Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease [ID6459]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease [ID6459]

Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Ferrer International
   a. Submission addendum

2. **Company summary of information for patients (SIP)** from Ferrer International

3. **Clarification questions and company responses**

4. **Patient group, professional group and NHS organisation submissions** from:
   a. Action for Pulmonary Fibrosis
   b. Association of Respiratory Nurses (ARNS)
   c. British Thoracic Society*
   d. NHS England (specialised commissioning)

5. **Expert personal perspectives** from:
   a. Professor David G Kiely, Director of Sheffield Pulmonary Vascular Disease Unit – clinical expert, nominated by Ferrer
   b. Dr Colin Church, pulmonary vascular physician – clinical expert, nominated by British Thoracic Society (*see item 4c)
   c. Dr Iain Armstrong – patient expert, nominated by Pulmonary Hypertension Association UK (PHA UK)
   d. Steve Jones – patient expert, nominated by Action for Pulmonary Fibrosis

6. **External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science
   a. EAG report addendum

7. **External Assessment Report – factual accuracy check**

8. **Managed access feasibility assessment**
   a. Managed access proposal - post submission

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease ID6459

Company evidence submission

File name	Version	Contains confidential information	Date
ID6459 inhaled treprostinil in PH-ILD	**2.0**	**Yes**	**2 December 2025**

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Abbreviations

Abbreviation	Definition
6MWD	6-minute walk distance
AE	Adverse event
AF	Adjustment factor
ANCOVA	Analysis of covariance
BIC	Bayesian Information Criterion
BNF	British National Formulary
BNP	Brain natriuretic peptide
BSA	Body surface area
BSC	Best supportive care
CE	Conformité Européenne
CEM	Cost-effectiveness model
CHP	Chronic hypersensitivity pneumonitis
CI	Confidence interval
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPFE	Combined pulmonary fibrosis and emphysema
CPI	Composite physiologic index
CT	Computed tomography
CW	Clinical worsening
CW1	First clinical worsening event
CWF	Clinical worsening-free
CW≥2	Two or more clinical worsening events
DLCO	Diffusing capacity of the lungs for carbon monoxide
DSU	Decision Support Unit
ECG	Electrocardiogram
EQ-5D	EuroQol 5-Dimensions questionnaire
ERA	Endothelin receptor antagonist
ESC/ERS	European Society of Cardiology/European Respiratory Society
FC	Functional class
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
FVC% pred	Forced vital capacity percentage predicted
Furos/Spiro/Bumet	Furosemide/Spironolactone/Bumetanide
GLM	Generalized linear model
HCRU	Healthcare resource utilisation
HP	Hypersensitivity pneumonitis

HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ILD	Interstitial lung disease
IM	Intramuscular
INCREASE	INCREASE clinical trial
IPD	Individual participant data
IPF	Idiopathic pulmonary fibrosis
IQR	Interquartile range
ITT	Intent-to-treat
IV	Intravenous
JBI	Joanna Briggs Institute
KM	Kaplan-Meier
LS	Least squares
LTOT	Long-term oxygen therapy
MCID	Minimal clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimal important difference
MMRM	Mixed-model repeat-measurement
NCC	National Cost Collection
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NSIP	Non-specific interstitial pneumonia
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label extension
OS	Overall survival
PAH	Pulmonary arterial hypertension
PAS	Patient Access Scheme
PCWP	Pulmonary capillary wedge pressure
PDE5i	Phosphodiesterase Type 5 Inhibitors
PFT	Pulmonary function test
PH	Pulmonary Hypertension
PH-ILD	Pulmonary Hypertension associated with Interstitial Lung Disease
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVR	Pulmonary vascular resistance

QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RHC	Right heart catheterisation
RPSFT	Rank-preserving structural failure time
RV	Right ventricle
SD	Standard deviation
SE	Standard error
SGRQ	Saint George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TAPSE	Tricuspid annular plane systolic excursion
TLC	Total lung capacity
VOP	Voice of the Patient
WHO	World Health Organization
WU	Wood units
mPAP	Mean pulmonary arterial pressure

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. A summary of how the decision problem is addressed by this submission is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with a confirmed diagnosis of pulmonary hypertension with interstitial lung disease.	Adult with a confirmed diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD WHO Group 3)	Inhaled treprostinil is anticipated to be indicated specifically for PH-ILD, within WHO Group 3.
Intervention	Inhaled treprostinil	As per NICE final scope	N/A
Comparator(s)	• Established clinical management without inhaled treprostinil • Phosphodiesterase 5 inhibitors (PDE5is): sildenafil and tadalafil	Established clinical management, without inhaled treprostinil (best supportive care)	European guidelines state that PDE5is (such as sildenafil and tadalafil) may be considered on a case-by-case basis in patients with severe PH-ILD (defined in the guidelines as patients with a PVR ≥5 WU).[1] The use of PDE5is in patients with non-severe PH-ILD is not recommended. These recommendations are based on conflicting and limited evidence. Additionally, expert clinical insights from the UK advisory board indicated that PDE5is are only used in a small percentage of very severe PH-ILD patients (in the absence of any licensed treatment), with low expectations of effectiveness and are not considered standard of care in the overall patient population.[2] This is supported by results from the UK-based epidemiological study (commissioned by Ferrer), which reported that only 8% of patients with PH-ILD received

			PDE5is (sildenafil or tadalafil).[3] As such, PDE5is are not considered to be relevant comparators.
Outcomes	The outcome measures to be considered include: • exercise capacity (for example 6-minute walk distance – 6MWD) and other measures of physical function • time to clinical worsening • hospitalisations • overall survival • lung function • breathlessness • haemodynamic assessment (for example cardiac index, cardiac output, right atrial pressure, pulmonary arterial pressure and pulmonary vascular resistance) • fatigue • transplant-free survival • adverse effects of treatment • health-related quality of life	The outcome measures to be considered in the company submission are: • exercise capacity • time to clinical worsening • hospitalisations • overall survival • lung function • breathlessness • haemodynamic assessment • fatigue • adverse effects of treatment • health-related quality of life	The following outcomes were not assessed in the trial: • transplant-free survival

Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Different types of interstitial lung disease, for example idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, idiopathic interstitial pneumonia, sarcoidosis, hypersensitivity pneumonitis	A subgroup analysis of patients with PH-ILD, excluding those with combined pulmonary fibrosis and emphysema (CPFE) is considered	Considering the number of patients in the trial and the number of different types of interstitial lung disease (ILD) (>200), it was not feasible to conduct further subgroup analyses
Key: CPFE: combined pulmonary fibrosis and emphysema; ILD: Interstitial Lung Disease, NICE: National Institute for Health and Care Excellence, PDE5i: Phosphodiesterase Type 5 Inhibitors, PH: Pulmonary Hypertension, PH-ILD: Pulmonary Hypertension associated with Interstitial Lung Disease, PVR: Pulmonary Vascular Resistance, WHO: World Health Organization, WU: Wood Units.			

1.2 Description of the technology being evaluated

The technology being evaluated in the submission (inhaled treprostinil [[redacted]®]) is described in Table 2. Please see Appendix A for the draft Summary of Product characteristics (SmPC).

Table 2. Technology being evaluated

UK approved name and brand name	UK approved name: Inhaled treprostinil Brand name: [redacted]®
Mechanism of action	Treprostinil is a stable analogue of prostacyclin, which promotes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. The targeted delivery of inhaled treprostinil in the lungs is expected to result in higher concentrations in the pulmonary vasculature to enhance blood flow and reduce off-site systemic exposure.
Marketing authorisation/CE mark status	Inhaled treprostinil does not yet have marketing authorisation for any indication in the UK. The expected date of Medicines and Healthcare products Regulatory Agency (MHRA) approval is [redacted] Inhaled treprostinil is administered via a CE-marked ultrasonic nebuliser.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Inhaled treprostinil is expected to be indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3).
Method of administration and dosage	Solution for oral inhalation administered through an ultrasonic, pulsed-delivery nebuliser. Initial dose 3 breaths per session, 4 sessions daily, titrated up to target dose of 9 breaths per session, 4 sessions daily and a maximum dose of 12 breaths per session, 4 sessions daily.
Additional tests or investigations	The anticipated indication for inhaled treprostinil is patients with a diagnosis of PH-ILD. This includes individuals with a confirmed diagnosis of diffuse parenchymal lung disease, such as any form of ILD or CPFE, established through imaging or histological confirmation (e.g., tissue biopsy). RHC is standard practice within the PH-ILD pathway and is required to confirm diagnosis of PH in patients with ILD. As such, no additional tests or investigations outside current practice are expected.
List price and average cost of a course of treatment*	• Starter kit: [redacted] per kit • Refill kit: [redacted] per kit

	Treatment is typically ongoing as long as the patient remains eligible and benefits from the therapy. The exact duration depends on clinical outcomes.
Patient access scheme (if applicable)	A simple PAS discount will be applied to the list price of inhaled treprostinil, providing a fixed discounted price of [redacted] per kit.
Key: CE: Conformité Européenne; CPFE: combined pulmonary fibrosis and emphysema; ILD: Interstitial Lung Disease; MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health Service; PAS: Patient Access Scheme; PH: Pulmonary Hypertension; PH-ILD: Pulmonary Hypertension associated with Interstitial Lung Disease; RHC: Right heart catheterisation; SmPC: Summary of Product Characteristics. **Notes:** * Price calculated based on one course of treatment. List prices are yet to be confirmed with DHSC. **Source:** Inhaled treprostinil Draft SmPC.[4]	

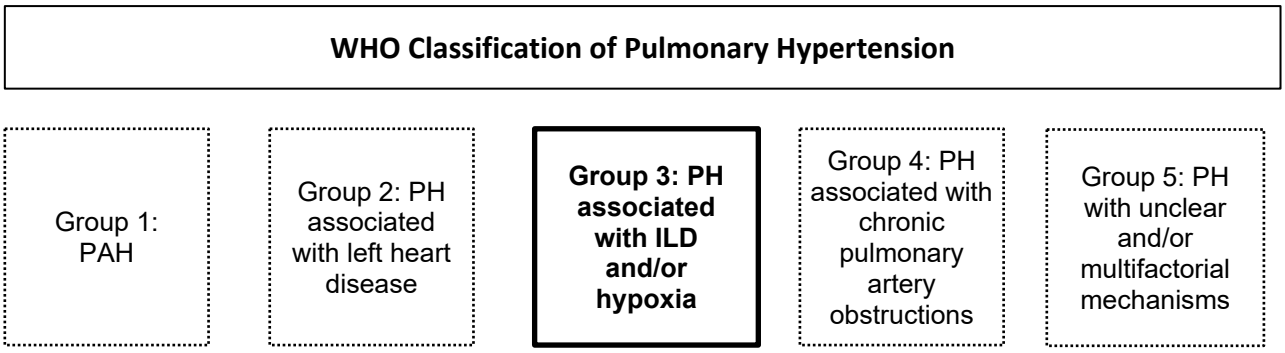
1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Overview of PH-ILD

Pulmonary hypertension (PH) refers to a group of conditions that result in increased pressure within the pulmonary arteries. It is defined across all forms by a mean pulmonary artery pressure (mPAP) greater than 20 mmHg. The World Health Organization (WHO) categorises PH into five clinical groups to enable differential diagnoses that guide decisions on appropriate treatment (Figure 1). Of these, PH WHO Group 3 refers to PH associated with lung diseases and/or hypoxia and has the worst prognosis of all PH groups. PH WHO Group 3 can include PH associated with chronic obstructive pulmonary disease, sleep-disordered breathing or interstitial lung disease (ILD).[1] Inhaled treprostinil is anticipated to be indicated specifically for PH associated with ILD (PH-ILD), within WHO Group 3.[5]

ILDs are a group of diffuse parenchymal lung conditions, resulting from damaged lung parenchyma by inflammation and fibrosis, that share similar clinical, radiological and pulmonary functional characteristics.[6] In England, the most common forms of ILD include idiopathic pulmonary fibrosis (IPF), sarcoidosis, and extrinsic allergic alveolitis.[7] PH frequently arises as a complication of ILD, affecting over 60% of individuals with end-stage ILD, and its presence significantly worsens ILD prognosis.[8-11]

Figure 1. Classification of Pulmonary Hypertension by the World Health Organization



Key: ILD: Interstitial Lung Disease; PAH: Pulmonary Arterial Hypertension; PH: Pulmonary Hypertension; WHO: World Health Organization

Notes: WHO Group 3 (in bold) is PH secondary to chronic lung diseases (ILD), hypoxia or both.

Source: Humbert et al. 2022.[1]

1.3.1.1 Epidemiology

The prevalence of PH-ILD varies substantially depending on the underlying ILD and data sources. The annual prevalence and incidence of PH-ILD in the UK during 2019 was estimated at 0.36 and 0.19 per 10,000 people, respectively.[12] However, this figure may underestimate the true burden of disease in the UK.

Studies conducted across Europe (including the UK) and North America have reported higher prevalence estimates, with PH-ILD prevalence reported to be around 4 in 10,000 and between 0.8 and 1 per 10,000, respectively.[13-16]

1.3.2 Burden of disease

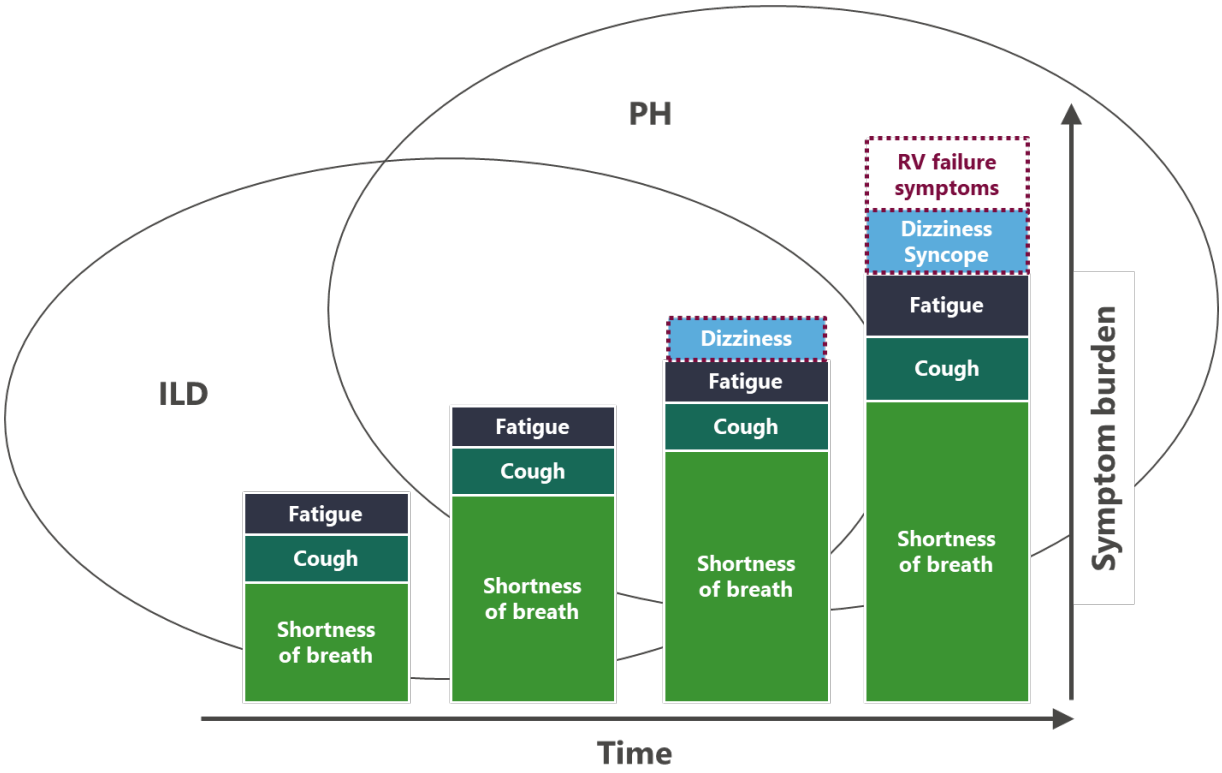
1.3.2.1 Clinical burden and survival associated with PH-ILD

The most common symptom in PH-ILD is dyspnoea, caused by chronic remodelling of small pulmonary arteries, leading to narrowing of the vascular lumen. This leads to a decline in functional capacity, evident through reductions in clinical outcomes such as six-minute walk distance (6MWD), forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DLCO). The decline in functional capacity is a characteristic of PH-ILD progression and correlates with increased mortality risk.[17-27] A univariate Cox regression analysis of baseline variables that may predict clinical outcomes in patients

with PH-ILD has indicated that 6MWD predicts overall survival (hazard ratio [HR]: 0.958; 95% confidence interval [CI]: 0.934, 0.983; p=0.001). Notably, an improvement in 6MWD (≥20m) has been shown to be associated with improved survival rates in patients with PH-ILD versus patients who do not demonstrate improved 6MWD.[17]

Patients with ILD and PH-ILD have an overlapping symptom burden, including dyspnoea, cough and fatigue, with PH-ILD resulting in exacerbated respiratory symptoms compared with ILD alone (Figure 2).[28] Over time, patients with PH-ILD may present with dizziness, syncope and symptoms resulting from right ventricular (RV) failure.[28] Acute exacerbations are common in patients with PH-ILD and may result in rapid deterioration and death.[29-31]

Figure 2. Symptom burden associated with ILD and PH-ILD over time



Key: ILD: Interstitial Lung Disease; PH: Pulmonary Hypertension; RV: Right Ventricle

Notes: X-axis represents the progression of symptoms over time. Y-axis illustrates the overall severity of the symptom burden caused by ILD and PH. Dashed symptoms indicate those that are less common and not experienced by all patients.

Source: Nikkho et al. 2022.[28]

Patients with PH-ILD have worse outcomes compared to those with PH or ILD alone, with 1-, 3-, and 5-year transplant-free survival rates of 71.9%, 40.3%, and 22.5%, respectively.[32] This is associated with over 50% reduction in survival compared to other PH WHO Groups.[32] Overall, median survival for patients with PH-ILD has been reported from 0.7 to 1.7 years.[18,28,32-34]

Prognosis of PH-ILD is poor irrespective of disease severity.[35] In a retrospective study of patients in PH centres across Spain, Italy, and the UK between January 2000 and March 2020, reduced 3-year survival rates were reported in patients with borderline PH-ILD (32%, n=29), mild PH-ILD (29%, n=52) and severe PH-ILD (33%, n=30) versus patients without PH.[35]

The symptoms of PH-ILD (notably dyspnoea and fatigue) impact daily activities, such as patients' ability to cook, clean or go to the shops. Furthermore, physical functioning is reduced with patients reporting difficulties walking or climbing stairs.[8,18,20] Patients' social and family life are also impacted, along with their emotions with patients reporting frustration, depression, anxiety, isolation and sadness.[19,36] Overall, PH-ILD substantially reduces patients' health-related quality of life compared with patients without the disease.

1.3.2.2 Economic and societal burden

PH-ILD is associated with a considerable economic burden largely driven by high healthcare resource utilisation (HCRU), including increased hospitalisations, accidents and emergency visits, and intensive care unit admissions, relative to patients with ILD without PH.[5,37-39] Notably, in the fiscal year 2022 to 2023, secondary PH (including but not specific to PH-ILD) was associated with 5,711 consultant episodes across the UK, according to Hospital Episode Statistics.[40]

A UK-based epidemiological study (commissioned by Ferrer), which included 2,217 patients with PH-ILD between 01 January 2017 and 31 December 2019, revealed that patients with PH-ILD experienced an all-cause hospitalisation rate of 1.36 per patient-year (95% CI: 1.31 - 1.4).[3] The median length of stay for PH-ILD patients was 6 days (interquartile range [IQR]: 6-9), with a mean stay of 10 days (standard deviation [SD]: 13). Furthermore, PH-ILD patients required an average of 11.53 outpatient visits, and 1.39 emergency room visits per patient-year. Frequent specialist interactions were also

observed, with 2.31 pulmonologist visits and 0.87 cardiologist visits reported per patient-year.

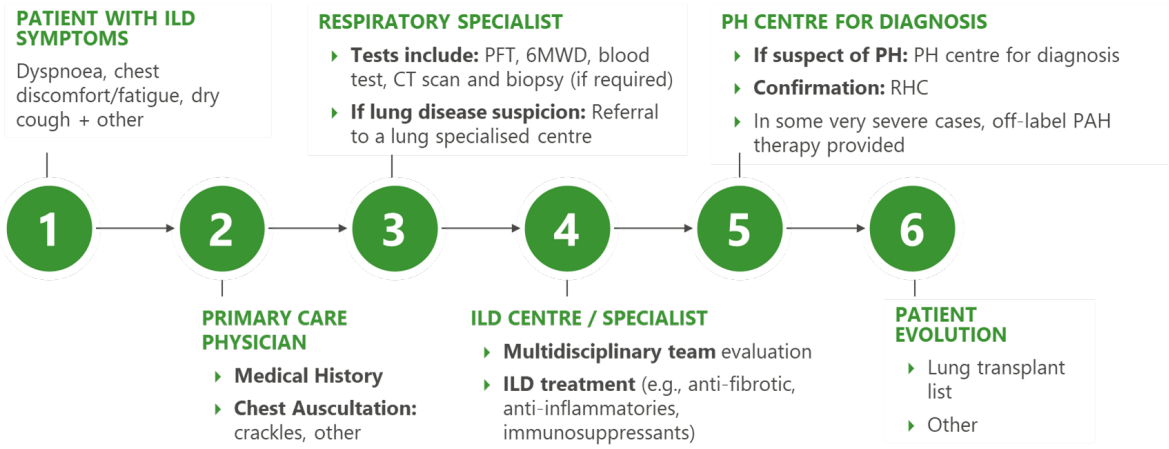
PH-ILD has a profound impact beyond direct clinical outcomes, notably through reduced work capacity, early retirement, and impaired participation in daily and social activities.[36] Patients frequently report severe limitations due to breathlessness and fatigue, with some becoming housebound or reliant on mobility aids within a year of diagnosis. These impairments hinder the ability to engage in employment, fulfil domestic responsibilities, or maintain social relationships, resulting in broader societal costs related to lost productivity.[36]

In addition, carers face significant physical, emotional, and financial strain. As reported in the European Voice of the Patient (VOP) study, carers—often close relatives—assume responsibilities that include managing oxygen therapy, assisting with mobility, and providing continuous emotional support. This leads to reduced independence, social isolation, and disruption to their own employment and daily lives.[36] These indirect burdens on both patients and carers highlight the need for holistic care approaches and support services that address the wider societal impact of PH-ILD.

1.3.3 Clinical pathway of care

Currently, there are no approved treatment options for patients with PH-ILD. Management of PH-ILD is fragmented between specialist ILD and PH centres within the National Health Service (NHS). The overall patient journey can be seen in Figure 3.

Figure 3. Overview of PH-ILD pathway



Key: CT: Computed Tomography, ILD: Interstitial Lung Disease, 6MWD: 6-Minute Walk Distance, PFT: Pulmonary Function Test, PH: Pulmonary Hypertension, RHC: Right Heart Catheterisation.

1.3.3.1 Diagnosis and management of ILD

Typically, patients present to general practitioners with unspecified ILD symptoms, including dyspnoea, chest discomfort, fatigue, and dry cough. Diagnosis involves several investigations (Figure 3, steps 2-4), including but not limited to full pulmonary function tests, 6-minute walk test (6MWT), high resolution computed tomography (CT) of the thorax and others.

There are several national and international guidelines[41-43] that are considered for the management of ILD. Based on these, treatment options for ILD can involve:

- Parenteral cytotoxic agents (e.g., intravenous [IV] cyclophosphamide, intramuscular [IM] methotrexate)
- Biological agents
- Chemotherapeutic agents
- Plasmapheresis
- IV immunoglobulins

In addition, both nintedanib and pirfenidone are recommended by NICE for treating IPF, the most common form of ILD:

- Nintedanib is recommended as an option for treating IPF in adults, only if they have a forced vital capacity of above 80% predicted (NICE TA864)[44]
- Pirfenidone is recommended as an option for treating IPF in adults, only if the person has a FVC between 50% and 80% predicted (NICE TA504)[45]

Patients with ILD who are suspected of having PH (e.g., due to NT-proBNP levels and/or echocardiogram results, among other tests) are referred to PH specialist centres for diagnosis.[80] The standard test for diagnosis is right heart catheterisation (RHC). Overall, the following confirms a diagnosis of PH:

- A mPAP of >20 mmHg
- A pulmonary vascular resistance (PVR) ≥2 Wood Units (WU)
- A pulmonary artery wedge pressure (PAWP) of <15 mmHg

PVR is a key haemodynamic parameter used to assess the presence and severity of pulmonary vascular disease. It is calculated as mPAP – PAWP / cardiac output (CO) to

provide a PVR value in Wood units.[46] PVR provides important prognostic information. In the context of PH-ILD, elevated PVR has been shown to be an independent predictor of mortality.[47]

Referral rates of patients with ILD and suspected PH to PH specialist centres for diagnostic evaluation and management remain low. This is understood to be primarily driven by the lack of approved treatment options for PH-ILD and the need to avoid placing additional pressure on the limited capacity and resources available within PH specialist centres.[2]

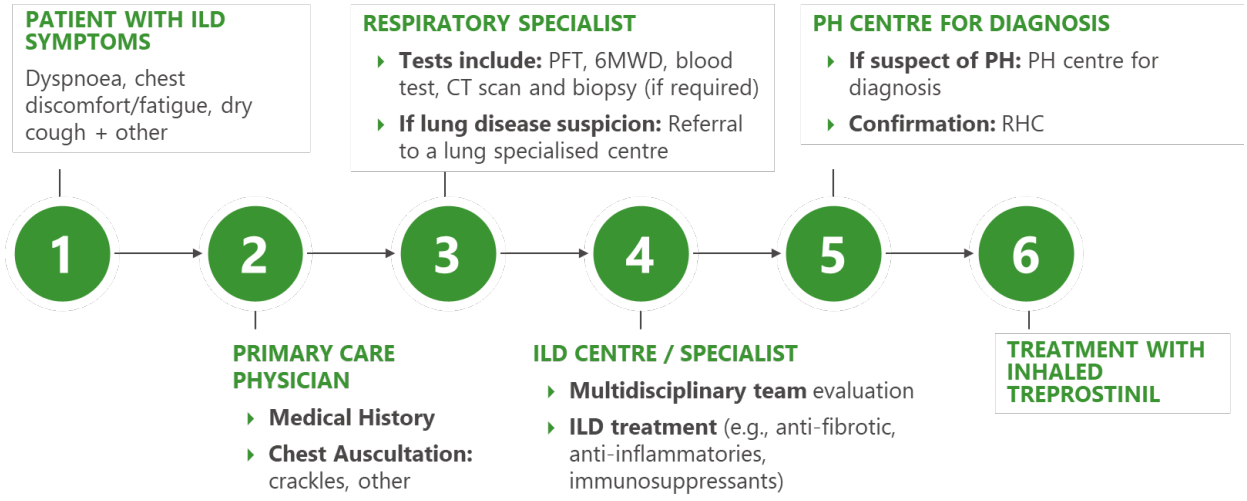
There are currently no approved treatment options for PH-ILD and there are no treatment guidelines for the management of PH-ILD in England. Following diagnosis of PH-ILD at a PH specialist centre, patients with PH-ILD who have a PVR between 2 and 5 WU are typically monitored at ILD specialist centres. Insights from clinicians engaged during a NICE Advice stakeholder engagement meeting and from the UK advisory board suggest that these individuals are generally only provided with treatment options targeting the ILD aspects of the disease.[2] In contrast, patients diagnosed with severe PH-ILD (i.e., a PVR ≥ 5 WU) may receive care at a PH specialist centre and, in some cases, may continue to be monitored at ILD centres. Expert clinical insights from the UK advisory board highlighted notable regional variation in the referral and management of patients with PH-ILD across the UK.[2]

As there are no approved treatments for PH-ILD, therapies for Pulmonary Arterial Hypertension (PAH, WHO Group 1) are sometimes used off-label for patients with severe PH-ILD (PVR ≥ 5 WU) on a case-by-case basis. The 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of PH recommend consideration of phosphodiesterase 5 inhibitors (PDE5i) such as sildenafil or tadalafil upon referral to a PH-centre for an individualised treatment approach.[1] The quality of evidence supporting the use of PDE5is is considered “very low”, with guidelines reiterating that data on use of these treatments for patients with PH-ILD are limited and conflicting. Further, the guidelines suggest that treatment options for PAH are not efficacious in the PH-ILD population and in some cases may even be harmful.

Clinical experts consulted during the UK advisory board noted that only a very small proportion of patients with severe PH-ILD may be treated with off-label PAH therapies, such as PDE5is, in an attempt to provide some symptom relief. ERS This is supported by results from the UK-based epidemiological study (commissioned by Ferrer), which reported that only 8% of patients with PH-ILD received PDE5is (sildenafil or tadalafil).[3] The effectiveness of PDE5is in this population is reported to be limited and variable, and their off-label use reflects the lack of licensed treatment options for PH-ILD.[2]

Inhaled treprostinil will be the first approved treatment option for PH-ILD in the UK. It is intended for use in adult patients diagnosed with PH-ILD. Depending on the patients' underlying ILD, inhaled treprostinil can be administered alone or in addition to concomitant treatments for ILD (e.g., pirfenidone or nintedanib). As such, inhaled treprostinil is not expected to replace or reduce the use of concomitant treatments for patients' underlying ILD. Figure 4 presents the proposed place of inhaled treprostinil in the current treatment pathway. During an advisory board in February 2025, UK clinicians (N=8) discussed the need for PH and ILD centres to closely collaborate to allow the smooth implementation of inhaled treprostinil and reduce current fragmentation between services.[2]

Figure 4. Proposed place of treprostinil in the PH-ILD diagnosis and treatment pathway



Key: BNP: Brain natriuretic peptide; CT: Computed tomography; ILD: Interstitial lung disease; MDT: Multidisciplinary team; NT-proBNP: N-terminal pro B-type natriuretic peptide; PDE5i: Phosphodiesterase-5 inhibitors; PH: Pulmonary hypertension; QoL: Quality of life

Source: Ferrer International UK Advisory board report. 2025.[2]

1.3.4 Unmet need

PH-ILD is a severe and progressive condition that is associated with a high risk of mortality, with median survival from diagnosis ranging from 0.7 to 1.7 years.[18,28,32-34] As aforementioned, there are currently no approved treatments for patients with PH-ILD in the UK. PAH therapies are sometimes used off-label for a small proportion of patients with severe PH-ILD in the UK.[2,3] However, they are not efficacious in the PH-ILD population,[2,48,49] and in some cases may even be harmful.[1,50] This has been shown in previous clinical trials for pulmonary vasodilator therapies in PH-ILD (e.g., sildenafil, bosentan, ambrisentan and riociguat), where the primary efficacy endpoints were not achieved and/or the trial was terminated due to serious adverse events (AEs).[51-57] Clinician feedback in a UK advisory board also described the limited effectiveness of these treatments for relieving symptoms and improving survival in patients with PH-ILD.[2] In addition, the absence of effective, licensed therapies for PH-ILD contributes to under-referral of patients for diagnostic evaluation.[2] As such, there remains a significant unmet need for a targeted, clinically effective and well-tolerated therapy that can improve exercise capacity, delay disease progression and extend survival in patients with PH-ILD.

Inhaled treprostinil is currently recommended within European guidelines for treatment of PH-ILD.[1] Therefore, it has the potential to address the significant unmet need in patients with PH-ILD within the UK context.

1.4 Equality considerations

It is not anticipated that this evaluation would: exclude any individuals protected by equality legislation from consideration for treatment; lead to a recommendation with a different impact for people protected by equality legislation versus the wider population; or lead to recommendations with an adverse impact on people with a particular disability or disabilities.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

A systematic literature review was conducted to identify published randomised controlled trials (RCTs) and observational studies for treatments of PH-ILD. Published study type filters for RCTs and observational studies from the Scottish Intercollegiate Guidelines Network (SIGN) were used to identify relevant RCTs and observational studies (see Appendix B for more details). An initial search in January 2024 retrieved only two relevant studies (INCREASE and INCREASE open-label extension (OLE). A subsequent search was conducted in December 2024 to identify any additional evidence to support an indirect or mixed comparison.

The search identified 45 relevant reports after duplicate removal and screening, yielding 35 studies in total. Of these, 19 of the studies are relevant to the decision problem, as they report on inhaled treprostinil or best supportive care (BSC). However, only 3 are pertinent to the remainder of this section, because any other studies that reported BSC included only sub-populations of patients with PH-ILD, which do not reflect the full patient population in the decision problem. The INCREASE and INCREASE OLE trials were identified that evaluated the safety and efficacy of inhaled treprostinil in combination with BSC compared to placebo with BSC. In addition, the retrospective observational cohort analysis by Dawes *et al.* (2022) was identified. This study examined patients with PH-ILD treated with or without PDE5is, where patients treated without PDE5is are assumed to be untreated patients.

The studies identified in the clinical SLR were assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist and the overall risk of bias was considered to be low across the included studies. Full results of this assessment are presented in Appendix B. See Appendix B also for full details of the process and methods used to identify and select the clinical evidence relevant to inhaled treprostinil.

2.2 List of relevant clinical effectiveness evidence

2.2.1 Inhaled treprostinil studies

The pivotal trials for inhaled treprostinil in adult patients with PH-ILD include the Phase 3 RCT INCREASE, and the Phase 3 extension trial, INCREASE OLE. A summary of the clinical effectiveness evidence for inhaled treprostinil is presented in Table 3.

Table 3. Clinical effectiveness evidence

Study title	**INCREASE (NCT02630316)**	**INCREASE OLE (NCT02633293)**
Study design	Phase 2/3, multicentre, randomised, double-blind, placebo-controlled study	Phase 2/3, open-label extension study
Population	Adults with PH-ILD, including CPFE (n=326). Eligible patients were adults with Group 3 PH with evidence of parenchymal lung disease and who had a 6MWD of ≥100 m. Patients with underlying connective tissue disease were required to have a baseline FVC of <70%. No approved therapy for PAH was permitted within 60 days of randomisation.	Adults with PH-ILD, including CPFE (n=242). Eligible patients 1) had received inhaled treprostinil for the duration of the 16-week INCREASE and completed all scheduled study visits; or 2) had discontinued inhaled treprostinil due to clinical worsening during the RCT and completed all remaining scheduled study visits; or 3) were enrolled in the RCT and their participation was discontinued by the sponsor [a]. For OLE, new medications were allowed, but if a patient required infused prostacyclin lasting ≥ 29 days, they were discontinued from the OLE.
Intervention(s)	Inhaled treprostinil (n=163), administered via an ultrasonic, pulsed-delivery nebuliser in up to 12 breaths (total, 72 µg) four times daily	Inhaled treprostinil (n=242), all patients discontinued treatment received during the RCT and received inhaled treprostinil via an ultrasonic, pulsed-delivery nebuliser at 6 µg per breath. Dose escalations were up to a maximum of 15 breaths per session (90 µg) four times daily, as tolerated
Comparator(s)	Placebo (n=163)	None
Indicate if study supports application for marketing authorisation	Yes	Yes

Study title	INCREASE (NCT02630316)	INCREASE OLE (NCT02633293)
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	Not applicable	Not applicable
Reported outcomes specified in the decision problem	• Exercise capacity (for example 6-minute walking distance) • **Time to clinical worsening** [b] • **Hospitalisations** • Haemodynamic assessment (e.g. cardiac index, cardiac output, right atrial pressure, pulmonary arterial pressure and pulmonary vascular resistance) • **Adverse effects of treatment** • **Health-related quality of life**	• Exercise capacity (for example 6-minute walking distance) • **Time to clinical worsening** [b] • **Hospitalisations** • **Overall survival** • Haemodynamic assessment (e.g. cardiac index, cardiac output, right atrial pressure, pulmonary arterial pressure and pulmonary vascular resistance) • **Adverse effects of treatment** • **Health-related quality of life**
All other reported outcomes	• Change in plasma NT-proBNP levels • Change in distance saturation product • Risk of disease progression events [c]	• Event-free survival • Change in plasma NT-proBNP levels • Change in distance saturation product

Key: 6MWD, six-minute walk distance; CI, confidence interval; CPFE, combined pulmonary fibrosis and emphysema; FVC, forced vital capacity; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; OLE, open-label study; PH-ILD, pulmonary hypertension associated with interstitial lung disease; QoL, quality of life; SGRQ, St George's Respiratory Questionnaire.

Notes: Bolded outcomes are those used in the economic modelling. a Patients enrolled in the RCT but discontinued by the sponsor were those who discontinued the OLE study after inhaled treprostinil for PH-ILD was approved by the US FDA and the inhaled treprostinil was commercially available, in accordance with the final clinical study report. b Clinical worsening is defined as the occurrence of any of the following events: hospitalisation for a cardiopulmonary indication, decrease in 6MWD of >15% from baseline (directly related to the disease at two consecutive visits occurring ≥24 hours apart), death from any cause, lung transplantation. c Disease progression defined as the occurrence of any of the following events: decrease in 6MWD of >15% from baseline, hospitalisation for a cardiopulmonary indication, lung transplantation, death from any cause, >10% decline in FVC, acute exacerbation of underlying lung disease.

Source: Waxman et al. 2021[58]; INCREASE clinical study report[59]; Waxman et al. 2023[60]; INCREASE OLE clinical study report.[61]

2.3 Summary of methodology of the relevant clinical effectiveness evidence

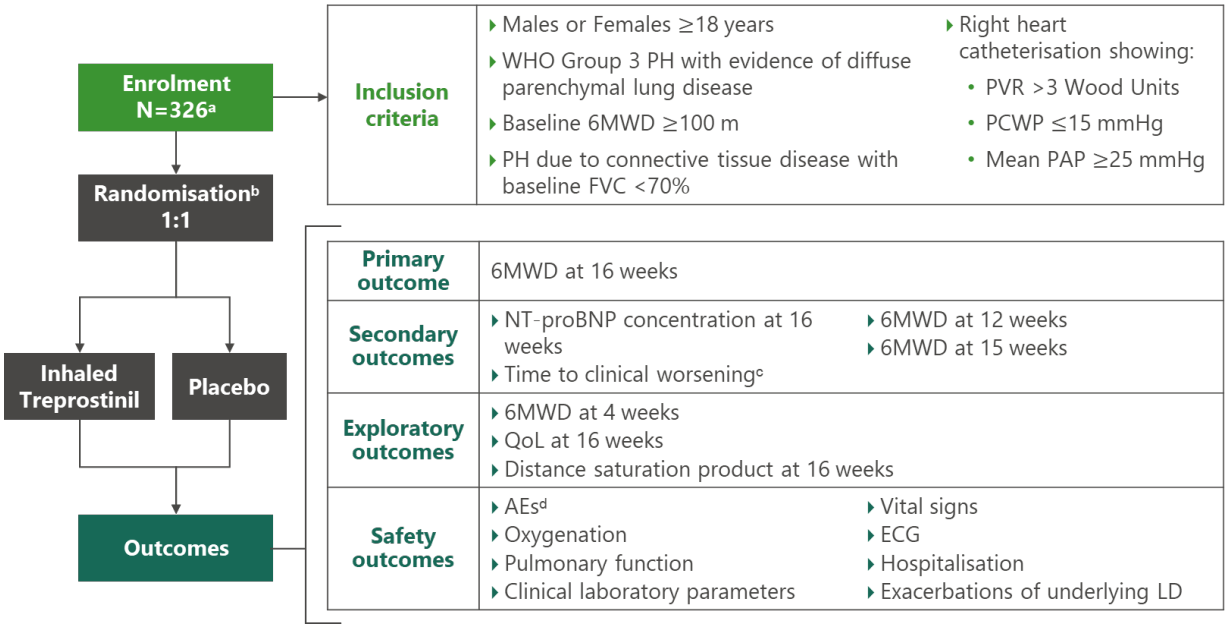
2.3.1 INCREASE

2.3.1.1 Study design

INCREASE was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, 16-week, parallel-group study designed to investigate the safety and efficacy of inhaled treprostinil versus placebo in patients with PH-ILD.[58,59] The study was conducted at 119 sites in the US and Puerto Rico.[59] Although no UK patients were included in either study, UK clinicians agreed that patients treated in INCREASE and INCREASE OLE are generalisable to UK patients seen in clinical practice.[62] The patients were of similar age to that of Dawes *et al.* (2022), as shown in Table 10. In addition, the outcomes assessed in the trial and background anti-fibrotic treatments received in patients at baseline are considered consistent with standard practice in the NHS England at the time of trial.[62]

The final database lock occurred on 18 February 2020.[58] The INCREASE study design is presented in Figure 5 and a summary of the trial methodology is presented in Appendix J.

Figure 5. Study design of INCREASE



Key: 6MWD, six-minute walk distance; AE, adverse event; ECG, electrocardiogram; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; WHO, World Health Organisation.

Notes: a Patients who were receiving a stable dose of medication therapy for underlying lung disease (i.e., pirfenidone or nintedanib) for ≥30 days were included in the trial. Patients treated with approved treatment for PAH within 60 days of randomisation and/or receiving >10 L/min of supplemental oxygen at baseline and/or initiated pulmonary rehabilitation within 12 weeks prior to randomisation were excluded from the trial. b Stratified by 6MWD. c Clinical worsening included the following criteria: hospitalisation due to a cardiopulmonary indication, decrease in 6MWD >15% from baseline and directly related to disease under study, all-cause mortality, and lung transplantation. d The use of concomitant medications was permitted and recorded during the trial.

Source: Waxman et al. 2021.[58]

For inclusion in INCREASE, patients had to be ≥ 18 years of age with a confirmed diagnosis of WHO group 3 PH based on computed tomography imaging, performed within 6 months prior to randomisation demonstrating evidence of diffuse parenchymal lung disease. Patients could have any form of ILD or combined pulmonary fibrosis and emphysema (CPFE). Patients were also required to have a RHC within 1 year prior to randomisation to confirm a PVR >3 WU, a PCWP of <15 mmHg, and a mPAP of >25 mmHg. Patients with WHO group 3 PH due to connective tissue disease were required to have a baseline FVC of less than 70%. Eligible patients also had to walk at least 100 metres during a 6MWT.

Eligible patients were randomised in a 1:1 ratio to receive either inhaled treprostinil (6µg/breath) or placebo.[58,59] All patients were randomised using a centrally administered stratified permuted block randomisation, stratified by baseline 6MWD (≤ 350 metres and > 350 metres).

The study consisted of three phases: a screening phase, a baseline visit, and a 16-week treatment phase. The treatment phase consisted of five visits to the clinic at weeks 4, 8, 12, 15, and 16. Patients were contacted at least once weekly to assess patients' tolerance to study drugs, adverse events (AEs), and changes to concomitant medications. At the end of the treatment phase, eligible patients could enrol in the OLE trial, INCREASE OLE, to evaluate the long-term safety and efficacy of inhaled treprostinil in patients with PH-ILD. See Section 2.3.2 for further details.

The primary efficacy endpoint in INCREASE was the change in peak 6MWD from baseline to Week 16.[58,59] Secondary efficacy endpoints included:

- Change in B-type natriuretic peptide (NT-proBNP) level from baseline to Week 16
- Time to clinical worsening (CW), calculated as the time from randomisation until one of the following criteria were met:
    - Hospitalisation due to a cardiopulmonary indication
    - Decrease in peak 6MWD >15% from baseline (directly related to the disease at two consecutive visits occurring ≥24 hours apart)
    - Death
    - Lung transplantation
- Change in 6MWD at peak plasma treprostinil level at Week 12
- Change in 6MWD at trough treprostinil level at Week 15

Details of all endpoints are provided in Figure 5 and Appendix J.

2.3.1.2 Patient characteristics

The baseline characteristics for patients in INCREASE are presented in Table 4. Baseline characteristics were similar between the two treatment arms.[58,59] The mean age of patients was 66.5 years, and the majority of patients (65.6%) were aged 65

years or older. Overall, 46.9% of patients were female, and the most common cause of lung disease was idiopathic interstitial pneumonia, occurring in 44.8% of patients. Median 6MWD at baseline was 259 metres, mean PVR was 6.191 WU and median NT-proBNP level was 503.85 pg/mL. The majority of patients (77.3%) were not receiving background therapy (e.g., pirfenidone or nintedanib) at baseline.

Table 4. Baseline demographics and disease characteristics in INCREASE

Characteristic	**Inhaled treprostinil (n=163)**	**Placebo (n=163)**	**All Patients (n=326)**
Female sex, n (%)	85 (52.1)	68 (41.7)	153 (46.9)
Age at randomisation, mean (range), years	65.6 (26–90)	67.4 (36–85)	66.5 (26–90)
Age distribution, n (%)			
65 years	64 (39.3)	48 (29.4)	112 (34.4)
< 65 to < 80 years	83 (50.9)	100 (61.3)	183 (56.1)
≥ 80 years	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group, n (%) †			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3)	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.3)
Hispanic or Latino ethnic group, n (%) †			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Time since diagnosis, mean (SD), years	0.54 (1.16)	0.54 (1.31)	0.54 (1.23)
Cause of lung disease, n (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)

Characteristic	Inhaled treprostinil (n=163)	Placebo (n=163)	All Patients (n=326)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory, n (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)
Use of supplemental oxygen, n (%)	119 (73.0)	114 (69.9)	233 (71.5)
Background therapy, n (%)			
None	133 (81.6)	119 (73.0)	252 (77.3)
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)
6MWD, metres			
Mean (range)	254.1 (100-538)	265.1 (30-505)	259.6 (30-538)
Median	256.0	260.0	259.0
PVR, WU			
Mean (range)	6.369 (3.11-18.05)	6.013 (3.06-17.62)	6.191 (3.06-18.05)
Median	5.570	5.060	5.275
NT-proBNP, pg/mL			
Mean (range)	1,857.53 (10.2-21,942.0)	1,808.86 (23.0-16,297.0)	1,832.88 (10.2-21,942.0)
Median	550.50	420.80	503.85
PAP, mmHg			
Mean (range)	37.2 (25-74)	36.0 (25-61)	36.6 (25-74)
Median	35.0	35.0	35.0
PCWP, mmHg			

Characteristic	Inhaled treprostinil (n=163)	Placebo (n=163)	All Patients (n=326)
Mean (range)	10.1 (2-20)	9.6 (0-15)	9.8 (0-20)
Median	10.0	10.0	10.0
Pulmonary function tests			
FEV1 % Predicted			
Mean (range)	63.9 (23, 120)	65.0 (22, 145)	-
Median	63.0	63.0	-
FVC % Predicted			
Mean (range)	62.5 (24, 130)	63.8 (20, 134)	-
Median	60.0	61.0	-
TLC % Predicted			
Mean (range)	62.9 (25, 126)	64.2 (30, 109)	-
Median	62.0	62.5	-
DLCO % Predicted			
Mean (range)	30.0 (5, 86)	28.1 (1, 86)	-
Median	29.0	26.0	-

Key: 6MWD, six-minute walking distance; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SD, standard deviation; TLC, total lung capacity; WU, woods units.

Notes: † Race and ethnic group were reported by the patient.

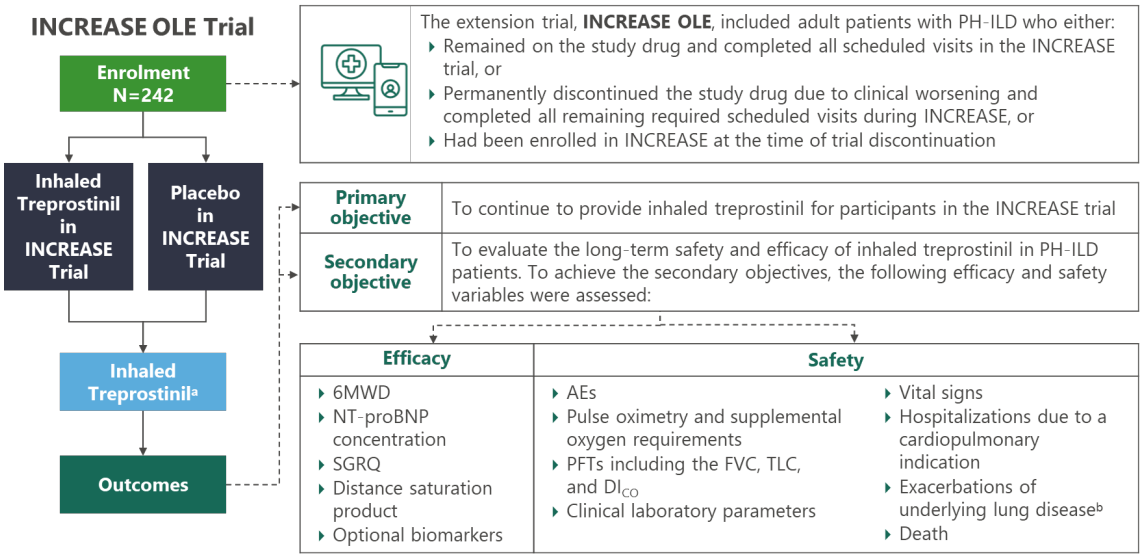
Source: Waxman et al. 2021[58]; INCREASE clinical study report.[59]

2.3.2 INCREASE OLE

2.3.2.1 Study design

INCREASE OLE was a Phase 3, multicentre, OLE study designed to assess the long-term safety and efficacy of inhaled treprostinil in patients with PH-ILD.[60,61] The study was conducted at 119 sites in the US and Puerto Rico and completed on 1 August 2021.[61] The INCREASE OLE study design is presented in Figure 6, and a summary of the trial methodology is presented in Appendix J.

Figure 6. Study design of INCREASE OLE



Key: 6MWD, six-minute walk distance; AE, adverse event; NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, open label extension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; SGRQ, St. George's Respiratory Questionnaire.

Notes: [a]All patients initiated inhaled treprostinil during the OLE study. [b]Defined as an acute, clinically significant, respiratory deterioration characterised by evidence of new widespread alveolar infiltrates on chest imaging.

Source: Waxman et al. 2023[60]; Nathan et al. 2022.[63]

For inclusion in INCREASE OLE, eligible patients must have:

- remained on study drug or placebo and completed all scheduled study visits during 16-week INCREASE RCT, or
- permanently discontinued study drug or placebo during the INCREASE RCT due to CW and completed all remaining scheduled study visits, or
- been enrolled in the INCREASE RCT and their participation was discontinued by the Sponsor[60,61]

Eligible patients discontinued the treatment received during the INCREASE RCT and received inhaled treprostinil (6µg/breath) regardless of their previously assigned treatment arm.[60,61] To preserve prior blinding, all patients initiated inhaled treprostinil at three breaths per session (18µg) four times daily. Recommended dose escalations were an additional one breath per session four times daily every three days, per the investigator's discretion, to a maximum of 15 breaths per session (90µg) four times daily as tolerated.

Initial assessments for INCREASE OLE were collected at the INCREASE RCT study termination visit (Week 16) before inhaled treprostinil was initiated. Patients were assessed at Week 20 (i.e. four weeks into INCREASE OLE), Week 28 and then every 12 weeks up to Week 124.[60,61]

There were no prespecified analyses as the objective of INCREASE OLE was to provide inhaled treprostinil to study patients and capture observational long-term safety and efficacy data in the open-label setting.[60,61] The observational efficacy data captured included 6MWD, NT-proBNP, QoL as measured by the St. George's Respiratory Questionnaire (SGRQ), and change in distance saturation point from baseline to week 64 (or study discontinuation if earlier). Safety data collected included AEs, hospitalisations due to cardiopulmonary indication, exacerbations of underlying lung disease, and death. Details of all endpoints are provided in Appendix J

2.3.2.2 Patient characteristics

The baseline characteristics for patients in INCREASE OLE are presented in Table 5. The median age of patients was 70.0 years, and the majority of patients (57.9%) were aged between 65 and 79 years.[60,61] Overall, 47.9% of patients were female, and the most common ILD diagnosis was idiopathic interstitial pneumonia, occurring in 44.6% of patients. Baseline characteristics of patients at the start of the OLE reflected the differential treatment received during the INCREASE RCT, with a mean 6MWD of 281.8 metres in the inhaled treprostinil arm and 266.3 metres in the placebo arm, and a median NT-proBNP of 1,312.9 pg/mL−1 in the inhaled treprostinil arm and 3,115.2 pg/mL−1 in the placebo arm.

