsaklis K, Singhvi A, and Salerno E L. Selexipag, an Oral Prostacyclin-Receptor Agonist for Pulmonary Arterial Hypertension. Annals of Pharmacotherapy. 2017; 51 (6): 488-495	Review of studies covered within CER document
Baldoni D, Bruderer S, Muhsen N, and Dingemanse J. Bioequivalence of different dose-strength tablets of selexipag, a selective prostacyclin receptor agonist, in a multiple-dose up-titration study. International Journal of Clinical Pharmacology & Therapeutics. 2015; 53 (9): 788-98	Not population of interest (Healthy volunteers)
Channick R; Chin K; Di Scala; L; Frey A; Preiss R; Gaine S; Galie N; Ghofrani H A; Hoeper M; Lang I; McLaughlin V; Rubin L; Simonneau G; Sitbon O; Tapson V. Individualized dosing of selexipag based on tolerability in the GRIPHON study shows consistent efficacy and safety in patients with Pulmonary Arterial Hypertension (PAH). 2015; VOL 148	Abstract
Chin K M; Channick R; Frey A; Gaine S; Ghofrani H A; Hoeper M; Lang I; McLaughlin V; Preiss R; Simonneau G; Sitbon O; Stefani M; Tapson V; Galie N; Rubin L J Selexipag prolongs the time to morbidity/mortality events in key subgroup populations: Results from griphon, a randomized controlled study in pulmonary arterial hypertension. American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS. 2015; VOL 191	Abstract
Coghlan G, Gaine S, Channick R, Di Scala L, Galie N, Ghofrani H A, Hoeper M M, Lang I, McLaughlin V, Preiss R, Rubin L J, Simonneau G, Sitbon O, Tapson V F, and Chin K. Targeting the prostacyclin pathway in the treatment of connective tissue disease associated pulmonary arterial hypertension (PAH): Insights from the randomised controlled griphon trial with selexipag. 2016; 71 PP A65	Poster
Dakwa D S, Mella L, Mella N, and Poulakos M N. Selexipag in pulmonary arterial hypertension: A comprehensive review. Pharmacotherapy. 2016; 36 (12) PP e301	Abstract
Del Pozo; R; Hernandez Gonzalez; I; Escribano-Subias P. The prostacyclin pathway in pulmonary arterial hypertension: a clinical review. Expert Review	Paper unavailable

of Respiratory Medicine. 2017; 11 (6): 491-503	
Edriss H; Schuller D; Nugent K; Huizar I. Safe, successful, and effective transition from a prostacyclin analog (treprostinil) to oral prostacyclin receptor agonist (selexipag). American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS. 2017; VOL 195	Abstract
El-Kersh K, and Smith J S. Transition From Inhaled Treprostinil to Selexipag in Pulmonary Arterial Hypertension. American Journal of Therapeutics. 2017; 24 (5) PP e620-e621	Commentary/Editorial
Fox B D, Shtraichman O, Langleben D, Shimony A, and Kramer M R. Combination Therapy for Pulmonary Arterial Hypertension: A Systematic Review and Meta-analysis. Canadian Journal of Cardiology. 2016; 32 (12): 1520-1530	Review of studies covered within CER document
Frost AE, Janmohamed M, Fritz J, McConnell JW, Poch D, Fortin T, Miller C, Chin K, Fisher Mr, Eggert M, McEvoy C, Benza Rl, Farber Hw, Kim Nh, Hartline B, Pfister T, Shiraga Y, and McLaughlin V. Tolerability and safety of transition from inhaled treprostinil to oral selexipag in pulmonary arterial hypertension: results from the transit-1 study. American journal of respiratory and critical care medicine. Conference: American thoracic society international conference, and ATS. 2017; VOL 195	Abstract
Ghosh R K, Ball S, Das A, Bandyopadhyay D, Mondal S, Saha D, and Gupta A. Selexipag in Pulmonary Arterial Hypertension: Most Updated Evidence From Recent Preclinical and Clinical Studies. Journal of Clinical Pharmacology. 2017; 57 (5): 547-557	Review of studies covered within CER document
Jain S, Khera R, Girotra S, Badesch D, Wang Z, Murad M H, Blevins A, Schmidt G A, Singh S, and Gerke A K. Comparative Effectiveness of Pharmacologic Interventions for Pulmonary Arterial Hypertension: A Systematic Review and Network Meta-Analysis. 2017; 151 (1) 90-105	No outcomes of interest for selexipag in isolation against comparator.
Krause A, Machacek M, Lott D, Hurst N, Bruderer S, and Dingemanse J. Population Modeling of Selexipag Pharmacokinetics and Clinical Response Parameters in Patients With Pulmonary Arterial Hypertension. CPT: Pharmacometrics & Systems Pharmacology. 2017; 6 (7): 477-485	Review of studies covered within CER document
Lajoie A C, Lauziere G, Lega J C, Lacasse Y, Martin S, Simard S, Bonnet S, and Provencher S. Combination therapy versus monotherapy for pulmonary arterial hypertension: A meta-analysis. The Lancet Respiratory Medicine. 2016; 4 (4): 291-305	No outcomes of interest for selexipag in isolation against comparator (combination vs monotherapy)