Table 5. Baseline demographics and disease characteristics in INCREASE OLE

Characteristic	Received inhaled treprostinil in INCREASE (n=119)	Received placebo in INCREASE (n=121)	All Patients (n=242)¶
Age, median (range), years	70.0 (27–90)	71.0 (36–86)	70.0 (27–90)
Female, n (%)	63 (52.9)	52 (43.0)	116 (47.9)
Race or ethnicity, n (%)			
White	78 (65.5)	98 (81.0)	178 (73.6)
Black or African American	33 (27.7)	20 (16.5)	53 (21.9)

Characteristic	Received inhaled treprostinil in INCREASE (n=119)	Received placebo in INCREASE (n=121)	All Patients (n=242)¶
American Indian or Alaska Native	2 (1.7)	1 (0.8)	3 (1.2)
Asian	6 (5.0)	2 (1.7)	8 (3.3)
Hispanic or Latino	7 (5.9)	10 (8.3)	17 (7.0)
Time since PH-ILD diagnosis, mean (SD), years	0.9 (1.1)	0.9 (1.5)	0.9 (1.3)
Current ILD diagnosis, n (%)			
Idiopathic interstitial pneumonia	47 (39.5)	61 (50.4)	108 (44.6)
Combined pulmonary fibrosis and emphysema	29 (24.4)	29 (24.0)	59 (24.4)
Connective tissue disease	33 (27.7)	24 (19.8)	57 (23.6)
Chronic hypersensitivity pneumonitis	7 (5.9)	6 (5.0)	13 (5.4)
Occupational lung disease	3 (2.5)	1 (0.8)	5 (2.1)
Idiopathic interstitial pneumonia subcategory, n (%)			
Idiopathic pulmonary fibrosis	25 (21.0)	42 (34.7)	67 (27.7)
Idiopathic nonspecific interstitial pneumonia	16 (13.4)	13 (10.7)	29 (12.0)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.7)	0	2 (0.8)
Desquamative interstitial pneumonia	0	1 (0.8)	1 (0.4)
Acute interstitial pneumonia	0	1 (0.8)	1 (0.4)
Unclassified idiopathic interstitial pneumonia	4 (3.4)	4 (3.3)	8 (3.3)
6MWD, mean (SD), metres	281.8 (99.6)	266.3 (113.2)	274.2 (106.3)
6MWD at start of 16-week RCT, mean (SD), metres	256.2 (101.3)	269.5 (90.1)	262.0 (95.9)
FVC % Predicted, mean (SD)	64.7 (22.3)	63.4 (19.7)	64.3 (21.1)
NT-proBNP, mean (SD), pg/mL	1,312.9 (2,242.8)	3,115.2 (9,461.4)	2,231.9 (6,943.0)
Antifibrotic therapy, n (%)			
None	100 (84.0)	88 (72.7)	190 (78.5)
Pirfenidone only	12 (10.1)	18 (14.9)	30 (12.4)
Nintedanib only	7 (5.9)	15 (12.4)	22 (9.1)

Characteristic	Received inhaled treprostinil in INCREASE (n=119)	Received placebo in INCREASE (n=121)	All Patients (n=242)¶
Key: 6MWD, 6-minute walk distance; FVC, forced vital capacity; ILD, interstitial lung disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, open-label extension; PH, pulmonary hypertension; RCT, randomised controlled trial. **Notes:** #, baseline is defined as the last measurement before the first dose of inhaled treprostinil in the OLE unless otherwise specified; ¶, two patients were not previously enrolled in the INCREASE RCT. **Source:** Waxman et al. 2023[60]; INCREASE OLE clinical study report.[61]			

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 INCREASE

2.4.1.1 Trial populations

The following predefined analysis populations were included in INCREASE[59]:

- **Modified Intent-to-Treat (ITT) Population:** consisted of all patients who were randomised into the study and received at least one dose of study drug. All modified ITT patients were counted in the arm to which they were randomised, regardless of the study drug they were given. Unless otherwise specified, all efficacy analyses were performed on the modified ITT Population
- **Safety Population:** consisted of all patients enrolled into the study who received at least one dose of study drug. All Safety Population patients were counted in the arm corresponding to the study drug received, regardless of randomised assignment. Unless otherwise specified, all safety analyses were performed on the Safety Population
- **Per-protocol (PP) Population:** consisted of all patients in the ITT Population, excluding patients with major protocol deviations that could have impacted the primary efficacy analyses

2.4.1.2 Statistical analysis

No interim efficacy analyses were conducted for this study.[59] Interim safety analyses were performed according to the Data Monitoring Committee (DMC) Charter. Interim safety analyses occurred following the enrolment of approximately 25%, 50%, and 75%

of patients in the study. All analyses were prepared by an independent external consultant and reviewed only by the independent DMC as defined in the DMC Charter. The Sponsor only had access to the blinded study data during this process.

2.4.1.3 Patient disposition

Between 3 February 2017 and 30 August 2019, 326 patients were randomised and treated in INCREASE, including 163 patients in the inhaled treprostinil arm and 163 patients in the placebo arm.[58,59] At the time of the final database lock (18 February 2020), 130 (79.8%) patients in the inhaled treprostinil arm and 128 (78.5%) patients in the placebo arm completed the study through 16 weeks. Overall, 40 (24.5%) patients in the inhaled treprostinil arm and 38 (23.3%) patients in the placebo arm discontinued study treatment; the most frequent reason for discontinuation was due to an AE (9.8% in the inhaled treprostinil arm and 8.0% in the placebo arm). Of the 258 patients who completed INCREASE through 16 weeks, 240 (73.6%) entered the extension trial, INCREASE OLE, including 119 (73.0%) in the inhaled treprostinil arm and 121 (74.2%) in the placebo arm.[60]

Further information on patient disposition is presented in Appendix B.

2.4.2 INCREASE OLE

2.4.2.1 Trial populations

The Safety Population included any patient who received inhaled treprostinil at any time during the course of the INCREASE OLE.[60,61] All analyses were based on the Safety Population.

2.4.2.2 Statistical analysis

No interim efficacy analyses were conducted for this study.[61] Interim safety analyses were performed according to the DMC Charter. The DMC met for formal data reviews following the enrolment of approximately 25%, 50%, and 75% of patients in INCREASE. At the scheduled meetings for INCREASE, data from INCREASE OLE were also reviewed. All analyses were prepared by an independent external consultant and reviewed only by the DMC as defined in the DMC Charter. Following each review by the DMC (19 July 2017, 30 November 2017, 04 June 2018, and 07 January 2019), the DMC recommended continuation of both studies without modification.

2.4.2.3 Patient disposition

A total of 243 patients were enrolled in the INCREASE OLE; 241 were previously enrolled and analysed in the INCREASE RCT, and two were excluded from the INCREASE RCT analysis due to a study drug labelling issue and enrolled directly into the INCREASE OLE.[60,61] A total of 242 patients received at least one dose of study drug and were included in the Safety Population.

Of the 242 patients included in the Safety Population, 70 (28.8%) completed INCREASE OLE.[60,61] A total of 173 patients (71.2%) discontinued the study early. The primary reasons for discontinuing the study were death (56 [23.0%] patients), withdrawal by the patient (41 [16.9%] patients), AEs (29 [11.9%] patients), and progressive disease (12 [4.9%] patients). There were 24 (9.9%) patients who discontinued when the study was terminated by the Sponsor.

Further information on patient disposition is presented in Appendix B.

2.5 Critical appraisal of the relevant clinical effectiveness evidence

INCREASE was conducted in accordance with the ethical principles of Good Clinical Practice (GCP) and is considered to be a good-quality study. The quality assessment of the INCREASE study is presented in Appendix B.3 and was conducted using the JBI critical appraisal checklist for RCTs, and it was carried out using the primary publication only. The overall risk of bias was considered to be low.

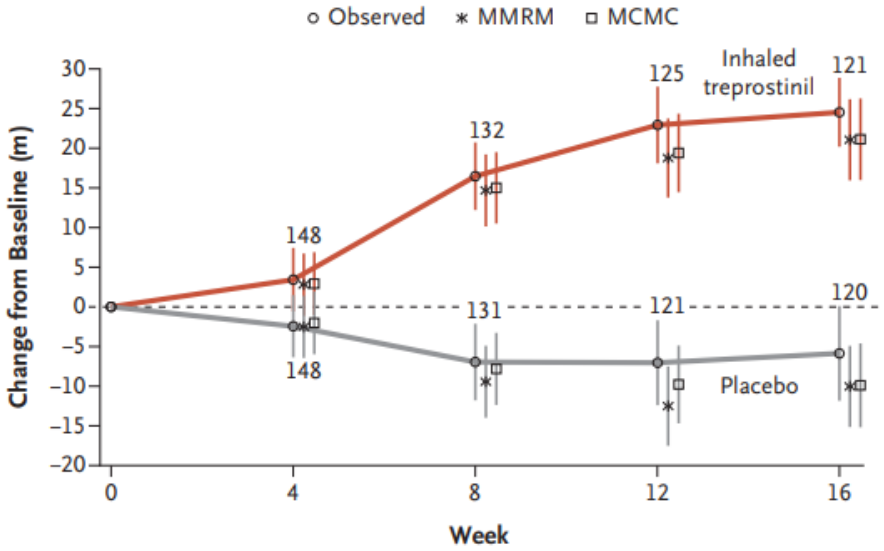
2.6 Clinical effectiveness results of the relevant studies

2.6.1 INCREASE

2.6.1.1 Primary efficacy endpoint

Treatment with inhaled treprostinil produced statistically significant improvements in exercise capacity (measured by 6MWD) from baseline to Week 16 versus placebo (Figure 7).[58,59] At Week 16, the least-squares (LS) mean difference in peak 6MWD between the inhaled treprostinil arm and the placebo arm was 31.12 metres (95% CI: 16.85, 45.39; $p < 0.001$). This is above the estimated minimal important difference (MID) threshold for the 6MWD in patients with PH-ILD of 18.7 metres to 24.7 metres.[64]

Figure 7. Mean change from baseline in peak 6MWD through Week 16 in INCREASE – ITT Population (n=326)



Key: 6MWD, 6-Minute Walk Distance; CI, confidence Interval; ITT, intent-to-treat population; MCMC, Markov chain Monte Carlo; MMRM, mixed-model repeat-measurement; SE, standard error.

Notes: Shown are mean (±SE) changes from baseline (dashed line) in peak 6MWD over the 16-week trial period. The data shown are for patients with available data (observed) as well as for the results of two analysis methods used to account for missing data. The values shown at each data point indicate the number of patients assessed at that time point. The primary analysis used MMRM methods, with the assumption that missing data were missing at random. The model included the change from baseline to peak 6MWD as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects and the baseline 6MWD as a covariate. A sensitivity analysis for the primary endpoint was performed with the use of a multiple imputation approach with a multivariate normal imputation model using the MCMC method. The imputation model included treatment arm, all scheduled visits, patient's sex, and patient's age at randomisation. The CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

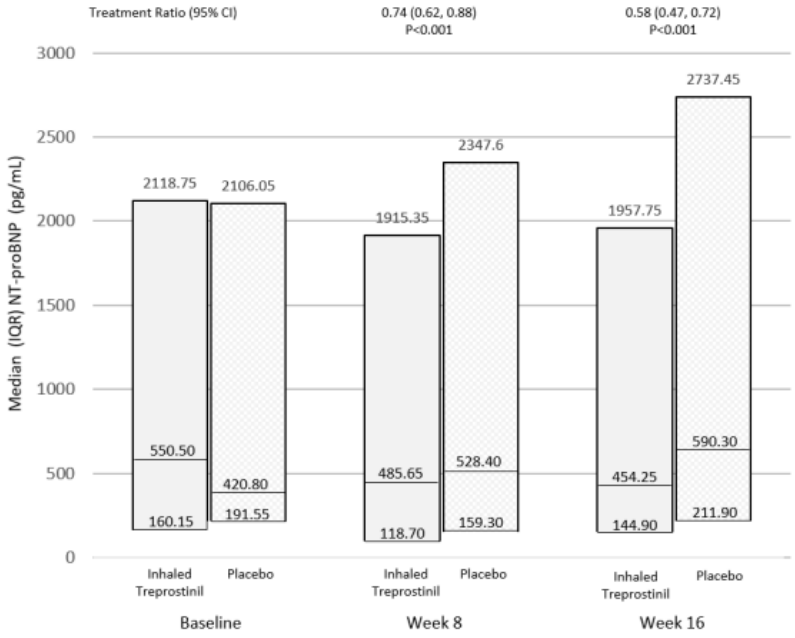
Source: Waxman et al. 2021.[58]

2.6.1.2 Secondary efficacy endpoints

Change in Plasma Concentration of NT-proBNP from baseline to Week 16

At Week 16, inhaled treprostinil statistically significantly decreased NT-proBNP, a biomarker associated with cardiac damage and heart failure, by 42% versus placebo (treatment ratio: 0.58 [95% CI: 0.47, 0.72]; p<0.001).[58,59] NT-proBNP decreased by 15% from baseline to Week 16 in the inhaled treprostinil arm and increased by 46% from baseline to Week 16 in the placebo arm (Figure 8).

Figure 8. NT-proBNP results by study visit (pg/mL) in INCREASE – ITT Population (n=326)



Key: CI, confidence interval; IQR, interquartile range; ITT, intent-to-treat population; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Notes: Only patients with a baseline NT-proBNP measurement are included in this analysis. P-values, estimated treatment ratio, and associated 95% CIs (LS Mean difference expressed as ratio) are obtained from the analysis of covariance with change from baseline in log-transformed data in NT-proBNP as the dependent variable, treatment as the fixed effect, and log-transformed baseline NT-proBNP as a covariate. The CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Source: Waxman et al. 2021.[58]

Number and time to CW events

The INCREASE trial defined CW as any of the following events:

- Hospitalisation due to a cardiopulmonary indication
- Decrease in peak 6MWD >15% from baseline (directly related to the disease at two consecutive visits occurring ≥24 hours apart)
- Lung transplantation
- Death

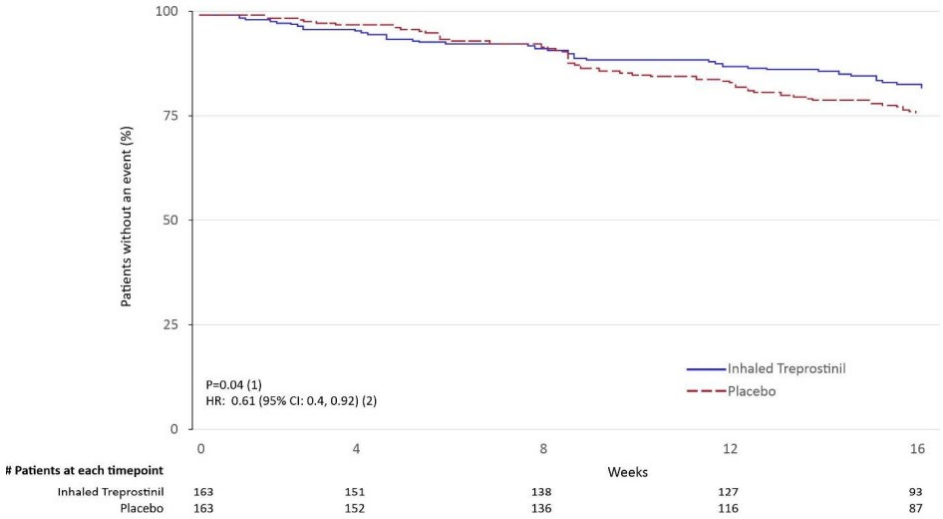
Patients treated with inhaled treprostinil experienced fewer CW events throughout the 16-week treatment period versus placebo.[58,59] CW was reported in 22.7% of patients in the inhaled treprostinil arm compared to 33.1% of patients in the placebo arm (Table 6).

The time to first CW event was significantly different between patients in the inhaled treprostinil arm versus placebo (Figure 9). Overall, inhaled treprostinil significantly decreased the risk of CW by 39% versus placebo over the 16-week trial (HR: 0.61 [95% CI: 0.4, 0.92]; p=0.041).

Table 6. Summary and analysis of number of clinical worsening events in INCREASE – ITT Population (n=326)

Occurrence of clinical worsening, n (%)	Inhaled treprostinil (n=163)	Placebo (n=163)
Any event	37 (22.7)	54 (33.1)
Hospitalisation for cardiopulmonary indication	18 (11.0)	24 (14.7)
Decrease in 6MWD of >15% from baseline	13 (8.0)	26 (16.0)
Death from any cause	4 (2.5)	4 (2.5)
Lung transplantation	2 (1.2)	0
Treatment effect (95% CI) p-value	0.61 (0.4, 0.92)* 0.04	
Key: 6MWD, 6-minute walk distance; CI, confidence interval; ITT, intent-to-treat population. **Notes:** *, this is a hazard ratio, calculated from a Cox proportional-hazards model. The p-value was calculated with the use of a log-rank test stratified by the baseline 6MWD category. **Source:** Waxman et al. 2021.[58]		

Figure 9. Kaplan-Meier plot of time to first clinical worsening event in INCREASE – ITT Population (n=326)



Key: CI, Confidence interval; HR, Hazard ratio; ITT, Intent-to-treat.

Notes: Subjects who discontinued from the study early had their time to first clinical worsening event censored at their last visit. Subjects who did not experience a clinical worsening event had their time to clinical worsening censored at the study termination date.

Source: Waxman et al. 2021.[58]

The CW events outlined above constitute some of the components that comprise the definition of CW used in the economic model, which is described in Section 3.2.3.7. In addition, the definition of a CW event for the cost-effectiveness model includes a decrease in FVC% of ≥10% from baseline, and acute lung-disease exacerbation events. These endpoints were captured in the post hoc analyses of disease progression events described in Section 2.6.1.4.

Change in 6MWD at peak plasma treprostinil level at Week 12

At Week 12, the LS mean difference in peak 6MWD between the inhaled treprostinil arm and the placebo arm was 31.29 metres (95% CI: 17.37, 45.21; $p < 0.001$).[58,59] The observed improvement was statistically significant and clinically meaningful based on an MID of 18.7 to 24.7 metres.[64]

Change in 6MWD at trough treprostinil level at Week 15

At Week 15, the LS mean difference in trough 6MWD between the inhaled treprostinil arm and the placebo arm was 21.99 metres (95% CI: 6.85, 37.14; $p=0.005$).[58,59] The observed improvement was statistically significant and clinically meaningful based on an MID of 18.7 to 24.7 metres.[64]

2.6.1.3 Exploratory efficacy endpoints

Change in distance-saturation product

Exploratory analysis of change from baseline in distance-saturation product showed improvement in the inhaled treprostinil arm beginning at Week 8 and continuing to Week 16.[58,59]

The distance-saturation product is calculated by multiplying the total distance walked by the lowest oxygen saturation measurement during the 6MWT. This measure is clinically relevant because it indicates how long patients can maintain adequate oxygen levels during exertion. An improvement in distance saturation point suggests enhanced exercise capacity, potentially translating into better daily functioning and quality of life.

The median changes from baseline in the inhaled treprostinil arm was 8.385 m% at Week 16 compared to -1.950 m% in the placebo arm, but these differences were not statistically significant (LS mean difference: 11.51 [95% CI: -1.33, 24.35]).[58,59]

2.6.1.4 Post hoc efficacy analyses

Disease progression events

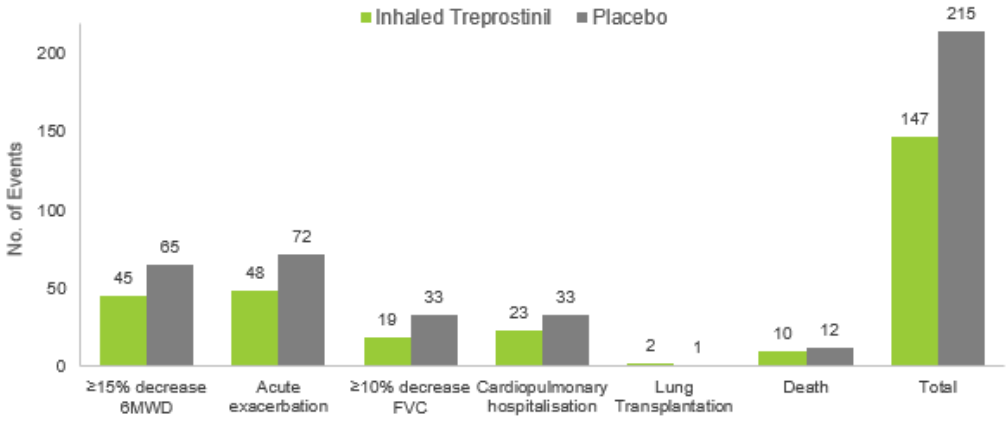
In the INCREASE trial, a disease progression event was defined as any of the following[65]:

- ≥15% or more decline in 6MWD from baseline
- ≥10% or more decline in FVC from baseline
- Acute lung-disease exacerbation
- Cardiopulmonary hospitalisation
- Lung transplantation
- Death

The disease progression events outlined above align with the definition of clinical worsening used to inform the economic model (Section 3.2.3.7).

Patients treated with inhaled treprostinil experienced fewer disease progression events throughout the 16-week treatment period versus placebo.[65] In a post hoc analysis, patients in the inhaled treprostinil arm experienced significantly fewer disease progression events throughout the 16-week treatment period versus patients in the placebo arm (rate ratio 0.69 [95% CI: 0.51, 0.94]; p=0.018) (Figure 10).[65]

Figure 10. Number of disease progression events by treatment arm in INCREASE – ITT Population (n=326)

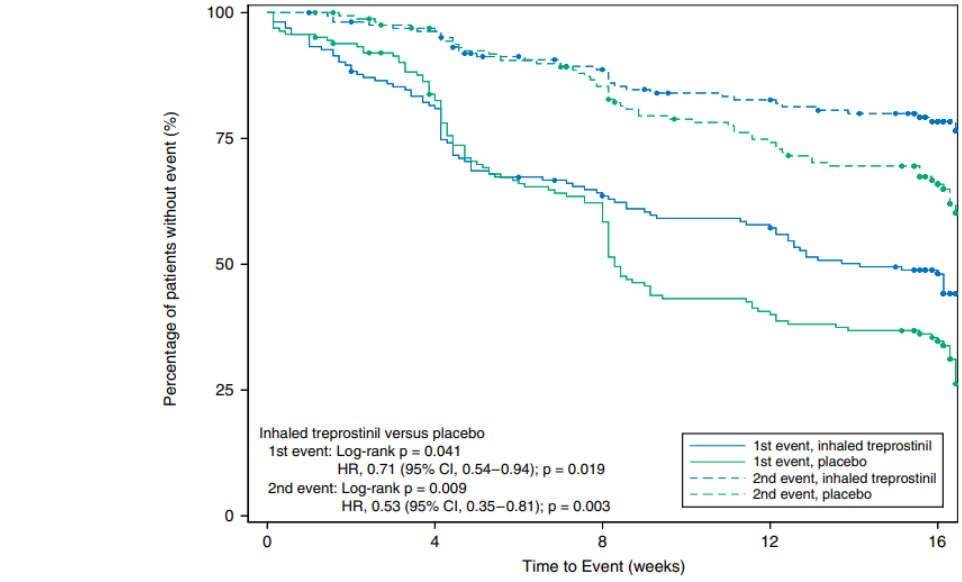


Key: 6MWD, 6-minute-walk distance; FVC, forced vital capacity; ITT, intent-to-treat population.

Source: Nathan et al. 2022.[65]

Inhaled treprostinil significantly decreased the risk of single disease progression events by 29% versus placebo over the 16-week trial period (HR 0.71 [95% CI: 0.54, 0.94]; p=0.019) (Figure 11).[65] Additionally, inhaled treprostinil significantly decreased the risk of multiple disease progression events by 47% versus placebo (HR 0.53 [95% CI, 0.35, 0.81]; p=0.003) (Figure 11).[65] Kaplan-Meier curves for inhaled treprostinil and placebo arms separated between 6 to 8 weeks for the time to first and second event, respectively, and this was maintained up to 16 weeks.

Figure 11. Kaplan-Meier estimates of time to first and time to second disease progression events up to 16 weeks in INCREASE – ITT Population



No. at Risk:

1st event, inhaled treprostinil	163	132	102	91	61
1st event, placebo	163	132	98	64	49
2nd event, inhaled treprostinil	163	155	135	122	92
2nd event, placebo	163	152	132	113	84

Key: CI, confidence interval; HR, hazard ratio.

Source: Nathan et al. 2022.[65]

2.6.1.5 Health-related quality of life

St. George's Respiratory Questionnaire

Exploratory analyses using the SGRQ were conducted to assess the effects of inhaled treprostinil on health-related quality of life (HRQoL) versus placebo.[58,59] The SGRQ is a patient-reported outcome measure used to assess HRQoL in patients with obstructive airway diseases and was developed and validated for use in patients with asthma and chronic obstructive pulmonary disease (COPD).[66] The SGRQ is also validated in ILD,

however the SGRQ may not fully capture disease-specific aspects of PH-ILD.[67] At the time of study design and initiation of INCREASE, there were no validated measures for assessing HRQoL in patients with PH-ILD. Therefore, the SGRQ was deemed the most appropriate measure to capture the impacts of PH-ILD on HRQoL, over generic measures such as the EQ-5D. The SGRQ has a range of results from 0 to 100, with where 0 indicates best health and 100 indicates worst health, and with an MID of four points.[68] In COPD, a score of 50 or more indicates moderate to severe impairment of quality of life; this suggests that the patients recruited into INCREASE (with a mean score of 55 to 57) were severely impacted by their PH-ILD.

At Week 16, exploratory analysis of the patient-reported SGRQ revealed a trend of improved HRQoL for patients with PH-ILD receiving inhaled treprostinil versus placebo (Table 7).[58,59] A slightly higher number of patients in the inhaled treprostinil arm (52 patients) reported a ≥ 4-unit improvement in SGRQ total score at Week 16 compared with placebo (47 patients).[59] All SGRQ domain scores (symptoms, activity, and impacts) were lower for patients in the inhaled treprostinil arm versus patients in the placebo arm, but these differences were not significant.

Table 7. St. George's Respiratory Questionnaire in INCREASE – ITT population (n=326)

	Inhaled treprostinil (n=163)		**Placebo (n=163)**	
	Value	**Change from baseline**	**Value**	**Change from baseline**
Baseline				
N	143	-	134	-
Mean (SD)	57.17 (15.77)	-	57.67 (15.78)	-
Median	59.80	-	56.30	-
IQR	45.60, 67.90	-	46.50, 70.70	-
Min, max	14.7, 94.9	-	18.4, 88.6	-
Week 16				
N	143	143	134	134
Mean (SD)	55.91 (17.07)	-1.25 (10.99)	57.49 (15.33)	-0.18 (10.72)
Median	56.30	-0.70	55.50	0.10
IQR	40.50, 67.00	-7.10, 5.20	46.80, 69.70	-6.50, 6.10
Min, max	3.5, 92.0	-40.4, 29.0	16.9, 96.5	-31.9, 33.3

	Inhaled treprostinil (n=163)	Placebo (n=163)
LS mean (SE)	-1.30 (0.87)	-0.13 (0.90)
LS Mean Difference (SE) (95% CI)	-1.18 (1.25) (-3.63, 1.28)	

Key: ANCOVA, analysis of covariance; CI, confidence interval; LS Mean, least squares mean; SD, standard deviation; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

Notes: The SGRQ has a range of results from 0 to 100, with higher scores indicating greater impairment and with a minimum clinically important difference of 4 points. The changes from baseline in Total Score and each of the 3 domain scores were analysed by parametric ANCOVA with no imputation for missing data. The CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

Source: Waxman et al. 2021.[58]

2.6.2 INCREASE OLE

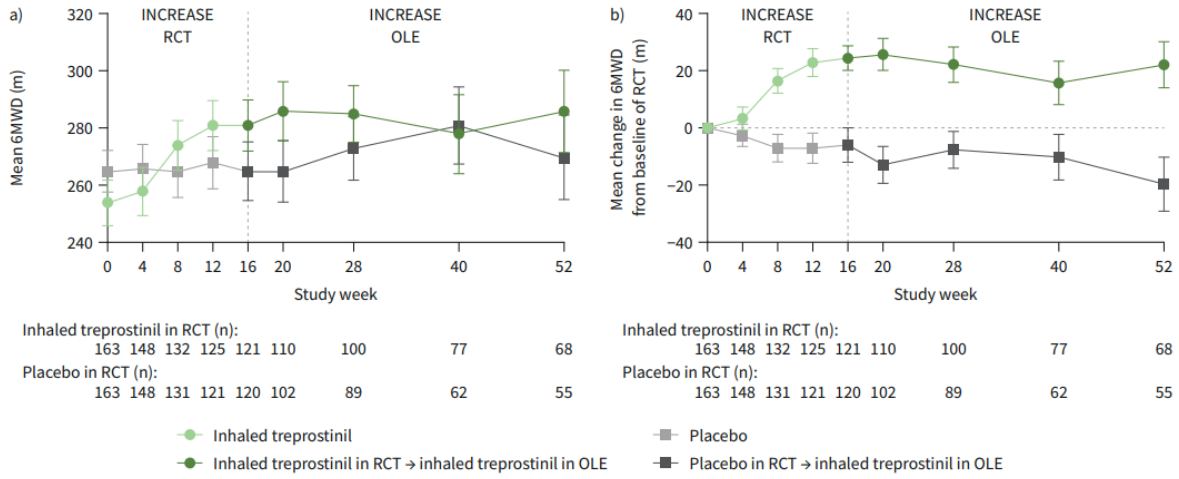
2.6.2.1 Efficacy endpoints

Changes in 6MWD

The mean (SD) change from baseline of the INCREASE RCT to week 52 in INCREASE OLE for 6MWD was 3.5 (70.7) metres for the overall population, 22.1 (66.3) metres in the former inhaled treprostinil arm and −19.5 (69.8) metres in the former placebo arm.[60,61]

Patients treated with inhaled treprostinil in the INCREASE RCT experienced sustained improvements in 6MWD in INCREASE OLE, indicating that inhaled treprostinil has a durable, long-lasting response (Figure 12).[60,61] There was minimal further deterioration of 6MWD for those patients initially treated with placebo who transitioned to inhaled treprostinil in the INCREASE OLE (Figure 12).

Figure 12. Summary of 6MWD in INCREASE OLE by prior treatment arm – Safety Population



Key: 6MWD, 6-minute walk distance; OLE, open-label extension; RCT, randomised controlled trial; SEM, standard error of mean.

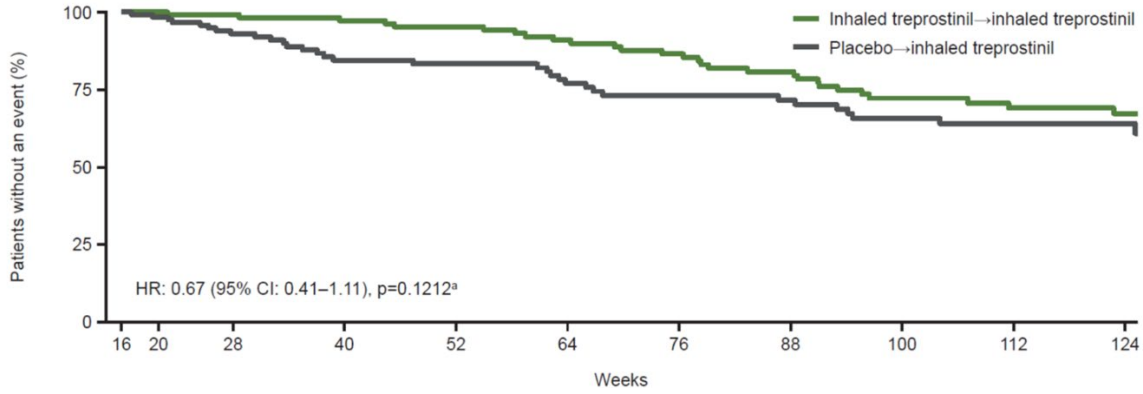
Notes: a) Mean 6MWD by study visit starting from baseline of the 16-week INCREASE RCT. Data are mean observed values. b) Mean change from baseline in 6MWD by study visit starting at baseline of the 16-week RCT. Time 0 for the OLE is also week 16 for the RCT; all available data at each time point are included in the figure. Errors bars indicate the SEM.

Source: Waxman et al. 2023.[60]

Overall survival (unadjusted for crossover)

Patients previously treated with inhaled treprostinil had a numerically reduced risk of death vs. patients who previously received placebo (Safety Population HR: 0.67; 95% CI: 0.41, 1.11; p=0.12).[60] Among the patients who died, the median time to death was 62 weeks for the 29 patients (24.4%) who had previously received inhaled treprostinil vs. 31 weeks for the 33 patients (27.3%) who had previously received placebo.[60] As the overall survival outcomes were confounded by patients switching from placebo to inhaled treprostinil, crossover adjustment was explored and is described in Section 2.6.2.2.

Figure 13: Time to death in INCREASE-OLE in patients previously treated with inhaled treprostinil or placebo – Safety Population



Key: CI, confidence interval; HR, hazard ratio; OLE, open-label extension.

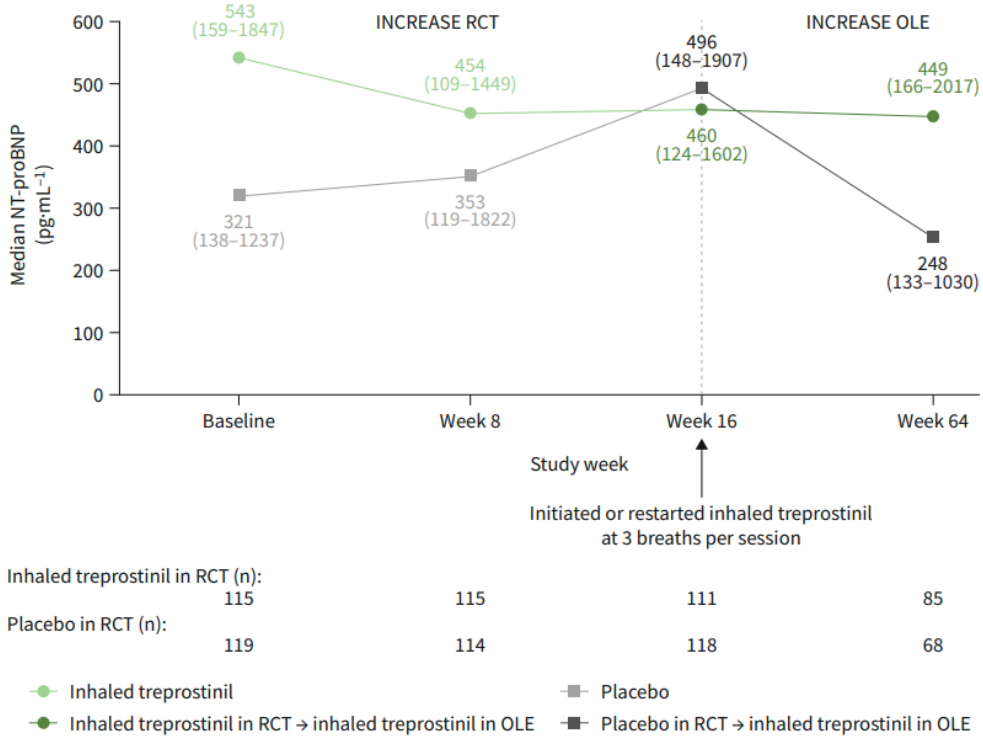
Source: Waxman et al. 2023.[60]

Changes in NT-proBNP

The median (interquartile range [IQR]) change from baseline of the INCREASE RCT to week 64 in INCREASE OLE for NT-proBNP was 10.2 (-148.20–284.80) for the overall population. In the former inhaled treprostinil and placebo arms, the median change was 21.85 (-194.90–269.50) pg/mL−1 and 6.85 (-100.40–300.60) pg/mL−1, respectively.[60,61]

INCREASE OLE demonstrated sustained benefit in NT-proBNP changes for patients treated with inhaled treprostinil in the INCREASE RCT, with a 17% decrease in NT-proBNP by week 64. Meanwhile, patients who transitioned from placebo to inhaled treprostinil in INCREASE OLE had a 50% decrease in NT-proBNP by week 64 (Figure 14).[60,61]

Figure 14. Median serum NT-proBNP levels in INCREASE OLE by prior treatment arm – safety population



Key: NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, open-label extension; RCT, randomised controlled trial.

Notes: The interquartile range is given in parentheses.

Source: Waxman et al. 2023.[60]

Change in distance saturation point

No deterioration in the distance saturation point was observed during INCREASE OLE (Table 8).[60,61]

Table 8. Distance saturation point in INCREASE OLE by prior treatment arm – safety population

	Received inhaled treprostinil in INCREASE RCT (n=119)		Received placebo in INCREASE RCT (n=121)	
	Median Score (IQR)	**Mean Change from Week 16 (SD)**	**Median Score (IQR)**	**Mean Change from Week 16 (SD)**
Week 16[a]	N=109 202.5 (153.9–275.4)	-	N=105 210.6 (153.9–275.4)	-
Week 64	N=63	N=58	N=40	N=37

	218.7 (137.7–283.5)	-16.2 (54.0)	226.8 (170.1–267.3)	-15.3 (52.8)
Week 124	N=28 202.5 (153.9–287.6)	N=27 -35.4 (64.6)	N=26 210.6 (145.8–251.1)	N=23 -19.7 (71.9)

Key: 6MWD, 6- minute walk distance; 6MWT, 6-minute walk test; RCT, randomised controlled trial; IQR, interquartile range; SD, standard deviation.

Notes: Distance saturation point is the product of the 6MWD and the lowest room air oxygen saturation during the 6MWT. Lower values indicate worse prognosis. [a] Week 16 reflects the baseline of INCREASE OLE.

Source: Waxman et al. 2023.[60]

2.6.2.2 Post hoc efficacy analyses

Event-free survival

In a post hoc analysis, event-free survival was improved in patients who were previously treated with inhaled treprostinil in the INCREASE RCT compared to those who received placebo.[63] Patients in the inhaled treprostinil arm had a 27% reduction in the risk of hospitalisation, exacerbation, or death compared to the former placebo arm (HR 0.73 [95% CI: 0.54, 0.99]; p=0.0454). Median time to first event was 37.1 and 21.3 weeks (p=0.0443) in the placebo and inhaled treprostinil arms, respectively.

Overall survival

A post-hoc analysis of the INCREASE RCT and INCREASE OLE was performed to evaluate whether inhaled treprostinil has a long-term survival benefit in patients with PH-ILD.[69] To adjust for the treatment crossover between the INCREASE RCT and INCREASE OLE, two adjustment methods (the observational-based inverse probability of censoring weighting [IPCW] and randomised-based rank-preserving structural failure time [RPSFT]) were explored to demonstrate the impact of inhaled treprostinil on the risk of death in patients with PH-ILD.

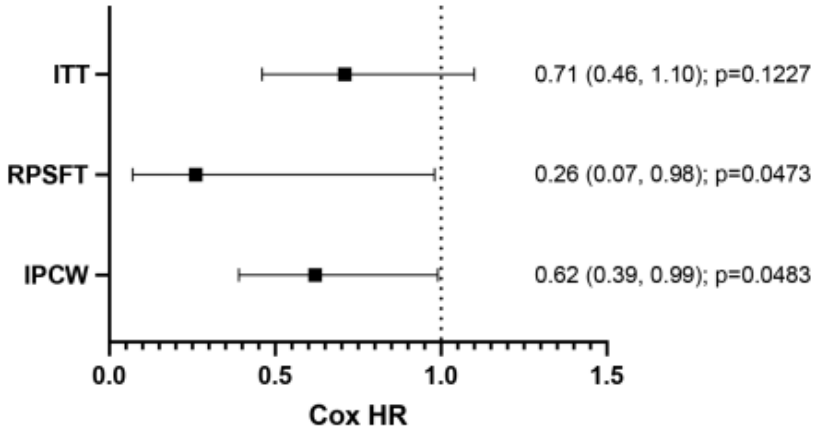
Given all control patients switched to inhaled treprostinil, the RPSFT approach is the most appropriate crossover adjustment methodology, in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 16 and 24 recommendations.[70,71] In such scenarios, inverse probability of censoring weighting (IPCW) can be prone to heightened bias due to the large number of crossovers,

whereas RPSFT provides a more robust, randomisation-based method for adjusting survival estimates when treatment switching is extensive. The RPSFT method is used in the base case for the cost-effectiveness model, as described in Section 3.

The RPSFT method assumes each patient follows their own trajectory of disease progression, and that the experimental treatment slows progression by a single factor ('common treatment effect'), regardless of whether treatment starts at randomisation or crossover. This factor is estimated and then applied to placebo crossover subjects to model what their survival might have been without switching treatments. A Cox proportional hazards model then uses these adjusted times, plus the original survival times for non-crossover placebo and inhaled treprostinil patients, to estimate an adjusted hazard ratio. As a sensitivity check, the analysis was repeated using week 4 as time zero, excluding early deaths during dose uptitration.[69]

The HRs from the analyses adjusted for treatment crossover are provided in Figure 15.[69] With a conventional ITT analysis, the HR for death was 0.71. When using the RPSFT method to calculate overall survival, there was a significant overall survival benefit associated with inhaled treprostinil treatment, with a HR of 0.26 (p=0.047).

Figure 15. Estimates of overall survival HR in a post-hoc analysis of the INCREASE and INCREASE-OLE: ITT population vs crossover adjusted



Key: IPCW, the observational-based inverse probability of censoring weighting; ITT, intention to treat; RPSFT, randomised-based rank-preserving structural failure time.

Source: Nathan et al. 2024.[69]

2.6.2.3 Health-related quality of life

St. George's Respiratory Questionnaire

No deterioration in HRQoL, as measured by the SGRQ was observed during INCREASE OLE (Table 9).[60,61]

Table 9. St. George's Respiratory Questionnaire in INCREASE OLE by prior treatment arm – safety population

	Received inhaled treprostinil in INCREASE RCT (n=119)		Received placebo in INCREASE RCT (n=121)	
	Median Score (IQR)	**Mean Change from Week 16 (SD)**	**Median Score (IQR)**	**Mean Change from Week 16 (SD)**
Week 16[a]	n=116 55.3 (40.2–66.8)	-	n=118 54.8 (46.3–69.4)	-
Week 64	n=84 54.2 (39.8–69.3)	n=82 0.8 (11.3)	n=71 56.1 (44.7–70.2)	n=71 1.3 (12.5)
Week 124	n=47 46.0 (34.6–64.1)	n=45 1.7 (13.0)	n=38 56.0 (38.6–66.4)	n=38 -3.2 (12.0)

Key: RCT, randomised controlled trial; IQR, interquartile range; MID, minimal important difference; SD, standard deviation.

Notes: [a] Week 16 reflects the baseline of INCREASE OLE. The St. George's Respiratory Questionnaire has a range of results from 0 to 100, with higher scores indicating greater impairment and with a MID of 4 points.

Source: Waxman et al. 2023.[60]

2.7 Subsequent treatments used in the relevant studies

No subsequent treatments were given following inhaled treprostinil in the trial. As there are currently no approved therapies for PH-ILD, this section is not applicable.

2.8 Subgroup analysis

2.8.1 INCREASE

Pre-specified subgroup analyses were conducted for the primary efficacy endpoint in INCREASE based on the following factors:[58,59]

- Age group (< 65 years of age, 65 to < 80 years of age, and ≥ 80 years of age)
- Sex (male versus female)

- Baseline 6MWD categories (≤ 350 metres versus > 350 metres)
- Aetiology of ILD (IIP, CHP, Occupational, CPFE, CTD, and Other)
- ILD disease severity as measured by baseline diffusing capacity of the lungs for carbon monoxide (DLCO) (< 40% predicted versus ≥ 40% predicted)
- PVR (< 4 WU versus ≥ 4 WU)
- Study drug dose at Week 16 (0 to 3 breaths, 4 to 6 breaths, 7 to 9 breaths, and 10 to 12 breaths)

A consistent benefit was observed for inhaled treprostinil versus placebo for improvements in 6MWD across all prespecified subgroups.[58,59] Further details on the pre-specified subgroup analyses are presented in Appendix C.

Post-hoc subgroup analyses

A post hoc subgroup analysis was conducted to investigate the clinical outcomes within patient subgroups in INCREASE.[72] These subgroups were delineated by baseline characteristics:

- PVR (< 5 WU, ≥ 5WU)
- PCWP (< 10 mmHg, ≥ 10 mmHg)
- mPAP (< 35 mmHg, ≥ 35 mmHg)
- DLCO (< 27% predicted, ≥ 27% predicted)
- FVC (< 60% predicted, ≥ 60% predicted)
- NT-proBNP (< 504 pg/mL, ≥ 504 pg/mL)

Of note, the PVR threshold for this post-hoc subgroup analysis was increased from 4 WU to 5 WU to align with European treatment guidelines in PH-ILD that defined patients with severe PH-ILD as those with a PVR score above 5.[1]

The post hoc analysis demonstrated 6MWD improvements across all subgroups.[72] Statistically significant improvements occurred in patients with above median PVR (i.e., PVR of 5 or more), PCWP, mPAP; lower than median DLCO; and in both above median and below median FVC and NT-proBNP cohorts (p≤0.013 for all).

Statistically significant reductions in NT-proBNP were demonstrated in all subgroups (p≤0.028 for all). In addition, a statistically significant benefit in time to CW following treatment with inhaled treprostinil was observed in above median PVR, mPAP, and NT-proBNP; and lower PCWP (p ≤ 0.0493 for all).

Overall, these analyses demonstrated improvements with inhaled treprostinil across patient subgroups. Further details on this post hoc subgroup analysis are presented in Appendix C.

Post hoc analysis in patients with less severe haemodynamics

Another post hoc analysis was conducted to evaluate change from baseline in NT-proBNP, exacerbation of underlying lung disease, CW events and disease progression in patients with less severe haemodynamics in INCREASE.[73] Patients were stratified by baseline PVR of < 4 WU versus ≥ 4 WU and ≤ 5 WU versus > 5 WU. Inhaled treprostinil treatment was associated with consistent benefits in clinical outcomes in patients with PH-ILD and less severe haemodynamics in INCREASE. Further details on this post hoc subgroup analysis are presented in Appendix C.

Post hoc analysis of the effects on FVC

In a separate post hoc analysis, the effects of inhaled treprostinil on FVC were assessed in the overall population and in subgroups of interest, defined by cause of ILD or baseline characteristics.[74] Improvements in lung function were demonstrated with inhaled treprostinil in the ITT population, with placebo-corrected mean improvements of 28.5mL (p=0.35) at week 8 and 44.4mL (p=0.21) at week 16, although these changes were not statistically significant.

Greater improvements in FVC were reported in patients with idiopathic interstitial pneumonia (46.5mL [p=0.25] at week 8 and 108.2mL [p=0.023] at week 16), although the improvement at week 8 was not statistically significant. The most evident improvement in lung function was observed in patients with idiopathic pulmonary fibrosis, showing an increase in FVC of 84.5mL [p=0.11] at week 8 (not statistically significant) and 168.5mL [p=0.011] at week 16), where the difference became statistically significant. Further details on this post hoc subgroup analysis are presented in Appendix C.

2.8.2 INCREASE OLE

A post hoc analysis was conducted to evaluate 6MWD and clinical events in patients with less severe haemodynamics in INCREASE OLE.[73] Patients were stratified by baseline PVR of < 4 WU versus ≥ 4 WU and ≤ 5 WU versus > 5 WU. Patients previously assigned to the placebo group in the INCREASE RCT were considered to have a 16-week treatment delay to elucidate the impact of delayed treatment on 6MWD after 1 year. Results from this post hoc analysis suggest 6MWD remained stable over 1 year with little evidence of deterioration. Of note, these analyses were underpowered and were not statistically significant. Further details on this post hoc subgroup analysis are presented in Appendix C.

2.9 Meta-analysis

INCREASE and INCREASE OLE were the only trials identified that evaluated inhaled treprostinil in this setting and provided data versus the relevant comparator (BSC). As such, a meta-analysis was not appropriate. A matching-adjusted indirect comparison (MAIC) was conducted and is detailed in Section 2.10.

2.10 Indirect and mixed treatment comparisons

To provide additional supportive evidence for the effectiveness of inhaled treprostinil versus BSC in PH-ILD, a MAIC was conducted using real-world evidence for patients with PH-ILD in the UK.[75] The MAIC provides a comparison of outcomes in patients receiving inhaled treprostinil in INCREASE and INCREASE OLE to those receiving BSC in a retrospective study in the UK (N=78). By matching the INCREASE population to a UK cohort, the analysis supports the generalisability of the trial findings to NHS practice and offers longer-term survival data for BSC to supplement the RCT evidence.

A feasibility assessment for a population-adjusted MAIC was conducted based on assumptions outlined by the NICE DSU TSD18.[76] Three relevant clinical studies were identified and assessed for inclusion (INCREASE, INCREASE OLE, and Dawes *et al.* (2022)).[75] Additional studies identified in the clinical SLR reporting on the efficacy of BSC (see Appendix B) included only sub-populations of patients with PH-ILD. Therefore, these studies do not reflect the full patient population specified in the

decision problem (Section 1.1) and were not appropriate for an indirect comparison of inhaled treprostinil versus BSC.

The level of heterogeneity across INCREASE, INCREASE OLE, and Dawes *et al.* (2022) was assessed by comparing study designs, population characteristics, treatment arms, and outcomes to determine the feasibility of an ITC. The feasibility assessment highlighted minor heterogeneity between the studies and therefore no studies were excluded. Overall, an unanchored MAIC using the three studies was deemed feasible, with sufficient data reported in each study to evaluate OS following treatment. Further details on the feasibility assessment are provided in Appendix B.

2.10.1 Matching-adjusted indirect comparison versus BSC

An unanchored MAIC was conducted against BSC to assess the comparative effectiveness of inhaled treprostinil in PH-ILD. The outcome considered was OS and the analysis was conducted on:

- Patients treated with inhaled treprostinil in the INCREASE and INCREASE OLE studies
- Untreated patients in the Dawes *et al.* (2022) study

Data were available for patients treated with PDE5is in the Dawes *et al.* (2022) study, but outcomes are not presented for inhaled treprostinil versus PDE5is as PDE5is are not considered a relevant comparator (see details in Section 1.1).

2.10.1.1 Methods

Full methods and data inputs for the MAIC are reported in Appendix B. Analyses for the MAIC were conducted in R, using code modified from NICE TSD18.[76]

The baseline characteristics that were considered prognostic variables and possible effect modifiers for an ITC included: age (baseline/screening), sex, body mass index, smoking history, PH-ILD severity (% predicted DLCO), time since diagnosis, pulmonary function (% predicted FEV), aetiology of lung disease, comorbidities, 6MWD at baseline, and oxygenation. It is assumed that there were no unmeasured confounding variables.

Insufficient data were reported for body mass index and smoking history to determine the sufficiency of overlap and the need for adjustment. The greatest observed

difference between the studies was the time since diagnosis of PH-ILD. Patients were assumed to have a time since diagnosis of zero in Dawes *et al.* (2022), whilst there was a delay from diagnosis to study entry of up to 13 years in the INCREASE trial. To allow for meaningful comparisons, patients with a time since diagnosis of >2 years in the INCREASE studies were excluded based on real-world evidence that shows patients typically receive treatment two years after symptom onset.[77] Furthermore, patients with CTD in the INCREASE studies were excluded from the analysis to align with the population in Dawes *et al.* (2022).

Indirect measures of treatment effect were estimated following the guidance in the NICE DSU TSD 2.[78] Statistical modelling was based on individual patient data (IPD) from INCREASE and INCREASE OLE, along with aggregate KM data obtained from the Dawes *et al.* (2022) study.

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE to the Dawes *et al.* (2022) population. The distribution of effect modifiers at baseline and after matching are presented in Table 10.

Table 10. Distribution of effect modifiers at baseline and after matching

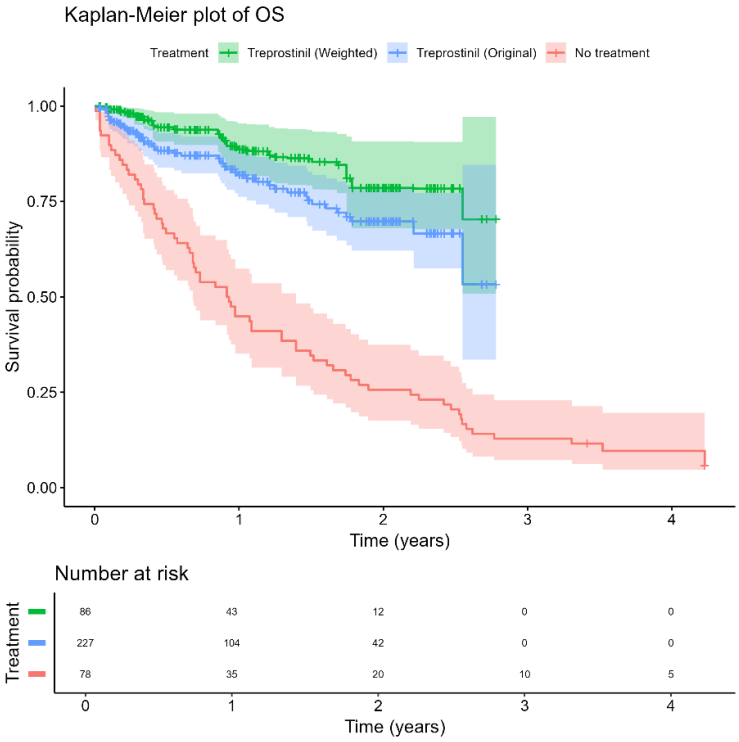
Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (% male)	0.59	0.26	0.26
Hypertension (% with)	0.50	0.33	0.33
Oxygenation (% receiving)	0.46	0.68	0.68
6MWD	261.0	222.0	222.0
DLCO	28.4	26.0	26.0
FEV1	67.0	55.0	55.0
IPF	0.33	0.69	0.69
NSIP	0.33	0.69	0.090
Other	0.55	0.22	0.22

Key: 6MWD, 6-minute walk distance; DLCO, Diffusing capacity of the lungs for carbon monoxide; FEV1, Forced expiratory volume in 1 second; IPF, Idiopathic pulmonary fibrosis; NSIP, Non-specific interstitial pneumonia.

2.10.1.2 Results

The MAIC demonstrated a significant OS benefit for patients treated with inhaled treprostinil versus BSC over 2.5 years, as shown in the KM curves presented in Figure 16.

Figure 16. KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population



Key: ITT, intention-to-treat; KM, Kaplan-Meier; OS, overall survival.

Table 11 provides a summary of the OS statistics from the MAIC. An incremental benefit was observed in median OS with inhaled treprostinil (median not reached) versus BSC (0.92 years), with a HR of 0.16 (95% CI: 0.09 to 0.28).

Table 11. Summary of OS statistics

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=86.3)	11.80 (10.2/86.3)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (N/A to N/A)	2.39 (0.11)	0.16 (0.09 to 0.28; 2.61E-10)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (2.55 to N/A)	2.15 (0.08)	0.28 (0.19 to 0.40; 3.75E-11)
No treatment (n=78)	92.3 (72/78)	0.88 (0.97 to 1.50)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Key: CI, confidence intervals; HR, hazard ratio; NA, not applicable; OS, overall survival; PDE5i, phosphodiesterase type 5 inhibitors; SE, standard error

The empiric hazards were assessed and the proportional hazard assumption was tested between inhaled treprostinil and BSC to ensure a constant HR can describe the difference in OS. The empiric hazard rate of OS over time for inhaled treprostinil and BSC are presented in Appendix B.

Log-log, Schoenfeld residuals, and Cox-Snell plots were generated for inhaled treprostinil versus BSC, and provided supportive evidence that the HRs are constant and the proportional hazard assumption holds (see Appendix B for details).

2.11 Adverse reactions

2.11.1 INCREASE

2.11.1.1 Extent of exposure to study treatment

The median number of breaths per session increased during weeks 4 (8.0 and 9.0 in the inhaled treprostinil and placebo arms, respectively), 8 (10.0 and 11.0, respectively), and 12 (11.0 and 12.0, respectively), reaching the maximum allowable 12.0 breaths (72 µg) per session at Weeks 15 and 16 in both arms.[58,59] The percentage of patients achieving 10 to 12 breaths (60 to 72 µg) per session at Week 16 was 57.8% in the inhaled treprostinil and 68.6% in the placebo arm. Further details on extent of exposure are presented in Appendix J.

2.11.1.2 Adverse events

A summary of the most common AEs occurring in ≥ 10% of patients in either treatment arm is provided in Appendix J. Most patients in the inhaled treprostinil arm (93.3%) and placebo arm (91.4%) experienced at least one AE during the study.[58,59] In the inhaled treprostinil arm, the most commonly reported AEs were cough (43.6%), headache (27.6%), dyspnoea (25.2%), dizziness (18.4%), nausea (15.3%), fatigue (14.1%), diarrhoea (13.5%), throat irritation (12.3%), and oropharyngeal pain (11.0%). In the placebo arm, the most commonly reported AEs were cough (33.1%), dyspnoea (31.3%), headache (19.6%), nausea (16.0%), NT-proBNP increased (15.3%), dizziness and fatigue (14.1% each), and diarrhoea (11.7%).

2.11.1.3 Treatment-related adverse events

A summary of the most common treatment-related AEs occurring in ≥ 10% of patients in either treatment arm is provided in Appendix J. Overall, [redacted] of patients in the inhaled treprostinil arm and [redacted] of patients in the placebo arm experienced at least one treatment-related AE.[59] In the inhaled treprostinil arm, the most commonly reported treatment-related AEs were cough ([redacted]), headache ([redacted]), dyspnoea ([redacted]), dizziness ([redacted]), throat irritation ([redacted]), and diarrhoea ([redacted]). In the placebo arm, the most commonly reported treatment-related AEs were cough ([redacted]), headache ([redacted]), dyspnoea ([redacted]), and nausea ([redacted]).

2.11.1.4 Serious adverse events

Serious AEs were reported in 23.3% of patients in the inhaled treprostinil arm and 25.8% of patients in placebo arm.[58,59] The most frequently reported serious AE (≥ 2% of patients) in the inhaled treprostinil arm was acute respiratory failure (2.5%). The most frequently reported serious AEs (≥ 2% of patients) in the placebo arm were pneumonia (5.5%), dyspnoea (4.3%), acute respiratory failure (3.1%), respiratory failure (3.1%), idiopathic pulmonary fibrosis (2.5%), and fluid overload (2.5%).

2.11.1.5 Adverse events leading to permanent discontinuation of study drug

Overall, [redacted] of patients in both the inhaled treprostinil and placebo arms experienced AEs leading to permanent discontinuation of study drug.[59] The most common AEs leading to discontinuation (≥ 2% of patients) in the inhaled treprostinil arm

were dyspnoea ([redacted]) and cough ([redacted]). The most common AE leading to discontinuation (≥ 2%) in the placebo arm was dyspnoea ([redacted]).

2.11.1.6 Deaths

Overall, there were [redacted] deaths in the inhaled treprostinil arm and [redacted] deaths in the placebo arm.[59] The primary cause of death was disease progression, occurring in [redacted] patients in the inhaled treprostinil arm and [redacted] patients in the placebo arm.

2.11.1.7 Exacerbation of underlying lung disease

Significantly fewer patients in the inhaled treprostinil arm experienced an exacerbation of underlying lung disease than in the placebo arm (43 [26.4%] versus 63 [38.7%]; p=0.02).[58,59] Overall, treatment with inhaled treprostinil provided a 34% overall reduction in the risk of an exacerbation of underlying lung disease after 16 weeks of treatment compared with placebo (HR 0.66 [95% CI: 0.45, 0.97]; p=0.0338).[59]

2.11.2 INCREASE OLE

2.11.2.1 Extent of exposure to study treatment

Total median inhaled treprostinil exposure duration in INCREASE OLE was 62.1 weeks (77.3 weeks in the inhaled treprostinil arm and 47.0 weeks in the placebo arm of INCREASE).[58,59] The reduced exposure in the prior placebo arm was likely due to the higher number of patients who discontinued the study drug due to an AE compared to patients from the inhaled treprostinil arm (28.1% versus 16.8%, respectively). From week 28 to week 76, the median number of breaths per session was 12 at all-time points. Overall, 80.6%, 60.7% and 26.9% of patients had achieved a maximum dose of ≥ 9, ≥ 12 and ≥ 15 breaths per session four times daily, respectively, by the end of the study. Further details on the extent of exposure are presented in Appendix J.

2.11.2.2 Adverse events

A summary of the most common AEs occurring in ≥ 10% of patients in INCREASE OLE is provided in Appendix J. The majority of patients (94.6%) experienced at least one AE during INCREASE OLE.[60,61] Consistent with INCREASE, the most common AEs were cough, dyspnoea and headache were cough (26.9%), dyspnoea (26.0%), headache (18.6%). Other most frequently reported AEs (> 10% of patients) included diarrhoea (15.3%), dizziness (14.9%), upper respiratory tract infection (14.0%), fatigue (13.2%),

nausea (13.2%), acute respiratory failure (12.4%), pneumonia (12.4%), urinary tract infection (11.2%), back pain (10.7%) and productive cough (10.3%).

A similar proportion of patients previously treated with inhaled treprostinil (94.1%) or placebo (95.0%) experienced at least one AE during INCREASE OLE.[60,61] However, patients previously treated with placebo were more likely to experience cough (35.5% versus 18.5%, respectively) and headache (27.3% versus 10.1%, respectively) than patients previously treated with inhaled treprostinil.

2.11.2.3 Treatment-related adverse events

A summary of the most common treatment-related AEs occurring in ≥ 10% of patients in INCREASE OLE is provided in Appendix J. Overall [redacted] of patients experienced at least one treatment-related AE during INCREASE OLE.[61] Consistent with INCREASE, the most commonly reported treatment-related AEs were cough ([redacted]), dyspnoea ([redacted]), and headache ([redacted]).

A higher proportion of patients previously treated with placebo in INCREASE experienced at least one treatment-related AE during INCREASE OLE compared to those who were previously treated with inhaled treprostinil ([redacted] versus [redacted], respectively.[61] Patients previously treated with placebo were more likely to experience treatment-related cough ([redacted] versus [redacted], respectively), dyspnoea ([redacted] versus [redacted], respectively) and headache ([redacted] versus [redacted], respectively) than patients previously treated with inhaled treprostinil.

2.11.2.4 Serious adverse events

Serious AEs were reported in 55.0% of patients in INCREASE OLE.[60,61] The most frequently reported serious AEs (≥ 2% of patients) included acute respiratory failure ([redacted]), pneumonia [redacted]), respiratory failure ([redacted]), RV failure ([redacted]), acute kidney injury ([redacted]), cardiac arrest ([redacted]), fluid overload ([redacted]), interstitial lung disease ([redacted]), dyspnoea ([redacted]), sepsis ([redacted]), pulmonary hypertension ([redacted]), syncope ([redacted]), cardiac failure congestive ([redacted]), idiopathic pulmonary fibrosis ([redacted]), and urinary tract infection ([redacted]).[61]

2.11.2.5 Adverse events leading to permanent discontinuation of study

Overall, 22.3% of patients experienced AEs leading to permanent discontinuation of study drug in INCREASE OLE, with a higher incidence occurring in patients who had

previously received placebo rather than inhaled treprostinil in INCREASE (28.1% versus 16.8%, respectively).[60,61] The most common AEs leading to discontinuation (≥ 2%) of inhaled treprostinil were dyspnoea ([redacted]), hypoxia ([redacted]) and RV failure ([redacted]).[61]

2.11.2.6 Deaths

Overall, there were 62 (25.6%) deaths during INCREASE OLE.[60,61] Among the patients who died, 29 (24.4%) deaths occurred in patients who had previously received inhaled treprostinil in INCREASE, and 33 (27.3%) deaths occurred in the patients who previously received placebo in INCREASE. The primary cause of death was disease progression, occurring in [redacted] patients, including [redacted] patients who previously received inhaled treprostinil and [redacted] who previously received placebo.[61]

2.11.2.7 Exacerbation of underlying lung disease

Overall, 133 (55.0%) patients experienced at least one exacerbation of underlying lung disease during INCREASE OLE.[60,61] Patients who previously received inhaled treprostinil in the INCREASE RCT had a 31% reduction in risk of an exacerbation of underlying lung disease in INCREASE OLE compared with patients who previously received placebo (HR 0.69 [95% CI: 0.49, 0.97]; p=0.0321; median 67.0 versus 32.9 weeks).

2.11.3 Safety overview

Safety data from INCREASE and INCREASE OLE demonstrated that inhaled treprostinil has a well-characterised and generally manageable safety profile in patients with PH-ILD that is consistent with the known effects of inhaled treprostinil in patients with PAH.[58-61] Safety outcomes were generally consistent between INCREASE and INCREASE OLE, and no new safety signals were observed.

The majority of patients in the inhaled treprostinil arm (93.3%) and placebo arm (91.4%) in INCREASE experienced at least one AE during the study.[58,59] The most frequently reported AEs in both treatment arms were cough, headache, dyspnoea, dizziness, nausea, fatigue, and diarrhoea; the majority of these AEs were mild-to-moderate in severity. The majority of patients in INCREASE OLE (94.6%) experienced an AE during the study.[60,61] Consistent with INCREASE, the most common AEs were cough, dyspnoea, and headache. However, AEs, such as cough and headache, were

less frequently reported in patients who continued to receive inhaled treprostinil versus patients who had switched from placebo to inhaled treprostinil treatment during the OLE period. This demonstrates improved responses to these AEs with longer exposure to treatment.

2.12 Ongoing studies

An ITC using propensity score weighting is currently ongoing to assess the effectiveness of inhaled treprostinil versus BSC in patients with PH-ILD. This study will compare outcomes in patients from the INCREASE and INCREASE OLE trials with real-world data from the Royal Brompton Hospital Pulmonary Hypertension Registry in the UK and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) that spans multiple countries in Europe. Further evidence on the long-term comparative effectiveness of inhaled treprostinil versus BSC will be generated from this external control arm study. However, developing a robust ITC has been complex and several methodological challenges have been faced, including limited sample sizes, high variability in real-world data completeness, and differences in eligibility criteria (e.g., 6MWD not routinely measured in clinical practice) and assessment timing between the trial and real-world populations. These complexities reduce the feasibility of generating reliable comparative estimates. As such, the ITC analyses are ongoing and results are not yet available.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence

Inhaled treprostinil has been assessed for efficacy and safety in the Phase 3 INCREASE RCT, which is the largest and most comprehensive study of adult patients with PH-ILD to date, and the INCREASE OLE.[58,59] The INCREASE RCT provides head-to-head data for inhaled treprostinil versus placebo (i.e., BSC), reflecting the relevant comparator for this submission (Section 1.1). Results from the INCREASE studies support the positioning of inhaled treprostinil as the first treatment for patients with PH-ILD that has the potential to address the substantial unmet need in this population.

Based on the primary efficacy analysis for INCREASE, inhaled treprostinil led to a statistically significant improvement in exercise capacity vs placebo, measured by 6MWD (31.1m, p<0.001).[58] This result is indicative of potential survival benefits with inhaled treprostinil as 6MWD is associated with mortality in patients with PH-ILD. An improvement in 6MWD of ≥20 m has been shown to be associated with improved survival in patients with PH-ILD versus patients who do not demonstrate improved 6MWD (see Section 1.3.2.1).[17] Additionally, the increase of 31.1 metres in 6MWD is above the estimated MID threshold in patients with PH-ILD of 18.7 metres to 24.7 metres.[64]

The improvement in 6MWD was maintained long-term, with a mean (SD) change from baseline to week 52 in INCREASE OLE of 22.1m (66.3m) in patients who were treated with inhaled treprostinil in INCREASE.[60] In patients who transitioned to inhaled treprostinil from placebo in the INCREASE OLE, mean (SD) change was -19.5m (69.8m) at 52 weeks, with minimal further deterioration in 6MWD over the study period.[60]

Furthermore, patients treated with inhaled treprostinil experienced a 15% reduction in NT-proBNP from baseline to Week 16, compared with a 46% increase in the placebo group. This favourable effect was maintained in the INCREASE OLE, with a 17% decrease in NT-proBNP observed at Week 64 in patients who received continuous inhaled treprostinil therapy. NT-proBNP is a well-established cardiac biomarker associated with disease severity and prognosis that has been shown to predict mortality and lung transplant risk.

Moreover, patients receiving inhaled treprostinil in INCREASE had a statistically significant decrease in the risk of CW (defined in section 2.3.1.1) vs placebo at 16 weeks (39%, HR: 0.61 [95% CI: 0.4,0.9]; p=0.04). Meanwhile, improved event-free survival was reported in INCREASE OLE, with a 27% reduction in the in the risk of hospitalisation, acute exacerbation or death in patients previously treated with inhaled treprostinil versus those previously treated with placebo (HR: 0.73 [95% CI: 0.54, 0.99]; p=0.0454).

With a conventional ITT analysis, the HR for death was 0.71. When using the crossover RPSFT method to calculate OS, there was a significant overall survival benefit associated with inhaled treprostinil treatment, with a HR of 0.26 (p=0.047).

Although no validated HRQoL measure in PH-ILD was available at the time of INCREASE, inhaled treprostinil was shown to have a positive impact on patient-relevant outcomes that may lead to improved HRQoL.[19,58,74] Results from the SGRQ showed a trend of improved HRQoL at week 16 with inhaled treprostinil vs placebo and no deterioration in SGRQ was observed during INCREASE OLE.[58-60]

Inhaled treprostinil has a well-characterised and generally manageable safety profile in patients with PH-ILD, with AEs reported in INCREASE being mild-to-moderate in severity.[58,60,63] In INCREASE OLE, AEs such as cough and headache were less frequently reported in patients formerly receiving inhaled treprostinil vs those in the former placebo arm.[60,63] This suggests improved responses to these AEs with longer exposure to treatment.

Overall, the INCREASE studies demonstrated the efficacy of inhaled treprostinil versus BSC in increasing exercise capacity and decreasing CW, while offering a well-characterised and generally manageable safety profile in patients with PH-ILD.[58,60]

In addition, the MAIC provides further supportive evidence for the comparative effectiveness of inhaled treprostinil versus BSC in patients with PH-ILD. Inhaled treprostinil was shown to provide greater OS (median not reached) versus patients receiving BSC, with a HR of 0.16 (95% CI: 0.09 to 0.28).

2.13.2 Strengths of the evidence base

INCREASE was a well-designed, Phase 3, multicentre, double-blind RCT providing head-to-head evidence of inhaled treprostinil versus a relevant comparator (placebo) in adult patients with PH-ILD.[58,59] Both INCREASE and INCREASE OLE studies were conducted in accordance with the ethical principles of Good Clinical Practice and were both considered to be good-quality studies, with steps taken to minimise the risk of bias. The overall risk of bias for both studies is considered to be low.

Although no UK-based patients were included in either study, clinicians from the UK agreed that patients treated in INCREASE and INCREASE OLE are generalisable to

patients seen in UK clinical practice. In addition, the outcomes assessed in the trial and background anti-fibrotic treatments received in patients at baseline are considered consistent with standard practice in the NHS England at the time of trial. The population age and other baselines characteristics matches closely that of Dawes *et al*. (2022), which is a retrospective study of UK PH-ILD patients (see Table 10). Clinically important outcomes were captured in INCREASE, including change in 6MWD that assesses functional exercise capacity and predicts prognosis, and the time to various patient-relevant CW events (defined in Section 2.3.1.1). The INCREASE OLE study provided long-term supportive evidence for the safety and efficacy of inhaled treprostinil across these outcomes.[60,61]Notably, INCREASE OLE demonstrated a survival benefit with inhaled treprostinil over 2 years (124 weeks).[69]

The MAIC provides another source of evidence for the incremental benefit of inhaled treprostinil on OS versus BSC. Strengths of the MAIC include that it uses a comparator arm derived from a UK-specific population, long-term OS data are available (approximately 5 years), and the effective sample size is relatively large after population matching (N=86.3 in the inhaled treprostinil arm versus 78 in the BSC arm).

2.13.3 Limitations of the evidence base

The double-blind phase of INCREASE was 16 weeks and 21% of patients discontinued the trial prematurely. Longer-term outcomes are primarily derived from the subsequent OLE (non-randomised), where the absence of a placebo arm can limit data interpretation on the degree of responses between different endpoints (e.g., 6MWD versus FVC). However, in progressive and high-mortality conditions like PH-ILD, maintaining a placebo arm beyond the short term is often not ethical or practical. As a result, OLEs are commonly used to assess durability of response. In INCREASE OLE, improvements in key outcomes such as 6MWD and NT-proBNP were largely maintained, supporting the likelihood of continued clinical benefit over time.

To assess the survival benefit associated with inhaled treprostinil, the RPSFT statistical method was required to adjust for the treatment crossover between the 16-week INCREASE RCT and the OLE phase.[69] This method relies on the ‘common treatment effect’ assumption and therefore there is some uncertainty around the true mortality benefit associated with inhaled treprostinil.[69] However, the cross-over adjustment was

necessary to assess the long-term survival benefit due to the practical (e.g., patient number, duration) and ethical considerations that prevent a long-term direct comparison of OS between inhaled treprostinil and placebo in PH-ILD.[69] In the absence of long-term randomised survival data, RPSFT is the most appropriate available method and follows established NICE guidance for crossover adjustment.

Patients' HRQoL was assessed using the SGRQ in the INCREASE and INCREASE OLE studies. The SGRQ was originally developed and validated for COPD and asthma.[79] There were no validated, disease-specific HRQoL measures available for PH-ILD at the time of the INCREASE trial and therefore the SGRQ was deemed the most appropriate measure. However, results from the SGRQ may not fully capture the impact of inhaled treprostinil on HRQoL in patients with PH-ILD (e.g., limited capture of the severity of breathlessness beyond frequency, no capture of the improvement in the vascular symptoms of the disease). Whilst the SGRQ captures several important domains, it may underestimate the true burden of disease in this population.

Considering the MAIC, data were utilised from Dawes *et al.* (2022), which is a real-world study, which meant creating a connected network was not possible. Given the absence of long-term head-to-head studies comparing inhaled treprostinil with BSC, an unanchored MAIC was conducted. This approach carries the potential for bias due to unobserved prognostic factors and effect modifiers that may differ between the INCREASE and Dawes *et al.* (2022) populations, as noted in NICE DSU TSD 18. In addition, incomplete reporting of certain baseline factors, such as body mass index and smoking history, limited the ability to adjust for these covariates, potentially introducing some residual confounding. To better align the populations, patients from INCREASE with a time since diagnosis >2 years were excluded. While this step improved comparability, it may also reduce the generalisability of these findings to PH-ILD populations with a longer disease history. Sensitivity analyses, including alternative data-trimming methods and various covariate sets, were performed to explore robustness. The overall direction and magnitude of the inhaled treprostinil benefit versus BSC remained consistent. Appendix B provides further details on these analyses and methods. Dawes *et al.* (2022) was the only UK-based study identified with an untreated PH-ILD population aligned with the decision problem. The MAIC

followed NICE DSU TSD 18 guidance, and sensitivity analyses showed consistent treatment effects across different assumptions.

3 Cost effectiveness

3.1 Published cost-effectiveness studies

During model conceptualisation, a targeted literature review was conducted to identify previously published economic models in PH-ILD. The NICE website was also searched to identify any previous appraisals of technologies for PH-ILD. The searches identified no models or submissions specific to PH-ILD. A systematic literature review was conducted in January 2024 and updated in January 2025 (Appendix E), which similarly identified no models or analyses specific to PH-ILD published or presented at conferences.

3.2 Economic analysis

In the absence of previously published economic models or health technology assessment (HTA) submissions specific to PH-ILD, a *de novo* cost-utility model was developed.

3.2.1 Patient population

The target patient population is adults with WHO Group 3 PH and in whom ILD was diagnosed. The modelled population was selected to align with the INCREASE study population, marketing authorisation, and NICE scope (adults with a confirmed diagnosis of PH with ILD), whilst also being generalisable to clinical practice in England.[80]

The baseline characteristics of patients upon entry to the model are based on the INCREASE study and presented in Table 12.

Table 12. Baseline characteristics in the cost-effectiveness model based on the INCREASE study

Variable	All participants (N=326)	Source
Age, mean (range)	66.45 years (26–90)	INCREASE[80]
Percentage male, % (number)	53.0 (173)	
Percentage of patients with CPFE, % (number)	25.2 (82)	
Percentage of patients with a PVR >5 Wood units, % (number)	54.0 (176)	
Percentage of patients with a PVR >5 Wood units and without CPFE, % (number)	39.6 (129)	
Key: CPFE, Combined pulmonary fibrosis and emphysema; PVR, Pulmonary vascular resistance.		

3.2.2 Clinical validation

Given that no PH-ILD economic models were identified from the initial targeted or subsequent systematic literature reviews, and inhaled treprostinil is expected to be the first treatment in this indication to be appraised by NICE, it was necessary to develop a *de novo* economic model. Clinical and health economic experts from the UK were consulted throughout the model conceptualisation phase to ensure the modelling approach was robust and valid, whilst providing the most appropriate option to capture disease progression and the effects of inhaled treprostinil. The methods and outcomes of the model concept validation have been presented previously.[81]

Two individual interviews were initially held with consultant respiratory physicians to gather information about the treatment pathway for PH-ILD in the UK.[82,83] Two advisory boards were subsequently held regarding the model conceptualisation. The first advisory board, held in March 2023, was attended by three UK-based consultant respiratory physicians and two health economic experts. The second advisory board, held in July 2023, was attended by two UK-based respiratory consultants (who also attended the first advisory board) and two different health economic experts from the UK.[84] An individual interview was also held with the consultant respiratory physician who attended the first advisory board but was unable to attend the second. An interview with a health economics expert was also conducted following an initial draft of the CEM to validate the modelling approach and initial results.

Furthermore, to validate the clinical assumptions for the CEM, including the time-to-event parameters, a workshop was conducted with two PH specialist physicians in the UK. The statistical models used to determine the long-term extrapolations for each time-to-event input, along with the utility values mapped from the SGRQ, were presented and validated with the physicians based on their experience managing patients with PH-ILD in the UK.[85] Their feedback was used to support the inputs detailed in Section 3.3.

3.2.3 Model structure

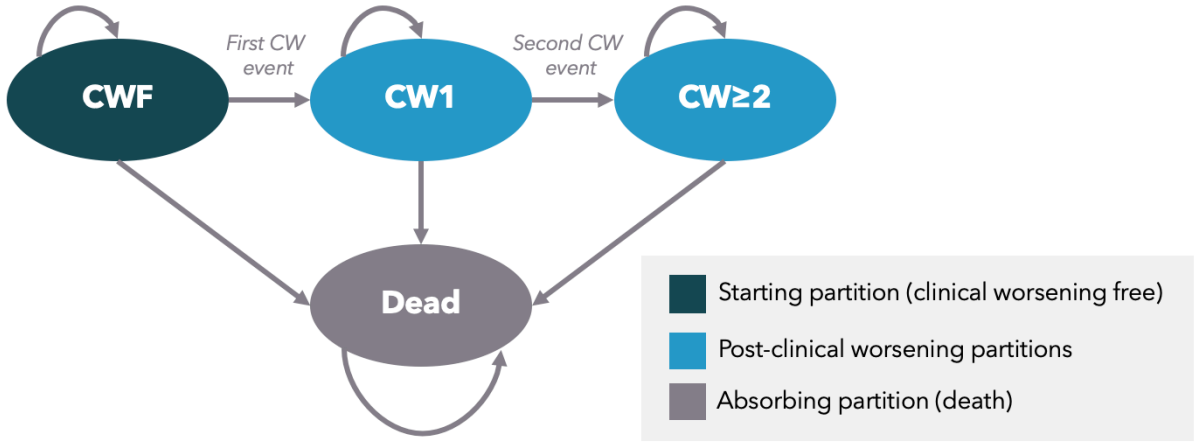
A *de novo* partitioned survival model (PSM) with the following four health states was built in Microsoft Excel® to estimate the cost-effectiveness of inhaled treprostinil compared with BSC, over a lifetime time horizon:

- No clinical worsening event, or clinical worsening free (CWF).
- First clinical worsening event (CW1).
- Two or more clinical worsening events (CW≥2).
- Dead.

A model schematic is presented in Figure 17. The cohort of patients with PH-ILD enters the model in the CWF health state and receive either inhaled treprostinil or BSC. Individual participant data (IPD) on times to events inform the proportion of patients with one clinical worsening event (CW1), two or more clinical worsening events (CW2), or death in each weekly cycle. Patients who do not experience a clinical worsening event but remain alive in each cycle occupy the CWF health state.

The definition of 'clinical worsening' is detailed in Section 3.2.3.7. The proportion of patients experiencing each event type is determined by analysis of the INCREASE 16-week trial time-to-event data for BSC and INCREASE OLE time-to-event data for inhaled treprostinil.

Figure 17. Model schematic



Key: CWF, clinical worsening-free; CW, Clinical worsening.

3.2.3.1 Model structure justification

The PSM structure captures the progressive nature of PH-ILD and results in an inherent, structural assumption that the simulated cohort cannot return to a previous health state once they have experienced a clinical worsening event (or died). Clinical worsening reflects key INCREASE trial endpoints directly whilst being considered

clinically meaningful and prognostic by clinical experts on the advisory boards.[81] This structure, while commonly used in cost-effectiveness analysis, is particularly prevalent in oncology models where disease progression is similarly treated as a one-way process.

A PSM structure may not have fully captured the benefits associated with inhaled treprostinil and can therefore be considered a conservative modelling approach. While clinical improvements following treatment initiation — such as those observed in the INCREASE trial, where patients in the inhaled treprostinil arm experienced a 21.08-metre improvement in 6MWD at 16 weeks (compared to a 10.04-metre decline in the placebo arm) — may occur based on specific criteria, these are not captured structurally in the model. Instead, such improvements are captured only by way of an increased to time first clinical worsening, and by capturing quality of life in patients who experienced the 6MWD improvement in the CWF partition. Structurally, the model is consistent with the progressive nature of PH, avoiding the structural complexity of introducing a fifth model partition, whilst still capturing the benefits of the improvement in 6MWD indirectly through increased time and quality of life in the CWF state.

3.2.3.2 Discontinuation

Discontinuation of inhaled treprostinil is determined by parametric models fitted to KM estimates and extrapolated using individual patient-level data analysis of the INCREASE and INCREASE OLE data (Section 3.3). Discontinuation only directly affects the cost of inhaled treprostinil in the model.

3.2.3.3 Cycle length

A cycle length of one week is adopted in the model to capture the possibility of patients with PH-ILD experiencing multiple clinical events in quick succession. A longer cycle length, such as one month, may underestimate the number of events because it would assume that only one event could occur per month. The selection of a weekly cycle length was validated by key opinion leaders during the advisory boards (see section 3.2.2). Half-cycle correction is applied to account for patients who may have experienced a clinical worsening event or die at any point within the weekly cycle.

3.2.3.4 Frequency of clinical worsening events

Patients with PH-ILD may experience more than two clinical worsening events over their lifetime (e.g., beyond the combined duration of INCREASE and INCREASE OLE), and discussions during the advisory boards therefore considered how many clinical worsening event health states should be included in the model. All participants agreed that two clinical worsening states would be sufficient. Moreover, there were insufficient data to support a robust survival analysis of time to additional events, given the low number of third and fourth events observed in the 16-week INCREASE and INCREASE OLE studies (Table 13).

To determine whether restricting the model structure to two clinical worsening events would make a substantial difference to the HRQoL estimations, statistical analyses were conducted to quantify the difference in HRQoL for patients who had no, one, two, three or four clinical worsening events within the INCREASE 16-week trial. This analysis was based on SGRQ, which was collected within the INCREASE study (Section 2.6.1.5) and the analysis was based on the INCREASE 16-week study only, incorporating patients in both arms of the study. Further details on the SQRQ are presented in Section 3.4.1.

As presented in Table 13, the SGRQ score between patients who had experienced three or more clinical worsening events was not statistically different from those who had experienced two, and the occurrence of more than two clinical worsening events would therefore not be expected to have a meaningful impact on patient outcomes. These HRQoL estimations, and the lack of robust data to inform the survival analysis, informed the decision not to include a third clinical worsening health state. A hospitalisation rate, and subsequent costs, were applied to the patients in the CW≥2 health state to account for the fact that patients could experience further costs of subsequent hospitalisations after the second clinical worsening event.

Table 13. SGRQ scores – INCREASE 16-week trial

	No event	One event	Two events	Three events	≥ Four events
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGRQ: Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: N, number; SD, standard deviation; SGRQ, Saint George's Respiratory Questionnaire.

3.2.3.5 Resource use and HRQoL

Resource use and unit cost inputs used in the model are described further in Section 3.5. Patients in the inhaled treprostinil arm incur the cost of treatment until they discontinue or die. One-off event costs are applied when a person enters either of the clinical worsening event health states to capture the acute cost of care associated with cardiopulmonary hospitalisations, lung-disease exacerbations and lung transplants (Section 3.5.2). Patients who experience clinical worsening events are stratified by the event type (as defined in Section 3.2.3.7) to capture the difference in costs and health outcomes associated with each specific event. Patients also incur ongoing health-state-dependent resource use. Aside from the direct cost of treatment, i.e. inhaled treprostinil and background medications, the healthcare resource use, costs and HRQoL inputs are health-state dependent.

3.2.3.6 Approach to modelling time to events

The proportion of patients occupying each health state over a lifetime horizon is informed by parametric models fitted to KM estimates and extrapolated based on individual patient-level data analysis of the INCREASE and INCREASE OLE trial data.[86] Parametric survival models are used to estimate the following time-to-event data:

- Time to first clinical worsening (informing occupancy of the “1st clinical worsening event” health state).
- Time to second clinical worsening (informing occupancy of the “Two or more clinical worsening events” health state).
- Time to death (all-cause) (informing occupancy of the “dead” health state).

Further details on the inputs used to inform the efficacy data used to populate the model can be found in Section 3.3

3.2.3.7 Definition of clinical worsening

Clinical worsening, for the purposes of modelling, is a composite endpoint defined as any of the following events, with patients allocated to the five CW subtypes based on the overall percentage of events observed across the trial, assuming this distribution remains constant over time:

- Decrease in 6MWD of ≥15% from baseline.
- Decrease in FVC% of ≥10% from baseline.
- Cardiopulmonary hospitalisation: Defined as any episode of care requiring a hospital admission directly caused by an indication related to the heart and lungs.[59]
- Acute lung-disease exacerbation: Defined as a clinically significant respiratory deterioration characterised by evidence of new widespread alveolar abnormality.[59]
- Lung transplant.
- Death.

The definition of clinical worsening was based on the secondary outcome measure in the INCREASE trial.[80] Decrease in 6MWD of ≥15% from baseline and cardiopulmonary hospitalisations are included in the clinical worsening event definition to capture the decline in PH. However, some adaptations were made to the definition from Waxman 2021 (see Section 2.6.1.2) to align with the *post hoc* analysis undertaken by Nathan 2022.[80,87] Within the Nathan 2022 study, the authors explored the number of clinical worsening events that occurred, based on a *post hoc* analysis, and found the number of events was substantially higher in the placebo group than in the inhaled treprostinil group; 67% and 55% respectively (p=0.018).

Adaptations in the Nathan 2022 study (versus the Waxman 2021), were as follows:

- A decrease in FVC% was recorded in the INCREASE trial but not included in the trial definition of the composite endpoint ‘clinical worsening’. This was incorporated into the model definition because, during the advisory boards, clinical experts noted

that the inclusion of this outcome was important to capture the impact of treatment on underlying ILD.

- An exacerbation was recorded in the trial but not included in the trial definition of the composite endpoint 'clinical worsening'. This was incorporated in the model definition, following the advice of the clinical and health economic experts during the advisory boards that the cost and HRQoL impact of this event should be captured. The experts also commented that whilst exacerbations would be a strong predictor of death, the impact of this would be captured through the overall survival KM extrapolations.

Table 14. Clinical worsening and disease progression event definitions in each analysis

Clinical worsening event definition	Current analysis	Waxman 2021[87]	Nathan 2022[74]
Fall in 6MWD of ≥15% from baseline	Included	Included	Included
Fall in FVC% of ≥10% from baseline	Included	Not included	Included
Cardiopulmonary hospitalisation	Included	Included	Included
Acute lung-disease exacerbation	Included	Not included	Included
Lung transplant	Included	Included	Included
Death	Included	Included	Included

Key: 6MWD: Six-minute walking distance; FVC: Forced vital capacity.

Note: Justification for the choices listed above

The definition of clinical worsening events used in the CEM includes lung transplants. The mean age of the cohort of the INCREASE trial is 66.45 years old (SE=0.67).[80] Clinical experts at the advisory board confirmed that patients in the UK are not indicated for transplant if they are over the age of 65 years.[88,89] Therefore, it is very rare that patients with PH-ILD undergo a lung transplant in the UK. This is further evidenced by the NHS Audit 2024 of PH (which includes other groups of PH such as PAH and chronic thromboembolic pulmonary hypertension), which stated that only one person with PH (not PH-ILD specific) received a lung transplant over the previous year in the UK.[90] Additionally, two patients required a lung transplant in the 16-week follow-up period of the INCREASE trial; this represented <1% of the original study population (n=326).[91] Therefore, transplants were not expected to be relevant to a UK-based cost-

effectiveness analysis and it was agreed with the experts at the advisory boards that the cost of lung transplants would not be considered in the base case analysis. However, the model contains the functionality for the costs of lung transplants to be considered in a scenario analysis.

Note that, while separate overall survival curves are modelled (Section 3.3.2), death is included in the definition of the clinical worsening events to account for the competing risk of mortality. Partitioned survival analysis relies on non-mutually exclusive curves and uses proportions to determine the type of event experienced. Deaths are not censored (i.e. excluded from the clinical worsening survival curves) to avoid double counting. The exclusion of death from this definition would overestimate the frequency of clinical worsening events because the competing risks are accounted for by using the partitioned survival approach.

3.2.3.8 Time horizon

The time horizon in the CEM can be set to between 6 months to 30 years. In the base-case analysis, cost-effectiveness is estimated over a lifetime horizon of 30 years to capture all potential differences in costs and HRQoL between the two treatment options. The lifetime time horizon was determined as the point at which all of the modelled cohort has died, in line with the NICE reference case.[92]

As detailed in Section 3.3, the model also includes the option to use the KM data from the INCREASE 16-week trial directly in a within-trial analysis. When this option is selected, the time horizon is capped by the KM data.

3.2.3.9 Perspective

The model evaluates cost-effectiveness from the perspective of the UK NHS and PSS, in line with the NICE reference case.[92] The model also includes functionality to evaluate cost-effectiveness from a societal perspective, considering costs of unemployment due to PH-ILD and absenteeism from workdays missed; this functionality is not used in the base case analysis.

3.2.4 Intervention technology and Comparators

The intervention of interest is inhaled treprostinil, administered through an ultrasonic, pulsed-delivery nebuliser (see Table 2). The target dose of inhaled treprostinil in the INCREASE 16-week trial is nine to twelve breaths per session, four times daily.[87] Some

patients reached 15 breaths per session in the INCREASE OLE trial.[93] However, the dose of inhaled treprostinil reached in the trial does not affect the total cost in the model as each person is assumed to receive one ampule per day, which is loaded into the nebuliser device (independently of the number of breaths per session). One ampule is considered sufficient to cover the full dose in all patients. The ampule is single-use and is discarded at the end of each day, even if residual medication remains.

Based on expert insights from UK clinicians (N=8), wording in the European treatment guidelines (Section 1.3.3.1), and in line with the first comparator listed in the NICE scope, the cost-effectiveness of inhaled treprostinil is compared against established clinical management (without inhaled treprostinil), considered to be BSC. BSC was chosen to align with the comparator arm (placebo) of the INCREASE trial, where patients received no treatment other than background medications for ILD management. While other immunomodulatory or immunosuppressive treatments (e.g. rituximab) were used and could contribute additional costs, only pirfenidone and nintedanib are considered in the model, as these were the treatments with notable cost implications and meaningful use.[80] NICE had not published guidance on any specific treatment for PH-ILD at the time of model development and no drugs for PH-ILD are available in the UK.

3.3 Clinical parameters and variables

3.3.1 Time-to-event parameters

As described in Section 3.2, the primary clinical data source for the economic model was the INCREASE trial. Additionally, a matching-adjusted indirect comparison of OS based on data from the Dawes et al. study was included as a scenario analysis.[75]

Parametric survival models were used to estimate the following time-to-event curves:

- Time to first clinical worsening events.
- Time to second clinical worsening events.
- Time to death.
- Time to treatment discontinuation (inhaled treprostinil only).

The curves were modelled independently and informed the proportion of the cohort in each health state during each cycle. Therefore, it was not necessary to calculate transition probabilities to determine the movement of patients between the health states.

In line with the methods outlined in the NICE Decision Support Unit TSD 14, the following parametric models were fitted to the individual patient survival data: exponential, Weibull, Gompertz, log-normal, log-logistic and generalised Gamma.[94] Coefficients were produced for each parametric model and used to extrapolate the survival models beyond the original trial period. The Akaike information criterion (AIC), Bayesian information criterion (BIC), visual inspection of the curve fits, and consultation with clinical experts were used to determine the best-fitting and most clinically plausible parametric model for each endpoint. More complex (flexible or spline-based) models were not considered owing to the complexities of fitting in a four-state PSM, the sensitivity of spline-based models to the number and placement of knots, and the possibility of overfitting to the 16-week data from INCREASE.

The hazard functions in both INCREASE and INCREASE OLE for inhaled treprostinil and placebo (assumed to be equivalent to BSC in the CEM) were not proportional, as shown by the time-to-event curves crossing, which indicates that the proportional hazard assumption (PHA) did not hold. This meant that a treatment group was not included as a covariate in the analysis. TSD 14 states that it is most appropriate to fit separate parametric models of the same type (e.g., exponential for both arms of the model) where the PHA does not hold. Therefore, as per this recommendation, the data were split by treatment arm and individual parametric models, without a treatment group covariate, were fitted to each treatment arm.[94]

Overall, the CEM includes the functionality for the cost-effectiveness of inhaled treprostinil to be estimated for the following subgroups:

- All patients with PH-ILD excluding those with CPFE.
- Including only those that met the target dose of inhaled treprostinil: titrated up to a dose of nine breaths per session four times daily at any point during the 16-week study or OLE extension (depending on the curves selected).

It was possible to analyse data from all subgroups using the data from the INCREASE 16-week trial and the INCREASE OLE for the following survival analysis: time to death, time to CW1, and time to CW2. The CEM contained all the following data that were specific to each subgroup: coefficients, KM, goodness-of-fit statistics and Cholesky matrices.

Please note that it was possible to use subgroup-specific time to treatment discontinuation (TTD) data for the CPFE-excluded subgroup only. Data for the full population were used for TTD when any other subgroups were selected.

The model also contains the option for the KM data from the INCREASE 16-week trial to inform the modelled cohort in a within-trial analysis. The time horizon is set to 16 weeks (0.32 years) when this option is selected for the INCREASE trial. This was the maximum time point that KM data were available for all four endpoints.

3.3.1.1 Inhaled treprostinil

INCREASE OLE was an extended crossover trial, with all participants receiving inhaled treprostinil after the initial 16-week trial. All participants, regardless of prior treatment and dosage during the 16-week INCREASE trial, started the OLE on the same initial inhaled treprostinil dose of three breaths, four times daily. It was possible to split the study cohort by whether they received inhaled treprostinil or the placebo in the prior 16-week trial. A set of parametric distributions was generated for the INCREASE OLE study inhaled treprostinil arm to dictate health state membership for those patients getting inhaled treprostinil in the cost-effectiveness model

3.3.1.2 BSC

The following curves for the BSC arm in the model were informed from the placebo arm of the INCREASE 16-week study:

- Time to the first clinical worsening event.
- Time to the second clinical worsening event.
- Time to death.

In the base case, overall survival is informed by the placebo arm of the INCREASE OLE study. As patients within the placebo arm of the INCREASE 16-week study crossed over to inhaled treprostinil when entering INCREASE OLE, it was necessary to

adjust survival for treatment crossover. The model supports the following options for modelling OS in the BSC arm:

- **Base case:** Nathan 2023: A *post hoc* analysis of OS using the INCREASE and INCREASE OLE trials to examine the impact of treatment crossover.[95]
- Matching-adjusted naïve indirect comparison based on data from Dawes *et al.* 2022: A retrospective observational cohort study which reported separate mortality estimates of patients who received PDE5is and those who did not (defined as receiving BSC).[75]
- User-defined hazard ratios compared to inhaled treprostinil (assuming the PHA holds).

Nathan 2023 was selected as the base case as it provides a *post hoc* analysis of overall survival using data from the INCREASE and INCREASE OLE studies, with adjustments for treatment crossover from placebo to inhaled treprostinil. As this approach uses data from the randomised controlled trial and directly addresses crossover to inhaled treprostinil, it was preferred over the unadjusted MAIC (using observational data from Dawes *et al.* 2022) as the basis of the base case analysis.

The options selected for the base case analysis are presented in Section 3.9.

3.3.2 Overall survival

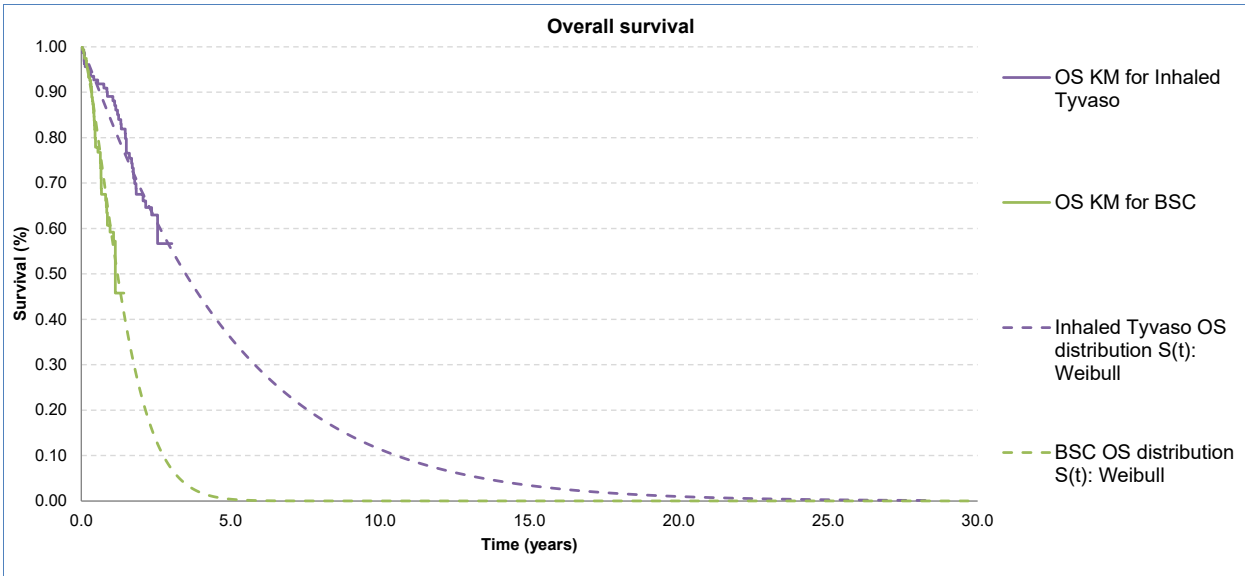
The options available to model OS are presented in Table 15. The base-case analysis selection is underlined and highlighted in bold. The base-case analysis extrapolations for OS in both arms of the model, along with the respective KM data, are presented in Figure 18.

Table 15. Options for determining overall survival

Source options	Subgroups available	Options available
Parametric Analysis: Inhaled Treprostinil Options		
• INCREASE 16-weeks • **INCREASE OLE**	• **Full population** • CPFE excluded • Met target dose	• Exponential • **Weibull** • Gompertz • Log-normal • Log-logistic • Generalised gamma
Parametric Analysis: Comparator Arm Options		
• **Nathan 2023 RPSFT Crossover Model** • INCREASE 16-weeks • Matching-adjusted indirect comparison (MAIC)	• **Full population** • CPFE excluded	• Exponential • **Weibull** • Gompertz • Log-normal • Log-logistic • Generalised gamma
• Nathan 2023 Crossover RPSFT HR vs. inhaled treprostinil		
Within-Trial Analysis Options: Sources set to the same across both arms		
• INCREASE 16-weeks	• Full population	

Key: CPFE, Combined pulmonary fibrosis and emphysema; HR, hazard ratio; OLE, open-label extension; RPSFT, rank-preserving structural failure time.

Figure 18. Long-term OS extrapolations: Base-case analysis (INCREASE OLE vs *post hoc* adjustment for inhaled treprostinil and BSC respectively)



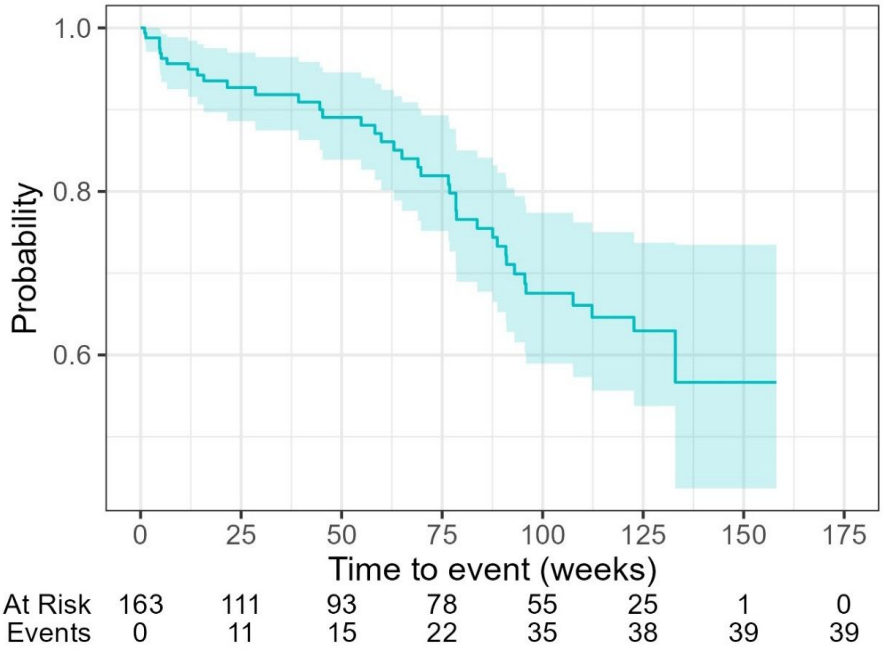
Multiple options are included in the model for extrapolating OS, particularly for the BSC arm. These options are described in detail in the following sub-sections, with the selected base-case analysis detailed in Section 3.9.

3.3.2.1 Inhaled treprostinil overall survival

3.3.2.1.1 INCREASE OLE trial OS (base-case analysis: inhaled treprostinil arm)

The OS KM curve for inhaled treprostinil in the INCREASE OLE trial is presented in Figure 19. Time 0 responds to the start date of the initial 16-week INCREASE trial (as opposed to the start of the OLE). Exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised gamma models were fitted to the curves, the AIC and BIC statistics for which are presented in Table 16. The best-fitting models, according to AIC and BIC, were the exponential and Gompertz models, respectively. The long-term extrapolation estimated with all distributions and the KM data for inhaled treprostinil from INCREASE OLE is presented in Figure 20.