Lajoie A C, Bonnet S, and Provencher S. Combination therapy in pulmonary arterial hypertension: Recent accomplishments and future challenges. Pulmonary Circulation. 2017; 7 (2): 312-325	Not reporting selexipag in isolation against a comparator
Lang I; Torbicki A; Hoeper M; Delcroix M; Karlocai K; Galia N. Outcomes of a phase II study of ACT-293987, an oral IP receptor agonist, in pulmonary arterial hypertension (PAH). European respiratory society annual congress, Barcelona, Spain, September 18-22 2010; [202]	Abstract
Lang I, Gaine S, Galie N, Ghofrani H A, Le Brun , F O, McLaughlin V, Rubin L J, Simonneau G, Sitbon O, and Hoeper M M. Effect of selexipag on long-term outcomes in patients with pulmonary arterial hypertension (PAH) receiving one, two or no PAH therapies at baseline: Results from the GRIPHON study. European Heart Journal. 2015; 36: 381-382	Poster
Langleben D, Beghetti M, Channick R, Chin K, DiScala L, Gaine S, Ghofrani H, Hoeper M, Lang I, McLaughlin V, Preiss R, Rubin L, Simonneau G, Sitbon O, Tapson V, and Galie N. Selexipag for pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) after defect correction: Insights from the randomised controlled griphon study. Canadian Journal of Cardiology. 2016 VOL 32 (10 Supplement 1) PP S162	Poster
Liu H L, Chen X Y, Li J R, Su S W, Ding T, Shi C X, Jiang Y F, and Zhu Z N. Efficacy and Safety of Pulmonary Arterial Hypertension-specific Therapy in Pulmonary Arterial Hypertension: A Meta-analysis of Randomized Controlled Trials. 2016; 150 (2): 353-366	Not reporting selexipag in isolation against a comparator
Miller C. Transition from parenteral prostacyclin to selexipag in patients with pulmonary arterial hypertension. American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS. 2017; VOL 195	Abstract
Nitsche A; Diez M; Echazarreta D; Mazzei J; Haag D; Babini A; Casado G; Lescano A; Coronel M; Perna E Pulmonary hypertension: First collaborative registry in Argentina (recopilar). Journal of Clinical Rheumatology 2016; VOL 22 (3):112	No outcomes of interest
Noel Z R, Kido K, and Macaulay T E. Selexipag for the treatment of pulmonary arterial hypertension. American Journal of Health-System Pharmacy. 2017; 74 (15): 1135-1141	Review of studies covered within CER document
Pallazola V A; Visovatti S; McLaughlin V. Functional outcomes of selexipag versus inhaled treprostinil for the treatment of pulmonary arterial hypertension.	Abstract

American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS. 2017; VOL 195	
Safdar Z. Single center experience in transitioning pulmonary arterial hypertension patients from intravenous epoprostenol to oral selexipag. American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS. 2017; VOL 195	Abstract
Sharma K. Selexipag for the treatment of pulmonary arterial hypertension. Expert Review of Respiratory Medicine. 2016;10 (1): 1-3	Review of studies covered within CER document / Commentary
Simonneau G; Lang I; Torbicki A; Hoeper M M; Delcroix M; Karlocai K; Galie N. Efficacy, safety and tolerability of ACT-293987, a novel oral, non-prostanoid, prostaglandin I2 (IP) receptor agonist: Results from a phase IIa study in pulmonary arterial hypertension (PAH). American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS. 2010; VOL 181 PT 1	Abstract
Sitbon O; Channick R; Chin K; Frey A; Galie N; Ghofrani H A; Hoeper M M; Lang I; Brun F O. L; McLaughlin V; Preiss R; Rubin L J; Simonneau G; Tapson V; Gaine S. Effect of selexipag on longterm outcomes in key subgroups of patients with pulmonary arterial hypertension (PAH): GRIPHON study results. European Respiratory Journal. Conference: European Respiratory Society Annual Congress. 2015; VOL 46	Abstract
Sitbon O, and Gaine S. Beyond a single pathway: Combination therapy in pulmonary arterial hypertension. European Respiratory Review. 2016; 25 (142): 408-417	Review of studies covered within CER document
Skoro-Sajer N; Lang I. Selexipag, an orally available IP receptor agonist, in the treatment of pulmonary arterial hypertension: current evidence and future prospects. Expert Opinion on Orphan Drugs. 2017; VOL 5 (2): 193-200	Abstract
Torbicki A, Lang I, Hoeper M, Delcroix M, Karlocai K, Galie N, and Simonneau G. A new drug class for Pulmonary Arterial Hypertension (PAH): Results from a phase II study of ACT 293987, an oral IP receptor agonist. European Heart Journal. 2010; VOL 31 PP 22	Abstract