Figure 19. KM curve showing OS with inhaled treprostinil in INCREASE OLE



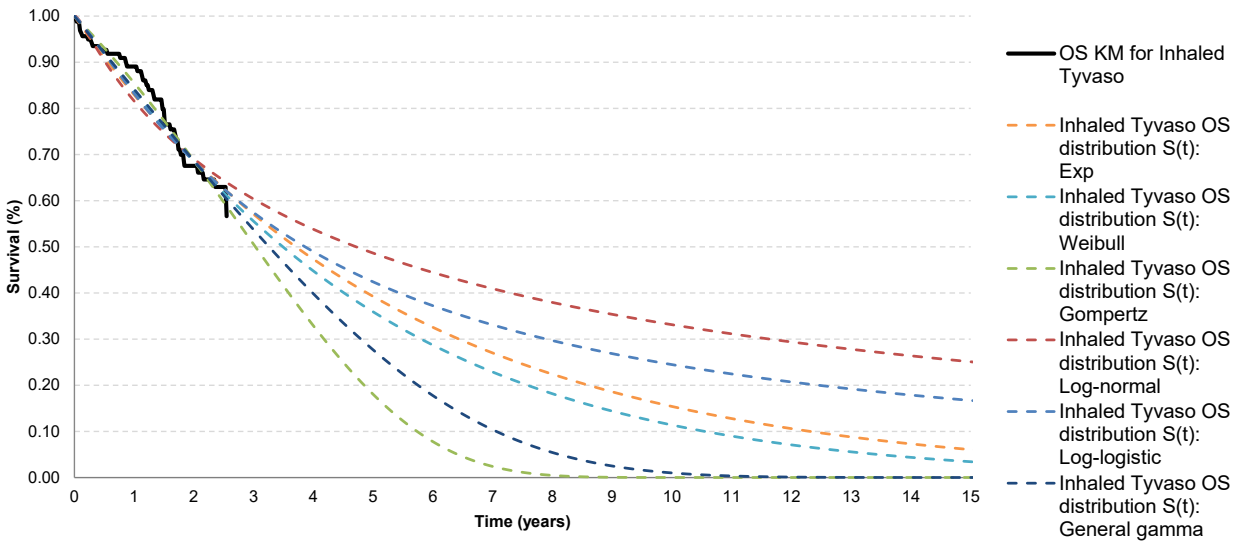
The base-case analysis used the INCREASE OLE data to inform the inhaled treprostinil arm as this was considered to be the most mature and relevant OS data available for inhaled treprostinil. While the exponential distribution provided the best statistical fit to the base-case KM data based on BIC and the second-best based on AIC (Table 16), expert opinion during a workshop with UK clinicians (N=2) in April 2025 considered it

too optimistic, as it failed to reflect the steep early drop observed in the KM curves. Similarly, although the Gompertz distribution ranked second by BIC and first by AIC, experts felt it overestimated mortality and was therefore not appropriate. Given that the Weibull distribution ranked third by both BIC and AIC, with generalised gamma performing poorly on both metrics, and to enable consistent distributional assumptions across treatment arms (see Section 3.3.2.2) in line with best practice, the Weibull distribution was selected as the basis of the base-case OS model.[94]

Table 16. AIC and BIC values for OS for INCREASE OLE

Distribution	Inhaled treprostinil	
	AIC	BIC
Exponential	521.03	**533.41**
Weibull	522.68	538.15
Gompertz	**520.87**	536.34
Log-normal	527.13	542.60
Log-logistic	523.85	539.32
Generalised gamma	523.99	542.55
Key: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, OS: Overall Survival		

Figure 20. Overall survival extrapolation based on INCREASE



3.3.2.2 BSC overall survival

3.3.2.2.1 Nathan 2023 Crossover Analysis for OS (base-case analysis: BSC arm)

A *post hoc* analysis of OS based the INCREASE 16-week data and INCREASE OLE was conducted to adjust for the effects of crossover to inhaled treprostinil, as reported in Nathan *et al.* 2023.[95] This was to account for participants that received the placebo during the 16 weeks of the INCREASE trial switching to inhaled treprostinil at the start of the OLE and, thus, to adjust for the effect of inhaled treprostinil in the long-term placebo survival extrapolations. Survival times for participants in the placebo arm were adjusted using the rank-preserving structural failure time (RPSFT) approach. The INCREASE crossover-adjusted data were considered the most appropriate source for informing OS in the BSC arm, as both arms were derived from the same RCT, and the RPSFT is a standard, commonly used, and well-accepted method of adjustment (NICE TSD 24 and Gurskyte *et al.* 2018).[71,96]

IPD with adjusted survival times for the placebo crossover subjects was utilised to generate survival analysis extrapolations of the placebo OS. This crossover-adjusted extrapolation of OS was intended to simulate the OS outcomes for patients in the placebo arm if they had not switched treatment during the OLE. The generated survival analysis extrapolations, in the form of the six standard parametric distributions, were incorporated into the model. This analysis refers to OS only and does not include an analysis of the clinical worsening or treatment discontinuation curves. The crossover analysis utilised the below parametric regression equation for the time to event since randomisation:

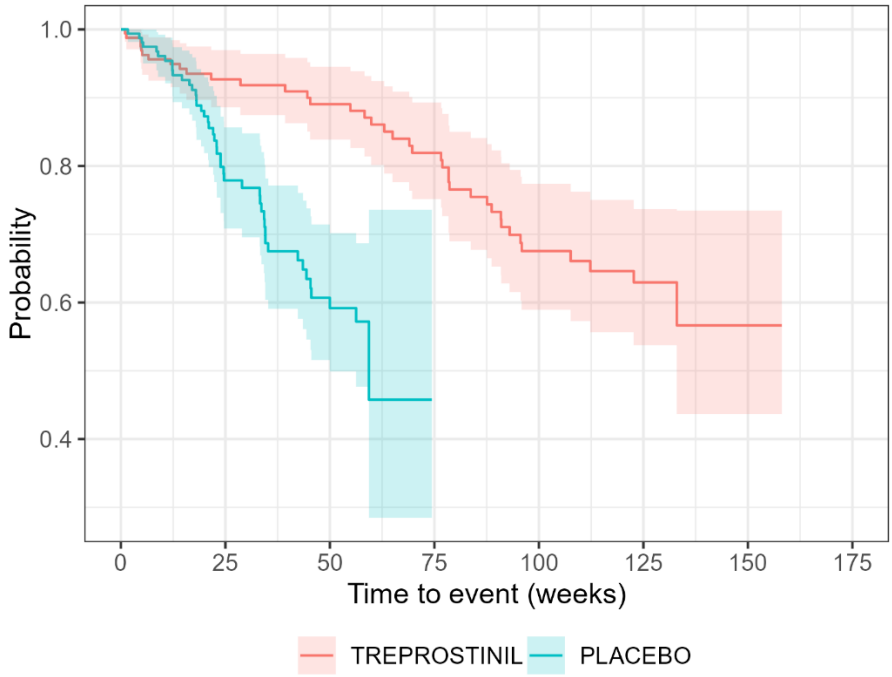
$$S(t)_{death} = B_1 Age_i + B_2 Sex_i + B_3 CPFEYes_i + B_4 PVR > 5_i$$

Where i is the ith individual in the data set.

The crossover analysis for the placebo arm and the original inhaled treprostinil arm from the INCREASE OLE are presented in Figure 21. The AIC and BIC statistical outputs are displayed in Table 17. While the log-logistic distribution provided the best statistical fit based on AIC and BIC, expert opinion during a workshop with UK clinicians (N=2) indicated that clinical practice is characterised by high rates of early mortality, with almost no patients alive at five years. This reflects data from Dawes *et al.* (2022), where most patients not treated with PDE5 inhibitors died within five years and median survival was 0.94 years (95% CI: 0.69 - 1.51).[75] As such, the log-logistic distribution was considered inappropriate. In contrast, the Gompertz and Weibull distributions

produced extrapolations more aligned with clinical expectations, showing low survival at five years. Given that the Weibull distribution was the second-best fitting model statistically based on AIC and BIC, it was selected for the BSC arm and, on the basis of the recommendation to fit separate parametric models of the same type in TSD 14, the Weibull distribution was therefore also adopted in the inhaled treprostinil arm. These distributions are reflected in Table 16, where the inhaled treprostinil arm of the INCREASE OLE is used and the crossover analysis data were used for the BSC arm in the base-case analysis. The long-term extrapolation estimated for all distributions is presented in Figure 22.

Figure 21. KM curve of overall survival for each arm in crossover analysis of the INCREASE OLE

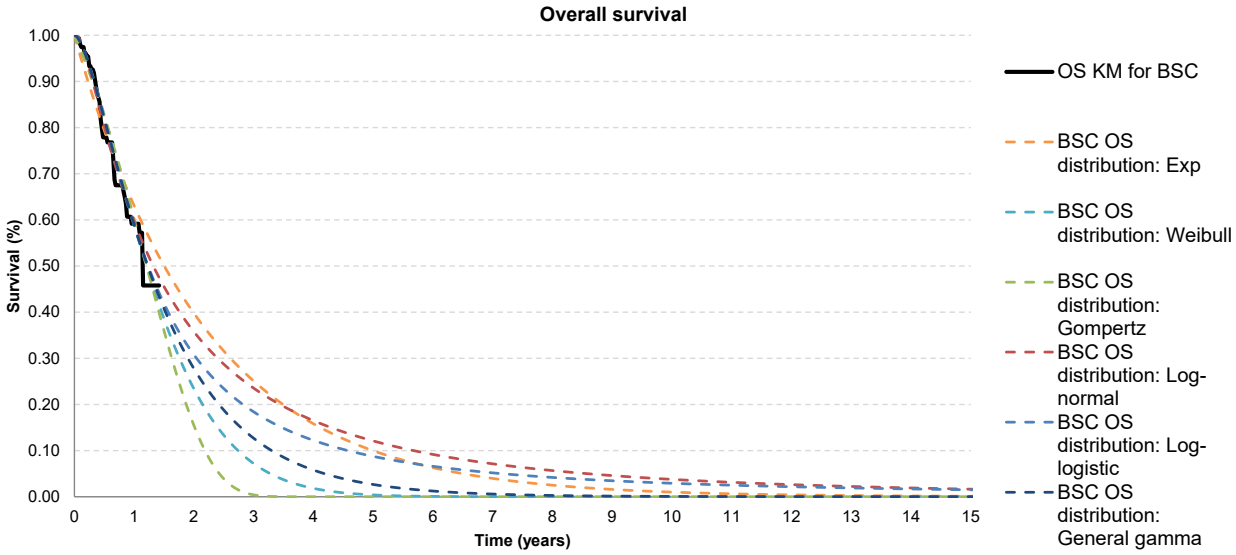


TREPROSTINIL								
At Risk	163	111	93	78	55	25	1	0
Events	0	11	15	22	35	38	39	39
PLACEBO								
At Risk	163	77	39	0	0	0	0	0
Events	0	28	43	45	45	45	45	45

Table 17. AIC and BIC values for time-to-death models using the crossover analysis of the INCREASE OLE

Distribution	Placebo	
	AIC	BIC
Exponential	520.11	535.58
Weibull	513.98	532.54
Gompertz	517.90	536.46
Log-normal	514.81	533.37
Log-logistic	**513.29**	**531.86**
Generalised gamma	515.62	537.28
Key: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion		

Figure 22. Overall survival extrapolation based on crossover analysis of the INCREASE OLE

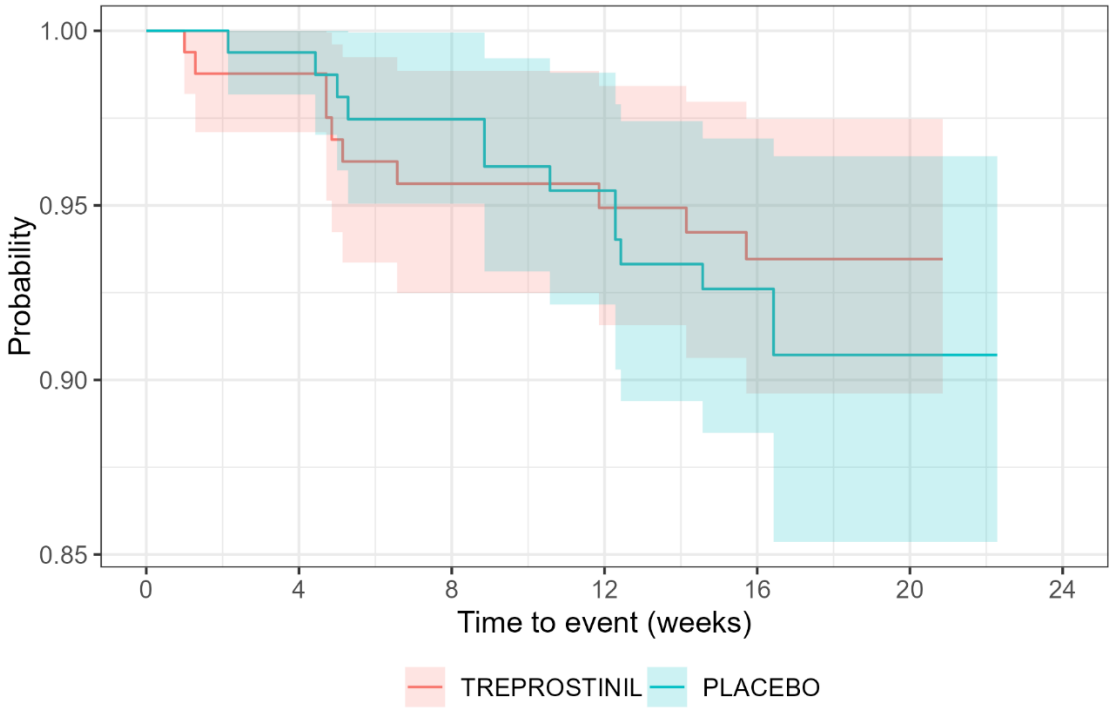


3.3.2.2.2 INCREASE (16-week) trial OS

All information presented in this section was sourced from the ad-hoc IPD analysis of INCREASE. The KM curves for OS by treatment arm for INCREASE are presented in Figure 23. The survival curves crossed, which indicated a departure from the PHA. The AIC and BIC statistics are presented in Table 18 and indicate that the exponential distribution is the best-fitting model for both the inhaled treprostinil and placebo data. The long-term extrapolations estimated for all distributions for inhaled treprostinil and BSC are presented in Figure 24.

Overall, the INCREASE OS KM data were less mature than the INCREASE OLE and the Dawes 2022 study. Therefore, neither arm of INCREASE was used in the base-case analysis but can be used as the basis of a within-trial scenario analysis.

Figure 23. KM curve of OS by treatment arm in INCREASE (16 weeks)

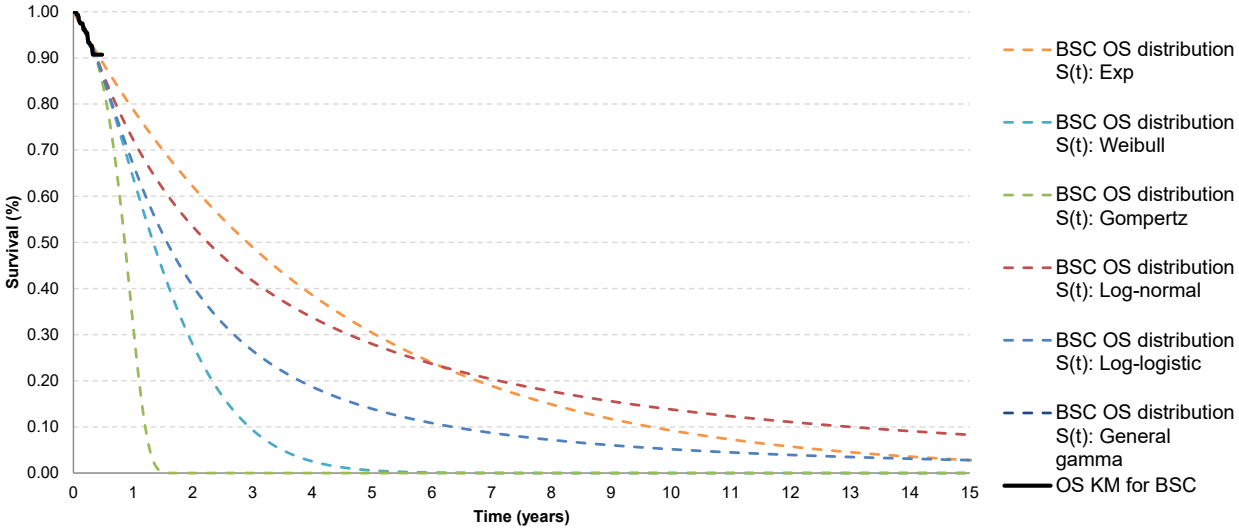


TREPROSTINIL							
At Risk	163	159	147	138	109	2	0
Events	0	2	7	8	10	10	10
PLACEBO							
At Risk	163	156	146	137	106	4	1
Events	0	1	4	7	11	12	12

Table 18. AIC and BIC values for OS by treatment arm for INCREASE (16 weeks)

Distribution	Inhaled treprostinil		Placebo	
	AIC	BIC	AIC	BIC
Exponential	**131.22**	**143.60**	156.02	**168.39**
Weibull	133.15	148.62	156.01	171.48
Gompertz	132.94	148.40	156.83	172.29
Log-normal	132.51	147.97	**154.68**	170.15
Log-logistic	133.00	148.47	155.78	171.25
Generalised gamma	135.32	153.88	Not applicable	Not applicable
Key: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion				

Figure 24. Long-term OS extrapolations for BSC using INCREASE (16 weeks) data



3.3.2.2.3 Dawes 2022 approximate KM OS and MAIC

Dawes 2022 approximate KM OS

Overall survival KM data from the Dawes 2022 study have also been incorporated into the model via a naïve indirect comparison.[75,97] The OS KM curves for patients receiving BSC were uploaded to the web application "WebPlotDigitizer", which was used to generate approximate coordinates for the KM curve.[75,98] Pseudo-IPD datasets were constructed using the extracted data with the Guyot algorithm (available in the 'survHE' R package).[99,100] Once pseudo-IPD were generated, the six standard parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were fit using the R package 'flexsurv',[101] as with all other survival analyses undertaken within the cost-effectiveness model. No treatment group covariate was included in the parametric models, and each was independent of the other. The extrapolated curves were then added to the economic model.

The recreated pseudo-KM for Dawes 2022 for patients receiving BSC is presented in Figure 25. The AIC and BIC statistical outputs are displayed in Table 19.

The long-term extrapolations estimated for all distributions are presented in Figure 26. Overall, the results of this analysis showed that the exponential curve was the best-fitting distribution for the BSC arm of Dawes 2022.[75] This was then presented as a scenario analysis to facilitate comparison with the BSC arm in INCREASE.

Figure 25. KM curve of overall survival for those who received BSC in Dawes *et al.* 2022[75]

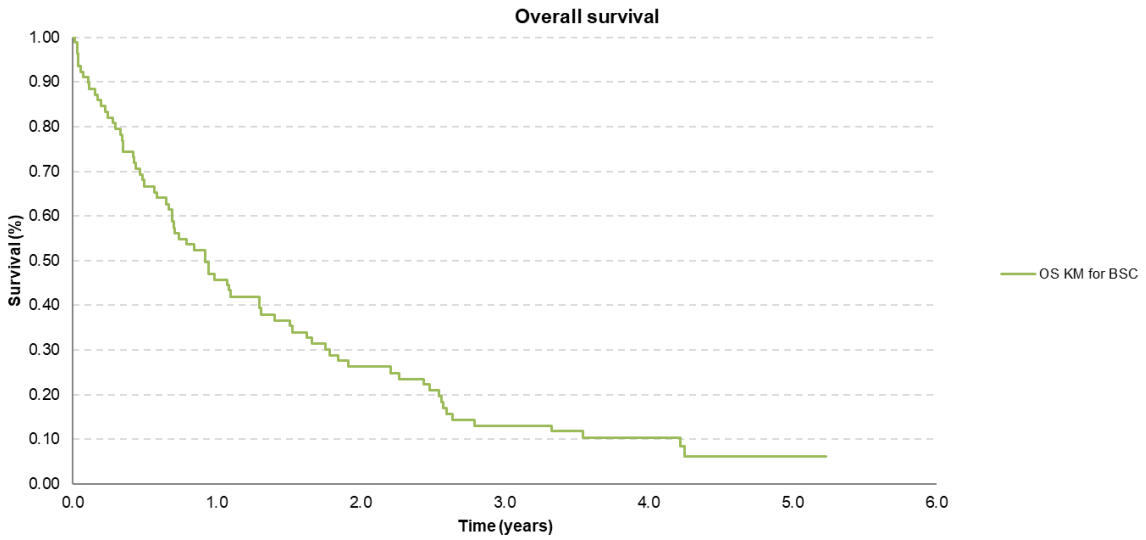
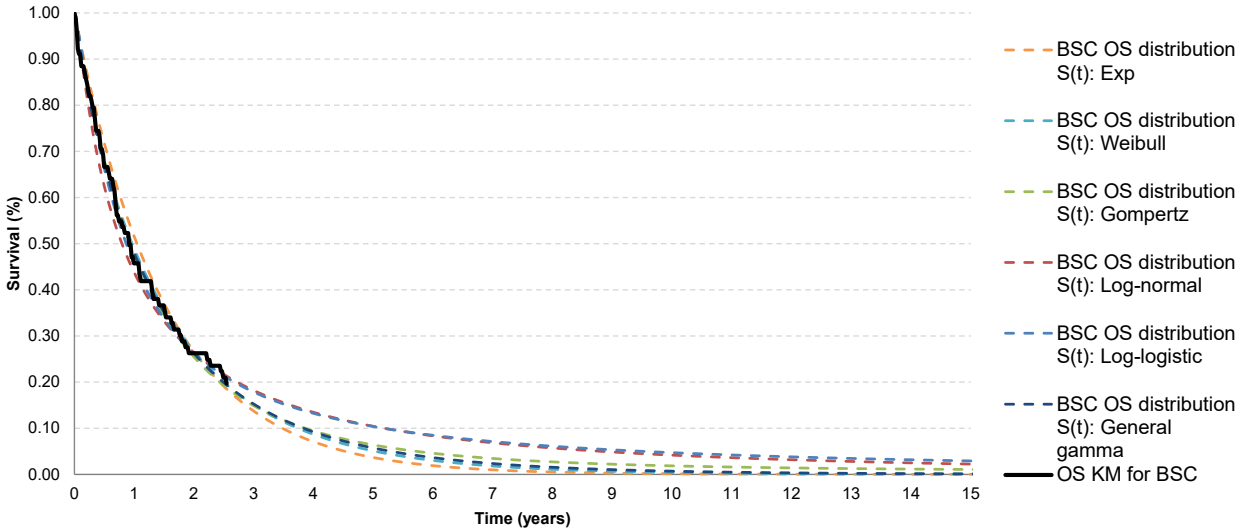


Table 19. AIC and BIC values for OS in the BSC arm for Dawes 2022[75]

Distribution	BSC arm	
	AIC	BIC
Exponential	**753.39**	**755.74**
Weibull	753.77	758.48
Gompertz	753.64	758.35
Log-normal	759.29	764.00
Log-logistic	756.96	761.67
Generalised gamma	755.57	762.64
Key: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion		

Figure 26. Overall survival extrapolations using Dawes 2022 (BSC arm)[20]



Key: BSC: Best Supportive Care, Exp: Exponential, Gompertz: Gompertz Distribution, ILD: Interstitial Lung Disease, KM: Kaplan–Meier, Log-normal: Log-Normal Distribution, OS: Overall Survival.

Dawes 2022 MAIC

Outcomes from the MAIC versus BSC based on INCREASE and Dawes *et al.* 2022 (Section 2.10.1) were also incorporated into the model by way of the inverse HR versus no treatment (Table 11; HR of 6.29 based on reciprocal HR of 0.16 from the MAIC). The MAIC was used as the basis of a scenario analysis.

3.3.2.2.4 Hazard ratios to inform comparator arm OS

The model incorporates functionality for a hazard ratio to inform overall survival in the comparator arm of the CEM. The RPSFT hazard ratio is included in the model (see Table 20), informed by Nathan 2023.[22] The model also includes the option for a user-defined hazard ratio for the purposes of conducting scenario analyses.

Table 20. BSC OS hazard ratios from Nathan 2023 [22]

Approach	Hazard ratio	Standard error	Notes
Rank-preserving structural failure time (RPSFT)	3.85	3.39	A hazard ratio of 0.26 converted to 3.85 (1/0.26) [22]
Note: a hazard ratio greater than one favours inhaled treprostinil.			

3.3.2.3 General population mortality

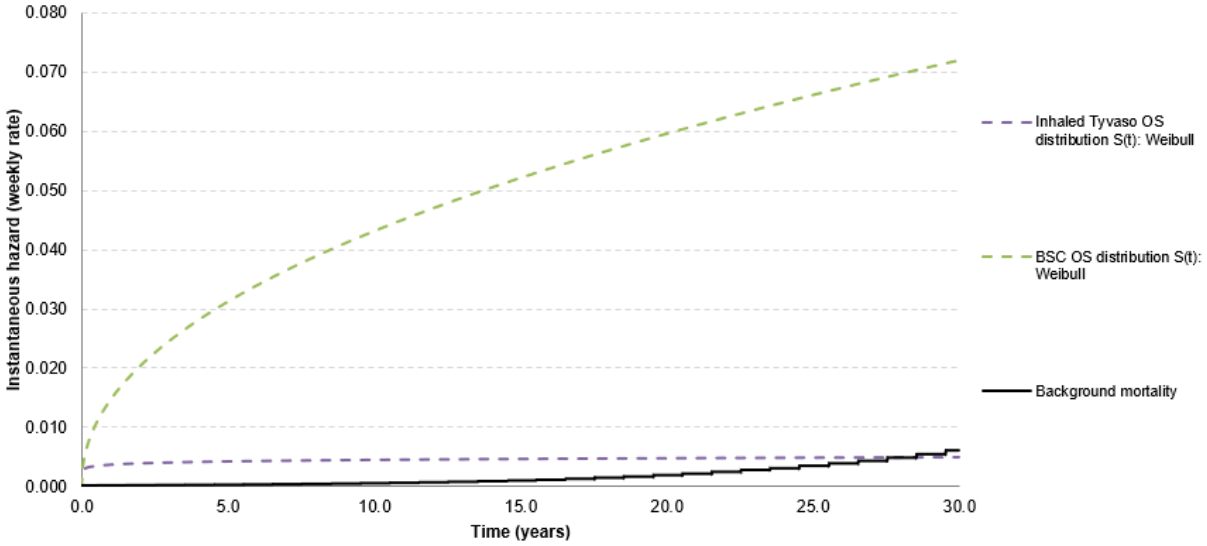
Survival was adjusted to ensure that the instantaneous hazard of death for those with PH-ILD could never be lower than general population mortality rates for an age- and

sex-matched cohort in the UK.[102] Specifically, the annual general population mortality rates were adjusted by the gender distribution reported in the INCREASE trial (53.1% male) and converted to weekly mortality rates.[87] The 2017-19 UK general mortality rates were used because they are the most recent UK national-level source available that was not impacted by the COVID-19 global pandemic.

In the base-case analysis, this cap on the instantaneous hazard was not applicable until year 28, as the weekly rate of death for either arm was higher than the weekly hazard in the general population for most of the time horizon.

Figure 27 shows the instantaneous weekly hazard of death, including the point at which mortality in the inhaled treprostinil arm is capped by general population mortality (~28 years).

Figure 27. Instantaneous hazard of death in the base-case analysis



3.3.3 Time to first clinical worsening

The options available to model time to first clinical worsening are presented in Table 21. The base-case analysis selection is underlined and highlighted in bold. The base-case analysis extrapolations in both arms of the model are presented in

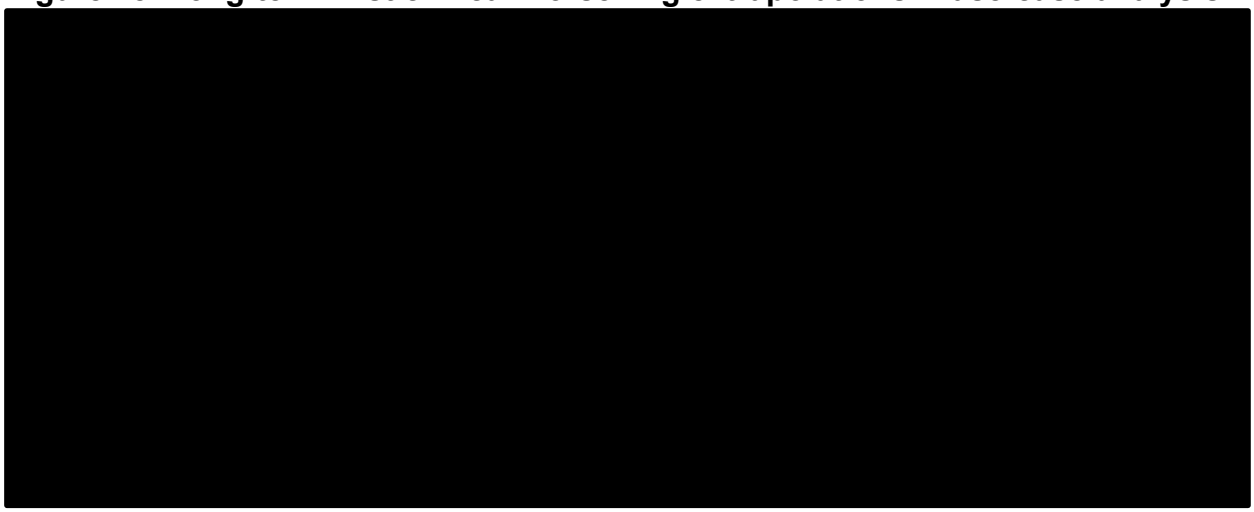
Figure 28.

Table 21. Options for determining time to first clinical worsening event

Source options	Subgroups available	Options available
Parametric Analysis: Inhaled Treprostinil Options		

• INCREASE 16-weeks • **<u>INCREASE OLE</u>**	• **<u>Full population</u>** • CPFE excluded	• Exponential • Weibull • Gompertz • **<u>Log-normal</u>** • Log-logistic • Generalised gamma
• **<u>Clinical worsening event stratification</u>**		• Treatment-dependent • **<u>Independent</u>**
Parametric Analysis: Comparator Arm Options		
• **<u>INCREASE 16-weeks</u>**	• **<u>Full population</u>** • CPFE excluded	• **<u>Exponential</u>** • Weibull • Gompertz • Log-normal • Log-logistic • Generalised gamma
• **<u>Clinical worsening event stratification</u>**		• Treatment-dependent • **<u>Independent</u>**
Within-Trial Analysis Options: Sources set to the same across both arms		
• INCREASE 16-weeks	• Full population	
Key: CPFE, Combined pulmonary fibrosis and emphysema; HR, hazard ratio; OLE, open-label extension. **Notes:** Base-case analysis selected settings are underlined and in bold.		

Figure 28. Long-term first clinical worsening extrapolations: Base-case analysis



The time to first clinical worsening curves were used to determine the proportion of the total cohort that occupied the 'CW1' state per cycle. As the occupancy of the CW1 and

CW≥2 are dependent on which curves are selected, it could be possible that the predicted occupancy of CW1 is higher than CW≥2. Therefore, the health state occupancy of CW1 was capped by the CW≥2 state in the CEM to ensure the occupancy of the CW1 state could never be higher than the CW≥2 state.

The modelled cohort were stratified into the different types of clinical worsening events to capture the differences in initial and ongoing resource use associated with the different events. These stratifications were informed from the ad-hoc IPD analysis of the INCREASE 16-week trial as treatment-dependent data from the INCREASE trial could be utilised. The model included the option for the distribution of events to be equivalent across treatment arms or to be treatment-specific (as presented in Table 22). The distributions were assumed to be equivalent across treatment arms in the base case analysis. In the base case analysis, lung transplant costs were not explicitly modelled, due to the very low numbers (as described previously).

Table 22. Distribution of first clinical worsening events from INCREASE 16-week

Stratification of events: % (n)	Lung transplant	Exacerbation	Hospitalisation	Fall in FVC%	Fall in 6MWD
Treatment independent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment dependent: Inhaled treprostinil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment dependent: BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: 6MWD, 6-minute walking distance; FVC, forced vital capacity.					

3.3.3.1 INCREASE OLE trial and INCREASE OLE 16-week trial CW1 (Base-case analysis: inhaled treprostinil arm and BSC)

All information presented in this section was sourced from the ad-hoc IPD analysis of the INCREASE OLE trial.

The KM curve for time to first clinical worsening for inhaled treprostinil from the INCREASE OLE study is presented in Figure 29. The time 0 responds to the start date of the initial 16-week INCREASE trial, rather than the start of the OLE.

The KM curve for time to first clinical worsening for inhaled treprostinil and BSC from the INCREASE OLE 16-week trial is presented in Figure 30.The KM curves crossed

which indicated a departure from the PHA. Over 75% of patients had experienced an event by the end of the follow-up period. Therefore, the data were considered mature.

The AIC and BIC statistics for inhaled treprostinil from INCREASE OLE, as well as for inhaled treprostinil and BSC from the INCREASE 16-week trial, are presented in Table 23. These indicate that the log-normal distribution provided the best fit for inhaled treprostinil from INCREASE OLE, while an exponential distribution was the best fit for both treatments in the INCREASE 16-week trial. The long-term extrapolation estimated across all distributions for INCREASE OLE and INCREASE 16-week trial is presented in

Figure 31 and Figure 32, respectively.

The first clinical worsening event curves from the INCREASE OLE were used to inform the inhaled treprostinil arm in the base case analysis due to the maturity of the KM data and their relevance to clinical worsening events for inhaled treprostinil. Similarly, the time to first clinical worsening event curves informed from the INCREASE 16-week trial were used to inform the BSC arm in the base case analysis because the KM data were mature and the most robust data available.

Weibull was the preferred extrapolation for CW1 for inhaled treprostinil from the INCREASE OLE trial based on expert opinion from a clinician workshop (N=2), as it produced the CW1 rates consistent with clinical experience—99.5% of patients experiencing an event by five years and 100% by ten years. However, Weibull demonstrated poor statistical fit, with the second worst AIC and BIC values (see Table 23). In contrast, the log-normal distribution also aligned well with clinical expectations—97.2% of patients experiencing an event by five years and 99% by ten years—and offered a stronger statistical fit, with the second-best AIC and BIC. Accordingly, log-normal was selected for CW1 for inhaled treprostinil.

Exponential was the preferred extrapolation for CW1 for BSC from the INCREASE 16-week trial based on UK expert opinion (N=2 clinicians), as all patients were expected to experience a CW1 event within three years—consistent with clinical experience. Given that the exponential distribution demonstrated a good statistical fit (see Table 23), with the second-best AIC and the best BIC, it was selected for CW1 in the BSC arm.

Figure 29. KM curve of time to first clinical worsening event for inhaled treprostinil in INCREASE OLE

Figure 30. KM curve of time to first clinical worsening event by treatment arm in INCREASE (16 weeks)

Table 23. AIC and BIC for time to first clinical worsening: inhaled treprostinil from INCREASE OLE, and inhaled treprostinil plus BSC from the INCREASE 16-week trial.

Distribution	INCREASE OLE		INCREASE 16-week trial	
	Inhaled treprostinil		BSC (placebo)	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Key: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, BSC: Best Supportive Care, OLE: Open-Label Extension.				

Figure 31. Time to first clinical worsening event extrapolations for inhaled treprostinil, INCREASE OLE

Figure 32. Time to first clinical worsening event extrapolations for BSC using INCREASE (16 weeks)

3.3.4 Time to second clinical worsening

The options available to model time to second clinical worsening are presented in Table 24. The base case analysis selection is underlined and highlighted in bold. The base-case analysis extrapolations in both arms of the model are presented in

Figure 33.

Table 24. Options for determining time to second clinical worsening event

Source options	Subgroups available	Options available
Parametric Analysis: Inhaled Treprostinil Options		
• INCREASE 16-weeks • **INCREASE OLE**	• **Full population** • CPFE excluded	• Exponential • Weibull • Gompertz • **Log-normal** • Log-logistic • Generalised gamma
• **Clinical worsening event stratification**		• Treatment-dependent • **Independent**
Parametric Analysis: Comparator Arm Options		
• **INCREASE 16-weeks**	• **Full population** • CPFE excluded	• Exponential • Weibull • Gompertz • **Log-normal** • Log-logistic

		• Generalised gamma
• **<u>Clinical worsening event stratification</u>**		• Treatment-dependent • **<u>Independent</u>**
Within-Trial Analysis Options: Sources set to the same across both arms		
• INCREASE 16-weeks	• Full population	
Key: CPFE, Combined pulmonary fibrosis and emphysema; HR, hazard ratio; OLE, open-label extension. **Note:** Base-case analysis selected settings are underlined and in **bold**		

Figure 33. Long-term second clinical worsening extrapolations: Base-case analysis

The time-to-second clinical worsening curves were used to determine the proportion of the total cohort that occupied the 'CW≥2' state per cycle.

Similar to the CW1 state, the modelled cohort were stratified into different types of clinical worsening events to capture the differences in initial and ongoing resource use associated with the different events. These stratifications were informed from the ad-hoc IPD analysis of the INCREASE 16-week trial as treatment-dependent data from the INCREASE trial could be utilised.

Table 25. Distribution of second clinical worsening events

Stratification of events: % (n)	Lung transplant	Exacerbation	Hospitalisation	Fall in FVC%	Fall in 6MWD
Treatment independent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment dependent: Inhaled treprostinil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment dependent: BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: 6MWD: Six-minute walking distance; FVC: Forced Vital Capacity; n: number.					

3.3.4.1 INCREASE OLE trial and INCREASE 16-week trial CW2 (Base-case analysis: inhaled treprostinil arm and BSC)

All information presented in this section was sourced from the ad-hoc IPD analysis of the INCREASE OLE trial.

The KM curve of time to second clinical worsening event for inhaled treprostinil from the INCREASE OLE trial is presented in Figure 34. The time 0 responds to the start date of the initial 16-week INCREASE trial, rather than the start of the OLE. Approximately 75% of patients had experienced an event by the end of the follow-up period. Therefore, the data were considered mature.

The KM curves of time to second clinical worsening event by treatment arm for the 16-week INCREASE trial are presented in Figure 35. The survival curves crossed which indicated a departure from the PHA. Approximately 50% of patients had experienced an event by the end of the follow-up period. Therefore, the data were considered to be reasonably mature.

The AIC and BIC statistics for inhaled treprostinil from INCREASE OLE, as well as for inhaled treprostinil and BSC from the INCREASE 16-week trial, are presented in Table 26. These indicate that the log-normal distribution provided the best fit for inhaled treprostinil from INCREASE OLE and INCREASE 16-week trial, while the Weibull was the best fitting distribution for BSC from INCREASE 16-week trial. The long-term extrapolations estimated across all distributions for INCREASE OLE and INCREASE 16-week trial is presented in Figure 36 and Figure 37, respectively.

The second clinical worsening event curves informed from the INCREASE OLE trial were used for the inhaled treprostinil arm in the base case analysis because of the maturity of the KM and as they were the most reflective clinical worsening event data available for inhaled treprostinil. The time to second clinical worsening event curves informed from the INCREASE 16-week trial were used to inform the BSC arm in the base-case analysis because of the maturity of the KM and as they were the most reflective of the available clinical worsening event data for BSC.

As per the guidance described in TSD14, it is recommended that the same distribution is selected for both arms of the model unless it is clinically justified to do otherwise.[94] The log-normal distribution was selected for the base case analysis as it provided a good fit for BSC in the INCREASE 16-week trial (third-best option) and was the best-fitting option for inhaled treprostinil from the INCREASE OLE trial. UK clinicians (N=2) also confirmed the log-normal extrapolations for the time to second clinical worsening events were clinically plausible for the inhaled treprostinil and BSC arms.

Figure 34. KM curve of time to second clinical worsening event for inhaled treprostinil in INCREASE OLE

Figure 35. KM curve of time to second clinical worsening event by treatment arm in INCREASE (16 weeks)

Table 26. AIC and BIC for time to second clinical worsening: inhaled treprostinil from INCREASE OLE and BSC from the INCREASE 16-week trial.

Distribution	INCREASE OLE		INCREASE 16-week trial	
	Inhaled treprostinil		BSC (Placebo)	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, BSC: Best Supportive Care, OLE: Open-Label Extension.

Figure 36. Time to second clinical worsening event extrapolations for inhaled treprostinil using INCREASE OLE

Figure 37. Time to second clinical worsening event extrapolations for BSC using INCREASE (16 weeks)

3.3.5 Time to treatment discontinuation

The options available to model time to treatment discontinuation are presented in Table 27. The base-case analysis selection is underlined and highlighted in bold. All the extrapolations for the inhaled treprostinil arm of the model are presented in Figure 38.

Table 27. Options for determining time to treatment discontinuation

Source options	Subgroups available	Options available
Parametric Analysis: Inhaled Treprostinil Options		
• **INCREASE OLE**	• **Full population** • CPFE excluded	• Exponential • Weibull • Gompertz • Log-normal • Log-logistic • **Generalised gamma**
Key: CPFE, Combined pulmonary fibrosis and emphysema; OLE, open-label extension.		

Figure 38. Long-term time to treatment discontinuation (TTD) extrapolations

The time to treatment discontinuation of inhaled treprostinil is informed by survival analysis using a combination of the 16-week INCREASE and INCREASE OLE trial data. Please note that within the model the time to treatment discontinuation only directly impacts costs (i.e. patients do not switch to the placebo clinical worsening and survival curves after they have discontinued). This was because the other time-to-event curves for inhaled treprostinil already account for those participants who discontinued during the trial (i.e. the efficacy of discontinued patients was captured). Time to treatment discontinuation is informed from the INCREASE OLE study in the base case.

The KM curve and number at risk table for treatment discontinuation are presented in Figure 39. The time 0 corresponds to the start date of the initial 16-week INCREASE trial, rather than the start of the OLE. The preferred models, based on AIC and BIC outputs, were Weibull and exponential, as shown in the results in Table 28. However,

feedback from UK clinicians (N=2) suggested the generalised gamma would be more appropriate as it reflects a faster rate of discontinuation that is more closely aligned with the high mortality rates expected in patients with PH-ILD; the generalised gamma distribution was also the second-best fitting model by AIC. The long-term extrapolations presented using the generalised gamma distribution are presented in Figure 40. This was the distribution used in the base case analysis.

Discontinuation parameters were also applied for pirfenidone and nintedanib. However, only a small number of participants in the INCREASE trial received these treatments as concomitant medicines. Approximately 9% (44) and 13% (30) of participants were treated at baseline with nintedanib and pirfenidone, respectively. Given the small number of patients that received those treatments within the trial it was judged that the use of the trial data to inform the long-term discontinuation of the treatments would introduce high levels of uncertainty. Therefore, alternative data were sought for this parameter, as described further in Section 3.5.1.2.

Figure 39. KM curve time to discontinuation for inhaled treprostinil treatment in INCREASE OLE

Table 28. AIC and BIC values for time to inhaled treprostinil treatment discontinuation using INCREASE OLE

Distribution	Inhaled treprostinil	
	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Figure 40. Time to inhaled treprostinil discontinuation extrapolation based on INCREASE OLE: base-case analysis

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

The options available to capture HRQoL are presented in Table 29. The base-case analysis selection is underlined and highlighted in bold. The base-case analysis HRQoL inputs are presented in Table 30.

Table 29. All available options for HRQoL

Source options	Mapping algorithm	Type of utility
Options for HRQoL		
• INCREASE 16-week univariate SGRQ • **INCREASE OLE univariate SGRQ**	• Starkie 2011 • **Freemantle 2015**	• **Treatment-independent SGRQ** • Treatment-dependent SGRQ
• INCREASE OLE GLM		• Treatment-independent SGRQ

Key: GLM, generalized linear model; OLE, open-label extension; SGRQ, Saint George's Respiratory Questionnaire.
Note: Base-case analysis selected settings are underlined and in **bold**

Table 30. Base-case analysis HRQoL inputs

Health states	Inhaled treprostinil			BSC		
	SGRQ	EQ-5D	AF	SGRQ	EQ-5D	AF
Clinical worsening free (CWF)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one (CW1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two (CW≥2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AF, adjustment factor; CW, clinical worsening; CWF, clinical worsening-free; SGRQ, Saint George's Respiratory Questionnaire.
Note: Given the lack of treatment-dependent HRQoL data for best supportive care from INCREASE OLE, it was assumed to be the same as inhaled treprostinil

A pragmatic targeted literature search was undertaken to inform the HRQoL inputs in the CEM at the time of model conceptualisation followed by a full systematic literature review that was conducted in January 2024 and updated in January 2025 (Appendix F). However, there was a paucity of evidence regarding HRQoL in patients with PH-ILD. The lack of HRQoL data was discussed during the advisory boards. The clinical experts confirmed that it would not be appropriate to use HRQoL values associated with ILD or PH because they would not accurately depict the impact of PH-ILD. In consideration of this expert advice, an analysis of the INCREASE 16-week and INCREASE OLE study data was undertaken to estimate the HRQoL associated with the CWF, CW1 and CW≥2 health states (Section 3.2.3.1). HRQoL data in both trials were collected in the form of the SGRQ questionnaire. No EQ-5D data were collected in INCREASE.

As of writing, a study initiated by PHA UK in March 2025 is assessing the sensitivity of the EmPHasis-10 in PH-ILD, but results have not yet been published. While the SGRQ has not been validated for use in PH-ILD, there are no validated alternatives with

mapping algorithms to the EQ-5D to generate utility values. Therefore, the SGRQ was the most appropriate measure to inform the economic model, as corroborated by experts attending advisory board meetings. There is a possibility that the SGRQ will overestimate utility because patients will not complete the questionnaire whilst in hospital (i.e. during an exacerbation). However, this is expected to be conservative from the perspective of inhaled treprostinil, which is associated with fewer clinical worsening events. The same phenomenon would be expected to have occurred had the EQ-5D been used instead of the SGRQ.

HRQoL was analysed in both the INCREASE 16-week and INCREASE OLE using participant scores from the SGRQ. Two analyses were performed: univariate descriptive analysis (Section 3.4.3) and multivariate regression analysis (Section 3.4.4).

3.4.2 Mapping

Given that SGRQ data were collected during the INCREASE trial, it was necessary to convert the cohort-level SGRQ scores into EQ-5D-3L values that could be included as utilities within the model. A review of the literature was undertaken and three papers describing the mapping process were identified.[103-105] Two of those publications reported relevant algorithms which could be used to map from SGRQ to EQ-5D-3L. The Wilson 2016 abstract did not report the algorithm itself, so could not be used within the model.[104] Therefore, the model contained the functionality for the user to select one of these two algorithms (Freemantle or Starkie).

The algorithm used in the base-case analysis (Freemantle, 2015) was based on a double-blind multicentre study conducted in England and Wales in which 181 patients with IPF were enrolled and 202 pairs of data were collected recording both SGRQ and EQ-5D-3L.[105] The Freemantle algorithm was used in the base-case analysis given the similarity of characteristics between PH-ILD and IPF. The following formula was used for this algorithm:

$$EQ - 5D - 3L = 1.3246 - 0.01276 \times SGRQ$$

The second algorithm (Starkie, 2011) was estimated based on a large sample of patients with chronic obstructive pulmonary disease (COPD; 14,612 observations from 3,640 patients).[103] The following formula was used for this algorithm:

$$EQ - 5D - 3L = 0.9617 - (0.0013 \times SGRQ) - 0.001 \times SGRQ^2 + 0.0231 \times \%male$$

The Freemantle algorithm was selected over the Starkie algorithm on the grounds that IPF (the Freemantle patient population) is a form of ILD, which is characterised by progressive interstitial scarring and restrictive lung physiology, whereas COPD (the Starkie patient population) is defined by airway inflammation and emphysema leading to an obstructive defect (Ghosh, 2022). Mappings in COPD may therefore meaningfully differ from those in patients with IPF. In alignment with NICE guidelines, the estimated EQ-5D-3L values were age-adjusted, using Hernández-Alava (2022), to account for decreasing HRQoL as patients age and to prevent the overestimation of quality of life. To reflect disease-specific decrements, a relative adjustment factor was calculated by dividing the health state utility by the corresponding population norm utility. This factor was then applied to the general population utility values to derive age- and gender-adjusted utilities for each modelled health state, ensuring consistency with population ageing trends. These adjustment factors are detailed in section 3.4.3.

A population norm utility value of 0.81 was estimated from the EQ-5D-3L NICE DSU Health Survey for England data set.[106] The population norm was estimated using the baseline characteristics of the INCREASE trial (an average age of 66 years old and 53.1% male).

The model contained the option to use the extracted average SGRQ (treatment dependent or treatment independent) or to use SGRQ derived from regression analysis from the INCREASE 16-week and INCREASE OLE studies (Section 3.4.3 and Section 3.4.4 respectively). It was deemed unnecessary to apply one-off disutilities when a person experienced a clinical worsening event because the HRQoL impact of these events would have been captured within the HRQoL values derived directly from the INCREASE trial and INCREASE OLE data.

3.4.3 Extracted univariate SGRQ

The SGRQ inputs estimated from the INCREASE trial and OLE study are presented in Table 31. These were estimated using data from INCREASE and OLE at the last follow-up of 16-weeks and week 48, respectively. These time points were used because the population numbers in each health state were considered large enough to

be statistically relevant. SGRQ data were also collected at week 108 but there was a substantial number of missing data points for this visit. For example, only 14 and 17 patients in the CWF and CW1 health states, respectively, reported SGRQ data at week 108. Therefore, it was judged that any data from week 108 would not be robust, due to the small sample size, and the data were excluded from the analysis.

One-way analysis of variance (ANOVAs) was performed to test for any statistically significant differences between groups. The p-values from the ANOVAs were <0.001 at week 16, 0.001 at week 48 and 0.251 at week 108. This indicated a lack of statistical significance in the difference in SGRQ between health states at week 108, which further supported the exclusion of the data from this timepoint.

The analysis was performed for all participants as well as stratified by treatment arm. Therefore, both treatment-independent and treatment-dependent values were reported for each health state within INCREASE. INCREASE OLE treatment-independent values were used in the base case, with values for best supportive care assumed to be the same as those for inhaled treprostinil, due to the lack of HRQoL data for best supportive care from INCREASE OLE.

The estimations of the mapped EQ-5D-3L values using the Freemantle and Starkie algorithms are presented in Table 32 and Table 33, respectively. These mapped EQ-5D-3L values were then adjusted based on the EQ-5D-3L population norm for the same age group and gender distribution. For example, the population norm for the modelled cohort upon entry to the model (with a starting of 66.45 years old and 53.07% proportion male) was estimated to be 0.816. The health-state-specific EQ-5D-3L values were then divided by the population norm to estimate the adjustment factor. For example, a health state utility value of 0.408 would result in an adjustment factor of 0.50. The adjustment factors were multiplied by the population norm utility of the cohort in each cycle (which changed as the model cohort aged throughout the time horizon).

To populate the HRQoL inputs in the base case analysis, the univariate treatment-independent INCREASE OLE trial data were used to keep consistency between sources used for the base-case analysis time-to-event data.

Table 31. Summary of SGRQ data from the IPD analysis of the INCREASE trials

Treatment-independent	INCREASE (at 16 weeks)			INCREASE OLE (at week 48)		
	SGRQ	SD	N	SGRQ	SD	N
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inhaled treprostinil only	**INCREASE (at 16 weeks)**			**INCREASE OLE (at week 48)**		
	SGRQ	**SD**	**N**	**SGRQ**	**SD**	**N**
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC only	**INCREASE (at 16 weeks)**			**INCREASE OLE (at week 48)**		
	SGRQ	**SD**	**N**	**SGRQ**	**SD**	**N**
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: N, number; N/R, not reported; OLE, open-label extension; SGRQ, Saint George's Respiratory Questionnaire; SD, standard deviation

Note: Values underlined in **bold** indicate base case SGRQ scores, SDs, and patient numbers. Given the lack of treatment-dependent HRQoL data for best supportive care from INCREASE OLE, it is assumed to be the same as inhaled treprostinil

Table 32. Outcomes of mapping SGRQ values to EQ-5D values based on the Freemantle algorithm (IPF) and adjustment factors reflecting the mapped EQ-5D value as a proportion of an age- and sex-matched general population estimate [105]

Treatment-independent	INCREASE (at 16 weeks)			INCREASE OLE (at week 48)		
	SGRQ	EQ-5D	AF	SGRQ	EQ-5D	AF
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inhaled treprostinil only	**INCREASE (at 16 weeks)**			**INCREASE OLE (at week 48)**		
	SGRQ	**EQ-5D**	**AF**	**SGRQ**	**EQ-5D**	**AF**
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC only	**INCREASE (at 16 weeks)**			**INCREASE OLE (at week 48)**		
	SGRQ	**EQ-5D**	**AF**	**SGRQ**	**EQ-5D**	**AF**
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AF, Adjustment factor; N/R, not reported; SGRQ, Saint George's Respiratory Questionnaire

Note: Values underlined in **bold** indicate base case SGRQ scores, EQ-5D utilities and adjustment factors. Given the lack of treatment-dependent HRQoL data for best supportive care from INCREASE OLE, it is assumed to be the same as inhaled treprostinil

Table 33. Outcomes of mapping SGRQ values to EQ-5D values based on the Starkie algorithm (COPD) and adjustment factors reflecting the mapped EQ-5D value as a proportion of an age- and sex-matched general population estimate[103]

Treatment-independent	**INCREASE (at 16 weeks)**			**INCREASE OLE (at week 48)**		
	SGRQ	**EQ-5D**	**AF**	**SGRQ**	**EQ-5D**	**AF**
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inhaled treprostinil only	**INCREASE (at 16 weeks)**			**INCREASE OLE (at week 48)**		
	SGRQ	**EQ-5D**	**AF**	**SGRQ**	**EQ-5D**	**AF**
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC only	**INCREASE (at 16 weeks)**			**INCREASE OLE (at week 48)**		
	SGRQ	**EQ-5D**	**AF**	**SGRQ**	**EQ-5D**	**AF**
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AF, Adjustment factor; N/R, not reported; SGRQ, Saint George's Respiratory Questionnaire

3.4.4 Extracted multivariate analysis

There was a possibility of selection bias within the SGRQ data from the INCREASE OLE study. Therefore, the model also contained the functionality for utility data to be based on a generalised linear mixed regression model, which was treatment and time-

independent. The generalised linear model (GLM) with a beta distribution and logit link was used to estimate the mean SGRQ score at any given time point for each health state. As well as age and sex, baseline SGRQ was included as a model covariable as it was considered a predictor of future SGRQ scores. A random intercept model was used to account for the repeated measure nature of the outcome based on unique participant identification.

The output from the analysis was a regression equation incorporating the following coefficients: intercept, age, gender and SGRQ at baseline. The regression equation was used to estimate the mean SGRQ value by health state, which was then converted to the EQ-5D-3L. An adjustment factor to compare these utility values with those of the general population (based on age and gender) was then estimated.

The SGRQ outcomes from the regression analysis are presented in Table 34. These results show that there remained a distinction in the quality of life scores across health states (i.e. quality of life was higher in the CWF health state); however, the distinction between health states was smaller when using the GLM. For this reason, it was judged that it would be more appropriate to use the data from the univariate analysis (see Section 3.3.1) as it would be more clinically plausible to see a large distinction in quality of life between the health states, given the expected impact of clinical worsening events on patient outcomes. This decision was validated at a clinical advisory board in April 2025, at which the clinicians confirmed that the larger differences between clinical worsening states in the univariate analyses were more clinically plausible than those in the multivariate analysis.

Table 34. Outcome from the regression analysis

	Freemantle 2015			Starkie 2015		
	SGRQ	EQ-5D	AF	SGRQ	EQ-5D	AF
Clinical worsening free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening one	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical worsening two	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AF, Adjustment factor; SGRQ, Saint George's Respiratory Questionnaire.						

3.4.5 Health-related quality-of-life studies

During model conceptualisation, a targeted literature search was conducted to identify health-related quality of life (HRQoL) data for individuals with PH-ILD. A systematic

literature review (SLR) was then conducted in January 2024 and updated in 2025 (Appendix F). However, there was a paucity of relevant evidence, with no suitable studies identified that could inform the HRQoL inputs in the model. The absence of published data was discussed with clinical experts, who advised that HRQoL values from broader ILD or PH populations would not accurately reflect the experience of patients with PH-ILD.

3.4.6 Adverse reactions

More than 90% of the study population experienced an adverse event in the INCREASE trial. However, the vast majority of these events were minor (i.e. Grade 1 or 2) and, therefore, they would not have had a meaningful impact on either healthcare costs or HRQoL. In terms of serious adverse events (i.e. Grade 3 or 4), the percentage of the study population experiencing each event was very low. Acute respiratory failure was the most commonly occurring serious adverse event in the inhaled treprostinil arm of the INCREASE trial, with 2.45% and 4.29% of patients experiencing this event in the inhaled treprostinil and placebo arms, respectively. Acute respiratory failure and pneumonia were experienced by 3.0% and 5.5% of the inhaled treprostinil and placebo arms respectively.[87] No further adverse events had a frequency of over 5% in either arm. Dyspnoea, which was the adverse event with the second-highest frequency, occurred in 1.77% of the 163 patients in the inhaled treprostinil arm over the 16 weeks.

However, it was expected that the impact of these events would already be captured in the data utilised from the INCREASE trial (i.e. cardiopulmonary hospitalisations were captured in the model already) and, therefore, adverse events were not included as separate events in the model to prevent double counting.

3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic literature review was conducted to identify published studies reporting on unit costs and healthcare resource utilisation in patients with PH-ILD (Appendix G). Only two relevant studies were identified (Frank 2019 and Heresi 2024), but both were focussed on resource utilisation outside of the UK (in Germany and the USA, respectively) and were not therefore used to inform the UK base case analysis. The

options available to capture cost and resource use are presented in Table 35. The base-case analysis options are underlined and highlighted in bold.

Table 35. Available options for costs and resource use parameters

Parameter	Application
Include off-label PDE5i	• Include in the inhaled treprostinil arm • Include in the comparator arm • **Exclude**
Cost of hospitalisations	• **Costed per admission** • Costed per day
Cost of lung transplants	• Include • **Exclude**
Weekly rate of hospitalisation after CW≥2	• **Include** • Exclude (rate set equal to 0)
Application of background medication	• Treatment dependent • **Treatment independent**
Key: CW: Clinical worsening; PDE5i: Phosphodiesterase 5 inhibitors **Notes**: Base-case analysis selected settings are underlined and in bold.	

Unit cost and resource-use assumptions and inputs are detailed in the following section. The frequency of each resource use was multiplied by the unit costs. Costs were then aggregated to produce the total cost incurred by patients receiving treatment with inhaled treprostinil compared with the comparator arm. To ensure consistency with NICE methodology, unit costs were obtained through the latest standard publicly available sources wherever possible.[92] All costs were inflated to the 2023/24 cost year where necessary using the Personal Social Services Research Unit (PSSRU) inflation indices.[107]

Six types of costs were captured in the model:

- Inhaled treprostinil treatment costs.
- BSC treatment costs.
- Background medication costs.
- One-off event-specific costs.
- Ongoing health-state-specific resource use.
- One-off end-of-life costs.

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Inhaled treprostinil treatment costs

The annual cost of inhaled treprostinil was [redacted] per person assuming a dosage of one ampule per day (Table 36). Due to the stability of an opened ampule and that each ampule contains more treprostinil than the maximum dose, the cost per day (of one ampule) remains constant regardless of the dose required. Ferrer has submitted a proposal for a confidential simple PAS for inhaled treprostinil that will ensure a consistent net price for both the starter and refill kits.

Table 36. Cost of inhaled treprostinil

Drug name	Cost per ampule before PAS	Ampules per cycle	Cost per cycle before PAS	Cost per kit before PAS	Cost per kit after PAS	Annual cost before PAS	Annual cost after PAS
Inhaled treprostinil starter kit	[redacted]	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inhaled treprostinil refill kit	[redacted]	7	[redacted]	[redacted]	[redacted]		

3.5.1.2 Background medication costs

A proportion of patients in both arms of the model received background medications for the underlying progressive hypertension and lung disease. A review of the INCREASE 16-week clinical study report (CSR) was undertaken to examine which concomitant medications were being received at baseline and at the study follow-up.[59] The information from this review indicated that a very large number (≥50) of different medications were taken during the trial. However, the majority of these treatments were either taken by only a very small number of patients, were associated with a very low cost, or there was no meaningful difference between the treatment arms (or a combination of all three issues). Therefore, only the treatment costs of pirfenidone and nintedanib are included within the model. These treatments are included because they are relatively expensive medications and may be used to treat the underlying lung disease, specifically for the treatment of IPF. The proportion of patients receiving these medications upon entry to the trial was informed from the INCREASE 16-week trial (Table 37).[91]

The model contains the option for the inputs used to inform the proportion of patients on each medication at baseline to be treatment-dependent or treatment-independent. Treatment-dependent values were used to inform the base-case analysis to align with background medication utilisation in the INCREASE trial.

Table 37. Proportion of patients receiving pirfenidone and nintedanib on model entry

Proportion of patients on medication at baseline (n=326)	Treatment dependent		Treatment independent
	Inhaled treprostinil	BSC	
Pirfenidone: % (n)	[redacted]	[redacted]	[redacted]
Nintedanib: % (n)	[redacted]	[redacted]	[redacted]

The proportion of patients who discontinued pirfenidone and nintedanib over a three-year follow-up period was informed by a 2022 retrospective study of 261 patients with IPF (Takehara et al.).[108] These proportions were used to estimate the proportion of the cohort that discontinued treatment per week, assuming a linear decline in the proportion of patients on treatment between the reported annual time points (Table 38). Discontinuation was only relevant for the proportion of the cohort that started on each medication (Table 37). The data from Takehara 2022 were applied over the first four years of the model time horizon. It was conservatively assumed that there was no discontinuation of these treatments after four years, such that the proportion that remained on medication at the end of the fourth year would incur the cost of that medication until they died. It was not possible to conduct a survival analysis to inform the time-to-treatment discontinuation associated with pirfenidone and nintedanib because the number of patients receiving these treatments at baseline (as displayed in Table 37) were not sufficient.

Table 38: Pirfenidone and nintedanib discontinuation proportions

Yearly discontinuation	Pirfenidone	Nintedanib	Source
End of the first year, % (n)	48.5 (65)	50.0 (25)	Takehara 2022.[108]
End of the second year, % (n)	64.9 (87)	62.0 (31)	
End of the third year, % (n)	68.7 (92)	66.0 (33)	
End of the fourth year, % (n)	81.3 (109)	68.0 (34)	
After the fourth year, % (n)	81.3 (109)	68.0 (34)	

The unit costs of pirfenidone and nintedanib were obtained from the eMIT and the British National Formulary (BNF), respectively.[109,110] The weekly per-person costs of pirfenidone and nintedanib are presented in Table 39. Based on the summary of product characteristics from the BNF, a dosage of 801mg three times a day and 150mg twice a day for pirfenidone and nintedanib were used, respectively.[111,112]

Table 39: Pirfenidone and nintedanib treatment costs

Drug	Pack cost	Dose per tablet	Pack size	Cost per mg	Dose per cycle	Cost per cycle
Pirfenidone	£106	801 mg	84	£0.00	16,821 mg	**£26**
Nintedanib	£2,151	150 mg	60	£0.24	4,200 mg	**£1,004**

3.5.2 Event-specific one-off costs

One-off event costs were applied to patients at the beginning of the cycle in which they experienced the following events:

- A lung-disease exacerbations.
- A cardiopulmonary hospitalisation.
- A lung transplant (scenario analysis only).

The upfront unit costs associated with each of these clinical worsening events are presented in Table 40. Each of the unit costs was obtained from the National Cost Collection 2023/24 database.[113]

Table 40: Clinical worsening event unit costs

Cost parameter	Unit cost	Source
Lung-disease exacerbation	£2,662	NCC. Weighted average, using the activity per code, of all 'respiratory failure' codes (codes DZ27M-U). Total HRGs.[113]
Cardiopulmonary hospitalisation	£2,382	NCC. Weighted average, using the activity per code, of all 'cardiac arrest' codes (codes EB05A-C). Total HRGs.[113]
Lung transplant	£71,848	NCC. 'Lung transplant' (code DZ01Z). Total HRGs.[113]
Key: HRGs, Health-resource groups; NCC, National Cost Collection		

Whilst the model includes functionality for patients experiencing a fall in 6MWD or FVC% to incur an upfront cost, these costs were set to zero in the base case. These events were not anticipated to be associated with an immediate increase in resource

use as the events would not incur immediately and the person may not know the event had occurred.

3.5.3 Health-state unit costs and resource use

3.5.3.1 Ongoing background resource use

Ongoing background resource use was included in the model to capture the costs of additional healthcare resources incurred by patients with PH-ILD. The model included functionality to capture any differences in resource use depending on both the number and type of clinical worsening events experienced. No PH-ILD-specific resource use data were identified from the targeted literature review.

It was not possible to elicit UK-specific resource-use data from the INCREASE trials because data on the following categories were not collected: healthcare visits, supplemental oxygen use or wheelchair requirements. Furthermore, the key opinion leaders did not feel comfortable providing estimations during the advisory boards. Therefore, health-state-specific healthcare visit data were obtained from the ongoing resource-use RWE study in France and are detailed in Table 42.[114] This retrospective longitudinal cohort study used claims data from France, Germany, and the UK to analyse the epidemiology, patient profile, treatment patterns, resource utilisation, and associated costs of PH-LD, PH-ILD, and PAH from 2015 to 2021. Whilst the model contains functionality for the resource use to differ by health state, it was not possible to distinguish the different resource use categories by health state using this source. Therefore, the resource use incurred in specific health states is assumed to be equivalent across the health states and in both treatment arms.

The unit costs used to inform the ongoing background resource use and the resource use estimations per health state are presented in Table 41 and Table 42, respectively.

Table 41. Unit costs used to inform ongoing background resource use

Cost parameter	Unit cost	Source
General practitioner appointment	£49.00	PSSRU 2023. Per GP surgery consultation lasting an average of 10 minutes. [41]
Respiratory medicines service outpatient appointment	£194.30	NCC. 'Respiratory medicines services' (service code 340). Outpatient care, face-to-face, consultant-led follow-on appointment.[47]
Cardiology service outpatient appointment	£186.38	NCC. 'Cardiology services' (service code 320). Outpatient care, face-to-face, consultant-led follow-on appointment.[113]
Rheumatology service outpatient appointment	£188.16	NCC. 'Rheumatology services' (service code 410). Outpatient care, face-to-face, consultant-led follow-on appointment.[113]
Emergency room visit (no admission)	£345.81	NCC. 'Emergency care' codes. Weighted average of all non-admitted service codes (T01NA, T02NA and T03NA). Included all currency codes that involve treatment (VB01Z, VB02Z, BV03Z, VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z). (excluding 'no significant treatment' codes (VB11Z)). Dental care emergency codes (VB10Z) also excluded.[113]
Supplemental oxygen (cost per year)	£2,095	NICE TA821. Table 36. 2020 cost inflated using PSSRU 2023 inflation indices. Non-invasive ventilation.[107,115]
Key: GP, general practitioner. HRGs, Health-resource groups; NCC, National Cost Collection; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit.		

Table 42. Health-state specific resource use[3]

Clinical worsening free	**Clinical worsening Free**							
	Frequency per weekly cycle				**Proportion**			
General practitioner appointment	0.0192				100.0%			
Respiratory medicines outpatient appointment	0.0364				100.0%			
Cardiology service outpatient appointment	0.0115				100.0%			
Rheumatology service outpatient appointment	0.0057				100.0%			
Emergency room visit	0.0057				100.0%			
One clinical worsening event	**Fall in 6MWD ≥15%**		**Fall in FVC% ≥10%**		**Cardiopulmonary hospitalisation**		**Exacerbation**	
	Frequency	**Proportion**	**Frequency**	**Proportion**	**Frequency**	**Proportion**	**Frequency**	**Proportion**
General practitioner appointment	0.0192	100.0%	0.0192	100.0%	0.0192	100.0%	0.0192	100.0%
Respiratory medicines outpatient appointment	0.0364	100.0%	0.0364	100.0%	0.0364	100.0%	0.0364	100.0%
Cardiology service outpatient appointment	0.0115	100.0%	0.0115	100.0%	0.0115	100.0%	0.0115	100.0%
Rheumatology service outpatient appointment	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%
Emergency room visit	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%
Supplemental oxygen		50.0%*		50.0%*		50.0%*		50.0%*
Two or more clinical worsening events	**Fall in 6MWD ≥15%**		**Fall in FVC% ≥10%**		**Cardiopulmonary hospitalisation**		**Exacerbation**	
	Frequency	**Proportion**	**Frequency**	**Proportion**	**Frequency**	**Proportion**	**Frequency**	**Proportion**
General practitioner appointment	0.0192	100.0%	0.0192	100.0%	0.0192	100.0%	0.0192	100.0%
Respiratory medicines outpatient appointment	0.0364	100.0%	0.0364	100.0%	0.0364	100.0%	0.0364	100.0%
Cardiology service outpatient appointment	0.0115	100.0%	0.0115	100.0%	0.0115	100.0%	0.0115	100.0%
Emergency room visit	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%
Rheumatology service outpatient appointment	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%
Supplemental oxygen		50.0%*		50.0%*		50.0%*		50.0%*
Key: 6MWD: 6-Minute Walk Distance, FVC%: Forced Vital Capacity (percent predicted), GP: General Practitioner *Assumption								

3.5.3.2 Accounting for cardiopulmonary hospitalisations after the 2nd clinical worsening event

The *post hoc* analysis by Nathan 2022 reported that patients receiving inhaled treprostinil were at a lower risk of experiencing further cardiopulmonary hospitalisations when compared with BSC.[87] Therefore, to capture the cost implications of potential reductions in further hospitalisations, treatment-dependent ongoing weekly hospitalisation rates for the cohort in the CW≥2 state were included in the model. These rates were only applied to the CW≥2 group, as inhaled treprostinil was associated with a reduction in 'further' cardiopulmonary hospitalisations, and patients in the CW1 group were experiencing their first hospitalisation event. A risk ratio estimating the difference in weekly hospitalisation rates between inhaled treprostinil and BSC was applied to the inhaled treprostinil arm in the model.

The weekly rate of hospitalisation in the CW≥2 health state was estimated using IPD from the INCREASE 16-week and OLE trials. The weekly rate of hospitalisation was calculated as the total number of cardiopulmonary hospitalisations divided by the total person-weeks, for each treatment arm. For the inhaled treprostinil arm, there were 50 hospitalisations and a total of 3,866 person-weeks, resulting in a weekly rate of 0.0129. For the placebo arm, there were 49 hospitalisations and a total of 3,716 person-weeks, resulting in a weekly rate of 0.0132. The rate of hospitalisations by treatment arm was used to derive a risk ratio of 1.02.

3.5.3.3 Adverse reaction unit costs and resource use

Adverse event costs were not considered in the model due to the low incidence in the INCREASE 16-week and OLE trials (Section 3.4.6).

3.5.3.4 Miscellaneous unit costs and resource use: Wheelchair use

The cost of wheelchair use was included in the model because the NHS funds wheelchair services in the UK. Patients incurred the upfront cost of a wheelchair during the cycle in which the wheelchair was first required. For example, the model calculations were set up to prevent patients from incurring the upfront wheelchair cost twice (i.e. after two clinical worsening events). Patients then incurred an ongoing maintenance cost per week until they died (i.e. it was assumed that a person would require a wheelchair for the rest of their life). It was also assumed that patients would not require a wheelchair until they had experienced at least one clinical worsening

event. The unit costs and resource use used to inform the wheelchair costs are presented in Table 43 and Table 44, respectively.

Table 43. Wheelchair use unit costs

Cost parameter	Unit cost	Source
Non-powered wheelchair (upfront cost)	£712.34	NCC. Wheelchair services adults, equipment, high need, manual WC07.[113]
Non-powered wheelchair (ongoing cost per week)	£3.76	NCC. Wheelchair services adults, Repair And Maintenance, All Needs, Manual WC09.[113]
Powered wheelchair (upfront cost)	£1,219.12	NCC. Wheelchair services adults, equipment, high need, powered WC08.[113]
Powered wheelchair (ongoing cost per week)	£16.08	NCC. Wheelchair services adults, Repair And Maintenance, All Needs, Manual WC10.[113]
Key: NCC, National Cost Collection		

Table 44. Wheelchair resource use (all assumed inputs)

One clinical worsening event	Fall in 6MWD ≥15%		Fall in FVC% ≥10%		Cardiopulmonary hospitalisation		Exacerbation	
	Proportion	**SE**	**Proportion**	**SE**	**Proportion**	**SE**	**Proportion**	**SE**
Non-powered wheelchair	30.0%	0.03	10.0%	0.01	10.0%	0.01	30.0%	0.03
Powered wheelchair	20.0%	0.02	10.0%	0.01	10.0%	0.01	20.0%	0.02
Two clinical worsening events	**Fall in 6MWD ≥15%**		**Fall in FVC% ≥10%**		**Cardiopulmonary hospitalisation**		**Exacerbation**	
	Proportion	**SE**	**Proportion**	**SE**	**Proportion**	**SE**	**Proportion**	**SE**
Non-powered wheelchair	30.0%	0.03	10.0%	0.01	10.0%	0.01	30.0%	0.03
Powered wheelchair	20.0%	0.02	10.0%	0.01	10.0%	0.01	20.0%	0.02
Key: 6MWD, 6-minute walking distance; FVC%, forced vital capacity; SE, standard error.								

3.5.3.5 End-of-life costs

End-of-life costs were applied as a one-off cost to the modelled cohort upon entering the 'dead' health state. A cost of £15,427 was sourced from PSSRU, using the hospital and social care cost of dying from a respiratory infection.[107] Please note that since the time horizon of the analysis is set to a lifetime (30 years in the base case analysis), the end-of-life incremental cost differences were exclusively due to the impact of the discounted costs (set at 3.5% annually), given the differences in time-to-death between the treatment arms.

3.6 Severity

The severity modifier tool developed by SCHARR was used to calculate the absolute and proportional to determine the severity modifier applicable to inhaled treprostinil. Patients with PH-ILD would be anticipated to experience 0.86 discounted QALYs (0.89 undiscounted QALYs) on BSC over a period of 1.35 discounted life years (1.40 undiscounted life years) and based on a Weibull model of OS in the RPSFTM-adjusted BSC arm of the INCREASE trial. This would correspond to a 91.9% proportional shortfall versus an age- and sex-matched UK population, who would be anticipated to experience an average additional 10.59 QALYs based on an adjusted limited dependent variable mixture model (ALDVMM) of 2014 HSE data (Hernandez Alava *et al.;* the York QALY Shortfall Calculator reference case).

Sensitivity analyses around the general population estimates (using an EQ-5D-5L to EQ-5D-3L mapping from Hernandez Alava *et al.* with HSE 2017-18 data, a EQ-5D-5L to EQ-5D-3L mapping from van Hout *et al.* with HSE 2017-18 data, and two health state profile-based models) showed that no general population estimates would yield less than a 91.7% proportional shortfall in patients with PH-ILD receiving BSC (Table 47).

Sensitivity analyses around the crossover-adjusted survival distributions for BSC (exponential, Gompertz, log logistic, log normal, and generalised gamma) showed only small differences in the estimated QALY gain, with no survival distribution resulting in less than an [redacted] proportional shortfall in patients with PH-ILD receiving BSC, and therefore qualifying for a 1.2x severity multiplier regardless of the underlying survival distribution (Table 47).

Inhaled treprostinil would therefore be eligible for a 1.2x QALY weight based on the proportional shortfall rule, and the analyses of this appear to be robust to changes in both the general population and BSC population estimates. This 1.2x modifier is applied in the economic analysis results presented in Sections 3.10 and 3.11. Note that switching the utility estimation approach to use the SGRQ health state utility base regression model in concert with an unadjusted Gompertz OS extrapolation from the INCREASE RCT resulted in QALY shortfall estimates that exceeded the 95% relative shortfall required to justify a 1.7x modifier, but this utility estimation approach was not adopted in the base case analysis, and the 1.2x modifier was therefore adopted.

Table 45. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	53.07% male	Section B3.2 and B3.9
Starting age (years)	66.45	Section B3.2 and B3.9

Table 46. Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean	Undiscounted life years (Weibull model of RPSFT crossover-adjustment)
Clinical worsening free	[redacted]	[redacted]
Clinical worsening 1	[redacted]	[redacted]
Clinical worsening 2	[redacted]	[redacted]

Table 47. Summary of QALY shortfall analysis

Severity analysis	Expected total QALYs for the general population (QALYs)	Total QALYs that patients living with the condition would be expected to have with current treatment	QALY shortfall
Reference case	10.59	0.86	9.73 QALYs or 91.9%
EQ-5D-5L to EQ-5D-3L mapping from Hernandez Alava *et al.* with HSE 2017-18 data	10.43	0.86	9.57 QALYs or 91.8%
EQ-5D-5L to EQ-5D-3L mapping from van Hout *et al.* with HSE 2017-18 data	10.48	0.86	9.62 QALYs or 91.8%
Measurement and valuation of health value set and health state profile	10.33	0.86	9.47 QALYs or 91.7%
Crossover-adjusted exponential OS model	10.59	[redacted]	[redacted]
Crossover-adjusted Gompertz OS model	10.59	[redacted]	[redacted]
Crossover-adjusted log-normal OS model	10.59	[redacted]	[redacted]
Crossover-adjusted log-logistic OS model	10.59	[redacted]	[redacted]
Crossover-adjusted generalised gamma OS model	10.59	[redacted]	[redacted]

3.7 Uncertainty

PH-ILD is a rare and severe condition that makes robust evidence collection challenging. Prior to INCREASE the largest trial conducted in patients with group 3 PH was RISE-IIP, which investigated the soluble guanylate cyclase stimulator riociguat in a patient population with group 3 PH. In the trial, 127 patients were

randomly assigned to receive either riociguat or placebo, but the trial was ultimately terminated early due to the elevated incidence of serious adverse events with riociguat.[116] INCREASE, having randomly assigned 326 to treatment (163 to inhaled treprostinil and 163 to placebo) therefore now represents the largest randomised controlled trial conducted in patients with PH-ILD. The 16-week duration of the randomised portion of INCREASE makes extrapolation of the data over patient lifetimes challenging, but the duration was informed by power calculations based on a 90% power at a significance level of 0.05 (two-sided hypothesis) to detect a 30 metre between-treatment difference in the change from baseline to week 16 in 6MWD measured at peak exposure assuming a standard deviation of 75 meters. Furthermore, INCREASE OLE was designed to provide an additional 108 weeks of follow-up in patients who did not discontinue inhaled treprostinil.

3.8 Managed access proposal

3.8.1 Eligibility for the Innovative Medicines Fund

Ferrer considers that routine commissioning is the most appropriate route for inhaled treprostinil. However, it recognises that there is some uncertainty regarding the utility values used within the health economic model. This is due to the use of the SGRQ instrument in the INCREASE trial, which may not have fully captured the specific PH-ILD impacts on HRQoL.

The SGRQ was designed for use in obstructive pulmonary disease such as asthma and COPD, therefore the majority of its content reflects symptoms typical of these conditions. It assesses impact of symptoms such as cough, sputum production and wheezing, while the clinical features of PH-ILD such as dyspnoea, fatigue and even pre-syncope are underrepresented or absent. The SGRQ also does not reflect the specific psychological and functional burden associated with PH-ILD, such as the need for long-term oxygen therapy, anxiety related to progressive hypoxaemia, or limitations on exertion that result in social withdrawal and dependency.

Additionally, the 50-item length of the SGRQ can also be burdensome for patients with PH-ILD. Fatigue is a key symptom of PH-ILD, and this can lead to missing HRQoL data due to patients not completing the entire questionnaire (item nonresponse) or their lack of participation in data collection (unit nonresponse). Unit

nonresponse can be a particular issue during hospital admissions. Since inhaled treprostinil is associated with fewer hospitalisations than best supportive care, this could result in differential levels of missing data between the treatment arms, introducing bias into the HRQoL-related model inputs.

Should NICE's technology appraisal committee deem the evidence too uncertain to support a recommendation for routine commissioning, Ferrer is open to exploring a managed access agreement within the Innovative Medicines Fund.

Ferrer proposes collecting additional HRQoL data using the emPHasis-10. This instrument is shorter, simpler to complete, and specifically developed for PH, making it more sensitive to PH-specific HRQoL impacts. Furthermore, it is widely used in routine clinical practice at PH clinics. The most recent National Audit of Pulmonary Hypertension (2023) reported that nearly all patients (92%) who have had at least one consultation in the last year have had an emPHasis-10 quality of life score recorded. Incorporating emPHasis-10-based data into the health economic model is therefore anticipated to reduce uncertainty by improving the accuracy of the health state utility values (HSUVs).

A managed access agreement would be appropriate for inhaled treprostinil given its potential to address the substantial high unmet need in patients with PH-ILD and to deliver clinically meaningful benefits (see Table 53 within Section 3.10). Inhaled treprostinil demonstrates improvements in exercise capacity and reductions in disease progression.

3.8.2 Uncertainties that could prevent the committee from making a recommendation for routine use

Table 48. List of uncertainties and potential data collection

Clinical uncertainty	Outcome data	Data source
Accuracy of the utility values within the health economic model	• HRQoL scores from emPHasis-10 • Health state utility values mapped from emPHasis-10 to EQ-5D	• The Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre (ASPIRE) Registry, Sheffield Teaching Hospitals NHS Foundation Trust OR

Clinical uncertainty	Outcome data	Data source
		• The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)

3.8.3 Data collection

Ferrer plans to develop and validate an algorithm that predicts EQ-5D utilities from emPHasis-10 in patients with PH-ILD. Baseline utility values for the health economic model will be updated by HSUVs derived from a mapping of emPHasis-10 scores to EQ-5D-3L.

The proposed data collection is for a prospective study to assess the impact of inhaled treprostinil on HRQoL using emPHasis-10 and EQ-5D-3L. EQ-5D data is collected solely to support the development of a mapping algorithm rather than directly generate utilities since this generic patient-reported outcome measure (PROM) is not considered to fully capture PH-specific impacts on HRQoL (see Section 2.6.1.5).

3.8.4 Overview of the data sources: PH registries

Ferrer is currently exploring the feasibility of using either the ASPIRE registry or UKRB registry to address the uncertainty around the accuracy of the utility values within the economic model.

The Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre (ASPIRE) Registry

The Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre (ASPIRE) is a disease-specific patient registry, and was established in 2001.[1] The ASPIRE registry contains de-identified clinical data collected from patients undergoing investigations for suspected pulmonary vascular disease at the Sheffield Pulmonary Vascular Disease Unit (PVDU). The investigations include a systematic evaluation with multimodality imaging and right heart catheterisation, following annually audited national care standards.[2]

The PVDU has a referral population of over 20 million patients.[3] In 2016/17, the Sheffield PVDU evaluated over 2,300 patients and received over 800 new referrals.[4]

The following outcomes are routinely collected in the ASPIRE registry: emPHasis-10 score, distance walked (based on the incremental shuttle walk test, ISWT), and levels of N-terminal pro-B-type natriuretic peptide level (NT-pro-BNP). The ASPIRE registry is considered to have excellent data completeness.[1]

The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)

The UKRB registry is a disease-specific patient registry and was established in 2023.[5] It aims to understand the pathophysiology of PH related to chronic lung disease (WHO Group 3 PH patients). This registry contains anonymised patient data from the records of consecutive incident patients referred to the Royal Brompton Hospital National Pulmonary Hypertension Service. Treating clinicians or other healthcare professionals manually transcribe data from electronic health records.

This registry includes approximately 900 patients who have been referred to the Royal Brompton Pulmonary Hypertension Service. As of August 2024, there are currently 128 patients who have had their PH-ILD diagnosis confirmed by a multi-disciplinary team.[6]

The following outcomes are routinely collected: emPHasis-10 score, six-minute walk distance (6MWD), and levels of B-type natriuretic peptide (BNP). In the proposed study, additional data collection includes an increased number of emPHasis-10 assessments over time, as well as measurements on EQ-5D-3L, and cardiopulmonary hospitalisation and lung exacerbations occurrence. Data quality is assessed through medical review of the data. Highly skilled professionals (e.g., clinical research fellows) are trained to enter the data under close supervision from the senior physicians. Ad-hoc data verification may occur via discussion between the data-entry professional and senior physicians.

Table 49. Overview of the Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre Registry (ASPIRE)

Registry	The Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre Registry (ASPIRE) https://bit.ly/aspire-registry
Type of registry	Disease-specific patient registry
Population	Adult patients (aged ≥18 years at index date) diagnosed with PH associated with ILD of various aetiologies, documented by an RHC
Relevant data items collected	Clinical outcomes: 1. Distance walked (incremental shuttle walk test, ISWT) 2. Forced vital capacity (FVC) 3. Cardiopulmonary hospitalisation 4. Lung exacerbation 5. NT-proBNP 6. **PROs (emPHasis-10, EQ-5D-3L)**
Data analysis	The analysis will be devised based on the following study: **Proposed study**: Prospective study to assess the impact of inhaled treprostinil on HRQoL using emPHasis-10 and EQ-5D-3L
Governance	Sheffield Teaching Hospitals NHS Foundation Trust is the controller of the ASPIRE registry. This registry is an ethically approved research database managed by Sheffield Teaching Hospitals NHS Foundation Trust (STH14169, REC 22/EE/0011). A data access agreement signed by the lead researcher and a data sharing agreement between Sheffield Teaching Hospitals and the recipient institution will be required before data is shared.
Indicate if registry previously used within a NICE managed access	No

Table 50. Overview of the Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)

Registry	The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB) https://www.rbht.nhs.uk/ourservices/heart/pulmonary-hypertensionservice
Type of registry	Disease-specific patient registry

Population	Adult patients (aged ≥18 years at index date) diagnosed with PH associated with ILD of various aetiologies, documented by an RHC
Relevant data items collected	Clinical outcomes: 1. 6-minute walk distance (6MWD) 2. Forced vital capacity (FVC) 3. Cardiopulmonary hospitalisation 4. Lung exacerbation 5. NT-proBNP 6. **PROs (emPHasis-10, EQ-5D-3L)**
Data analysis	The analysis will be devised based on the following study: **Proposed study**: Prospective study to assess the impact of inhaled treprostinil on HRQoL using emPHasis-10 and EQ-5D-3L
Governance	The Royal Brompton Hospital research governance department is the controller of the UKRB registry data. The registry is supported by the NHS. To access the data, approval will be sought from the Health Research Authority (including Research Ethics Committee review)
Indicate if registry previously used within a NICE managed access	No

For either data source, the following will apply:

- The additional data collection would include an increased number of emPHasis-10 assessments over time as well as measurements on the EQ-5D-3L, and determining cardiopulmonary hospitalisation and lung exacerbations occurrence.
- During the managed access period, emPHasis-10 and EQ-5D will be self-administered by patients at baseline and at every 3 months thereafter. Patients will also be encouraged to complete these PROMs during hospitalisation.
- Cardiopulmonary hospitalisation and lung exacerbations occurrence will be derived from linking registry data to the HES database.
- The patient population for the proposed study will be closely aligned to the INCREASE trial eligibility criteria (see Appendix J for details)

3.8.5 Prior approach to the registry for the data specified in the managed access proposal

While Ferrer has had collaborations with stakeholders from the ASPIRE registry and the UKRB registry, it has not currently approached either registry owners regarding the data collection, analysis and sharing specified in this managed access proposal.

3.8.6 Timeframe of data collection

Following recommendation into the Innovative Medicines Fund, Ferrer anticipates that a timeframe of 2 years would be sufficient to address uncertainties about HRQoL.

The proposed study is expected to have an 18-month timeframe. This is a sufficient to obtain HSUVs for clinical worsening (CW) events (deterioration in 6MWD and/or FVC; cardiopulmonary hospitalisation, lung exacerbations).

Based on the INCREASE trial, modelling of time to first and second CW events shows that by the end of 18 months, approximately 90% and 60% of patients have had their first and second CW event, respectively (section 3.3.3 and 3.3.4). Additionally, a recent analysis of Hospital Episode Statistics (HES) data showed the mean annualised rate of all-cause hospitalisations for patients newly diagnosed with PH-ILD was approximately 3 per person-years within the first year of follow-up.[7]

In 2027, Ferrer anticipates incorporating results from the additional data collected during the managed access period into an evidence submission and updated economic model (Table 51).

Table 51. Duration of proposed managed access activities

Activity	Duration	Provisional study title
Proposed study	18 months	Prospective study to assess the impact of inhaled treprostinil on HRQoL
Resubmission	6 months	Update evidence submission and economic model

The study timeframe also includes the time needed to:

- Link registry data to Hospital Episode Statistics (HES) to obtain details on cardiopulmonary hospitalisation and lung exacerbations.

- Define a validated mapping algorithm between emPHasis-10 and EQ-5D-3L utility values.

3.8.7 Additional considerations that may impact feasibility of data collection

Ferrer has a good relationship with key opinion leaders from the ASPIRE registry who have developed emPHasis-10 with the Pulmonary Hypertension Association (PHA) UK as well as with stakeholders at the UKRB registry. Therefore, Ferrer does not anticipate any barriers to obtaining a data collection agreement with either registry or the use of emPHasis-10.

Listed below are specific considerations that may impact the feasibility of data collection within the managed access period:

Informed consent: Lack of patient consent to give access to their clinical data.

PRO data collection for patients and clinicians: PRO collection facilitates monitoring of patients' symptoms with PH-ILD and supports tailoring of treatment to patient needs. However, the proposed frequency of administration of PRO measurements over the data collection period is a potential burden to patients and clinicians. This may lead to poor data quality due to non-response or incomplete responses by patients. Ferrer aims to address this potential burden by having patients complete electronic PROs (ePROs) versions of emPHasis-10 and EQ-5D-3L. ePROs are considered easier and faster to complete than traditional pen and paper versions.

The interpretation of emPHasis-10 scores by clinicians over the course of the managed access period is unlikely to significantly burden clinicians. This is based on clinicians routinely collecting and using emPHasis-10 in patients attending PH clinics.[8]

To ensure adherence to HRQoL data collection, Ferrer will produce supportive educational materials for patients to explain the importance of data collection in PH-ILD.

Demographic characteristics of PH-ILD patients: In the UK, patients with PH-ILD have a mean age of 71 years,[7] therefore age-related physical or cognitive decline may be a barrier for elderly patients to complete the PROMs.

Ferrer will include interview support (telephone) for patients if needed to facilitate the collection of HRQoL data (such as those who are unable to complete ePROs).

3.9 Summary of base-case analysis inputs and assumptions

The model options utilised in the base case analysis are presented in Table 52.

Table 52. Base case analysis selections

Model option	Inhaled treprostinil	BSC	Justification
Population	Intention-to-treat population from INCREASE		Reflective of the target population.
Model structure	Partitioned survival model (PSM)		Structure reflects the progressive nature of PH-ILD, ensuring irreversible disease progression consistent with clinical and trial evidence
Discount rate	3.5% for costs and benefits		Per the NICE reference case[92]
Time horizon	Lifetime time horizon		Ensures all cost and HRQoL differences are captured, aligning with NICE guidance and reflecting the full disease course[92]
Cycle Length	Weekly cycle length		Ensures frequent clinical events are captured accurately, preventing underestimation and aligning with key opinion leaders validation
Severity	1.2x QALY weight modifier		Reflects the high proportional shortfall in PH-ILD, with sensitivity analyses confirming the robustness of this classification
Time to death (independently-fit distributions)			
Source	INCREASE OLE (inhaled treprostinil)	Crossover RPSFT analysis (placebo)	The two sources that offer the most mature data available.
Distribution or hazard ratio	Weibull	Weibull	Weibull was selected for both arms based on expert opinion, statistical fit and best practice.

Model option	Inhaled treprostinil	BSC	Justification
Time to first clinical worsening (independently-fit distributions)			
Source	INCREASE OLE (inhaled treprostinil)	INCREASE 16-week (placebo)	The two sources that offer the most mature data available. Log-normal and exponential were selected based on expert opinion and statistical fit.
Distribution or hazard ratio	Log-normal	Exponential	
Stratification of events	Independent		See Section 3.3.3.
Time to second clinical worsening (independently-fit distributions)			
Source	INCREASE OLE (inhaled treprostinil)	INCREASE 16-week (placebo)	The two sources that offer the most mature data available. Log-normal was the best fitting distribution for inhaled treprostinil and the third best for BSC.
Distribution or hazard ratio	Log-normal	Log-normal	
Stratification of events	Independent		See Section 3.3.4.
Time-to-discontinuation			
Source	INCREASE OLE (inhaled treprostinil)	Not applicable	Data only available for inhaled treprostinil from the INCRESE OLE. Generalised gamma was selected based on expert opinion and statistical fit.
Distribution	Generalised gamma	Not applicable	
Health-related quality of life			
Source	INCREASE OLE		INCREASE OLE was used to remain consistent with the source used to populate the intervention time-to-event parameters. Freemantle 2015 (for IPF) was deemed the most relevant mapping algorithm for PH-ILD. Treatment independent utilities were used as utility was assumed to be a function of health state, not of treatment.
Mapping algorithm	Freemantle 2015		
Type of utility	Treatment independent		

Model option	Inhaled treprostinil	BSC	Justification
Costs and healthcare resource use			
Include off-label PDE5i (proportion)	Excluded (0%)	Excluded (0%)	OS curves are for BSC only.
Cost method of hospitalisations	Full admission		Data not available to cost per day.
Cost of lung transplants	Excluded		See Section 3.2.3.8.
Weekly rate of hospitalisation after CW≥2	Treatment dependent Inhaled treprostinil ([redacted])	Treatment dependent BSC ([redacted])	The rate differed between treatment arms in the INCREASE trial.
Application of background medication at baseline	Treatment dependent	Treatment dependent	Reflective of background medication use in the INCREASE trial.
Key: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, CW1: Clinical Worsening One, CW2: Clinical Worsening Two, CWF: Clinical Worsening Free, HRQoL: Health-Related Quality of Life, IPF: Idiopathic Pulmonary Fibrosis, NICE: National Institute for Health and Care Excellence, OLE: Open-Label Extension, PDE5i: Phosphodiesterase Type 5 Inhibitors, PH-ILD: Pulmonary Hypertension associated with Interstitial Lung Disease, PSM: Partitioned Survival Model, QALY: Quality-Adjusted Life Year, RPSFT: Rank Preserving Structural Failure Time.			

3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

The results of the base case analysis are presented in Table 53 and Table 54. Note that QALY outcomes include the 1.2 severity multiplier (Section 3.6).

Table 53. Deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]					
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,000	£28,000
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 54. Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000 (QALYs)	NHB at £30,000 (QALYs)
Inhaled treprostinil	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-0.81	0.14
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years						

3.11 Exploring uncertainty

Uncertainty in the model was characterised through a combination of probabilistic sensitivity analysis, deterministic sensitivity analysis, and scenario analyses.

3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed based on sampling from distributions around key model parameters as detailed in Table 55.

Table 55. Distributions included in the model

Parameter type	Variation method
Time-to-death parametric coefficients	Cholesky matrix derived from the regression variance-covariance matrix
Time to first clinical worsening event parametric coefficients	
Time to second clinical worsening event coefficients	
Time to discontinuation parametric coefficients	
Clinical distributions after each clinical worsening event	Dirichlet (multivariate beta distribution)
Hazard ratios	Lognormal distribution
SGRQ score	Extended beta distribution
Listed unit costs	Fixed
Unit costs from sourced literature	Gamma distribution
Resource use proportions	Beta distribution
Calculated health state costs	Gamma distribution

One thousand model iterations were run and used to generate a cost-effectiveness scatterplot (Figure 41) and acceptability curve (Figure 42). The tabulated PSA results are displayed in Table 56.

The mean incremental costs were [redacted] (95% credible interval: [redacted]), while mean incremental quality-adjusted life expectancy was [redacted] QALYs (95% credible interval: [redacted] QALYs). The mean probabilistic ICER was £31,808 per QALY, which was [redacted] per QALY higher than the deterministic base case (£28,000 per QALY). This difference was driven by a higher modelled incremental cost in the probabilistic analysis ([redacted]) compared to the deterministic base case ([redacted]), and marginally lower

modelled incremental QALYs gained in the probabilistic analysis ([redacted]) compared to the deterministic base case ([redacted]).

Table 56. Probabilistic sensitivity analysis results and base case results to facilitate comparison

Analysis	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Base-case	Inhaled treprostinil	[redacted]	[redacted]	[redacted]			
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,000
PSA	Inhaled treprostinil	[redacted]	[redacted]	[redacted]			
	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,808

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 41. Cost-effectiveness scatterplot showing 1,000 model iterations from the probabilistic sensitivity analysis

Figure 42. Cost-effectiveness acceptability curve based on 1,000 model iterations in the probabilistic sensitivity analysis

3.11.2 Deterministic sensitivity analysis

Cost inputs, utilities and hazard ratios were explored in deterministic sensitivity analysis (DSA) to capture first-order uncertainty around the data used for all input parameter values. Some parameters were not included within the DSA, such as the

efficacy inputs used to inform the survival analysis or the inputs for the generalised linear model, as the impact of each of these parameters was examined within scenario analyses. DSA involved altering the value used for individual parameters, within realistic ranges, to see the impact on the model results. The main output from the DSA was a tornado diagram, which summarised the impact of changes to each parameter on the model results. This enabled the user to quickly identify the parameters that had the most significant impact on the results.

Where statistical parameters were not available from the literature, a range of values (±15%) were applied around the point estimate that has been applied in the base case analysis. Results from the deterministic sensitivity analysis are presented in Figure 43 and Table 57.

Figure 43. Tornado diagram showing the results of the 15 deterministic sensitivity analyses having the greatest effect on the ICER

Key: 6MWD, 6-Minute Walk Distance; BSC, Best Supportive Care; CW1, Clinical Worsening One; CW2, Clinical Worsening Two; CWF, Clinical Worsening Free; ICER, Incremental Cost-Effectiveness Ratio; PVR, Pulmonary Vascular Resistance; QALY, Quality-Adjusted Life Year; SGRQ, St. George's Respiratory Questionnaire.

Table 57. Tabulated results of the 15 deterministic sensitivity analyses having the greatest effect on the ICER

Parameters	Low ICER (£ per QALY)	High ICER (£ per QALY)	Spread
Base case (versus BSC)	**£28,000**		
Inhaled Tyvaso: CW2 SGRQ score (53.9; 64.9)	£25,495	£31,051	£5,557
Inhaled Tyvaso: CWF SGRQ score (33.2; 50.0)	£26,730	£29,397	£2,667
Inhaled Tyvaso: CW1 SGRQ score (44.4; 57.5)	£26,801	£29,312	£2,511
BSC: CW2 SGRQ score (53.9; 64.9)	£28,890	£27,163	£1,726
Discount rate: Benefits (3.0%; 4.0%)	£27,287	£28,717	£1,430
Starting age of population (65.1; 67.8)	£27,381	£28,500	£1,119
BSC: CWF SGRQ score (33.2; 50.0)	£28,485	£27,531	£954
BSC: CW1 SGRQ score (44.4; 57.5)	£28,469	£27,546	£922
Discount rate: Costs (3.0%; 4.0%)	£28,412	£27,603	£810
Inhaled Tyvaso: At least two clinical worsening events (CW2) costs: ↓ in 6MWD (£58; £79)	£27,746	£28,254	£507
Inhaled Tyvaso: proportion receiving Nintedanib at baseline (6.2%; 7.2%)	£27,745	£28,209	£464
Inhaled Tyvaso: At least two clinical worsening events (CW2) costs: Exacerbation (£58; £79)	£27,780	£28,220	£440
Nintedanib: proportion discontinued at the after the third year (66.0%; 78.2%)	£28,058	£27,707	£351
PVR>5 only (45.9%; 62.1%)	£28,170	£27,837	£333
Nintedanib: proportion discontinued at the end of the third year (62.0%; 75.9%)	£28,026	£27,708	£318

Key: 6MWD, 6-Minute Walk Distance; BSC, Best Supportive Care; CW1, Clinical Worsening One; CW2, Clinical Worsening Two; CWF, Clinical Worsening Free; ICER, Incremental Cost-Effectiveness Ratio; PVR, Pulmonary Vascular Resistance; QALY, Quality-Adjusted Life Year; SGRQ, St. George's Respiratory Questionnaire.

3.12 Scenario analysis

A series of scenario analyses were conducted in which the underlying time-to-event distributions were modified for the survival and clinical worsening models, alongside analyses in which the discount rates were modified to 0% and 6%, costs of lung

transplant were included, alternative methods of capturing health state utility values were employed, and alternative approaches to modelling overall survival for best supportive care.

Scenarios exploring alternative methods for capturing health state utility values included:

- Switching the SGRQ to EQ-5D mapping algorithm (using Starkie *et al. r*ather than Freemantle *et al*. as in the base case analysis)
- Adopting the SGRW utility regression approach.

Scenarios exploring alternative approaches to modelling OS for BSC included:

- OS: inhaled treprostinil Weibull, BSC Dawes 2022 Weibull (Section 3.3.2.2.3)
- OS: inhaled treprostinil Weibull, BSC MAIC (HR=6.29; Section 3.3.2.2.3)
- OS: inhaled treprostinil Weibull, BSC RPSFT from Nathan 2023[22] (HR=3.85; Section 3.3.2.2.4)

Results from all scenario analyses are presented in Table 58.

Table 58. Tabulated results of the scenario analysis

Analysis	BSC QALYs	Inhaled treprostinil QALYs	Incremental QALYs	BSC costs (£)	Inhaled treprostinil costs (£)	Incremental costs (£)	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,000
0% discounting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,897
6% discounting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,461
Lung transplant cost included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,572
Starkie *et al.* SGRQ mapping	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,294
Utility regression approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,455
OS model							
OS: inhaled treprostinil Weibull, BSC Dawes 2022 exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,747
OS: inhaled treprostinil Weibull, BSC MAIC (HR=6.29)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,487
OS: inhaled treprostinil Weibull, BSC RPSFT from Nathan 2023 [22] (HR=3.85)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,913
OS: exponential both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,883
OS: log-logistic both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,215
OS: log-normal both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,518
OS: Generalised gamma both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,565
CW1 model							
CW1: exponential both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,451
CW1: Weibull both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,292
CW1: Gompertz both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,219
CW1: log-normal both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,345

Analysis	BSC QALYs	Inhaled treprostinil QALYs	Incremental QALYs	BSC costs (£)	Inhaled treprostinil costs (£)	Incremental costs (£)	ICER (£/QALY)
CW1: Generalised gamma both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,943
CW2 model							
CW2: exponential both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,421
CW2: Weibull both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,408
CW2: Gompertz both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,569
CW2: log-logistic both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,715
CW2: Generalised gamma both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,869

Key: BSC, best supportive care; CW, clinical worsening; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MAIC, matching-adjusted indirect comparison; OS, overall survival; QALYs, quality-adjusted life years; SGRQ, St. George's Respiratory Questionnaire

3.13 Subgroup analysis

A subgroup analysis was conducted in which patients with CPFE were excluded from the analysis, the results of which are presented in Table 59. The CPFE exclusion analysis resulted in an ICER of £28,698 per QALY gained, or £698 per QALY higher than the deterministic base case analysis in the overall population, driven by an increase in incremental QALYs to [redacted] QALYs (from [redacted] QALYs in the base case) and an increase in incremental costs from [redacted] in the base case to [redacted] over the full time horizon.