Appendix 3: Evidence tables

Table 6: Coghlan et al. (2018)

Study reference	Gaine S, Coghlan G, Channick R et al. Targeting the prostacyclin pathway with selexipag in pulmonary arterial hypertension patients receiving double combination therapy: Insights from the randomized controlled GRIPHON study
Unique identifier	n/a
Study type (and NSF-LTC study code)	Post hoc subgroup analysis of a Randomised (event driven), double blind, placebo controlled phase III clinical trial (S2)
Aim of the study	To describe the response to selexipag of PAH patients receiving double combination background therapy
Study dates	Not reported
Setting	Multicentre (n=181) in 39 countries (evidence from GRIPHON trial)
Number of participants	376 adult patients with PAH and receiving double combination background therapy at baseline. Patient results taken from the GRIPHON trial (randomised to receive either selexipag (n=179 or placebo (n=197)
Population	PAH patients receiving double combination background therapy WHO Functional class: FC I (n=0) FC II (n=115) FC III (n=255) FC IV (n=6)
Inclusion criteria	• Pulmonary vascular resistance (PVR) of at least 5 Wood units (400 dyn · sec · cm−5) • 6-minute walk distance (6MWD) of 50 to 450 m. • Patients who were not receiving treatment for pulmonary arterial hypertension • Patients receiving an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both at a dose that had been stable for at least 3 months
Exclusion criteria	• Patients with pulmonary hypertension that were not covered by the inclusion criterion • Scheduled to receive or Intake of prostacyclin (epoprostenol) or prostacyclin analogs up to 1 month prior to the Baseline visit • moderate or severe obstructive lung disease: FEV1/FVC < 70% and FEV1 < 65% of predicted value after bronchodilator administration or moderate or severe restrictive lung disease: Total Lung Capacity < 70% of predicted value • moderate or severe hepatic impairment • documented left ventricular dysfunction (i.e., ejection fraction < 45%, clarified by amendment 1)

	• severe renal insufficiency (estimated creatinine clearance < 30 mL/min, or serum creatinine > 2.5 mg/dL) • BMI < 18.5 kg/m2 (modified by amendment 1) • Lactating or pregnant
Intervention(s)	Selexipag administered at a dose of 200 µg twice daily increased weekly in twice-daily increments of 200 µg until unmanageable adverse effects associated with prostacyclin use, such as headache or jaw pain, developed. The maximum dose allowed was 1600 µg twice daily.
Comparator(s)	Placebo
Length of follow-up	Median duration 62.0 weeks (placebo) Median duration 67.1 weeks (selexipag)
Outcomes	Primary outcome: Composite of death or a complication related to PAH (whichever occurred first) up to the end of the treatment period – defined as 7 days after the last intake of selexipag or placebo Secondary outcome: Death due to PAH or hospitalisation for worsening PAH
Source of funding	Actelion Pharmaceuticals

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Data reported and analysed but underpowered
5. Are the results generalisable?	1/2	The subgroup analysed represented 32% of the original GRIPHON trial population

Total	8/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 7: Gaine et al. (2017)

Study reference	Gaine S, Chin K, Coghlan G, Channick R et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. European Respiratory Journal. 2017; 50:1602493.
Unique identifier	n/a
Study type (and NSF-LTC study code)	Post hoc subgroup analysis of a Randomised (event driven), double blind, placebo controlled phase III clinical trial (S2)
Aim of the study	To describe the PAH-CTD patients enrolled in GRIPHON and to characterise their response to selexipag
Study dates	Not reported
Setting	Multicentre (n=181) in 39 countries (evidence from GRIPHON trial)
Number of participants	334 adult patients with PAH-CTD. Patient results taken from the GRIPHON trial (randomised to receive either selexipag (n=167 or placebo (n=167)
Population	Patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD). WHO Functional class: FC I (n=3) FC II (n=154) FC III (n=176) FC IV (n=1) Background therapy at baseline None (n=78) ERA (n=66) PDE-5 (n=94) ERA and PDE-5 (n=96)
Inclusion criteria	• Pulmonary vascular resistance (PVR) of at least 5 Wood units (400 dyn · sec · cm−5) • 6-minute walk distance (6MWD) of 50 to 450 m.