Table 59. Subgroup analysis excluding patients with CPFE

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,698

Key: CPFE, combined pulmonary fibrosis and emphysema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

3.14 Benefits not captured in the QALY calculation

Owing to lack of data, the quantitative economic analysis did not capture the burden of PH-ILD on caregivers. A 2024 study by Piccari *et al*. reported on patient and caregiver experiences with PH-ILD, which reported that "the severity and progressive nature of PH-ILD, these experiences left patients and carers feeling frustrated, insecure, ill-informed, and confused about their condition and symptoms".[36] This study built on previous research on patients and caregivers with ILD, such as Shah *et al.* 2018, which reported that "[c]aregiving for patients with ILD significantly impairs HRQoL, particularly, emotional health."[117] The model also did not capture any effect of death of the patient and bereavement on caregiver quality of life. While these effects have been reported as small and not sustained in other populations,[118] the extension of life with inhaled treprostinil would have deferred these effects to later in the model, when they would have been discounted further and therefore benefitted the economic case for inhaled treprostinil.

3.15 Validation

3.15.1 Validation of cost-effectiveness analysis

The model structure was validated clinically during conceptualisation and the UK base case parameters were subsequently validated. During the conceptualisation phase, two individual interviews were initially held with consultant respiratory physicians to gather information about the treatment pathway for PH-ILD in the UK. Two advisory boards were subsequently held. The first advisory board, held in March 2023, was attended by three UK-based consultant respiratory physicians and two health economic experts. The second advisory board, held in July 2023, was attended by two UK-based respiratory consultants (who also attended the first advisory board) and two different health economic experts. An individual interview was also held with the consultant respiratory physician who attended the first advisory board but was unable to attend the second. Following an initial draft of the CEM, an interview with a health economics expert was conducted to validate the modelling approach and initial results. Finally, a workshop with 2 UK clinicians was conducted in April 2025 to validate the clinical data, including the long-term extrapolations for time-to-event parameters and SGRQ-mapped utility values.

3.16 Interpretation and conclusions of economic evidence

The present economic evaluation was conducted specifically in the population described in the decision problem, namely adults with a confirmed diagnosis of PH-ILD. The SLR conducted during preparation of the appraisal did not identify any previously-published economic evaluations conducted in patients with PH-ILD. Direct comparisons with existing economic publicatons are therefore not possible. In the absence of prior studies, we believe the current analysis — utilising data from the INCREASE RCT and INCREASE OLE — represents the most credible and comprehensive economic assessment available in PH-ILD to-date.

The evaluation aligns with the entire patient population detailed in the decision problem, namely adult patients with a confirmed diagnosis of PH-ILD. The alignment of the economic analysis with this population stems from the INCREASE and INCREASE OLE inclusion criterion, which covered patients 18 years of age or older in whom interstitial lung disease was diagnosed and Group 3 pulmonary

hypertension had been confirmed by RHC within 1 year before randomisation. The PSM was based exclusively on data from these studies and is therefore clinically aligned with the patient population in the decision problem.

The analysis should generalise well to clinical practice in patients with PH-ILD in England. All economic inputs were explicitly derived from nationally recognised-sources specific to England, including eMIT and the BNF for drug costs, and the NHS England National Cost Collection for hospital event costing. Data on resource utilisation were obtained from a French study, but were also deemed by clinicians to be applicable to the UK setting. Consequently, the findings closely reflect the resource utilisation patterns, clinical pathways, and economic realities of the English healthcare system, strengthening the external validity of the evaluation.

The greatest strength of the base case analysis lies in the use homogeneous clinical data obtained directly from patients in the target population from INCREASE and INCREASE OLE, ensuring consistency between the overall survival and clinical worsening models used in the partitioned survival analysis. In the base case, the well-established rank preserving structural failure time (RPSFT) model was utilised to adjust for patient cross-over, providing robust adjustment for patients crossing over to the inhaled treprostinil arm.

There are, however, some limitations of the modelling approach. Namely, QoL data specific to this patient group collected directly via validated, generic instruments like EQ-5D, are currently absent from the literature and the INCREASE trial, restricting evaluation of patient experience and utility gains without employing mapping algorithms. Future economic evaluations in PH-ILD could therefore incorporate QoL measures collected via EQ-5D, if and when such data become available.

The results of this cost-effectiveness anlaysis demonstrated that, from an NHS and PSS perspective, inhaled treprostinil is a cost-effective treatment versus BSC in the treatment of patients with PH-ILD in the UK based on a WTP threshold of £30,000 per QALY gained. The analysis adopted a number of conservative assumptions, as evidenced by the high proportion of the scenario analyses yielding ICERs that were below the WTP threshold of £30,000 per QALY gained and, in many cases, below the base case ICER of £28,000 per QALY gained.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease ID6459

Addendum: Matching-adjusted indirect comparison versus PDE5is

October 2025

File name	Version	Contains confidential information	Date
ID6459 inhaled treprostinil in PH-ILD Addendum	**1.0**	**Yes**	**03 October 2025**

Contents

Tables and figures

Figures

Abbreviations

Abbreviation	Definition
6MWD	6-minute walk distance
BSC	Best supportive care
CI	Confidence interval
DLCO	Diffusing capacity of the lungs for carbon monoxide
DSU	Decision Support Unit
EAG	External Assessment Group
FEV	Forced expiratory volume
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ILD	Interstitial lung disease
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OLE	Open-label extension
OS	Overall survival
PDE5i	Phosphodiesterase Type 5 Inhibitors
PH	Pulmonary Hypertension
PH-ILD	Pulmonary Hypertension associated with Interstitial Lung Disease
QALY	Quality-adjusted life year
RPSFT	Rank-preserving structural failure time
WHO	World Health Organization

1. Clinical effectiveness

1.1 Matching-adjusted indirect comparison versus PDE5is

An unanchored matching-adjusted indirect comparison (MAIC) was conducted against phosphodiesterase type 5 inhibitors (PDE5is) to assess the comparative effectiveness of inhaled treprostinil in pulmonary hypertension associated with interstitial lung disease (PH-ILD).[1] The outcome considered was overall survival (OS) and the analysis was conducted on:

- Patients treated with inhaled treprostinil in the INCREASE and INCREASE open-label extension (OLE) studies
- Patients treated with PDE5i in the Dawes *et al.* (2022) study

Although Ferrer does not consider PDE5is to be a relevant comparator for inhaled treprostinil (see Section 1.1 of the Company submission), data from the MAIC versus PDE5is are presented to provide further supporting evidence on the effectiveness of inhaled treprostinil and to support scenario analyses in the cost-effectiveness model (see Section 2).

1.1.1 Methods

Full methods and data inputs for the MAIC are reported in Appendix B (Section B.1.3) of the Company submission. Analyses for the MAIC were conducted in R, using code modified from NICE TSD18.[2]

The baseline characteristics that were considered prognostic variables and possible effect modifiers for an indirect treatment comparison (ITC) included: age (baseline/screening), sex, body mass index, smoking history, PH-ILD severity (% predicted diffusing capacity of the lungs for carbon monoxide [DLCO]), time since diagnosis, pulmonary function (% predicted forced expiratory volume [FEV]), aetiology of lung disease, comorbidities, 6-minute walk distance (6MWD) at baseline, and oxygenation. It is assumed that there were no unmeasured confounding variables.

Insufficient data were reported in the Dawes *et al.* (2022) study for body mass index and smoking history to determine the sufficiency of overlap with the INCREASE population and the need for adjustment. The greatest observed difference between

the studies was the time since diagnosis of PH-ILD. Patients were assumed to have a time since diagnosis of zero in Dawes *et al.* (2022), whilst there was a delay from diagnosis to study entry of up to 13 years in the INCREASE trial. To allow for meaningful comparisons, patients with a time since diagnosis of >2 years in the INCREASE studies were excluded based on real-world evidence that shows patients typically receive treatment two years after symptom onset.[3] Furthermore, patients with connective tissue disease in the INCREASE studies were excluded from the analysis to align with the population in Dawes *et al.* (2022).

Indirect measures of treatment effect were estimated following the guidance in the NICE DSU TSD 2.[4] Statistical modelling was based on individual patient data (IPD) from INCREASE and INCREASE OLE, along with aggregate Kaplan-Meier (KM) data obtained from the Dawes *et al.* (2022) study.

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE to the Dawes *et al.* (2022) population. The distribution of effect modifiers at baseline and after matching are presented in Table 1.

Table 1. Distribution of effect modifiers at baseline and after matching

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	65.0	65.0
Sex (% male)	0.59	0.42	0.42
Hypertension (% with)	0.50	0.26	0.26
Oxygenation (% receiving)	0.46	0.76	0.76
6MWD	261.0	258.0	258.0
DLCO	28.4	25.0	25.0
FEV1	67.0	59.0	59.0
IPF	0.33	0.40	0.40
NSIP	0.33	0.10	0.10
Other	0.55	0.50	0.50

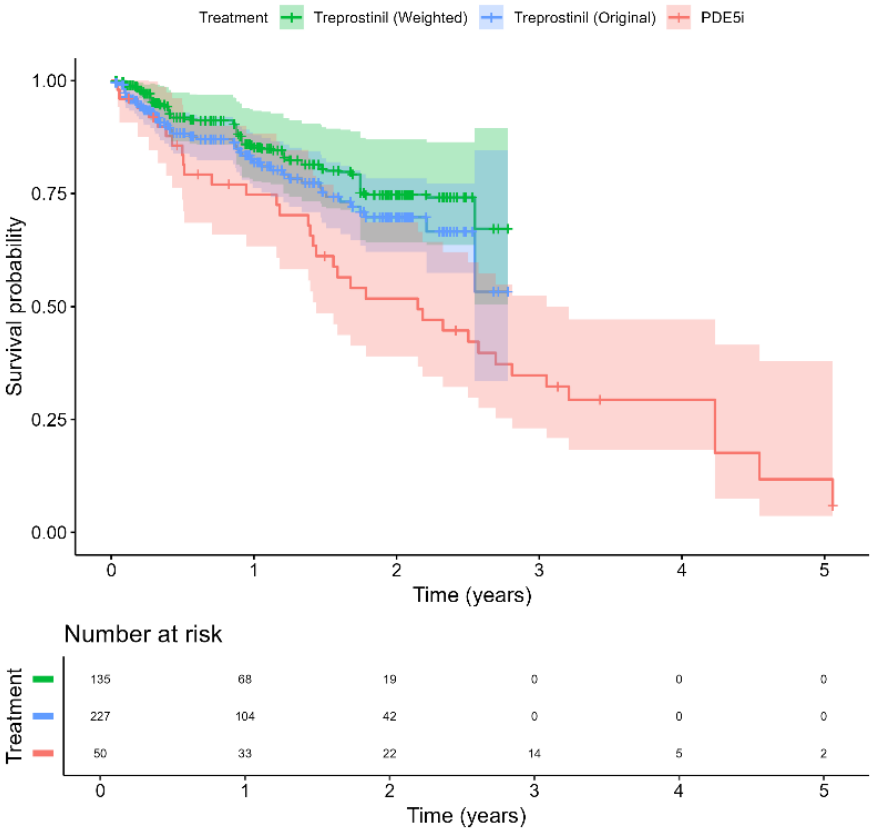
Key: 6MWD, 6-minute walk distance; DLCO, Diffusing capacity of the lungs for carbon monoxide; FEV1, Forced expiratory volume in 1 second; IPF, Idiopathic pulmonary fibrosis; NSIP, Non-specific interstitial pneumonia.

1.1.2 Results

Predicted outcomes after reweighting

The MAIC demonstrated that a larger proportion of patients treated with inhaled treprostinil remain alive compared to patients treated with PDE5is, indicating an OS benefit of inhaled treprostinil versus PDE5is over a 2.5-year period, as shown in the KM curves presented in Figure 1.

Figure 1: KM for inhaled treprostinil, weighted treprostinil and PDE5i OS in the ITT population



Key: ITT, intention-to-treat; KM, Kaplan-Meier; PDE5i: phosphodiesterase type 5 inhibitors; OS, overall survival.

Table 2 provides a summary of the OS statistics from the MAIC. An incremental benefit was observed in the median OS with inhaled treprostinil (median OS not reached) versus PDE5is (2.15 years), with a hazard ratio (HR) of 0.44 (95% confidence interval [CI]: 0.241 to 0.803). Notably, this HR is more favourable than that derived from the unadjusted ITT analysis of INCREASE OLE for inhaled treprostinil versus BSC (0.71).[5] This suggests that the EAG's selection of the ITT HR

to model OS with inhaled treprostinil versus BSC is likely to represent an inappropriately conservative scenario.

Table 2: Summary of OS statistics

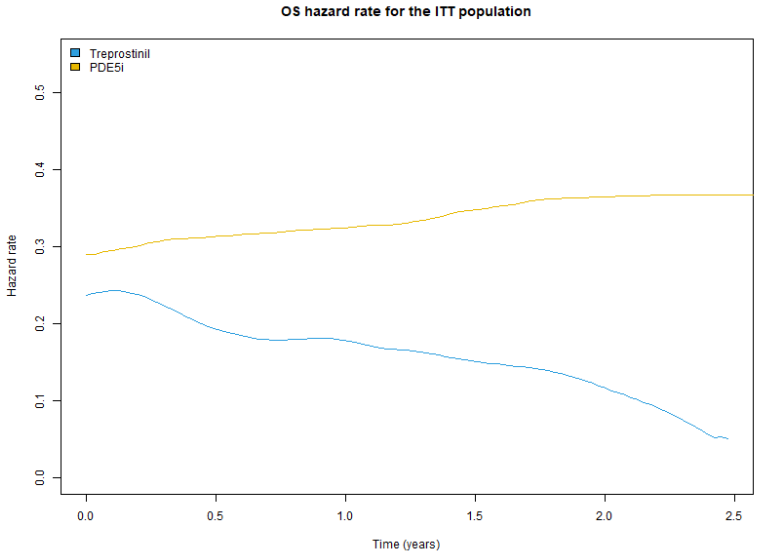
Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with PDE5i (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=135)	15.31 (21/135)	0.97 (0.96 to 1.19)	1.07 (0.80)	N/A (N/A to N/A)	2.30 (0.10)	0.44 (0.241 to 0.803; 0.030)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.97 to 1.17)	1.07 (0.80)	N/A (2.55 to N/A)	2.15 (0.08)	0.58 (0.355 to 0.949; 0.0074)
PDE5i (n=50)	70.00 (35/50)	1.42 (1.26 to 2.01)	1.62 (1.29)	2.15 (1.44 to 3.05)	2.39 (0.25)	-

Key: CI, confidence intervals; HR, hazard ratio; NA, not applicable; OS, overall survival; PDE5i, phosphodiesterase type 5 inhibitors; SE, standard error

Assessment of the PH assumption

The empiric hazards were assessed, and the proportional hazard (PH) assumptions were tested between inhaled treprostinil and PDE5is to ensure a constant HR can describe the difference in OS. Figure 2 presents the hazard rate of OS over time for inhaled treprostinil and PDE5i. The hazard rate for PDE5i is shown to be monotonically increasing. The hazard rate for inhaled treprostinil is also largely monotonic, with a constant decrease in hazard rate occurring from approximately year 1 onwards. These constant hazard rates over time for both arms suggest that applying a single HR to describe the OS difference between the two is appropriate.

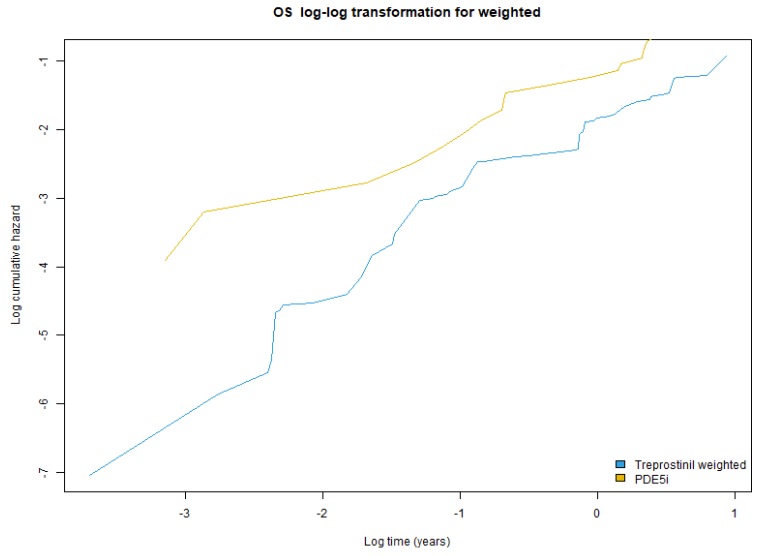
Figure 2: Empiric OS hazard rate for inhaled treprostinil and PDE5i in the ITT population



Key: ITT: intention to treat; OS: overall survival; PDE5i: phosphodiesterase type 5 inhibitors.

Figure 3 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and PDE5i groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

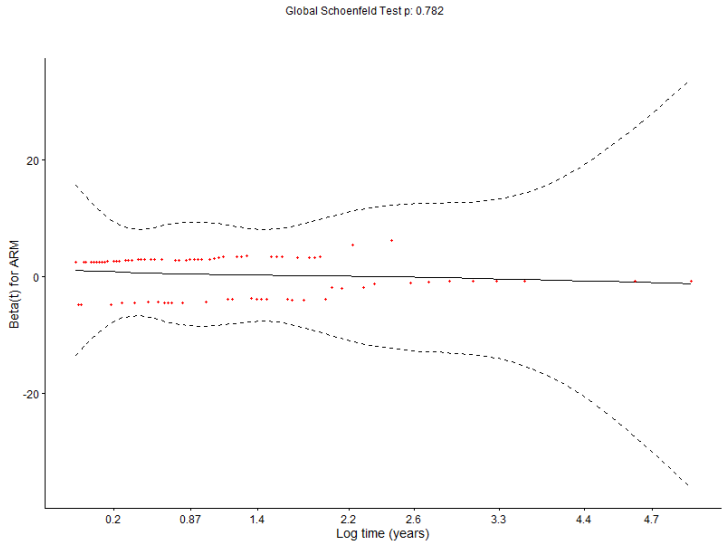
Figure 3: Log-log plot of OS in the ITT population



Key: ITT: intention to treat; OS: overall survival; PDE5i: phosphodiesterase type 5 inhibitors.

Figure 4 shows the Schoenfeld plot for inhaled treprostinil and PDE5i, further supporting that the PH assumption holds for the treatment covariate with a non-significant relationship between residuals and time (p=0.782).

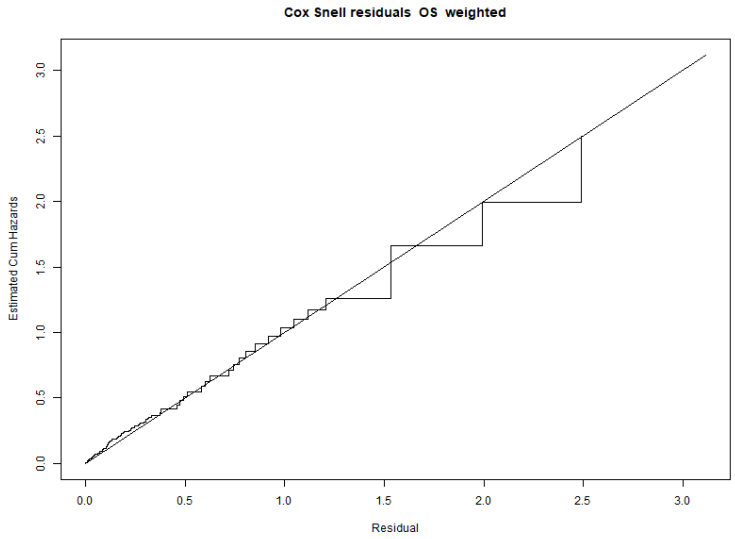
Figure 4: Schoenfeld plot of OS in the ITT population (p=0.782)



Key: ITT: intention to treat; OS: overall survival.

Figure 5 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie fully on the straight line with zero intercept and unit slope, this provides evidence of non violation of the PH assumption.

Figure 5: Cox-Snell residual plot of OS in the ITT population



Key: ITT: intention to treat; OS: overall survival.

2 Cost effectiveness

2.1 Methods

Cost-effectiveness analyses comparing inhaled treprostinil with mixed populations of patients treated with BSC or PDE5is were conducted by running analyses for the individual populations (i.e. inhaled treprostinil versus BSC and inhaled treprostinil versus PDE5is) and weighting the results (incremental costs and QALYs). An Excel workbook incorporating the functionality to perform this weighting is provided alongside the present addendum.

Results of comparisons with mixed populations of patients treated with PDE5is were performed in scenario populations in which 8% of the population were treated with PDE5is and 10% were treated with PDE5is, in line with the use of PDE5is reported in a UK-based epidemiology study using CPRD data and the NHSE estimate of PDE5i use in the budget impact model, respectively.[6] Each analysis versus BSC was run using the Weibull model of OS in the BSC arm (based on the RPSFT-adjusted crossover for INCREASE OLE) and either the Weibull or the generalised gamma distribution of OS in the inhaled treprostinil arm (based on the current company base case and the preferred OS distribution in the EAG report, respectively). Each analysis versus PDE5is was run using either the Weibull or generalised gamma model of OS in the inhaled treprostinil arm, with a hazard ratio of 2.27 (the reciprocal of 0.44) used to derive the corresponding model in the PDE5i arm based on the MAIC (see Section 1.1.2).

2.2 Results

The incremental quality-adjusted life years, incremental costs, and ICERs are presented in Table 3. These results demonstrate that in the scenarios applying the company's preferred Weibull curve for inhaled treprostinil OS, inhaled treprostinil is a cost-effective treatment versus a weighted BSC/PDE5i comparator reflecting NHSE's estimates of PDE5i usage in the NHS.

Table 3. Scenario analyses results of inhaled treprostinil versus 8% or 10% use of PDE5is and the remaining population on best supportive care

Base case (versus BSC) inhaled treprostinil OS model	PDE5i comparison inhaled treprostinil OS model	Incremental QALYs	Incremental costs (£)	ICER (£/QALY at [redacted]% PAS)
8% PDE5i use				
Weibull	Weibull	[redacted]	[redacted]	[redacted]
Generalised gamma	Generalised gamma	[redacted]	[redacted]	[redacted]
10% PDE5i use				
Weibull	Weibull	[redacted]	[redacted]	[redacted]
Generalised gamma	Generalised gamma	[redacted]	[redacted]	[redacted]

Key: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; OS: overall survival; QALYs: Quality adjusted life years.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

Summary of Information for Patients (SIP)

May 2025

File name	Version	Contains confidential information	Date
ID6459_inhaled treprostinil summary of information for patients_20052025	1.0	No	20/05/2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Inhaled treprostinil

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Inhaled treprostinil is a treatment for adult patients with pulmonary hypertension (i.e., high blood pressure in the blood vessels that connect the heart and lungs) associated with interstitial lung disease (i.e., lung disease causing scarring of the lungs).(1)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Inhaled treprostinil is expected to be indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD). The application for marketing authorisation with the UK Medicines and Healthcare products Regulatory Agency (MHRA) is currently ongoing. The current anticipated date of approval can be found in Table 2 of the NICE company submission document.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Ferrer has been in contact with Pulmonary Hypertension Association in the United Kingdom (PHA UK) and Action for Pulmonary Fibrosis (APF) during the last 3 years. The aim of these collaborations has been to understand the unmet need and burden of disease for people living with PH-ILD.

In 2023, Ferrer provided financial support for a meeting called PH Professionals Forum in London with the participation of nurses, pharmacists and physiotherapists (but not patients). PHA UK were involved in the organisation of this meeting. In 2022, Ferrer conducted a study to understand the burden of disease in patients with PH-ILD, for which patients received financial compensation for their time.(2) In addition, Ferrer is conducting a Get-on-Board project to analyse stakeholders' journey in PH-ILD and identify where different interventions could improve patients' experience. No financial contribution is provided by Ferrer to patient groups for this project.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

PH is a rare condition that causes high blood pressure in the blood vessels connecting the heart and lungs (the pulmonary arteries). When a person develops PH, the walls of the pulmonary arteries become stiff and thickened resulting in tightened, narrowed arteries. This makes it difficult for them to expand, and trying to pump blood through these arteries increases strain on the right side of the heart.(1)

PH often develops as a complication from ILD, which refers to a group of lung conditions that cause scarring of the lung tissues.(3-5) This scarring makes it difficult for the lungs to work properly, leading to breathing problems and reduced oxygen levels in the blood. People with ILD may experience symptoms like shortness of breath, dry cough, and fatigue.(3-5) PH affects over 60% of individuals with end-stage ILD and worsens the prognosis of the underlying ILD.(6, 7)

Current estimates show that around 0.66 in every 10,000 people in the UK has PH associated with ILD (PH-ILD).(8) However, this figure may not reflect the full scale of the disease in the UK. Studies from Europe (including the UK) and North America have reported higher prevalence rates—about 4 in 10,000 people in Europe, and between 0.8 and 1 in 10,000 in North America.(9)

PH-ILD is a progressive and life-limiting condition that poses substantial burden for patients and carers.(10-13) The median survival time in patients with PH-ILD is reported to be from 0.7 to 1.7 years.(14-17) The symptoms of PH-ILD, such as shortness of breath and tiredness, affect daily activities like cooking, cleaning, or going to the shops.(5, 13, 18-20) Additionally, physical abilities are reduced, with patients finding it hard to walk or climb stairs.(10-13)

Carers of patients with PH-ILD also experience significant physical, emotional, and financial stress. Carers—usually close family members—take on tasks such as managing oxygen therapy, helping with mobility, and offering constant emotional support. This can result in social isolation, anxiety and financial burden.(2)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Initially, people with ILD visit their GP with general symptoms such as shortness of breath, chest discomfort, tiredness, and a dry cough. Patients may require between 1 and 3 visits to specialist ILD centres before a diagnosis of ILD is made, with some patients waiting more than 12 months for their first appointment with a general respiratory clinician.(21) Diagnosis of ILD involves several tests, such as assessing the patients' lung function, physical ability, and computed tomography (CT) scans of the chest. When doctors suspect that someone with ILD might also have PH, they refer them to a specialist PH centre (of which there are 7 in the UK) for further testing. The main test to confirm PH is an invasive procedure called right heart catheterisation, which measures pressure in the heart and lung vessels. Doctors confirm a diagnosis of PH if:(22, 23) • The pressure in the lung's blood vessels is high (defined as an average pressure over 20 mmHg) • The heart is facing resistance when pumping blood through the lungs   ○ If resistance is 2 or more (in a unit called "Wood units"), it shows the right side of the heart is under strain • The pressure on the left side of the heart is normal (defined as an average pressure below 15 mmHg) No additional diagnostic tests will be required to identify patients for treatment with inhaled treprostinil.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:
• What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
• Please also consider:
  ○ if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  ○ are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There are currently no approved treatments for the management of PH-ILD. However, in patients with severe forms of PH-ILD, clinicians at specialist PH centres may consider treatments such as phosphodiesterase 5 inhibitors (PDE5is). These are approved for another type of pulmonary hypertension, called pulmonary arterial hypertension (PAH).(23) Although PDE5is are not approved for PH-ILD, clinicians administer these therapies to try to relieve symptoms in patients with severe disease due to the lack of alternative treatment options.(24) However, their effectiveness is limited and varies from patient to patient. Inhaled treprostinil is the first treatment for PH-ILD shown to improve physical function, decrease the risk of hospitalisation, improve lung function, and potentially prolong survival.(15, 25)

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A European Voice of the Patient (VOP) meeting was held in December 2022 to better understand the impact of PH-ILD on patients and their carers. The meeting was organised by Ferrer, with input from the patient organisations Pulmonary Hypertension Association-Europe (PHA-EU) and European Pulmonary Fibrosis Federation (EU-PFF).(2) People living with PH-ILD and carers were invited to attend an online meeting, along with representatives from the patient organisations and clinical experts. Following the meeting, researchers grouped what people said about PH-ILD into five key themes:

1. Patients reported experiencing severe symptoms that limit daily life
    - The most common symptoms were shortness of breath, cough and fatigue.
    - These made everyday tasks like walking, shopping, and housework very difficult.
    - Oxygen helped some people but didn't restore their ability to do their usual daily activities.
2. The disease has a considerable emotional and social impact
    - Many people felt isolated, anxious or sad because of how the disease had changed their lives.
    - They had to give up hobbies, reduce social contact, and some couples experienced strain on relationships.
3. Diagnosis is difficult and often delayed
    - Diagnosis was often delayed by more than a year.
    - Many people were misdiagnosed or told symptoms were due to something else.
    - Some were not told about PH until months after being diagnosed with ILD.
4. A high unmet need for an effective treatment
    - No approved treatment is currently available for PH-ILD.
    - Some patients receive medicines for other types of pulmonary hypertension, but these are used off-label (i.e., they are not approved for PH-ILD)
    - Patients said they were willing to try treatments with side effects if these could improve their quality of life (QoL) or help them live longer.
5. A need for joined-up care
    - Patients and carers called for a clear care pathway from diagnosis to end-of-life support.
    - Many said that care was disjointed, and that GPs and hospital doctors had limited knowledge of PH-ILD.

Carers of patients with PH-ILD also experience significant physical, emotional, and financial stress. Carers—usually close family members—take on tasks such as managing oxygen therapy, helping with mobility, and offering constant emotional support. This results in reduced independence, social isolation, and interruptions to their own jobs and daily lives.(2) Furthermore, giving patients more support closer to home will help free up space in specialist services so they can care for those with more complex needs.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Inhaled treprostinil is a synthetic version of a naturally occurring substance in the body known as prostacyclin, a hormone that helps to relax blood vessels and prevent blood clots. It is inhaled directly to the lungs where it works by:

- Widening (relaxing) the blood vessels in the lungs, so blood can flow more easily
- Reducing the pressure in the lung arteries, which means the heart does not have to work as hard
- Improving oxygen delivery throughout the body
- Reducing symptoms like shortness of breath and fatigue
- Improving the ability to exercise and carry out daily activities

Inhaled treprostinil does not require hospital visits – it is a non-invasive treatment that can be taken at home. It offers a treatment option that delays disease progression and reduce hospitalisations. It provides symptom relief and helps improve daily life and independence. Studies have shown that it improves exercise capacity, which is a key goal in managing pulmonary hypertension.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, inhaled treprostinil will not be used in combination with any other medication for PH-ILD. Inhaled treprostinil will be used alongside treatments for underlying lung disease, such as pirfenidone or nintedanib.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Inhaled treprostinil is taken at home or on the go using a portable inhalation device. Before starting treatment, patients are taught how use the inhalation device to administer inhaled treprostinil correctly.

The initial dose consists of 3 breaths of inhaled treprostinil (18 mcg of treprostinil) per treatment session 4 times per day. If 3 breaths are poorly tolerated, the initial dose should be reduced to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

The maintenance dosage should be increased under medical supervision in increments of 1 breath per treatment session, 4 times daily at a minimum of a 3 day interval. The target maintenance dose consists of 9 to 12 breaths per treatment session 4 times per day. Treatment is typically ongoing as long as the patient remains eligible and benefits from the therapy. The exact duration depends on clinical outcomes.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The pivotal trials for inhaled treprostinil in adult patients with PH-ILD were the Phase III randomised controlled trial (RCT) INCREASE and the Phase III INCREASE open-label extension (OLE).(14, 15, 25) These are summarised below.

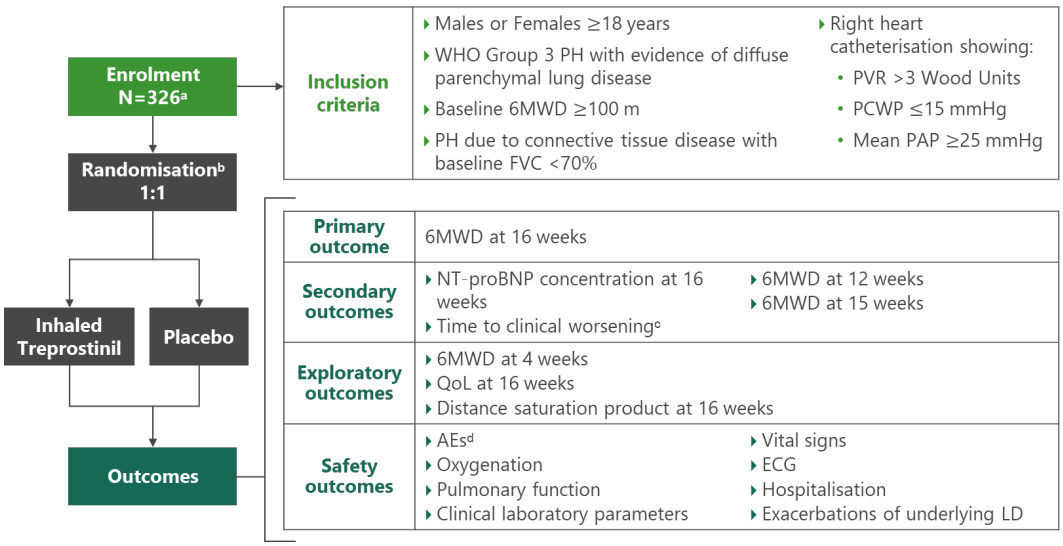
INCREASE

INCREASE was a 16-week Phase III, multicentre, randomised, double-blinded, placebo-controlled trial to investigate the safety and efficacy of inhaled treprostinil in PH-ILD (Figure 1).(15)

Study characteristics:

- Location: Conducted at 119 centres across the United States and Puerto Rico
- Population: Adult patients with PH-ILD.
- Patient Group Size: 326 participants.
- Comparators: Placebo.
- Key Inclusion Criteria: Adults aged 18-85 years with a confirmed diagnosis of PH-ILD.
- Key Exclusion Criteria: Patients with significant left heart disease or other severe comorbidities.
- Completion Dates: The trial was completed on 18 February 2020

Figure 1. Study design of INCREASE



Key: 6MWD, six-minute walk distance; AE, adverse event; ECG, electrocardiogram; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial

pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, quality of life; WHO, World Health Organisation.

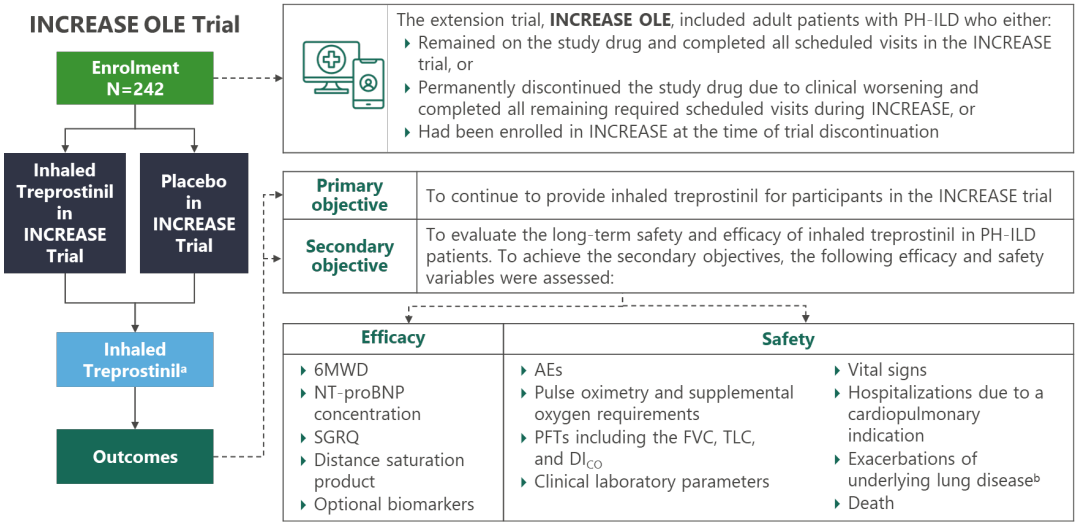
INCREASE OLE

INCREASE OLE was a Phase III, multicentre, open-label trial to evaluate the long-term safety and efficacy of inhaled treprostinil in patients who had completed the INCREASE 16-week trial (Figure 2).(25) All patients in INCREASE OLE had inhaled treprostinil, even if they had placebo in INCREASE.

Study characteristics:

- Location: Conducted at 119 centres across the United States and Puerto Rico.
- Population: Adult patients who completed the INCREASE NCT02630316 trial.
- Patient Group Size: 242 participants.
- Comparators: No comparator, as it is an open-label extension.
- Key Inclusion Criteria: Patients who completed the INCREASE NCT02630316 trial and met the continuation criteria.
- Key Exclusion Criteria: Patients with significant left heart disease or other severe comorbidities.
- Completion Dates: The trial was completed on 1 August 2021

Figure 2. Study design of INCREASE OLE



Key: 6MWD, six-minute walk distance; AE, adverse event; NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, open label extension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; SGRQ, St. George's Respiratory Questionnaire.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Key findings from INCREASE

<u>The primary endpoint: 6-Minute Walk Distance at 16 weeks</u>

The primary endpoint for INCREASE was the 6-Minute Walk Distance (6MWD) at 16 weeks. This measures how far a person can walk in six minutes. It is a standard way to assess physical ability in patients with lung disease.

After 16 weeks, patients using inhaled treprostinil were able to walk 31.1 metres further than those treated with placebo.(15) This improvement is both statistically significant and clinically

meaningful. It is above the threshold where patients are likely to feel a real difference in their day-to-day activities (18.7–24.7 metres).(26) Similar improvements were seen at other time points (e.g., 31.3 metres at Week 12 and 22.0 metres at Week 15).(15, 26)

Secondary efficacy endpoint: Change in Plasma Concentration of NT-proBNP from baseline to Week 16

A secondary endpoint for INCREASE was change in plasma concentration of NT-proBNP from baseline to Week 16. NT-proBNP is a blood marker, which indicates strain on the heart.

NT-proBNP was reduced by 42% in patients taking inhaled treprostinil.(15) In contrast, levels of NT-proBNP went up by 46% in patients taking placebo. This suggests that inhaled treprostinil may reduce strain on the heart.

Secondary efficacy endpoint: time to clinical worsening

Another secondary endpoint for INCREASE was the time it took for patients' condition to get worse (known as clinical worsening). Inhaled treprostinil decreased the risk of clinical worsening by 39% over the 16-week trial. Fewer patients needed hospitalisation, experienced a large drop in walking ability, or had other serious issues.(15)

Post-hoc efficacy analysis of INCREASE: disease progression

A further analysis of INCREASE assessed how many patients experienced disease progression during the 16-week treatment period. Disease progression was measured as clinical deterioration, indicated by reduced walking ability, acute exacerbations, decreased lung capacity, and the occurrence of hospitalisations, transplantation, and/or death. Acute exacerbations are defined as sudden and severe flare-ups of the lung disease that can quickly worsen breathing. Patients on inhaled treprostinil had significantly fewer disease progression events compared to placebo. The rate of disease progression was reduced by 31%, which was considered significant.(27)

Key findings from INCREASE OLE

6-Minute Walk Distance at 52 weeks

A key efficacy endpoint included in INCREASE OLE was the 6MWD at 52 weeks. This was included to evaluate long-term effects in patients who participated in the INCREASE RCT.

At week 52, patients using inhaled treprostinil in the overall population were able to walk 3.5 metres more than at the start of the INCREASE RCT.(25, 28) Those who had previously received inhaled treprostinil were able to walk 22.1 metres more, while those who had been on placebo walked 19.5 metres less than they did at the start the INCREASE RCT. These findings indicate that patients treated with inhaled treprostinil in the INCREASE RCT experienced sustained improvements in the 6MWD during INCREASE OLE, indicating that inhaled treprostinil has a durable, long-lasting response.(25, 28)

Change in Plasma Concentration of NT-proBNP from baseline to Week 64

Patients treated with inhaled treprostinil in the INCREASE RCT, had a 17% reduction in NT-proBNP by week 64.(25, 28) Patients treated with placebo in the INCREASE trial RCT but switched to inhaled treprostinil during the OLE showed a 50% reduction in NT-proBNP levels by week 64. These results suggest a sustained benefit in reducing heart strain for patients receiving inhaled treprostinil.

Overall survival (i.e., how long patients lived after starting treatment)

Around 2 years after starting treatment, patients treated with inhaled treprostinil in the INCREASE RCT had a 33% lower risk of death than those who had received placebo and then switched to inhaled treprostinil. On average, patients who had inhaled treprostinil in the INCREASE RCT lived for 62 weeks after starting the study whereas patients who started on placebo lived for 31 weeks. However, these results are likely to underestimate the true positive effect of inhaled treprostinil

on overall survival, because everyone starting on placebo in the INCREASE RCT switched over to inhaled treprostinil after 16 weeks.

A further analysis looked at whether inhaled treprostinil has survival in the INCREASE trial and INCREASE OLE, adjusting for patients switching from placebo to inhaled treprostinil.(29) When adjusting using a statistical method called Ranking Preserving Structural Failure Time (RPSFT), patients on inhaled treprostinil showed a 74% lower risk of death compared to what would be expected if they had stayed on placebo.

Further (post-hoc) efficacy analyses

Event-free survival:

A further analysis showed that patients who had received inhaled treprostinil in the INCREASE trial had better event-free survival than those who received placebo. On average, patients in the inhaled treprostinil group went 37.1 weeks before their first serious event (for example, hospitalisation or an exacerbation), compared to 21.3 weeks for the placebo group. Additional details of these results can be found in section 2.6.2.2 of the company submission.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Changes in QoL were measured in the INCREASE and INCREASE OLE studies using the St. George's Respiratory Questionnaire (SGRQ). The SGRQ is a measure used to assess QoL in patients with obstructive airway diseases and has been validated for use in patients with asthma and chronic obstructive pulmonary disease.(30) Therefore, the SGRQ may not fully capture the impact of PH-ILD on QoL, but was the most suitable option at the time of these studies due to the lack of validated measure for PH-ILD specifically.(31) The SGRQ provides a score from 0 to 100, where 0 equals best possible health and 100 equals worst possible health. A change of 4 points or more is considered meaningful to patients.

At Week 16 of the INCREASE RCT trial, an exploratory analysis of the patient-reported SGRQ revealed a trend of improved QoL for patients with PH-ILD receiving inhaled treprostinil versus placebo. A slightly higher number of patients on inhaled treprostinil (total of 52 patients) showed a meaningful improvement in their QoL (≥4-point improvement) compared with placebo (total of 47 patients).(14, 15) Furthermore, no deterioration in patient QoL, as measured by the SGRQ was observed during INCREASE OLE.(25, 28)

In conclusion, patients treated with inhaled treprostinil reported lower scores (i.e., better health) across all domain scores of the SGRQ (symptoms, activities, and impacts). However, the differences between the inhaled treprostinil and placebo arms were not statistically significant, meaning the difference could be due to chance and further research is required to demonstrate the impact of inhaled treprostinil on QoL.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where

possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Inhaled treprostinil has a generally manageable safety profile, with no new safety concerns identified in longer-term use.

INCREASE

In the INCREASE RCT, most patients experienced at least one side effect: 93.3% in the inhaled treprostinil arm and 91.4% in the placebo arm.(14, 15, 25, 28) In the inhaled treprostinil group, the most common side effects were cough (43.6%), headache (27.6%), shortness of breath (25.2%), dizziness (18.4%), nausea (15.3%), fatigue (14.1%), diarrhoea (13.5%), throat irritation (12.3%), and sore throat or mouth pain (11.0%). In the placebo group, the most frequently reported side effects were cough (33.1%), shortness of breath (31.3%), headache (19.6%), nausea (16.0%), an increase in NT-proBNP (heart strain biomarker) (15.3%), dizziness and fatigue (14.1% each), and diarrhoea (11.7%).

Very few patients stopped treatment due to side effects, indicating that most patients are able to continue therapy with appropriate management.(14, 15, 25, 28) Although side effects were common, they occurred at similar rates in the placebo group, and may reflect the underlying disease or method of drug delivery.

INCREASE OLE

Most patients in INCREASE OLE (94.6%) experienced at least one side effect during the study.(25, 28) Consistent with the INCREASE RCT, the most common side effects were cough (26.9%), breathlessness (26.0%), headache (18.6%). A similar proportion of patients who had taken inhaled treprostinil (94.1%) or placebo (95.0%) in the INCREASE RCT experienced at least one side effect during the INCREASE OLE study. However, those who had previously taken placebo were more likely to report a cough (35.5% compared to 18.5%) and headache (27.3% compared to 10.1%) than those who had taken inhaled Treprostinil, suggesting that tolerability may improve over time.

When considering the overall balance of benefits and risks, inhaled treprostinil offers meaningful clinical improvements in physical function, symptom control, and potentially longer-term outcomes such as reduced hospitalisations and heart strain. These benefits are considered to outweigh the risks for many patients with PH-ILD, particularly when side effects are closely monitored and managed by healthcare professionals.

Further safety information can be found in section 2.11 of the company submission.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

PH-ILD is a debilitating, progressive and life-limiting condition that poses substantial burden for patients and carers. There are currently no effective, approved treatments for PH-ILD.

Inhaled treprostinil is administered via a hand-held, user-friendly inhalation device.(32, 33) The inhalation device is designed for convenient 2 to 3-minute treatment sessions at home or on the go, allowing patients to receive treatment with minimal disruption to their daily lives and work.

The frequency of administration can be scheduled around daily activities every 4 waking hours, avoiding nighttime use with the benefit of only once daily set-up and cleaning.(32) Inhaled treprostinil is delivered directly to the lungs where it is needed, limiting widespread side effects.(15, 33, 34)

The INCREASE and INCREASE OLE studies have shown that inhaled treprostinil improves physical functioning (i.e., increased 6MWD) and reduces the risk of worsening in underlying lung disease symptoms. In addition, inhaled treprostinil is associated with improvements in lung function and provides a potential survival benefit.(35, 36)

Overall, inhaled treprostinil has been shown to have a positive impact on patient-relevant outcomes that may lead to improved QoL in patients with PH-ILD.(35-39) This is supported by the results from the SGRQ measure that assessed patients' QoL in the clinical trials. In INCREASE, a trend of improved QoL was reported in patients receiving inhaled treprostinil vs placebo and no deterioration in SGRQ scores was observed long-term in the INCREASE OLE study.(15, 25)

Inhaled treprostinil has been shown to be well tolerated, with similar rates of side effects reported between the placebo and inhaled treprostinil arm in INCREASE and INCREASE OLE.(14, 15, 33)

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The disadvantages seen with inhaled treprostinil treatment are minor and mainly relate to side effects, such as cough, headache, and dizziness. These side effects can be bothersome, especially for patients who are already dealing with breathlessness and fatigue from PH-ILD, however, they have been shown to decrease over time.

Inhaled treprostinil must be taken multiple times a day using a portable inhalation device, which can be time-consuming, but this can be done at home or on the go by the patient or carer.

Finally, there is currently no clear evidence that inhaled treprostinil has a clinically meaningful impact on patient QoL. However, the QoL tool in the INCREASE trial (SGRQ) was not developed for use in PH-ILD specifically and therefore may not fully reflect the QoL benefits associated with inhaled treprostinil.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by

patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

A new model was developed to reflect the experience of people with PH-ILD, as no previous models existed for this condition. The model is intended to compare the costs and benefits of inhaled treprostinil with the currently available standard of care (best supportive care), which was represented by the placebo arm of the INCREASE trial.

The model was developed in consultation with experts in treating PH-ILD, as well as health economists experienced in reviewing models for NICE, to check that the approach was appropriate. It uses a 'partitioned survival' approach, which allows data from the clinical trial to be used directly and also reflects the progressively worsening nature of PH-ILD.

Four health states are included in the model to reflect disease progression:

1) No clinical worsening,
2) After one clinical worsening event,
3) After two or more worsening events, and
4) Death.

A clinical worsening event is any of the following:

- A decrease in 6MWD of 15% or more from the start of the INCREASE trial
- A decrease in FVC of 10% or more from the start of the INCREASE trial
- A hospitalisation caused by an issue with the heart and lungs
- A clinically significant lung disease exacerbation
- Lung transplant
- Death

The modelled population was selected to align with the INCREASE study population and to align with patients with PH-ILD in UK clinical practice.

People in the model begin in the "no worsening" state and may move to a worsening state or die, based on how their condition progressed in INCREASE and INCREASE OLE. These changes reflect typical disease progression in PH-ILD. Once a person experiences a worsening event, they do not move back to a better state, which mirrors the irreversible nature of disease progression.

Although some patients in the trial improved (e.g. walked longer distances), the model does not include a separate "improvement" state. This means that the model may not have captured all the benefits associated with inhaled treprostinil.

Modelling how much inhaled treprostinil extends life

By slowing the progression of PH-ILD and reducing the likelihood of major respiratory and cardiovascular events, inhaled treprostinil is expected to extend patients' lives. The long-term overall survival for patients having inhaled treprostinil was modelled using data from the INCREASE OLE study, which followed patients over more than 2 years. For patients having best supportive care, the crossover adjusted data from INCREASE OLE were used to try to remove the benefit of inhaled treprostinil. These data were extended to represent a lifetime duration using statistical modelling approaches. This analysis showed that inhaled treprostinil increases the length of time patients live on average from around 2 years to 4.5 years.

Modelling how much inhaled treprostinil improves quality of life

Inhaled treprostinil may improve QoL by improving physical functioning, reducing the risk lung disease exacerbations (i.e., flare-ups) and improving lung function.

QoL was measured in the INCREASE trial using the SGRQ, which asks people about their symptoms and how their lung disease affects their daily life. This tool is commonly used in other lung conditions like COPD and asthma and was not designed specifically for patients with PH-ILD. Therefore, the model may not fully reflect the QoL benefits associated with inhaled treprostinil.

Modelling how the costs of treatment differ with the new treatment

Various costs are included in the model, including: the cost of inhaled treprostinil; costs of treatments for a patient's underlying ILD; costs associated with specific events such as hospitalisations; and ongoing care costs such as for GP and specialist appointments. As there are currently no treatments for PH-ILD, inhaled treprostinil will be associated with higher costs per patient per year compared to best supportive care. However, inhaled treprostinil is expected to offset some of these costs by reducing the frequency of hospitalisations required by patients with PH-ILD.

Inhaled treprostinil will be administered at home using a portable inhalation device by the patient themselves or caregivers. Therefore, there is no additional cost for administration.

Uncertainty

There are various assumptions that were made in the model, which can result in uncertainty in the results. These include:

- Long-term effects of treatment are based on statistical modelling assumptions following the trends shown in the INCREASE and INCREASE OLE studies. In addition, the best supportive care data had to be adjusted to account for patients switching from placebo to inhaled treprostinil in the clinical trial
- There are no PH-ILD-specific tools for measuring QoL so the SGRQ was used that may not fully reflect the benefits of inhaled treprostinil on QoL
- The burden of PH-ILD on caregivers was not captured in the model due to a lack of appropriate data, despite studies showing a substantial burden of the disease on carers

Alternative assumptions for survival estimates, disease progression, and QoL mapping (from the SGRQ to the EQ-5D, NICE's preferred tool) were tested. These analyses confirmed that the model results are sensitive to uncertainty, but the model outcomes with inhaled treprostinil versus best supportive care remained broadly consistent under different scenarios.

The model is based on data from the INCREASE and INCREASE OLE trials, which provided evidence on survival, QoL and disease progression. Adjustments were made using NICE-recommended methods, for example on the statistical methods used to account for patients switching from placebo to active treatment in the OLE study.

Cost-effectiveness results

Please see section 3.10 of the company evidence submission for the cost-effectiveness results.

Additional factors

A severity modifier was included in the model because PH-ILD is a serious and life-limiting condition that greatly reduces both how long people live and their QoL.

Using a NICE-endorsed severity modifier tool, it was estimated that people with PH-ILD who receive best supportive care would gain only a further 1.21 quality-adjusted life years (QALYs*) on average, compared to 8.97 QALYs expected for people of the same age and sex in the general population. This means that people with PH-ILD miss out on nearly 90% of their expected healthy life.

Because of this large shortfall, a 1.2 times weighting was applied to the QALYs gained with inhaled treprostinil. This helps reflect the high level of unmet need in this condition. The result was tested in different ways and remained consistent, supporting the use of the severity modifier.

** A QALY, or quality-adjusted life year, is a way of measuring both how long someone lives and how good their health is during that time—one QALY means one year of life in perfect health.*

The QALY calculation may not fully capture the QoL benefits associated with the use of inhaled treprostinil for patients with PH-ILD due to the use of the SGRQ and the model does not capture the impact of inhaled treprostinil on caregivers QoL.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Inhaled treprostinil is expected to be the first and only approved treatment option for PH-ILD in the UK, with demonstrated efficacy in increasing exercise capacity and decreasing clinical worsening, while also offering a well-characterised and generally manageable side effect profile. Additionally, inhaled treprostinil is associated with an improvement in lung function and a potential long-term survival benefit.

Inhaled treprostinil works by targeting blood vessels in the lungs, helping to reduce pressure and improve oxygen flow. This means that inhaled treprostinil works by a new and innovative mechanism compared with other treatments and provides benefits regardless of the underlying lung disease.

Owing to lack of data, the economic model did not capture QALY benefits related to caregiver burden.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics
More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

No equality issues were identified.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Related clinical trials:

INCREASE
Clinicaltrials.gov study number: NCT02630316
Publication: Waxman A, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. New England Journal of Medicine. 2021 Jan 28;384(4):325-34. https://www.nejm.org/doi/10.1056/NEJMoa2008470

INCREASE OLE
Clinicaltrials.gov study number: NCT02633293
Publication: Waxman A, et al. Long-term inhaled treprostinil for pulmonary hypertension due to interstitial lung disease: INCREASE open-label extension study. European Respiratory Journal. 2023 Jun 29;61(6). https://publications.ersnet.org/content/erj/61/6/2202414

Related technology appraisals:

Nintedanib for treating idiopathic pulmonary fibrosis when forced vital capacity is above 80% predicted (2023) NICE technology appraisal guidance 864.

Nintedanib for treating progressive fibrosing interstitial lung diseases (2021) NICE technology appraisal guidance 747.

Pirfenidone for treating idiopathic pulmonary fibrosis (2018) NICE technology appraisal guidance 504.

Nintedanib for treating idiopathic pulmonary fibrosis (2016) NICE technology appraisal guidance 379.

Related technology appraisals in development:

Sotatercept for treating pulmonary arterial hypertension. NICE technology appraisal guidance [ID6163]. Publication expected October 2025.

Related NICE guidelines:

Idiopathic pulmonary fibrosis in adults: diagnosis and management (2013; updated 2017) NICE guideline CG163.

Related interventional procedures:

Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (2016) NICE interventional procedures guidance 554

Related quality standards:

Idiopathic pulmonary fibrosis in adults (2015) NICE quality standard 79.

Related national policy:
The NHS Long Term Plan (2019) NHS Long Term Plan

NHS England (2023) Prescribed specialised services manual (version 6) Chapter 4 Adult specialist respiratory Services Chapter 14 Adult Specialist pulmonary hypertension services

NHS England (2018) Interstitial Lung Disease Service Adult Service Specification 17009/S

NHS England (2014) Clinical Commissioning Policy: National policy for the treatment of pulmonary hypertension in adults

NHS Commissioning Board (2013) Clinical Commissioning Policy: targeted Therapies for Pulmonary Hypertension Function Class 11 Ref NHSCB/A11/P/a

Related information on the disease area and living with the condition
PHA UK website Pulmonary Hypertension Association | PHA

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **6MWD (Six-Minute Walk Distance)**: A test that measures how far a person can walk in six minutes. It shows how well the heart and lungs are working
- **Adverse event**: Any unwanted or harmful effect experienced after taking a treatment, whether or not it was caused by the treatment.
- **Chronic Obstructive Pulmonary Disease (COPD)**: A group of lung conditions that cause breathing difficulties.
- **Clinically meaningful**: A change in a symptom or test result that makes a real difference to a patient's health or daily life.
- **Clinical worsening events**: Serious health setbacks that indicate a decline in a patient's condition, such as hospitalisation or lung function decline.
- **Chronic Obstructive Pulmonary Disease (COPD)**: a group of lung conditions that cause breathing difficulties.
- **EQ-5D**: A standardised instrument used to measure health-related QoL, recommended by NICE for evaluating treatments.
- **Interstitial lung disease (ILD)**: A group of lung conditions that cause scarring of the lung tissues, leading to breathing problems and reduced oxygen levels in the blood.
- **NICE**: National Institute for Health and Care Excellence.
- **N-terminal pro–B-type natriuretic peptide (NT-proBNP)**: A blood marker that indicates strain on the heart.
- **OLE**: Open-label extension, a type of clinical trial where all participants know which treatment they are receiving.

- **Pulmonary Arterial Hypertension (PAH)**: A rare type of high blood pressure that affects the arteries in the lungs and the right side of the heart.
- **Pulmonary Hypertension (PH)**: High blood pressure in the blood vessels that supply the lungs.
- **PH-ILD**: Pulmonary hypertension associated with interstitial lung disease, a progressive and life-limiting condition.
- **Quality-adjusted life years (QALYs)**: A measure that combines the quantity and QoL, used to evaluate the value of medical interventions.
- **Quality of Life (QoL)**: a measure of a person's overall well-being and daily functioning.
- **Rank-preserving structural failure time (RPSFT):** Statistical method used to estimate survival outcomes in clinical trials.
- **St. George's Respiratory Questionnaire** (**SGRQ)**: Tool used to measure QoL in people with lung conditions. Scores range from 0 to 100, with higher scores showing worse symptoms and poorer QoL. A drop in score means the person's condition has improved.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

Clarification questions

May 2025

File name	Version	Contains confidential information	Date
Clarification questions	1	Yes	04/07/2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Please provide a post-hoc analysis of overall survival, 6-minute walk distance (6MWD), clinical worsening, and event-free survival from the INCREASE and INCREASE OLE trials, stratified by patients with and without background therapies. Additionally, assess the impact of concomitant therapies on these outcomes, including PDE-5 inhibitors (e.g., sildenafil, tadalafil), ERAs (e.g., bosentan, ambrisentan, macitentan), and prostacyclins or prostacyclin analogues (e.g., epoprostenol, SC/IV/oral treprostinil, inhaled iloprost, and selexipag).

Thank you for sharing this question. However, we have not provided the requested the requested post-hoc analysis of outcomes stratified by patients with and without background therapies or assessing the impact of concomitant therapies. This is because these analyses are not considered valuable or feasible based on the available data.

A post-hoc analysis for overall survival, 6MWD and EFS stratified by patients with and without background therapies has not been provided due to the low proportion of patients receiving background therapies in the INCREASE trial (overall: 22.7%, pirfenidone: 13.5%, nintedanib: 9.2%) that would prevent these analyses being statistically powered.

Furthermore, pirfenidone and nintedanib are not expected to impact the effectiveness of inhaled treprostinil. Inhaled treprostinil acts as a selective pulmonary vasodilator to widen the blood vessels in the lungs to lower pressure and improve blood flow. [1] In contrast, anti-fibrotic treatments (pirfenidone and nintedanib) target TGF-β signalling to slow the progression of pulmonary fibrosis (i.e., scarring of the lungs).[2] The distinct and non-overlapping mechanisms of action between inhaled treprostinil and antifibrotic treatments support the assumption that concomitant use of these therapies will not impact the effectiveness of inhaled treprostinil in PH-ILD.

Of note, patients are expected to continue receiving antifibrotic therapies alongside inhaled treprostinil in UK clinical practice, as these treatments target the underlying lung disease (i.e., idiopathic pulmonary fibrosis [IPF]) but do not treat PH in patients with ILD.

Additionally, it is not possible to assess the impact of PDE5is, ERAs, prostacyclins or prostacyclin analogues on the outcomes with inhaled treprostinil as no patients received these therapies in the INCREASE and INCREASE OLE study. Patients were not eligible for enrolment in the INCREASE trial if they received treatments approved for pulmonary arterial hypertension (PAH) within 60 days before randomisation into INCREASE.[1]

A2. Please provide the reason for exclusion and a table of baseline characteristics of the 136 patients who were screened but not enrolled in the INCREASE trial (out of a total of 462 screened).

The 136 patients who were screened but not enrolled were screen failures or withdrew from the study during the screening period. These patients were not randomised and not included in the intention-to-treat population for the analyses. The reasons for exclusion included ‘failed inclusion/exclusion criteria’, ‘screening period past 30 days’, ‘consent withdrawn’, ‘adverse event’, ‘death’, ‘progressive disease’.

Information regarding baseline characteristics for patients who were not randomised into the trial was not collected in the clinical database. Therefore, it is not possible to provide a table of baseline characteristics for patients who were screened but not enrolled in the INCREASE trial.

A3. It appears that at least one person in the trial had a baseline 6-minute walk distance (6MWD) of less than 100 metres, despite the trial's eligibility criteria excluding patients with a baseline 6MWD below 100 metres. Please confirm how many people were included with 6MWD <100m, and how these people were included in the trial

Only a single patient with a baseline 6MWD of 30 metres was included in the trial; this was a protocol deviation. However, the inclusion of this single patient is unlikely to have had a significant impact on trial outcomes.

A4. Please provide the rationale for stratifying by baseline 6-minute walk distance (6MWD) using the thresholds of ≤ 350 metres and > 350 metres, and explain why other relevant prognostic factors were not considered in the stratification approach.

The 350-metre cut-off for baseline 6MWD used for randomisation was informed by prior evidence indicating that the average 6MWD in PH-ILD was approximately 350 metres.[3] Although this threshold was originally established in the context of chronic obstructive pulmonary disease rather than PH-ILD, it has been shown to inversely correlate with the risk of hospitalisation and mortality.[4] This threshold was used to stratify randomisation with the aim of achieving equal numbers randomised into inhaled treprostinil or placebo group within each stratum (i.e., 6MWD < 350 metres and 6MWD ≥350 metres).

Stratification was limited to baseline 6MWD as the key prognostic factor expected to impact the primary outcome. Other prognostic factors were not considered due to the small number of patients in these prognostic groups, which prevented stratification. Statistical adjustment models and subgroup analyses were therefore conducted to account for these prognostic factors.

A5. Please provide the distribution of patients in the INCREASE trial with baseline pulmonary vascular resistance (PVR) values of <5 Wood units (WU), 5–10 WU, and >10 WU, separately for the placebo and treprostinil arms.

The distribution of patients in the INCREASE trial with baseline PVR values is depicted in Figure 1. A higher number of patients in the inhaled treprostinil arm had a PVR between 5 and 10 WU (N=77) and >10 WU (N=17) compared to the placebo

arm (72 and 14, respectively, not statistically significant). This suggests patients receiving inhaled treprostinil had more severe PH-ILD and, therefore potentially a worse prognosis than those receiving placebo.[5]

Figure 1: Distribution of patients in the INCREASE trial with baseline PVR values

Abbreviations: PVR: pulmonary vascular resistance; WU: wood units.
Source: United Therapeutics.

A6. PRIORITY: Please explain the generalisability of the INCREASE findings, where all people seemingly underwent right heart catheterisation (RHC), to real-world patients who have not undergone RHC. How might implementation of treprostinil affect existing NHS services?

The INCREASE trial exclusively enrolled patients with a confirmed diagnosis of PH-ILD established by right heart catheterisation (RHC). RHC is considered the gold standard for diagnosing and classifying PH, in line with the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.[6] In the UK, people with ILD who are suspected of having PH are referred to PH specialist centres for diagnosis.[7] Because RHC is already required to confirm PH-ILD prior to starting any treatment, the patient population eligible for inhaled treprostinil in routine practice is expected to be aligned with that included in the INCREASE study.

Clinical experts agree that the implementation of inhaled treprostinil is anticipated to increase diagnosis of PH-ILD and therefore the number of patients managed in specialist PH centres.[7] Coordination between PH and ILD centres will be key for

effectively implementing inhaled treprostinil, and clinician feedback suggests they are keen to work closely together to facilitate its introduction into the treatment pathway.[7] Ferrer are continuing to communicate with and support stakeholders across PH and ILD centres to facilitate the implementation of inhaled treprostinil.

A7. PRIORITY: Please complete the baseline characteristics for the table below.

Baseline characteristics have been added to Table 1, where available. The comorbidities reported in the clinical study report (CSR) have been reviewed and grouped into the most appropriate category listed in Table 1 to provide this information. Of note, patients receiving PAH therapies were excluded from the INCREASE study.

Data on these characteristics are not available for the INCREASE OLE study.

Table 1. Baseline characteristics of patients in INCREASE and INCREASE OLE

Baseline characteristics		**INCREASE**			**INCREASE OLE**		
		Inhaled Treprostinil N=163	**Placebo N=163**	**Overall N=326**	**Inhaled Treprostinil N=119**	**Placebo N=121**	**Overall N=242**
Never smoked Tobacco (%)		0	0.6	0.3	NR	NR	NR
Comorbidities	**Mean (SD)**	NR	NR	NR	NR	NR	NR
	without comorbidities %	0	0	0	NR	NR	NR
Baseline comorbidities (%)	**Arterial Hypertension** *(Hypertension, Essential hypertension, Orthostatic hypertension)*	63.2	54.6	58.8	NR	NR	NR
	Cardiac arrhythmias and conduction disorders	29.3	30.4	29.8	NR	NR	NR

	Coronary heart disease	26.4	18.4	22.4	NR	NR	NR
	Diabetes	27.6	17.8	22.7	NR	NR	NR
	Morbid obesity	11.7	5.5	8.6	NR	NR	NR
	Neurological diseases	43.1	32.2	37.5	NR	NR	NR
	Peripheral artery disease *(Peripheral vascular disorder, Peripheral arterial occlusive disease)*	3.7	1.8	2.7	NR	NR	NR
	Sequelae of cerebrovascular disease of history of acute cerebrovascular disease *(Cerebrovascular accident, Cerebral small vessel ischaemic disease)*	3.7	1.2	2.3	NR	NR	NR
	Substance abuse disorders *(drugs, alcohol, cannabis)*	1.2	0	0.6	NR	NR	NR
Concomitant treatments (%)	**PDE-5 inhibitors (e.g., sildenafil, tadalafil)**	0	0	0	NR	NR	NR
	ERAs (e.g., bosentan, ambrisentan, macitentan)	0	0	0	NR	NR	NR
	Prostacyclin analogues (e.g., epoprostenol, SC/IV/oral treprostinil,	0	0	0	NR	NR	NR

	inhaled iloprost, and selexipag)						
	None of the above	100	100	100	NR	NR	NR

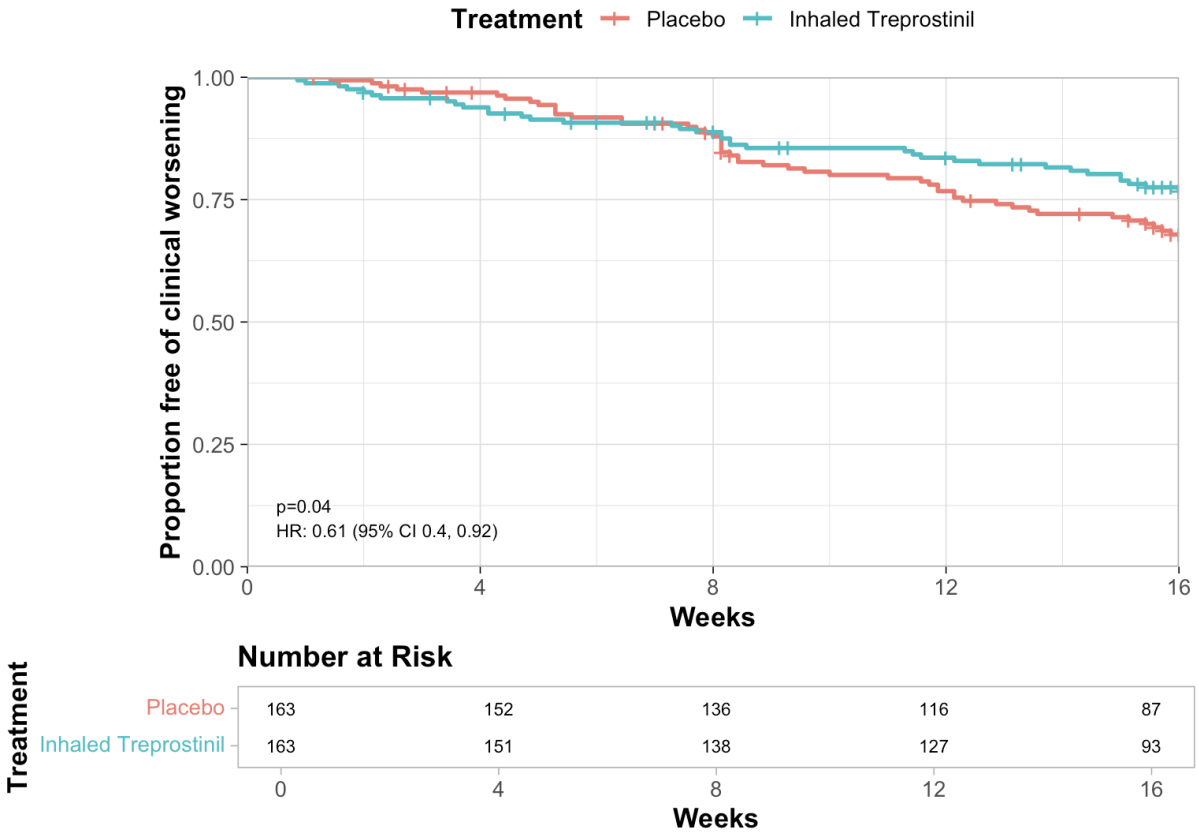
Abbreviations: NR: not reported. Note that Cardiac arrhythmias and conduction disorders include the following: Atrial Fibrillation, Palpitations, Bundle Branch Block Right, Arrhythmia, Sinus Node Dysfunction, Bradycardia, Sinus Tachycardia, Supraventricular Tachycardia, Tachycardia, Atrial Tachycardia, Right Atrial Dilation, Sinus Bradycardia, Ventricular Tachycardia, Atrial Flutter, Atrioventricular Block Complete, Atrioventricular Block First Degree, Bifascicular Block, Bundle Branch Block Right, Bundle Branch Block Left, Ventricular Extrasystoles. Note also that Neurological disease include the following: Neuropathy Peripheral, Cerebrovascular Accident, Dizziness, Sciatica, Carpal Tunnel Syndrome, Lumbar Rediculopathy, Migraine, Peroneal Nerve Palsy, Seizure, Diabetic Neuropathy, Hypoaethesia, Paraesthesia, Post Herpetic Neuralgia, Transient Ischaemic Attach, Ataxia, Balance disorder, Cervical Radiculopathy, Dizziness Exertional, Epilepsy, Guillain-Barre Syndrome, Hydrocephalus, Hypersomnia, Morton's Neuralgia, Myasthenia Gravis, Neuralgia, Occipital Neuralgia, Parkinson's dsiease, Periodic Limb Movement Disorder, Polyneuropathy, Somnolence, Tremor, Cerebral Small Vessel Ischaemic Disease, Cognitive Disorder, Dementia Alzheimer's Type, Essential Tremor, Facial Spasm, Intention Tremor, Ivth Nerve Paralysis, Nerve Compression, Polyneuropathy Alcoholic, Radial Nerve Palsy, Radiculopathy

Source:[8]

A8. Please add censoring marks to Figure 9.

Figure 9 with censoring marks is provided below. In response to question A26, further clarity has been provided on the differentiation between the definitions for clinical worsening events (figure below), disease progression events and EFS.

Figure 2: Kaplan-Meier plot of time to first clinical worsening event in INCREASE – ITT Population (n=326)

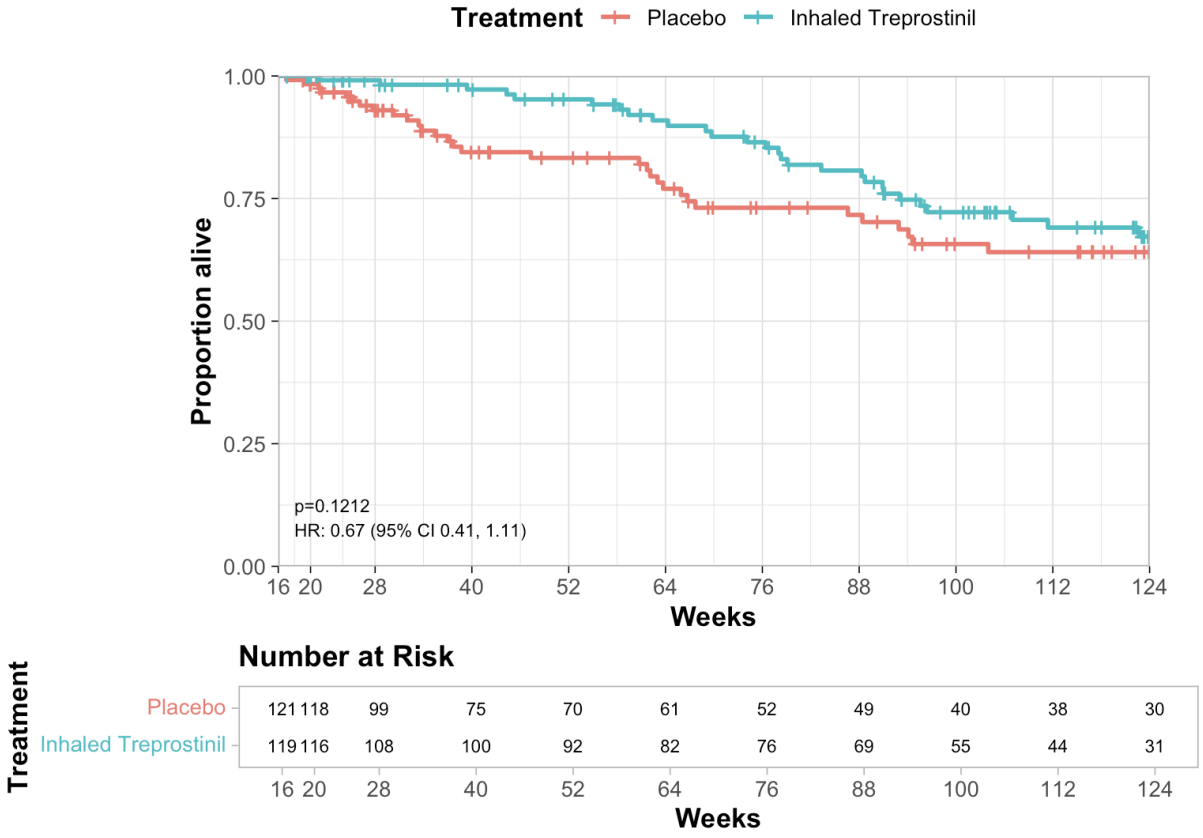


Please note that the above figure differs from the figure included in the original CS, due to distortion introduced into the figure that was taken from the publication. The above figure aligns with that in the CSR and the hazard ratio derivation, statistical significance calculations, and health economic analysis are unaffected by this distortion.

A9. Please add N at risk and censoring marks to Figure 13.

An updated version of Figure 13, showing time to death in INCREASE-OLE in patients previously treated with inhaled treprostinil or placebo in the Safety Population, is provided below.

Figure 3: Time to death in INCREASE-OLE in patients previously treated with inhaled treprostinil or placebo – Safety Population



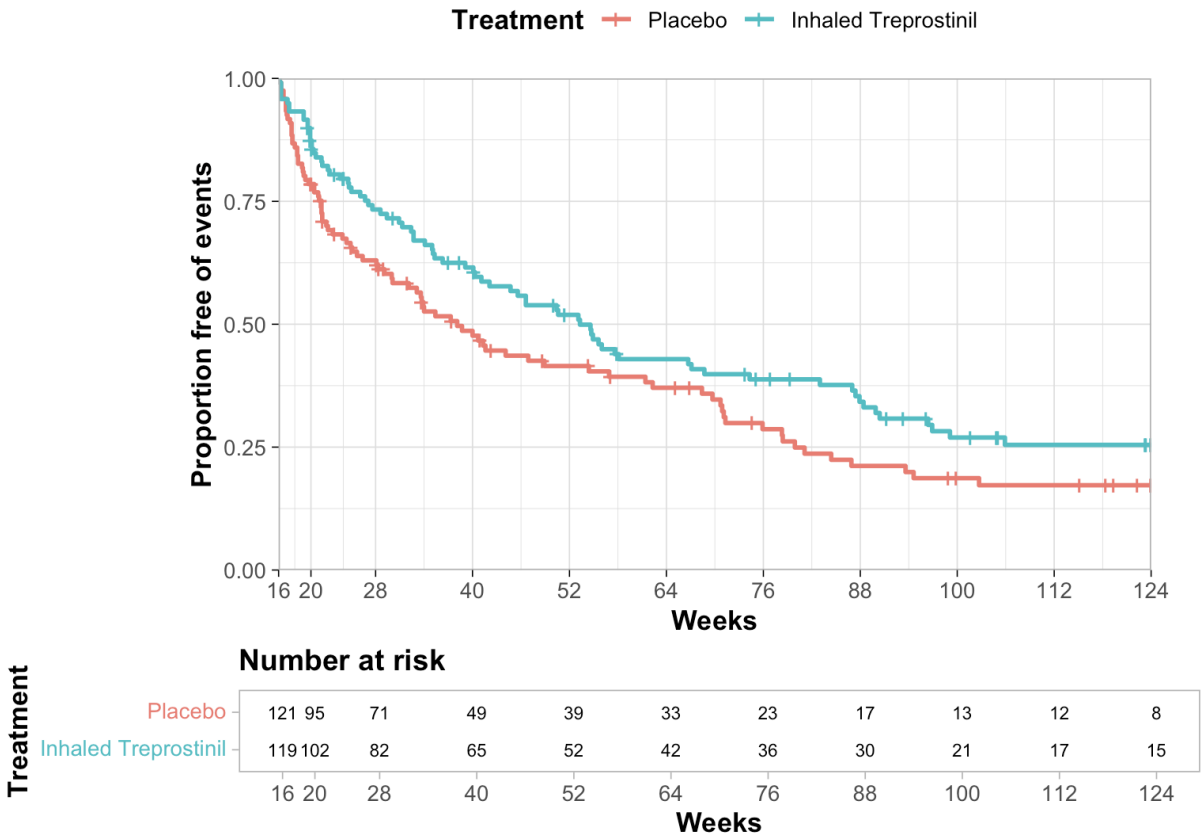
A10. Please provide a KM plot for EFS, including N at risk and censoring marks.

A KM plot of EFS has been generated from the INCREASE OLE data, where EFS is defined as time free of death, exacerbation of underlying disease, or hospitalisation. EFS was improved in patients who were previously treated with inhaled treprostinil in the INCREASE RCT (blue curve) compared to those who received placebo (red curve).

For further clarity on the difference between the definition of EFS, clinical worsening events and disease progression events in the clinical trials, please see the response to question A26 below. Of note, the definition of clinical worsening events for the

purposes of the model also comprised decrease in 6MWD of ≥15% from baseline, decrease in FVC% of ≥10% from baseline and lung transplant.

Figure 4: Kaplan-Meier plot of event free survival in INCREASE-OLE in patients previously treated with inhaled treprostinil or placebo



A11. Please provide an updated figure/label of Figure 7 to clearly define the different points on this figure.

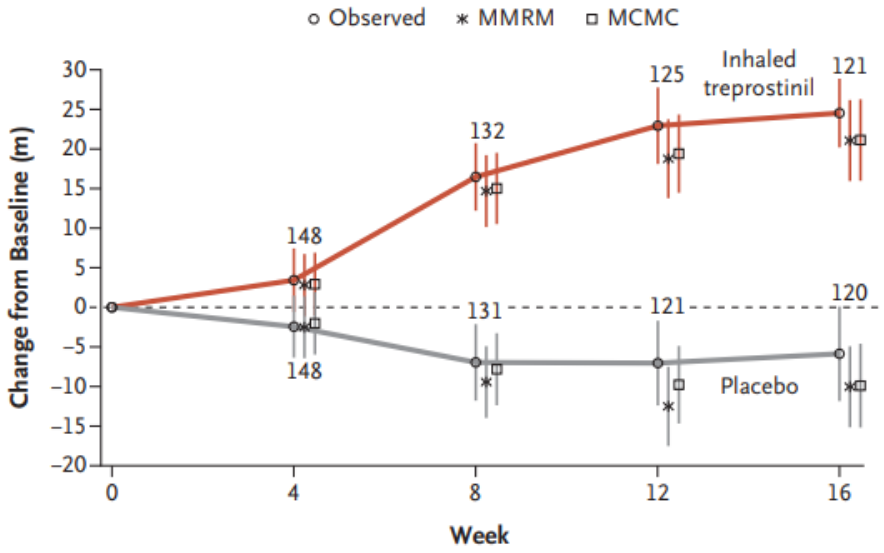
Figure 7 in the CS was reproduced from Waxman *et al.* 2021 and is presented below for context. In brief, the figure presents the mean (±SE) changes from baseline (dashed line) in peak 6MWD over the 16-week trial period for placebo (gray) and inhaled treprostinil (red). At each timepoint (weeks 4, 8, 12, and 16), mean and standard errors are presented for patients with available data ("observed") as well as for results of two different analysis methods used to account for missing data.

The primary analysis to account for missing data used a mixed model of repeat measures (MMRM), with the assumption that missing data were missing at random (MAR). The model included the change from baseline to peak 6MWD as the dependent variable, with treatment, week, and treatment-by-week interaction as

fixed effects and baseline 6MWD as a covariate. These values are presented as crosses on the figure.

A sensitivity analysis for the primary endpoint was performed with the use of a multiple imputation approach with a multivariate normal imputation model using the Markov chain Monte Carlo method. The MCMC imputation model included treatment arm, all scheduled visits, sex, and age at randomisation. These values are presented as squares on the figure.

Figure 5: Mean change from baseline in peak 6MWD through Week 16 in INCREASE – ITT Population (n=326)



A12. Please confirm the number of people with clinical worsening events in the placebo and the treprostinil arm of the INCREASE trial period, comparing those who entered the OLE with those who did not.

The table below presents the number of patients who received inhaled treprostinil or placebo in the INCREASE trial and the proportion of patients who experienced a clinical worsening event in those who entered the OLE versus those who did not.

Table 2: Number of individuals with clinical worsening events in the placebo and inhaled treprostinil arm of INCREASE entering the OLE in comparison to those who did not

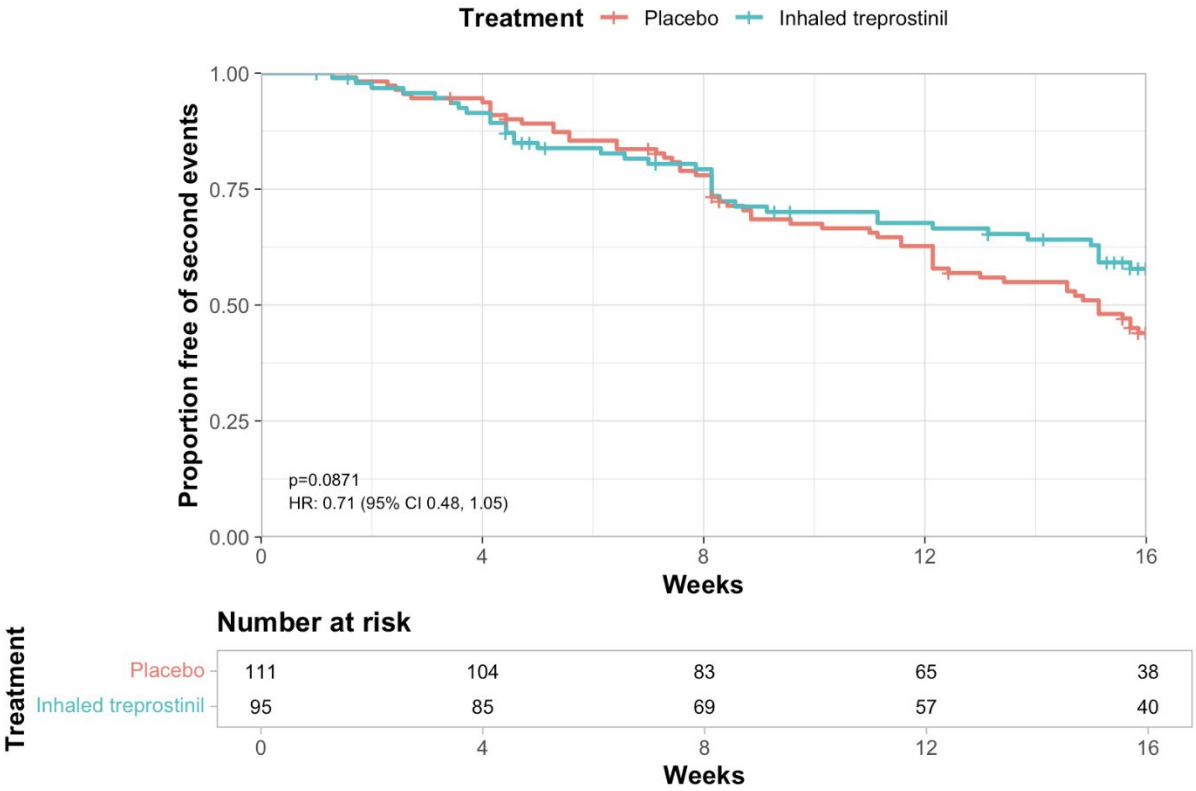
Treatment in INCREASE[1]	Entered OLE[9]	N	N with clinical worsening	Proportion with clinical worsening
Inhaled treprostinil	No	44	22	50.0%
Inhaled treprostinil	Yes	119	15	12.6%
Placebo	No	42	23	54.8%
Placebo	Yes	121	31	25.6%

A13. Please produce a figure similar to Figure 11, showing the Kaplan-Meier plot for second events, including only participants who experienced a first event.

A KM plot has been generated to show time free of second clinical worsening events in the subgroup of patients who had experienced a first event, based on the composite endpoint of:

- ≥15% or more decline in 6MWD from baseline
- ≥10% or more decline in FVC from baseline
- Acute lung-disease exacerbation
- Cardiopulmonary hospitalisation
- Lung transplantation
- Death

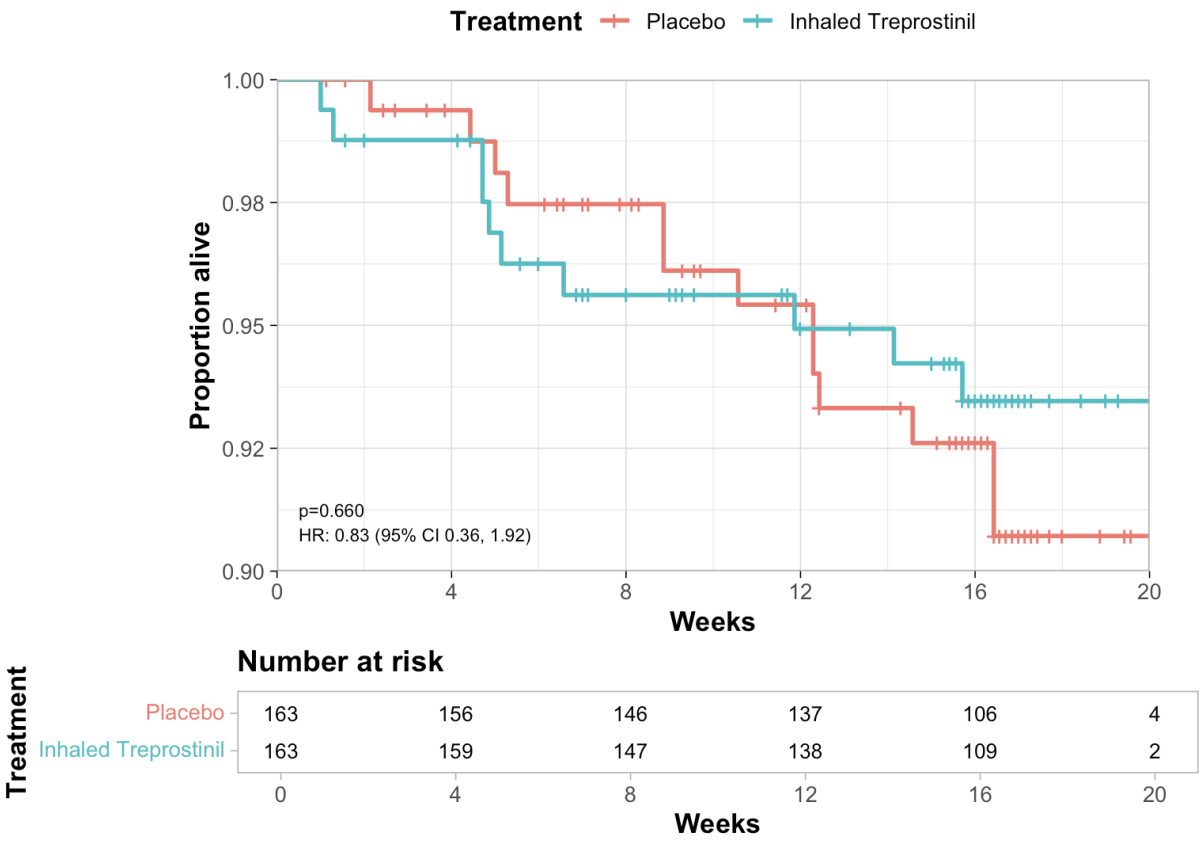
Figure 6: Kaplan-Meier plot of time free of second clinical worsening events in the subgroup of patients who had experienced a first event



A14. Please perform an overall survival analysis and for event-free survival using the 16-week follow-up data from the INCREASE study (e.g., Kaplan-Meier plot and hazard ratio).

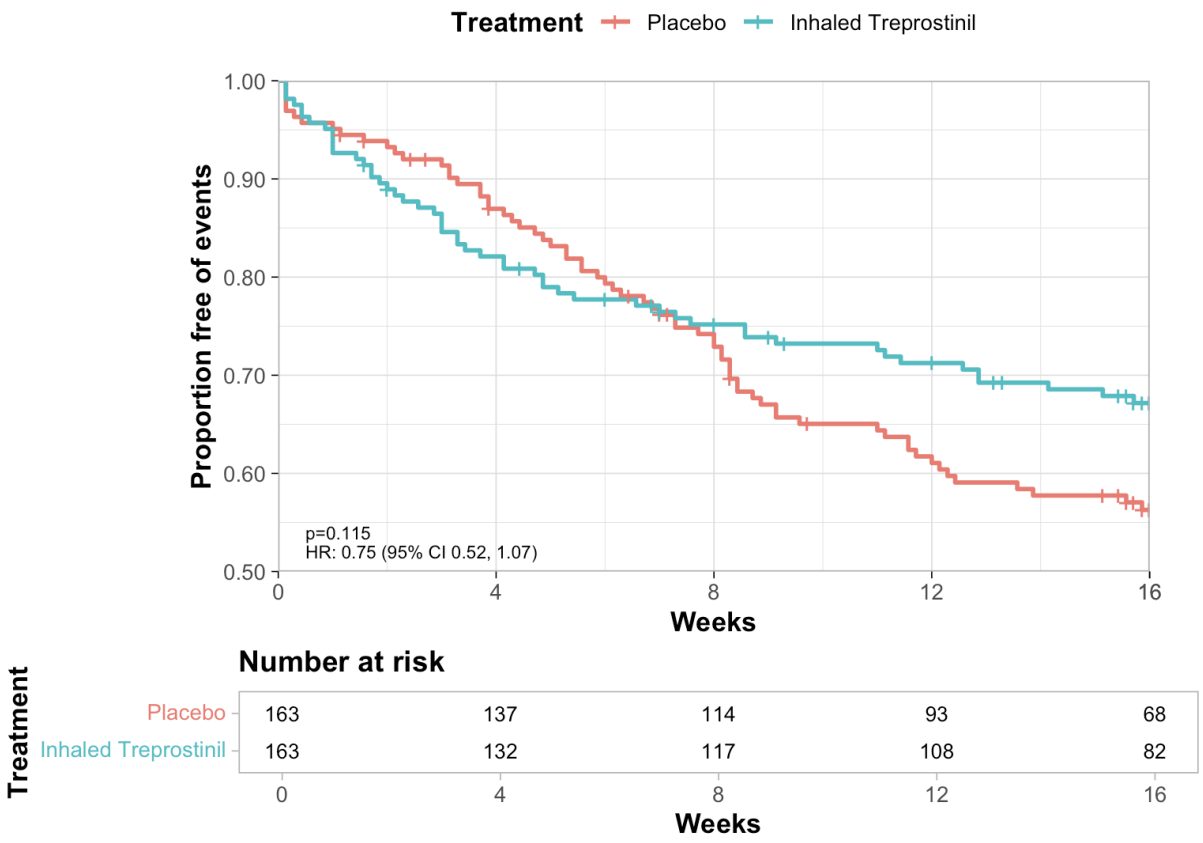
The KM plot with hazard ratio (based on an unadjusted Cox model) for overall survival within the INCREASE study is presented below. This corresponds to Figure 23 in the original submission, with the addition of censoring marks and a hazard ratio.

Figure 7: Kaplan-Meier plot of overall survival by treatment arm in INCREASE (16 weeks)



A KM plot and hazard ratio (based on an unadjusted Cox model) for event-free survival within the INCREASE study is presented below. Event-free survival is defined as time free of death, exacerbation of underlying disease, or hospitalisation.

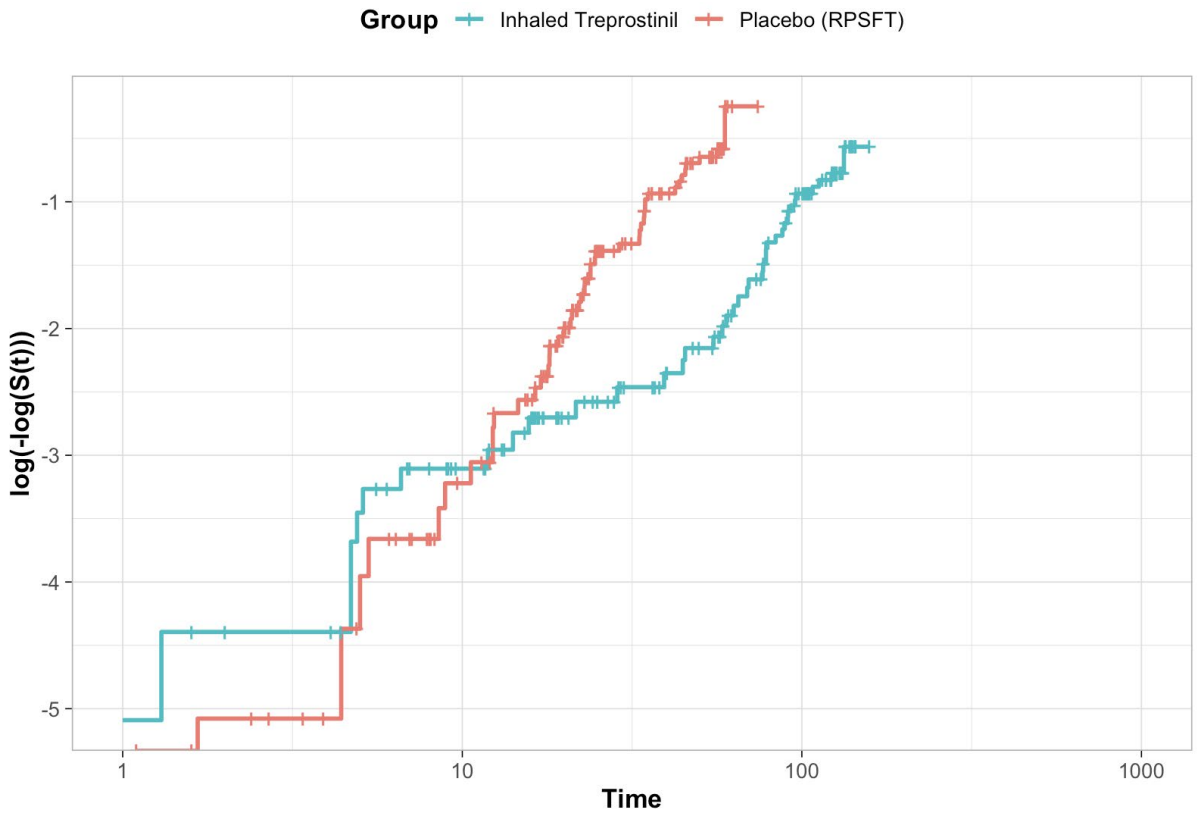
Figure 8: Kaplan-Meier plot of event-free survival by treatment arm in INCREASE trial



A15. Please confirm which comparison the graphs in Appendix B 1.3 refer to in relation to the assessment of proportional hazards. Additionally, please provide equivalent graphs for the INCREASE OLE comparison to support the content presented in Section B3.3.1 of the main submission.

Figure 2 to Figure 5 in Appendix 1.3.3 refer to the MAIC presented in Section 2.1 of the main submission. The MAIC provides a comparison of outcomes in patients receiving inhaled treprostinil in INCREASE and INCREASE OLE to those receiving BSC in a retrospective study in the UK (N=78).

We have presented a log-log hazard plot based on the survival data underpinning the base case analysis (inhaled treprostinil versus RPSFT-adjusted placebo), showing that the proportional hazards assumption would be violated and thereby supporting the use of independent parametric models in the inhaled treprostinil and placebo arms.



A16. For Figure 14, please confirm whether the Week 16 results for the placebo group were recorded before or after patients began receiving treprostinil. Additionally, clarify why the number of participants at baseline differs from the number at Week 16, and reproduce the graph using a consistent population across both time points to ensure comparability.

For Figure 14, Week 16 results for the placebo group were recorded before the initiation of inhaled treprostinil. The differences in patient numbers at Week 16 versus baseline is due to some patients choosing not to be enrolled in the OLE study. Furthermore, there were two patients who were not in the RCT study, but enrolled in the OLE study. Therefore, a graph using a consistent population has not been provided as this would not provide an accurate reflection of the outcomes reported in the INCREASE OLE.

A17. Please provide a Kaplan-Meier plot showing the impact of the different methods used to adjust for treatment switching, including implementing the 2-stage adjustment.

A Kaplan-Meier plot showing the impact of the different methods has not been provided as the IPCW and 2-stage approaches are not suitable to adjust for

treatment switching in INCREASE OLE. The IPCW approach relies on there being some patients within the study who do not switch, to determine the weighting to apply to non-switchers. Due to all patients receiving placebo in INCREASE switching to inhaled treprostinil in INCREASE OLE, the IPCW will be prone to increased bias and potential errors due to the large number of patient crossovers. Moreover, as described in NICE TSD 16, the 2-stage adjustment method is only applicable when switching occurs immediately after an appropriate secondary disease-related baseline, such as disease progression. However, all patients who received placebo during the 16-week INCREASE RCT switched to inhaled treprostinil at the start of the OLE rather than this being determined by a disease-related event (e.g., disease progression). In addition, NICE TSD 16 states that the 2-stage adjustment method is similarly prone to error and bias with very high proportions of patients switching.[10] Therefore, the RPSFT is considered the most appropriate approach, and the IPCW and 2-stage adjustment are not considered relevant for inclusion.

A18. Please provide the following information regarding the RPSFTM (Rank Preserving Structural Failure Time Model) adjustment:

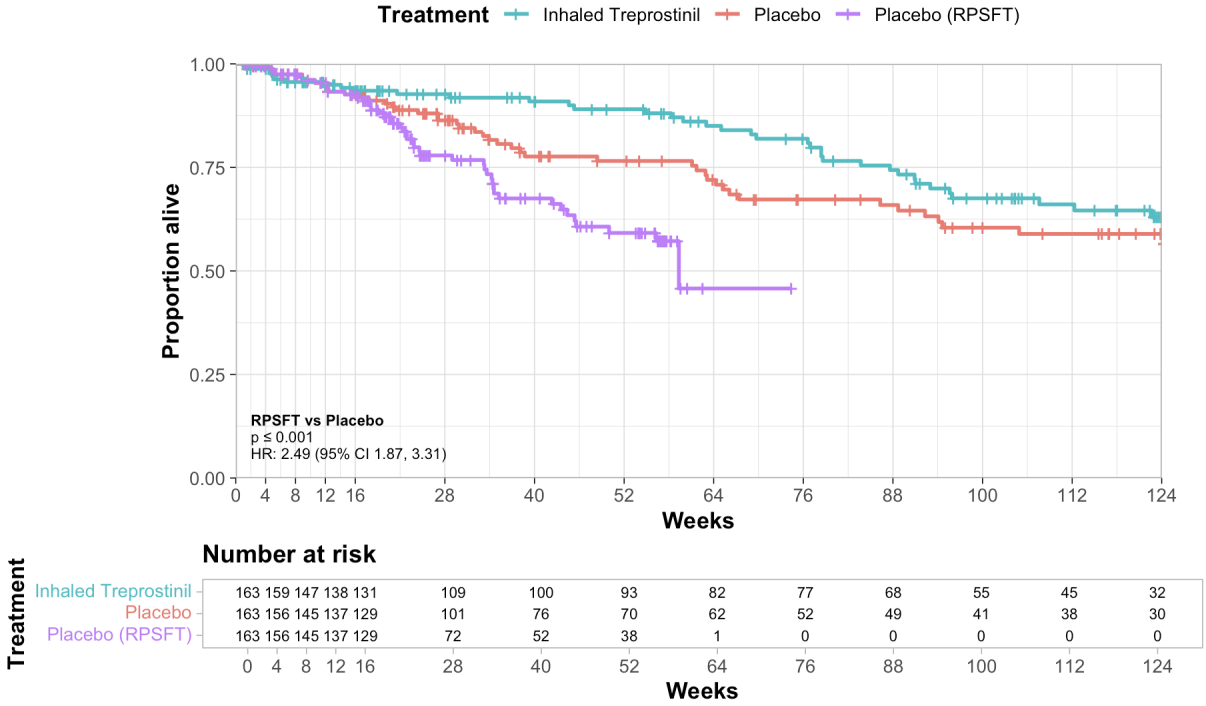
- **Details on the approach to RPSFTM adjustment taken, as recommended in TSD 16. (e.g. were any covariates adjusted for, re-censoring?)**
- **The hazard ratio and acceleration factor between the RPSFTM-adjusted treated and untreated populations**
- **The hazard ratio comparing the original placebo arm in INCREASE OLE with the RPSFTM-adjusted population**

No covariate adjustment was performed in the RPSFTM analysis, consistent with the approach taken in the INCREASE OLE publication. Re-censoring was also not applied, as all placebo subjects became eligible to switch to the active treatment after a fixed duration, as defined in the study protocol.

A hazard ratio for the RPSFTM-adjusted treated versus untreated populations cannot be provided as there are no RPSFTM-adjusted untreated patients. All patients receiving placebo in the INCREASE study switched to inhaled treprostinil in the INCREASE OLE study.

The KM curves with numbers at risk and censor marks are presented in the figure below, alongside the mortality hazard ratio for the RPSFT-adjusted patients versus the original placebo arm based on an unadjusted Cox model.

Figure 9: Kaplan-Meier plot comparing mortality in the RPSFT-adjusted patients versus the original placebo arm



A19. Please perform a MAIC and compare OS outcomes to Dawes et al. using people from the placebo arm of INCREASE who did not receive treprostinil.

Conducting a MAIC to compare OS outcomes between Dawes et al. and the placebo arm of INCREASE would require the use of 16-week RCT data from the INCREASE trial. We have assessed the feasibility of this and we do not propose conducting the analysis as the duration of trial data does not provide an appropriate time horizon to evaluate treatment effect on mortality. During the 16-week period, only 4 deaths in 163 patients receiving placebo (2.5%) were reported. This highlights the immaturity of the survival data from the INCREASE study that results in high uncertainty associated with survival estimates from this time period alone.