	• Patients who were not receiving treatment for pulmonary arterial hypertension • Patients receiving an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both at a dose that had been stable for at least 3 months
Exclusion criteria	• Patients with pulmonary hypertension that were not covered by the inclusion criterion • Scheduled to receive or Intake of prostacyclin (epoprostenol) or prostacyclin analogs up to 1 month prior to the Baseline visit • moderate or severe obstructive lung disease: FEV1/FVC < 70% and FEV1 < 65% of predicted value after bronchodilator administration or moderate or severe restrictive lung disease: Total Lung Capacity < 70% of predicted value • moderate or severe hepatic impairment • documented left ventricular dysfunction (i.e., ejection fraction < 45%, clarified by amendment 1) • severe renal insufficiency (estimated creatinine clearance < 30 mL/min, or serum creatinine > 2.5 mg/dL) • BMI < 18.5 kg/m2 (modified by amendment 1) • Lactating or pregnant
Intervention(s)	Selexipag administered at a dose of 200 µg twice daily increased weekly in twice-daily increments of 200 µg until unmanageable adverse effects associated with prostacyclin use, such as headache or jaw pain, developed. The maximum dose allowed was 1600 µg twice daily.
Comparator(s)	Placebo
Length of follow-up	Median duration 62.0 weeks (placebo) Median duration 67.1 weeks (selexipag)
Outcomes	Primary outcome: • Composite of death or a complication related to PAH (whichever occurred first) up to the end of the treatment period – defined as 7 days after the last intake of selexipag or placebo
Source of funding	Actelion Pharmaceuticals

NSF-LTC

Criteria	Score	Narrative description of study quality
Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Data reported and analysed but underpowered
5. Are the results generalisable?	1/2	The subgroup analysed represented 29% of the original GRIPHON trial population
Total	8/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 8: Simonneau et al. (2012)

Study reference	Simonneau G, Torbicki A, Hoeper M et al. Selexipag: an oral prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. European Respiratory Journal. 2012;40(4):874-880
Unique identifier	NCT00993408
Study type (and NSF-LTC study code)	Randomised, double blind, placebo controlled parallel group clinical trial (P1)
Aim of the study	To determine the safety and efficacy of selexipag as a treatment for pulmonary arterial hypertension (PAH)
Study dates	April 2008 and June 2009
Setting	Multicentre (n=7) in 7 countries

Number of participants	43 adult patients with symptomatic PAH (receiving stable endothelin receptor antagonist and/or a phosphodiesterase type-5 inhibitor therapy) were randomised three to one to receive either selexipag (n=33) or placebo (n=10)
Population	Adult patients (≥ 18 yrs) with symptomatic PAH of idiopathic or hereditary origin, associated with connective tissue diseases (PAH-CTD), corrected congenital heart disease (congenital systemic-to-pulmonary shunts surgically repaired ≥ 5 yrs previously), or anorexigen use. WHO Functional class: FC I (n=0) FC II (n=17) FC III (n=26) FC IV (n=0) Background therapy at baseline None (n=0) ERA (n=16) PDE-5 (n=12) ERA and PDE-5 (n=15)
Inclusion criteria	• Background targeted treatment with endothelin receptor antagonists (ERAs) and/or phosphodiesterase type 5 (PDE-5) inhibitors was mandatory and patients had to have been on stable doses for 12 weeks before screening. • Baseline pulmonary vascular resistance (PVR) of.400 dyn.s.cm^{-5} • Two 6-min walk tests of 150–500 m inclusive and within ±15% of each other.
Exclusion criteria	• Clinically unstable right heart failure within the last 3 months • World Health Organization functional class (WHO FC) IV • Received or were scheduled to receive long-term epoprostenol within 3 months of screening • Patients who had received a ventilation–perfusion lung scan • Patients with a pulmonary angiography indicative of thromboembolic disease • Evidence of left-sided heart disease • Patients who had received any investigational drug within 30 days of screening.
Intervention(s)	Patients received selexipag 200 µg twice daily on day 1. Dosage was then up-titrated to 400 µg twice daily on day 3, to 600 µg twice daily on day 7, and to 800 µg twice daily on day 21. Final dosage was required to be stable for ≥4 weeks prior to evaluation at week 17.

Comparator(s)	Placebo
Length of follow-up	17 weeks
Outcomes	Primary outcome: • Change in pulmonary vascular resistance (PVR)
	Secondary outcomes: • 6 minute walking distance (6MWD) • Aggravation of PAH (defined as death, transplantation, hospitalisation due to worsening PAH, or aggravation of PAH symptoms, i.e. a ≥10% deterioration in 6-min walk distance or the need for additional PAH-specific therapies • Borg dyspnea index • WHO functional class • NTpro-BNP level
	Safety outcomes: • Frequency of treatment-emergent adverse events • Premature discontinuation of study treatment • Change from baseline to last measurement during the treatment period in vital signs, ECG and laboratory parameters.
Source of funding	Not reported

NSF-LTC

Criteria	Score	Narrative description of study quality
Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
3. Are the methods clearly described?	1/2	Methods reasonably clear. Small sample size.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Not all statistical analysis of data reported
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion and exclusion criteria reduce this.

Total	7/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 9: Sitbon et al. (2015)

Study reference	Sitbon O, Channick R, Chin K, Frey A et al. Selexipag for the treatment of pulmonary arterial hypertension. New England Journal of Medicine 2015;373:2522-2533
Unique identifier	NCT01106014
Study type (and NSF-LTC study code)	Randomised (event driven), double blind, placebo controlled phase III clinical trial (P1)
Aim of the study	To investigate the safety and efficacy of selexipag in patients with pulmonary arterial hypertension (PAH) who were not receiving therapy at baseline and those who were already receiving one or two therapies for the disease at baseline
Study dates	December 2009 to May 2013
Setting	Multicentre (n=181) in 39 countries
Number of participants	1156 adult patients randomised to receive either selexipag (n=574) or placebo (n=582)
Population	Patients aged 18 to 72 with idiopathic or heritable pulmonary arterial hypertension or pulmonary arterial hypertension associated with human immunodeficiency virus infection, drug use or toxin exposure, connective tissue disease, or repaired congenital systemic-to-pulmonary shunts. Confirmation of the diagnosis by means of right heart catheterization was required before screening WHO Functional class: FC I (n=9) FC II (n=529) FC III (n=607) FC IV (n=11) Background therapy at baseline None (n=236) ERA (n=170) PDE-5 (n=374) ERA and PDE-5 (n=376)

Inclusion criteria	• Pulmonary vascular resistance (PVR) of at least 5 Wood units (400 dyn · sec · cm−5) • 6-minute walk distance (6MWD) of 50 to 450 m. • Patients who were not receiving treatment for pulmonary arterial hypertension • Patients receiving an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both at a dose that had been stable for at least 3 months
Exclusion criteria	• Patients with pulmonary hypertension that were not covered by the inclusion criterion • Scheduled to receive or Intake of prostacyclin (epoprostenol) or prostacyclin analogs up to 1 month prior to the Baseline visit • moderate or severe obstructive lung disease: FEV1/FVC < 70% and FEV1 < 65% of predicted value after bronchodilator administration or moderate or severe restrictive lung disease: Total Lung Capacity < 70% of predicted value • moderate or severe hepatic impairment • documented left ventricular dysfunction (i.e., ejection fraction < 45%, clarified by amendment 1) • severe renal insufficiency (estimated creatinine clearance < 30 mL/min, or serum creatinine > 2.5 mg/dL) • BMI < 18.5 kg/m2 (modified by amendment 1) • Lactating or pregnant
Intervention(s)	Selexipag administered at a dose of 200 µg twice daily increased weekly in twice-daily increments of 200 µg until unmanageable adverse effects associated with prostacyclin use, such as headache or jaw pain, developed. The maximum dose allowed was 1600 µg twice daily.
Comparator(s)	Placebo
Length of follow-up	Median duration 63.7 weeks (placebo) Median duration 70.7 weeks (selexipag)
Outcomes	Primary outcome: • Composite of death or a complication related to PAH (whichever occurred first) up to the end of the treatment period – defined as 7 days after the last intake of selexipag or placebo
	Secondary outcomes: • Change in 6 minute walking distance (6MWD) • Change in WHO functional class • Death due to PAH or hospitalisation for worsening PAH • NTpro-BNP level
	Safety outcomes:

	• Adverse events
Source of funding	Actelion Pharmaceuticals

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Some outcome measures had missing data imputed by the authors. .
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion and exclusion criteria reduce this.
Total	8/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 10: Tanabe et al. (2017)

Study reference	Tanabe N, Ikeda S, Tahara N, et al. Efficacy and safety of an orally administered selective prostacyclin receptor agonist, selexipag, in Japanese patients with pulmonary arterial hypertension. Journal of Circulation. 2017;81(9):1360-1367
Unique identifier	Not applicable
Study type (and NSF-LTC study code)	Open label, non-comparative phase II clinical study (P1)
Aim of the	To determine the efficacy and safety of selexipag in Japanese

study	patients with pulmonary arterial hypertension (PAH)
Study dates	Not reported
Setting	Multiple centres (n=26) in Japan
Number of participants	37 adult patients
Population	Patients aged 23 to 72 with Idiopathic PAH (n=25), Hereditary PAH (n=5), and PAH associated with other diseases (n=6 with connective tissue disease and n=1 with PAH repaired congenital shunts). Diagnosis of PAH was confirmed within 30 days prior to the beginning of selexipag administration by measurement of pulmonary hemodynamic at rest under right heart catheterization. WHO Functional class: FC I (n=2) FC II (n=21) FC III (n=14) FC IV (n=0) Background therapy at baseline None (n=6) ERA (n=2) PDE-5 (n=3) ERA and PDE-5 (n=26)
Inclusion criteria	• Japanese patients aged 18 years or older • Idiopathic PAH (IPAH), hereditary PAH (HPAH), drug- or toxin-induced PAH, or PAH associated with connective tissue disease, congenital heart disease with a shunt repair surgery, or HIV infection • WHO functional class I–III. • mean PAP (mPAP) ≥25 mmHg; pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure ≤15 mmHg; and PVR at rest >400 dyn · s/cm5. • Combined use of other PAH therapeutic drugs, such as ERAs, phosphodiesterase-5 inhibitors, and calcium antagonists at a constant dose for 90 days before baseline right cardiac catheterization.
Exclusion criteria	• Pregnant women • Patients with a total lung capacity (TLC) less than 70% of the predicted value • Child-Pugh class B or C patients • Serum creatinine value of 2.5 mg/dL (221 μmol/L) or higher • Use of prostacyclin (PGI_2) or its derivatives during the trial period

	• Patients who had received PGI_2 or its derivatives in the 4 weeks before the administration of the therapeutic drug • Patients who received Beraprost sodium within 1 week of administration of the therapeutic drug
Intervention(s)	Selexipag administered at 200 µg twice daily and titrated up to 1,600 µg by increments of 200 µg to reach the individual maximum tolerated dose.
Comparator(s)	None
Length of follow-up	192 weeks (efficacy evaluation period from baseline to week 16, and a long-term treatment period lasting from week 16 to week 136 (cut-off date))
Outcomes	Primary outcome: • Pulmonary vascular resistance (PVR)
	Secondary outcomes: • Mean pulmonary arterial pressure (mPAP) • Mean right atrial pressure (mRAP) • Cardiac Index (CI) • Mixed venous oxygen saturation (SvO2) • 6 minute walking distance (6MWD) • Borg dyspnea index • NTpro-BNP level
	Safety outcomes: • Adverse events
Source of funding	Actelion pharmaceuticals Japan Nippon Shinyaku

NSF-LTC

Criteria	Score	Narrative description of study quality
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	0/2	No comparator or placebo or randomisation of participants. Open label studies have inherently associated biases
3. Are the methods clearly described?	1/2	Methods reasonably clear. Open label studies can be prone to biases. Small sample size.

4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Limitations in study methods reduce the confidence in the data, and thus the conclusions.
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion and exclusion criteria reduce this.
Total	5/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Appendix 4: Results tables

Table 11. Coghlan et al. (2018)

	Placebo (n=133)	Selexipag (n=122)	Hazard Ratio (HR) 95% CI*	P value
N=370				
Primary Outcome – FC III at baseline patients / events				
Composite of death or complication related to PAH	133 / 59	122 / 41	HR 0.74 (0.50 to 01.10) – Unadjusted HR 0.67 (0.45 to 1.01) – Adjusted for baseline 6MWD	Not reported
Secondary Outcome – FC III at baseline patients / events				
Death due to PAH or hospitalisation due to PAH worsening	133 / 38	122 / 26	HR 0.71 (0.43 to 01.18) – Unadjusted HR 0.63 (0.38 to 1.05) – Adjusted for baseline 6MWD	Not reported

*Hazard Ratio estimated using Cox proportional-hazard models.

For all time-to-event endpoints, Kaplan-Meier estimates by treatment arm were calculated.

Table 12: Gaine et al. (2017)

	Placebo (n=167)	Selexipag (n=167)	Hazard Ratio (HR) 95% CI*	P value
N=334				
Primary Outcome – patients / events				
Composite of death or complication related to PAH	167 / 73	167 / 48	HR 0.59 (0.41 to 0.85)	Not reported

*Hazard Ratio estimated using Cox proportional-hazard models.

For all time-to-event endpoints, Kaplan-Meier estimates by treatment arm were calculated.

Table 13: Simonneau et al. (2012)

	Placebo (n=10)	Selexipag (n=33)		
N=43	Change from baseline to week 17		Treatment effect (95% CI)	P-value***
Primary Outcome (per-protocol analysis)				
PVR (dyn.s/cm^{-5})	223.6±355.4	-129.8±309.7[#]	-33% (-47 to -15.2)[^]	0.0022
Secondary Outcomes (per-protocol analysis)				
mPAP (mmHg)	5.7±13.3	-1.7±11.0[#]	-7.4 (-15.9 to 1.1)	0.1
CI (L/min/$^{m-2}$)	-0.2±0.2	0.3±0.5[#]	0.5 (0.13 to 0.83)	0.01
RAP (mmHg)	-2.9±2.8	0.3±3.5*	3.2 (0.8 to 5.7)	0.02
SvO_2 (%)	-2.1±4.1	1.9±10.6	4.1 (-3.8 to 11.9)	0.3
Pulmonary capillary wedge pressure (mmHg)	-1.6±2.7	0.6±3.4**	2.2 (-0.2 to 4.6)	0.07
SVR (dyn.s/cm^{-5})	287.9±227.8	-119.9±498.8*	-407.8 (-740.2 to -75.5)	0.01
6MWD (m)	24.7 (-1.6 to 50.9)	0.4 (-19.7 to 20.5)	24.2 (-23.7 to 72.2)	Not reported
Borg dyspnea index	Not reported	Not reported	-0.1 (-1.4 to 1.1)	Not reported
Plasma NT-pro-BNP (pg/ml)	Not reported	Not reported	-212.8 (-1,012.1 to 586.5)	Not reported
Change in WHO functional class	5 (15.6%) selexipag treated patients experienced an improvement in WHO FC compared with 1 (10%) placebo patient. Two patients in each group experienced a worsening of WHO FC			
Safety				
Adverse events	Almost all patients in both treatment groups experienced at least one adverse event, with headache, pain in jaw, pain in an extremity, nausea, and nasopharyngitis being the most frequently reported in the selexipag group. The majority of adverse events in the selexipag group were classified as mild (n=5; 15.2%) or moderate (n=20; 60.6%). Six (18.2%) patients in the selexipag group and four (40.0%) in the placebo groups experienced at least one serious adverse event. Serious adverse events considered by the investigator to be at least possibly related to selexipag treatment included headache, nausea, vomiting, myalgia, dyspnoea and chest pain. None of the events on placebo were considered to be related to the study drug. There were no deaths.			

Data shown as mean ±SD, unless otherwise stated. PVR: pulmonary vascular resistance; SVR: systemic vascular resistance. #: n=32; *: n=30; **: n=31; ^: treatment effect calculated at week 17 as the change in the geometric mean expressed as a percentage of the baseline value. Although p-values were calculated for secondary end-points, they are only exploratory in nature as there was no formal statistical hypothesis for secondary end-points. ***P-value determined using a Wilcoxon rank sum.

Table 14: Sitbon (2015)

	Placebo (n=582)	Selexipag (n=574)	Hazard Ratio (HR) / Odds Ratio (OR) (99% or 95% CI)*	P value+
N=1156				
Primary Outcome - no. of patients and (%)				
Composite of death or complication related to PAH (All events)	242 (41.6)	155 (27.0)	HR 0.60 (0.46 to 0.78)	<0.001
Secondary Outcomes - no. of patients and (%)				
Death due to PAH or hospitalisation for worsening of PAH up to end of treatment period (All events)	137 (23.5)	102 (17.8)	HR 0.70 (0.54 to 0.91)	0.003
Death up to the end of the study due to PAH ^	83 (14.3)	70 (12.2)	HR 0.86 (0.63 to 1.18)	0.18
Death up to the end of the study from any cause ^	105 (18.0)	100 (17.4)	HR 0.97 (0.74 to 1.28)	0.42
Secondary Outcomes - % of patients				
Absence of worsening in WHO functional class (at week 26)	74.9%	77.8%	OR 1.16 (0.81 to 1.66)**	0.28
Secondary Outcomes – change in distance (m)				
Median change in 6MWD # (baseline to week 26)	-9.0	+4.0	Treatment effect 12.0 (1 to 24)***	0.003
Safety				
Adverse events	Nearly all patients reported 1 or more adverse events (96.6% in the placebo group and 98.3% in the selexipag group) p=0.18. 272 (47.1%) in the placebo group and 252 (43.8%) in the selexipag group reported one or more serious adverse events.(p=0.26) 41 patients (7.1%) in the placebo group and 82 patients (14.3%) in the selexipag group discontinued their study regimen prematurely because of an adverse event (p<0.001). The most frequent adverse events leading to discontinuation in the selexipag group (events for which there was >1% difference between the selexipag and placebo groups) were headache (3.3%), diarrhoea (2.3%), and nausea (1.7%).			

	Hyperthyroidism occurred in 8 patients in the selexipag group and led to treatment discontinuation in 1 patient. No serious adverse events were reported more frequently (i.e., at a rate >1% higher) in the selexipag group than in the placebo group. The death from any cause measured as a first primary endpoint event was 28 patients (4.9%) in the selexipag group and 18 patients (3.1%) in the placebo group.

*Hazard ratios are for selexipag versus placebo, with a 99% confidence interval (CI) for the primary end point and 95% CIs for secondary end points. ** Note: Missing values were imputed for 18.3% of the patients in the analysis of WHO functional class. *** Missing values were imputed for 21.6% of the patients in the analysis of 6-minute walk distance. #: Measured at trough level of study drug. $^{+}$: P values were calculated with the use of a one-sided log-rank test. ^: On the basis of the testing hierarchy the secondary endpoints were analysed with 95% CIs and these results should be interpreted as exploratory. The analysis included patients who may have received other treatments for PAH including open label selexipag. A total of 155 patients from the placebo group who discontinued treatment after the occurrence of a primary endpoint event and 63 patients from the selexipag group who discontinued selexipag after the occurrence of a primary endpoint event received open-label selexipag.

Table 15: Tanabe (2017)

	Selexipag				No comparator
N=33					
Primary Outcome (per-protocol analysis)					
	Baseline	Week 16	Change from baseline to week 16	p-value*	
PVR (dyn.s/cm^5)	683.2±237.3 (408 to 1,351)	560.3±238.7 (240 to 1,103)	−122.9±115.2 (−402 to 90)	<0.0001	
Secondary Outcomes (per-protocol analysis)					
mPAP (mmHg)	41.8±9.2 (26 to 59)	38.8±8.9 (21 to 56)	−3.1±6.0 (−16 to 8)	0.0091	
CI (L/min)	2.63±0.50 (1.5 to 3.5)	2.96±0.74 (1.5 to 4.5)	0.33±0.57 (−0.6 to 1.7)	0.0025	
mRAP (mmHg)	4.5±2.5 (0 to 10)	4.7±2.7 (0 to 10)	0.2±3.7 (−8 to 6)	0.7010	
SvO_2 (%)	70.46±6.96 (50.5 to 82.8)	70.00±8.35 (39.0 to 82.9)	−0.41±5.38 (−16.4 to 13.7)	0.9771	
6MWD (m) **N=30**	445±102.2	459±112.8	Not reported	0.0324	
Borg dyspnea index	2.7±2.1	2.5±2.0	Not reported	Not reported	
Plasma NT-pro-BNP (pg/ml)	111.1 (71.4 to 172.8)	105.7 (66.4 to 168.4)	Not reported	0.5634	
Change in WHO functional class	Improved n=4 (12.1%) 95% CI = 3.4 to 28.1% Deteriorated n=0				
Safety					
Adverse events	**Dose-adjustment phase (Baseline to 16 weeks)** Overall, for 15 patients, a serious adverse event was reported. Two of these patients died due to right ventricular failure. A total of 9 patients discontinued selexipag due to the following adverse events: PAH 13.5% (5 patients), right ventricular failure 5.4% (2 patients), blood pressure decreased and systemic lupus erythematosus 2.7% (1 patient each). **Long term treatment phase** At the cut-off date for analysis (a maximum duration of selexipag treatment of 136 weeks), all 37 patients (100.0%) reported at least 1 adverse event. The most commonly reported adverse events were headache (73.0%), diarrhoea (45.9%), jaw pain (45.9%), nausea (37.8%), and flushing (32.4%). Six patients experienced adverse events related to low blood pressure (low blood pressure: 8.1%; decrease in blood pressure: 10.8%). Of these 6 events, 1 patient (2.7%) was reported as serious, and consequently the patient discontinued selexipag.				

Data shown as mean ± SD (95% confidence interval: min, max). CI, cardiac index; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation. *P-value determined using a Wilcoxon signed-rank test.

Appendix 5: Grading of the evidence base

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

NSF-LTC scoring notes

1. Are the research questions/aims and design clearly stated?	Score 2 points if the research aims and design are both clearly described Score 1 point if either the research aim or research design is clearly described Score 0 points if neither are clearly described
2. Is the research design appropriate for the aims and objectives of the research?	Score 2 points if the research design (e.g. RCT, cohort, before and after) is appropriate to the objectives Score 1 point if the research design is not clearly described but it can be inferred and appears appropriate, or if it is partially appropriate Score 0 points if it is not appropriate or very unclear
3. Are the methods clearly described?	Score 2 points if the methods are described and appropriate. Consider randomisation methods, blinding methods, the methods for handling bias and confounding, and the methods for calculating sample size, where appropriate Score 1 point if the methods are not clearly described but they can be inferred and appear appropriate, or if they are partially appropriate Score 0 points if they are not appropriate or very unclear
4. Are the data adequate to support the authors' interpretations / conclusions?	Score 2 points if the data supports the conclusions and issues of bias, confounding and study power have been sufficiently accounted for (either in study methods or analysis) Score 1 point if the data partially supports the conclusions Score 0 points if the data do not support conclusions or very unclear
5. Are the results generalisable?	Score 2 points if the study results are fully generalisable to the UK setting Score 1 point if the study results are partially generalisable Score 0 points if the results are not generalisable or very unclear

Overall grading by outcome

For each key outcome, studies were grouped and the following NSF-LTC criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.

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