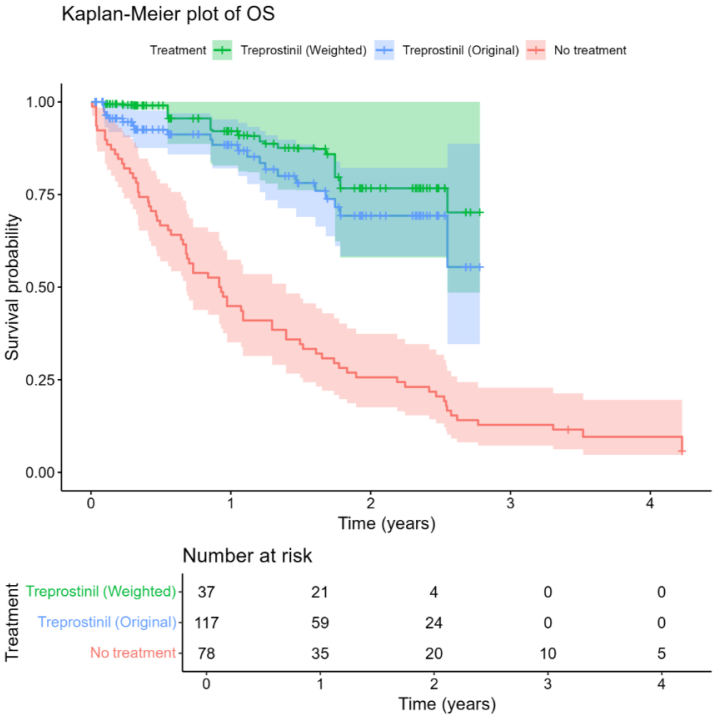
Literature indicates that survival modelling with follow-up periods of 12 months or less is highly uncertain.[11] The median survival in patients with PH-ILD receiving SOC in the study by Dawes et al. was 0.94 years, considerably longer than the duration of INCREASE (16 weeks [0.3 years]). As such, this further supports that a MAIC based

on the 16-week RCT data from INCREASE would be too uncertain to yield robust or meaningful conclusions.

A20. Please re-perform the MAIC analyses using only data from participants who were randomised to the treprostinil arm.

The overall survival (OS) Kaplan Meier (KM) data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 10. Only patients who were randomised to the inhaled treprostinil arm in the INCREASE RCT were included in the analysis. After excluding patients with CTD and patients with time since diagnosis >2 years, in line with the base case analysis, there were 117 patients included in the analysis. The covariates included in the MAIC were age, sex, hypertension, oxygenation, 6MWD, DLCO, FEV1, and aetiology (Idiopathic pulmonary fibrosis (IPF), Non-specific interstitial pneumonia (NSIP) and other). The HR of OS for patients treated with inhaled treprostinil was 0.162 (0.064 to 0.405) (Table ***3***), compared to an OS HR of 0.242 (0.149 to 0.393) for patients treated with inhaled treprostinil versus untreated patients from Dawes et al. (2022). The HR remained statistically significant in the scenario analysis provided.

Figure 10: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the intent-to-treat (ITT) population – scenario analysis using only patients randomised to the inhaled treprostinil arm



Abbreviations: OS – overall survival.

Table 3: Summary statistics OS - scenario analysis using only patients randomised to the inhaled treprostinil arm

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=37)	13.15 (4.8/36.7)	1.06 (1.01 to 1.32)	1.17 (0.08)	NA (2.55 to NA)	2.41 (0.16)	0.162 (0.064 to 0.405; p<0.001)
Inhaled treprostinil – unweighted (n=117)	18.80 (22/117)	1.06 (1.00 to 1.32)	1.17 (0.08)	NA (2.55 to NA)	2.22 (0.10)	0.242 (0.149 to 0.393; p<0.001)
No treatment (n=78)	92.3 (72/78)	0.88 (0.97 to 1.50)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error.

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel of Figure 11 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 5. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 16.5, which is approximately 14.1% of the total trial population of 117.

Figure 11: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – scenario analysis using only patients randomised to the inhaled treprostinil arm

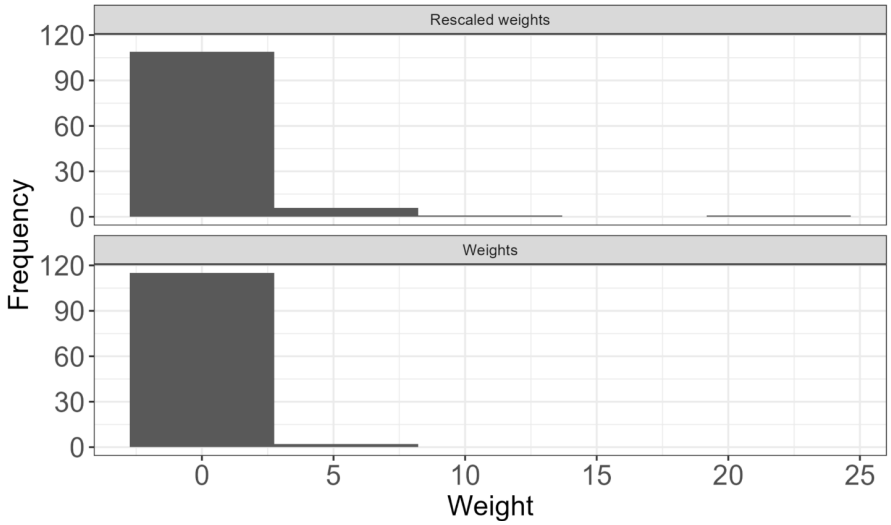


Table 4 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 4: Distribution of effect modifiers at baseline and after matching – scenario analysis using only patients randomised to the inhaled treprostinil arm

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.45	67.0	67.0
Sex (male %)	0.58	0.26	0.26
Hypertension	0.54	0.33	0.33
Oxygenation	0.45	0.68	0.68
6MWD	252.0	222.0	222.0
DLCO	30.2	26.0	26.0
FEV1	67.6	55.0	55.0
Aetiology-IPF	0.30	0.69	0.69
Aetiology-NSIP	0.15	0.09	0.09
Aetiology-other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

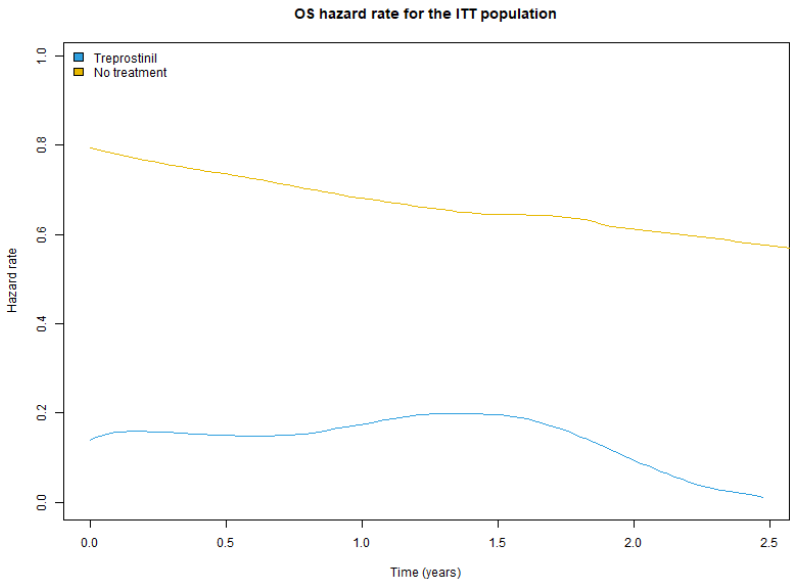
The baseline effect modifiers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the individual patient data (IPD) and aggregate study which will likely result in stable results.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 12 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

Figure 12: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population - scenario analysis using only patients randomised to the inhaled treprostinil arm

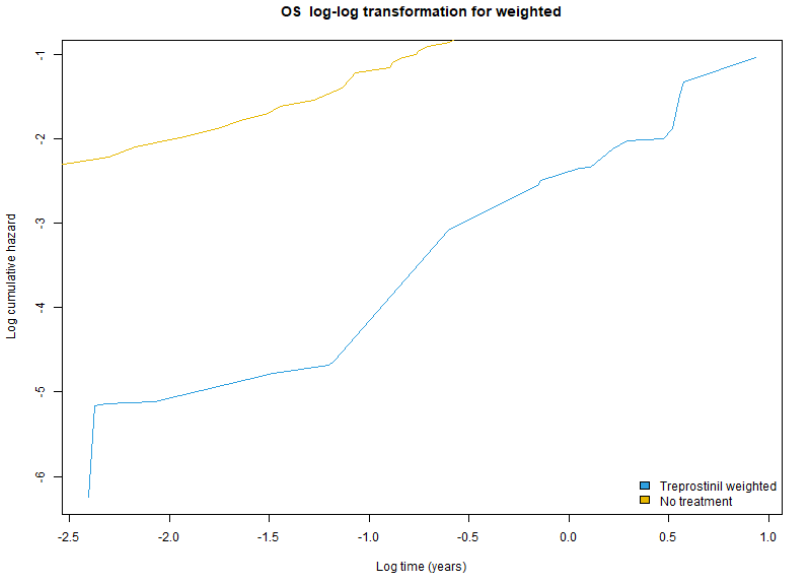


Abbreviations: ITT – intention to treat; OS – overall survival

Figure 13 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that

are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

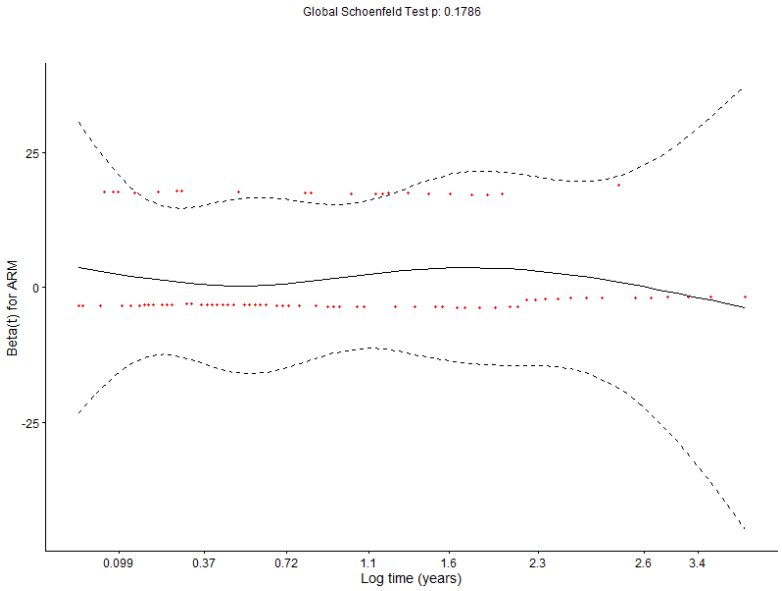
Figure 13: Log-log plot of OS in the ITT population – scenario analysis using only patients randomised to the inhaled treprostinil arm



Abbreviations: OS – overall survival

Figure 14 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows an approximately flat, linear relationship with a zero slope, giving evidence that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.1786).

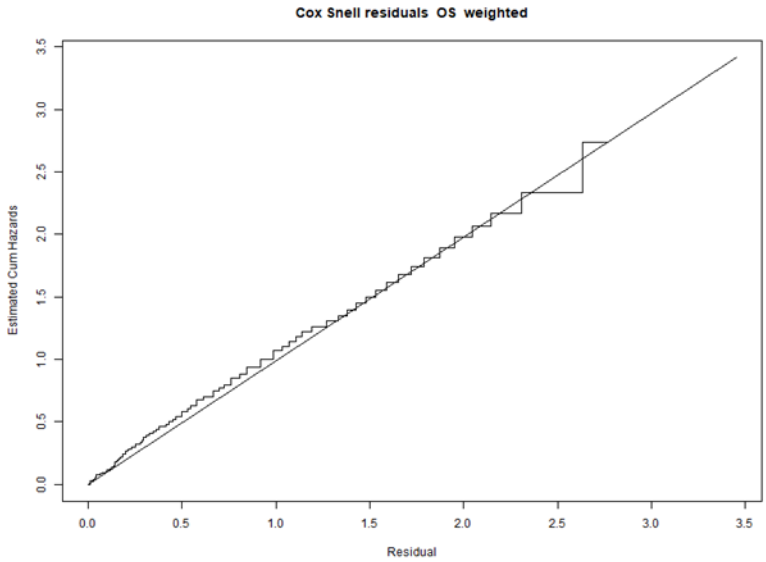
Figure 14: Schoenfeld plot of OS in the ITT population (p=0.1786) – scenario analysis using only patients randomised to the inhaled treprostinil arm



Abbreviations: ITT – intention to treat; OS - overall survival.

Figure 15 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 14: Cox-Snell residual plot of OS in the ITT population – scenario analysis using only patients randomised to the inhaled treprostinil arm



Abbreviations: ITT – intention to treat; OS – overall survival.

A21. Please confirm which variables were included in the company's preferred MAIC analysis, and clarify whether both the mean and standard deviation were used where applicable, or only the mean.

Only the mean is used for the proportional variables since they are binary and do not exhibit variability. The following variables and the mean/SD used for each variable were included in the MAIC analysis:

- Age (years): both mean and SD
- Sex (% male): only mean
- Hypertension (% with): only mean
- Oxygenation (% receiving): only mean
- 6MWD: both mean and SD
- DLCO: both mean and SD
- FEV1: both mean and SD
- IPF: only mean
- NSIP: only mean
- Other: only mean

A22. Please comment on the apparent lack of matching on Non-Specific Interstitial Pneumonia (NSIP) from the MAIC as shown in Table 10.

The NSIP variable was matched during the analysis, however, there were two typographical errors in values of the original distribution in INCREASE (before matching) and the weighted INCREASE distribution (after matching) shown in Table 5 below, which have now been corrected (highlighted in yellow).

Table 5: Updated summary table of all covariates

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.68	0.68
6MWD	261.0	222.0	222.0
DLCO	28.4	26.0	26.0
FEV1	67.0	55.0	55.0
IPF	0.33	0.69	0.69
NSIP	[redacted]	[redacted]	0.090
Other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

A23. Please provide results from MAIC sensitivity analyses to explore the stability of the relative effect output parameters when varying the set of matching parameters.

Summary of the scenario analyses

Consistent results were observed from all of the sensitivity analyses conducted, demonstrating that stepwise exclusion of each of the eight covariates do not alter the conclusion that OS is significantly greater for patients treated with inhaled treprostinil compared with patients who receive no treatment, as shown in Table 6.

Table 6: Summary statistics of OS

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (2.55 to N/A)	2.15 (0.08)	0.276 (0.188 to 0.404; p<0.001)
Inhaled treprostinil – reweighted including all covariates (n=86.3)	11.80 (10.2/86.3)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (N/A to N/A)	2.39 (0.11)	0.159 (0.090 to 0.280; p<0.001)
Inhaled treprostinil – reweighted excluding age as a covariate (n=87)	11.61 (10/87)	0.97 (0.97 to 1.18)	1.07 (0.05)	NA (NA to NA)	2.40 (0.11)	0.157 (0.089 to 0.276; p<0.001)
Inhaled treprostinil – reweighted excluding sex as a covariate (n=111)	19.42 (22/111)	0.97 (0.96 to 1.19)	1.07 (0.05)	NA (2.55 to NA)	2.15 (0.12)	0.276 (0.165 to 0.462; p<0.001)
Inhaled treprostinil – reweighted excluding hypertension as a covariate (n=99)	13.98 (14/99)	0.97 (0.97 to 1.18)	1.07 (0.05)	NA (2.55 to NA)	2.32 (0.12)	0.188 (0.112 to 0.315; p<0.001)
Inhaled treprostinil – reweighted excluding oxygenation as a covariate (n=98)	13.31 (13/98)	0.97 (0.97 to 1.19)	1.07 (0.05)	NA (2.55 to NA)	2.32 (0.12)	0.188 (0.111 to 0.316; p<0.001)
Inhaled treprostinil – reweighted excluding 6MWD as a covariate (n=87)	10.97 (9.5/86.8)	0.97 (0.96 to 1.19)	1.07 (0.05)	NA (NA to NA)	2.42 (0.11)	0.145 (0.081 to 0.260; p<0.001)
Inhaled treprostinil – reweighted excluding DLCO as a covariate (n=86)	11.73 (10.1/86.3)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (NA to NA)	2.39 (0.11)	0.158 (0.089 to 0.279; p<0.001)
Inhaled treprostinil – reweighted excluding FEV1 as a covariate (n=94)	13.40 (13/94)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (N/A to N/A)	2.34 (0.11)	0.183 (0.105 to 0.318; p<0.001)

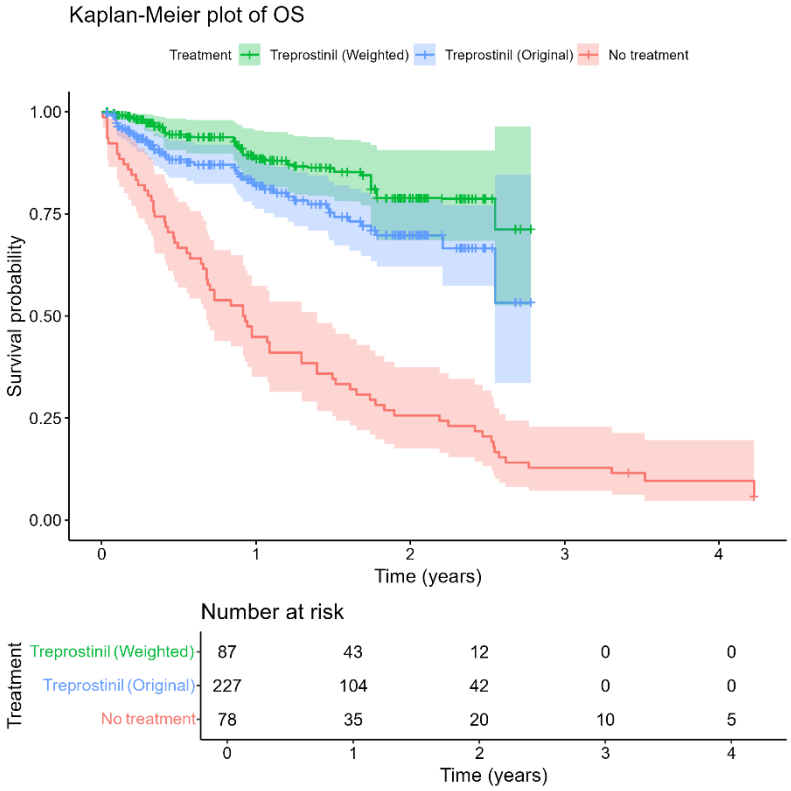
Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted excluding aetiology (IPF, NSIP or other) as a covariate (n=126)	18.52 (23.4/126.4)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (2.55 to NA)	2.24 (0.10)	0.233 (0.137 to 0.398; p<0.001)
No treatment (n=78)	92.3 (72/78)	0.88 (0.97 to 1.50)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: 6MWD – 6-minute walk distance; CI – Confidence intervals; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; N – Number; NSIP – Non-specific interstitial pneumonia; SE – Standard error

Sensitivity analysis 1 - Age

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 1616. The population considered from INCREASE was the same as the base case analysis (n=227), including patients from INCREASE and its OLE who were treated with inhaled treprostinil, without patients with CTD or patients with time since diagnosis >2 years, and the covariates included in the MAIC were sex, hypertension, oxygenation, 6MWD, DLCO, FEV1, and aetiology (IPF, NSIP, or other). After reweighting to match the Dawes et al. (2022) population and excluding age as a covariate, the HR of OS was 0.157 (0.089 to 0.276) in the weighted group of patients receiving inhaled treprostinil relative to patients receiving no treatment (Table). This is similar to the HR of OS of 0.159 (0.090 to 0.280) when age is included as a covariate. The HR remained statistically significant in the scenario analysis provided.

Figure 15: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – sensitivity analysis excluding age covariate



Abbreviations: OS – overall survival

Table 7: Summary statistics OS – sensitivity analysis excluding age covariate

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=87)	11.61 (10/87)	0.97 (0.97 to 1.18)	1.07 (0.05)	NA (NA to NA)	2.40 (0.11)	0.157 (0.089 to 0.276; p<0.001)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (2.55 to NA)	2.15 (0.08)	0.276 (0.188 to 0.404; p<0.001)
No treatment (n=78)	92.31 (72/78)	0.88 (0.96 to 1.47)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel in Figure shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 5. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 44.83, which is approximately 19.75% of the total trial population of 227.

Figure 16: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – sensitivity analysis excluding age covariate

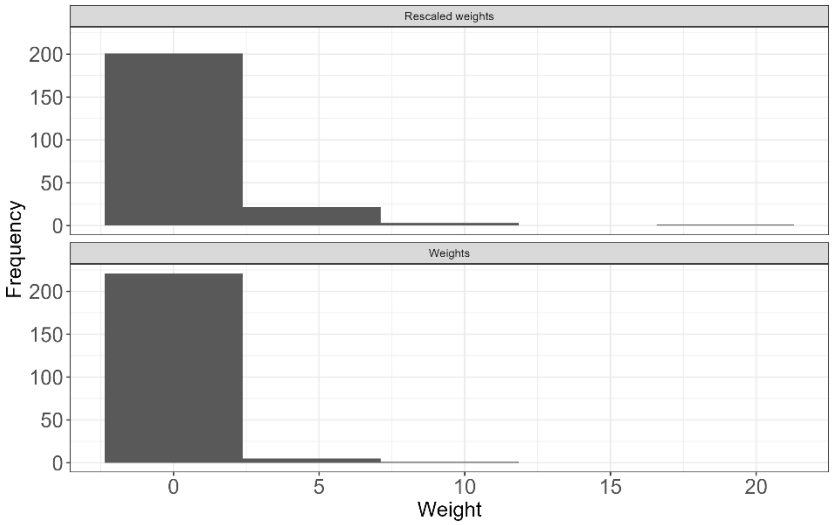


Table below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 8: Distribution of effect modifiers at baseline and after matching – sensitivity analysis excluding age covariate

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	66.31	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.68	0.68
6MWD	260.95	222.0	222.0
DLCO	28.36	26.0	26.0

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
FEV1	66.70	55.0	55.0
Aetiology-IPF	0.33	0.69	0.69
Aetiology-NSIP	0.12	0.09	0.09
Aetiology-other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

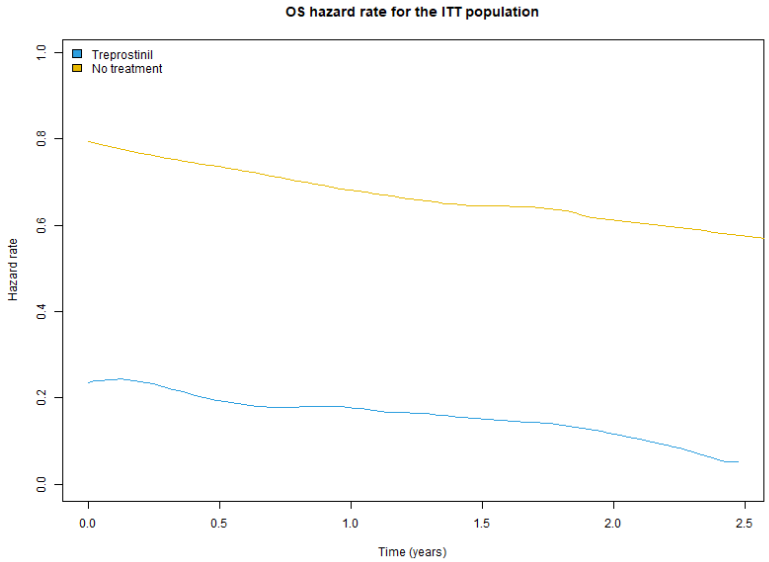
The baseline effect modifiers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were imbalanced when compared with those reported in the Dawes et al. study. These imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results. However, age is imbalanced between the INCREASE and Dawes et al. populations following matching, where patients in the reweighted INCREASE population are now slightly younger than those in the Dawes et al. Study population.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

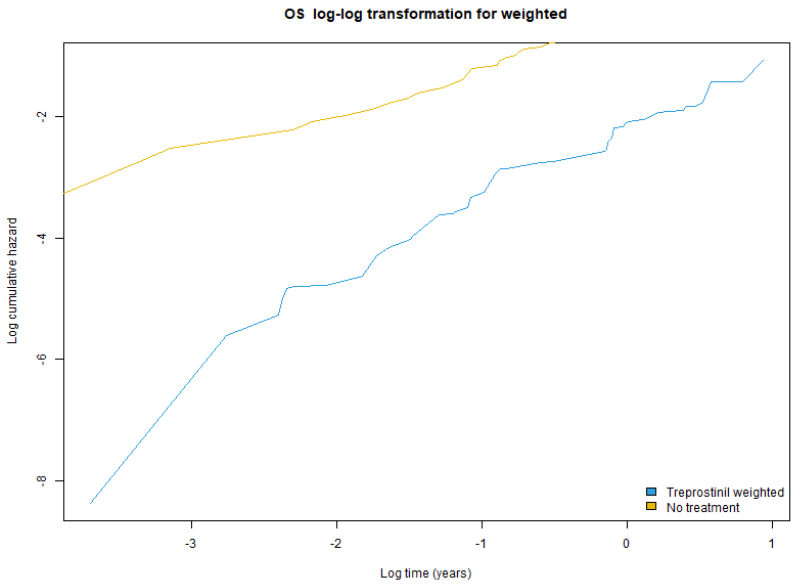
Figure 17: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population – sensitivity analysis excluding age covariate



Abbreviations: ITT – intention to treat; OS – overall survival; PDE5i – phosphodiesterase type 5 inhibitors

Figure shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

Figure 18: Log-log plot of OS in the ITT population – sensitivity analysis excluding age covariate

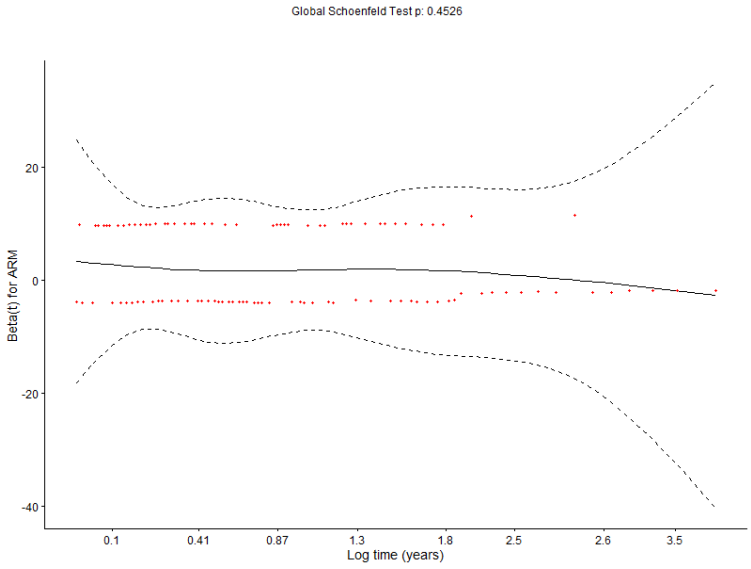


Abbreviations: OS – overall survival; PDE5i – phosphodiesterase type 5 inhibitors

Figure shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows non-random, monotonic linear relationship with a zero slope, giving evidence

that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.4526).

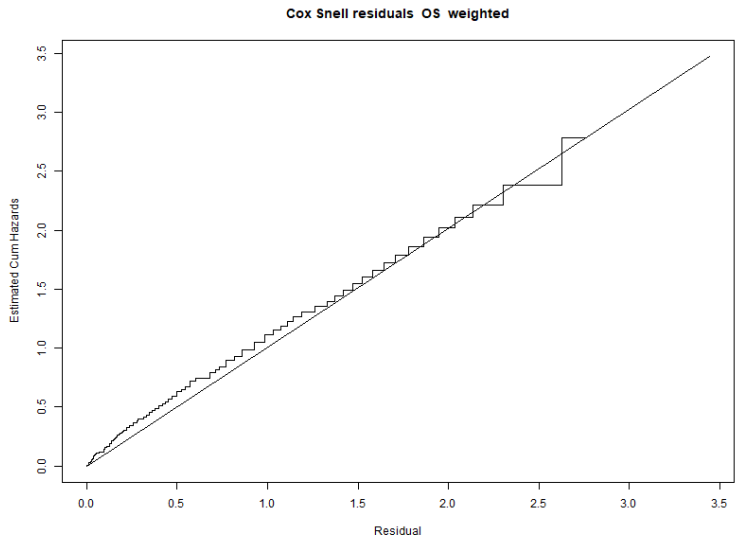
Figure 19: Schoenfeld plot of OS in the ITT population (p=0.4526) – sensitivity analysis excluding age covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 20: Cox-Snell residual plot of OS in the ITT population – sensitivity analysis excluding age covariate

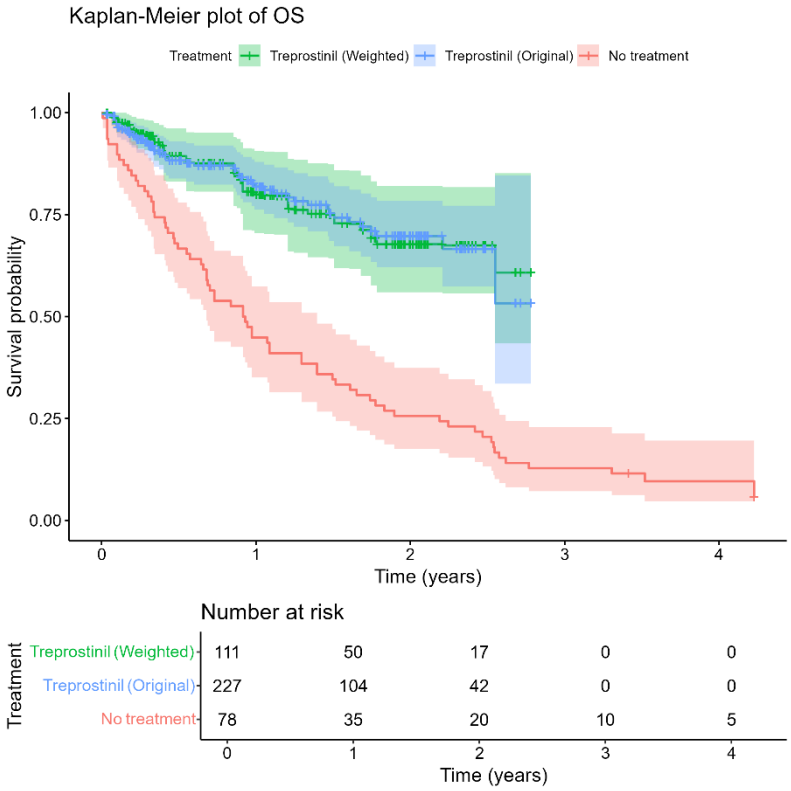


Abbreviations: ITT – intention to treat; OS – overall survival

Sensitivity analysis 2 - Sex

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 22. The population considered from INCREASE was the same as that in the base case analysis (n=227), including patients from INCREASE and its OLE who were treated with inhaled treprostinil, without patients with CTD or patients with time since diagnosis >2 years, and the covariates included in the MAIC were age, hypertension, oxygenation, 6MWD, DLCO, FEV1, and aetiology (IPF, NSIP, or other). After reweighting to match the Dawes et al. (2022) population and excluding sex as a covariate, the HR of OS was 0.276 (0.165 to 0.462) in the weighted group of patients receiving inhaled treprostinil relative to patients receiving no treatment (Table 9). This is similar to the HR of OS of 0.159 (0.090 to 0.280) when sex is included as a covariate. The HR remained statistically significant in the scenario analysis provided.

Figure 21: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – sensitivity analysis excluding sex covariate



Abbreviations: OS – overall survival

Table 9: Summary statistics OS – sensitivity analysis excluding sex covariate

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=111)	19.42 (22/111)	0.97 (0.96 to 1.19)	1.07 (0.05)	NA (2.55 to NA)	2.15 (0.12)	0.276 (0.165 to 0.462; p<0.001)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.97 to 1.18)	1.07 (0.05)	NA (2.55 to N/A)	2.15 (0.08)	0.276 (0.188 to 0.404; p<0.001)
No treatment (n=78)	92.3 (72/78)	0.88 (0.97 to 1.47)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The

first panel of Figure 23 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 2.5. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 69.10, which is approximately 30.44% of the total trial population of 227.

Figure 22: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – sensitivity analysis excluding sex covariate

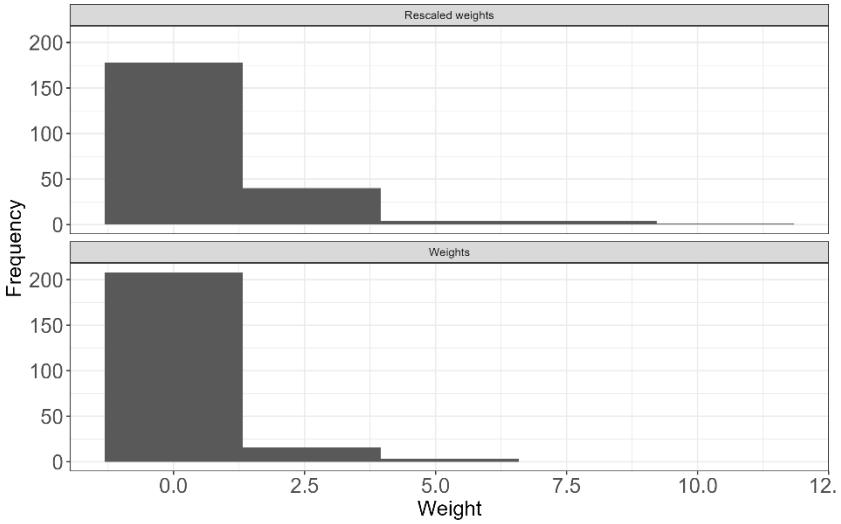


Table 10 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 10: Distribution of effect modifiers at baseline and after matching – sensitivity analysis excluding sex covariate

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.59	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.68	0.68
6MWD	260.95	222.0	222.0
DLCO	28.36	26.0	26.0
FEV1	66.70	55.0	55.0
Aetiology-IPF	0.33	0.69	0.69
Aetiology-NSIP	0.12	0.09	0.09
Aetiology-other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

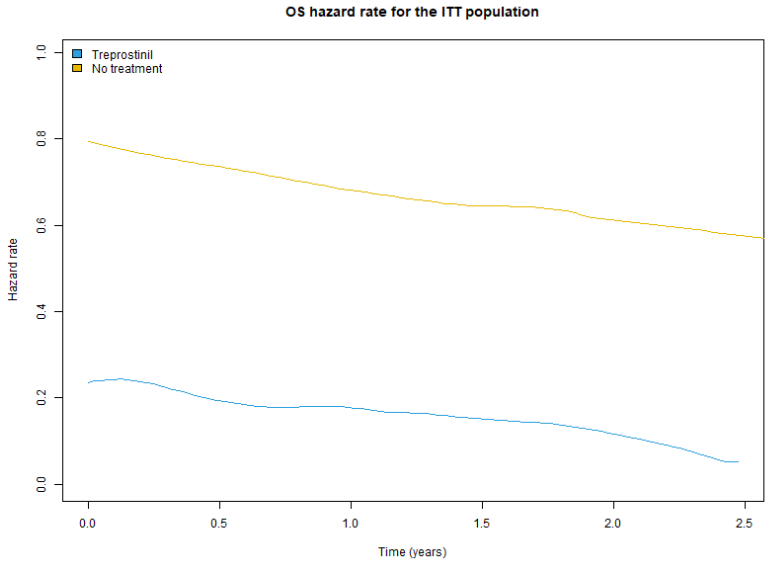
The baseline effect modifiers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 24 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

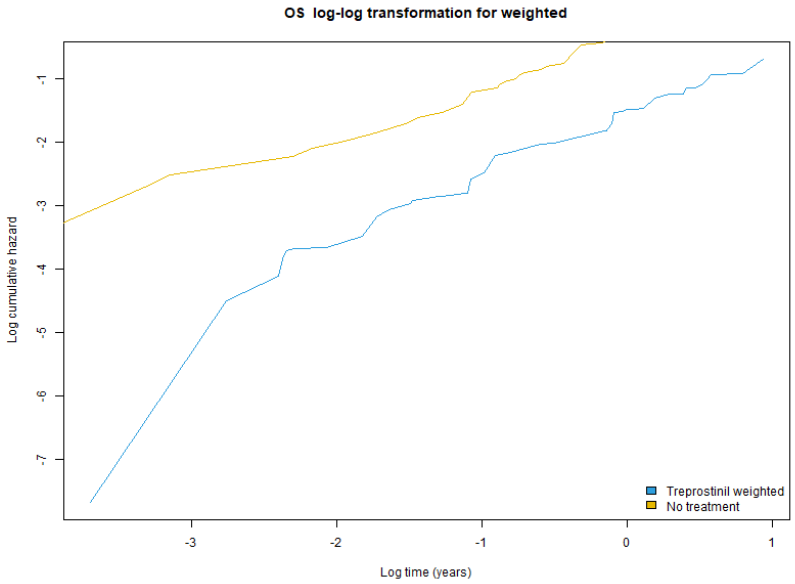
Figure 23: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population – sensitivity analysis excluding sex covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 25 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

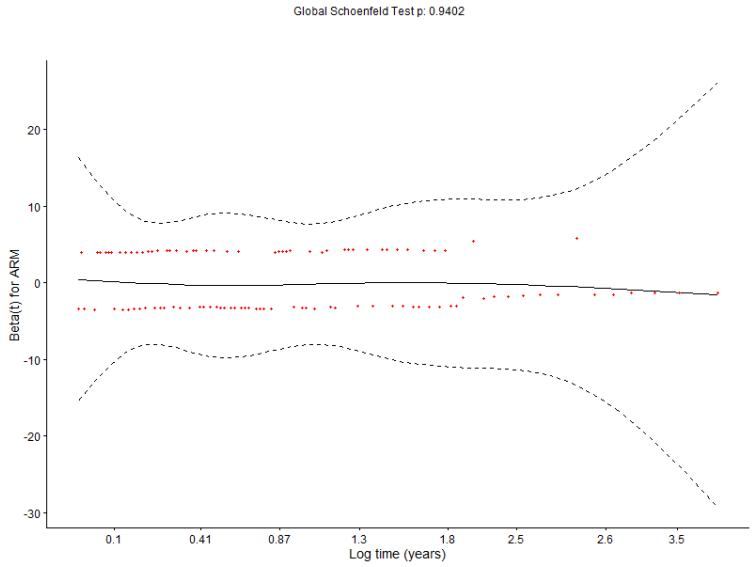
Figure 24: Log-log plot of OS in the ITT population – sensitivity analysis excluding sex covariate



Abbreviations: OS – overall survival

Figure 26 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows non-random, monotonic linear relationship with a zero slope, giving evidence that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.9402).

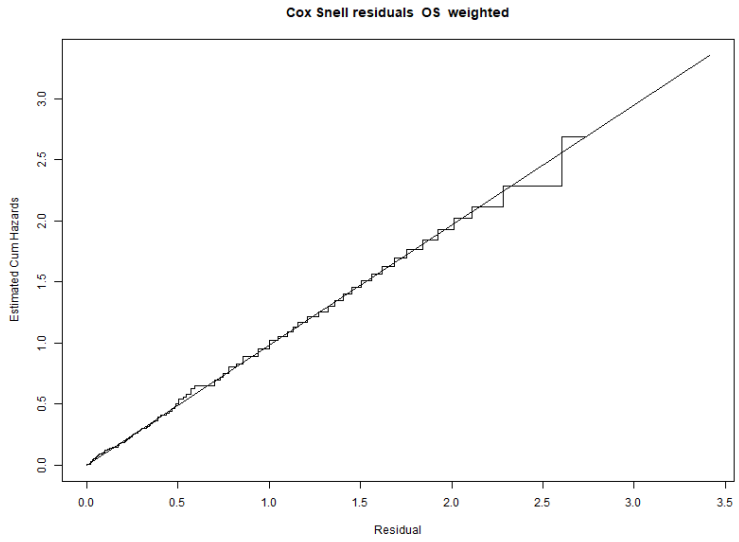
Figure 25: Schoenfeld plot of OS in the ITT population (p=0.9402) – sensitivity analysis excluding sex covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 27 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 26: Cox-Snell residual plot of OS in the ITT population – sensitivity analysis excluding sex covariate



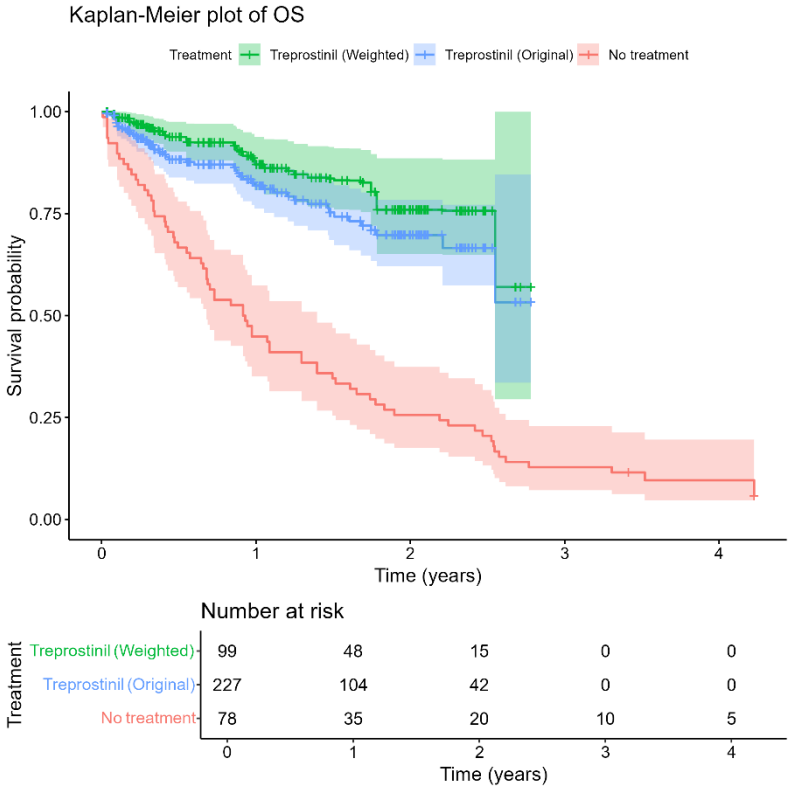
Abbreviations: ITT – intention to treat; OS – overall survival

Sensitivity analysis 3 - Hypertension

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 28. The population considered from INCREASE was the same as the base case analysis population (n=227), including patients from INCREASE

and its OLE who were treated with inhaled treprostinil, without patients with CTD or patients with time since diagnosis >2 years, and the covariates included in the MAIC were age, sex, oxygenation, 6MWD, DLCO, FEV1, and aetiology (IPF, NSIP, or other). After reweighting to match the Dawes et al. (2022) population and excluding hypertension as a covariate, the HR of OS was 0.188 (0.112 to 0.315) in the weighted group of patients receiving inhaled treprostinil relative to patients receiving no treatment (Table 11). This is similar to the HR of OS of 0.159 (0.090 to 0.280) when hypertension is included as a covariate. The HR remained statistically significant in the scenario analysis provided.

Figure 27: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – sensitivity analysis excluding hypertension covariate



Abbreviations: OS – overall survival

Table 11: Summary statistics OS – sensitivity analysis excluding hypertension covariate

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=99)	13.98 (14/99)	0.97 (0.97 to 1.18)	1.07 (0.05)	NA (2.55 to NA)	2.32 (0.12)	0.188 (0.112 to 0.315; 2.48E-10)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.97 to 1.18)	1.07 (0.05)	NA (2.55 to NA)	2.15 (0.08)	0.276 (0.188 to 0.404; 3.75E-11)
No treatment (n=78)	92.3 (72/78)	0.88 (0.98 to 1.50)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel of Figure 29 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 5. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 55.38, which is approximately 24.40% of the total trial population of 227.

Figure 28: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – sensitivity analysis excluding hypertension covariate

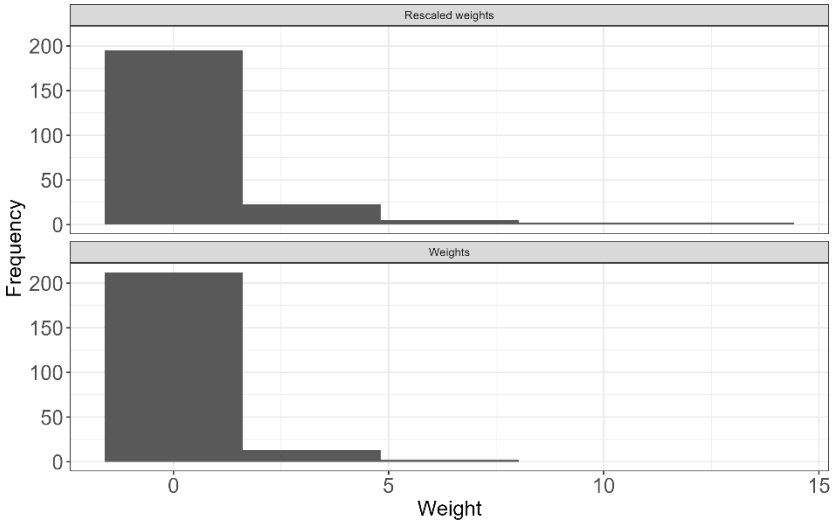


Table 12 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 12: Distribution of effect modifiers at baseline and after matching – sensitivity analysis excluding hypertension covariate

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.57	0.33
Oxygenation	0.46	0.68	0.68
6MWD	260.95	222.0	222.0
DLCO	28.36	26.0	26.0
FEV1	66.70	55.0	55.0
Aetiology-IPF	0.33	0.69	0.69
Aetiology-NSIP	0.12	0.09	0.09
Aetiology-other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

The baseline effect modifiers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

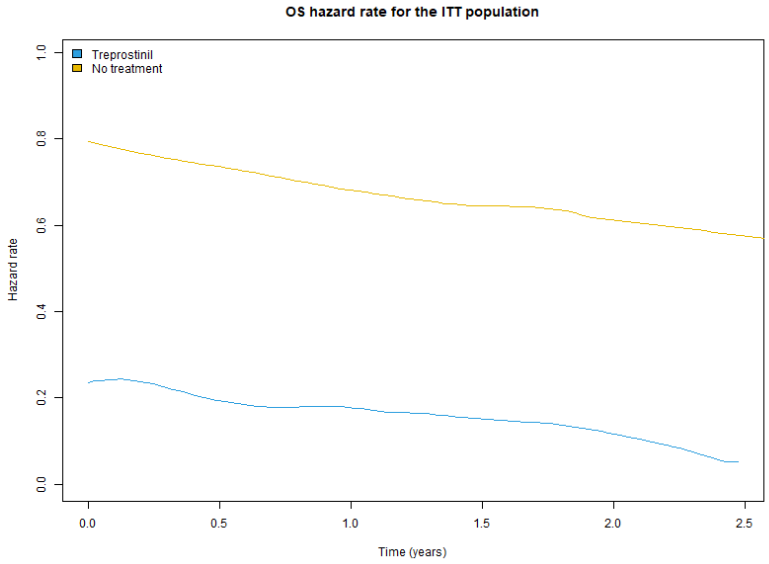
After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced

when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 30 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

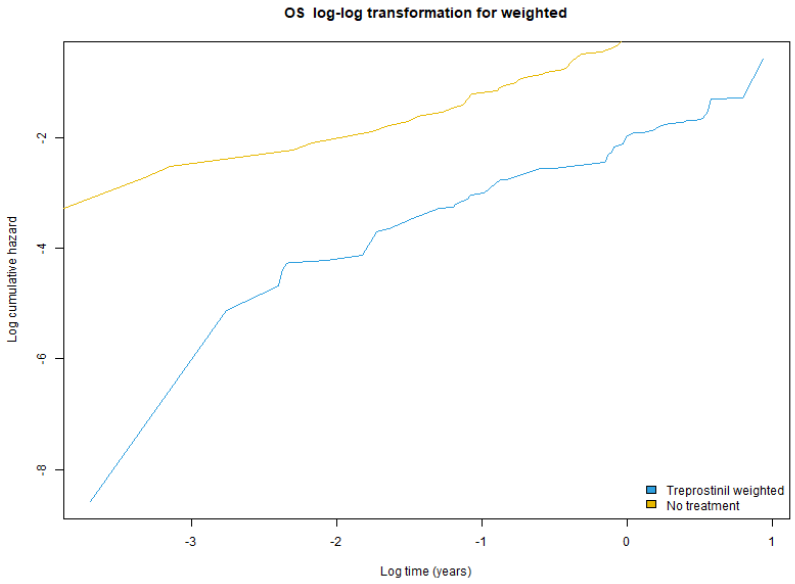
Figure 29: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population – sensitivity analysis excluding hypertension covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 31 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

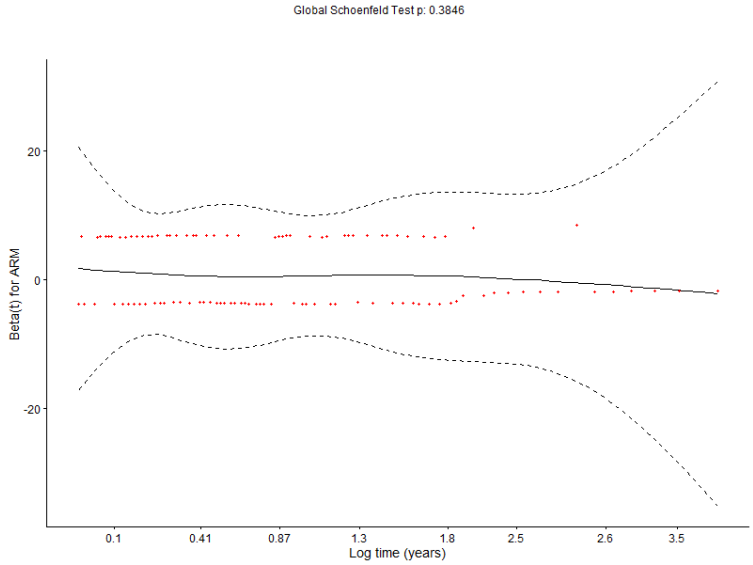
Figure 30: Log-log plot of OS in the ITT population – sensitivity analysis excluding hypertension covariate



Abbreviations: OS – overall survival

Figure 32 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows non-random, monotonic linear relationship with a zero slope, giving evidence that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.3846).

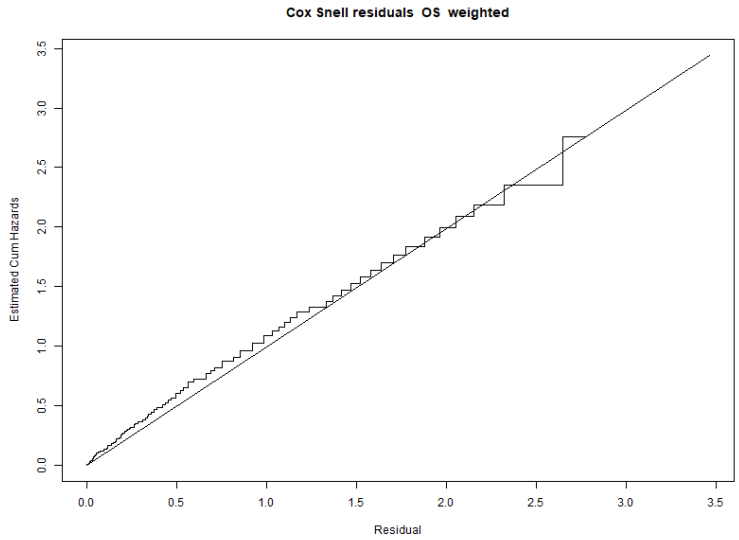
Figure 31: Schoenfeld plot of OS in the ITT population (p=0.3846) – sensitivity analysis excluding hypertension covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 33 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 32: Cox-Snell residual plot of OS in the ITT population – sensitivity analysis excluding hypertension covariate

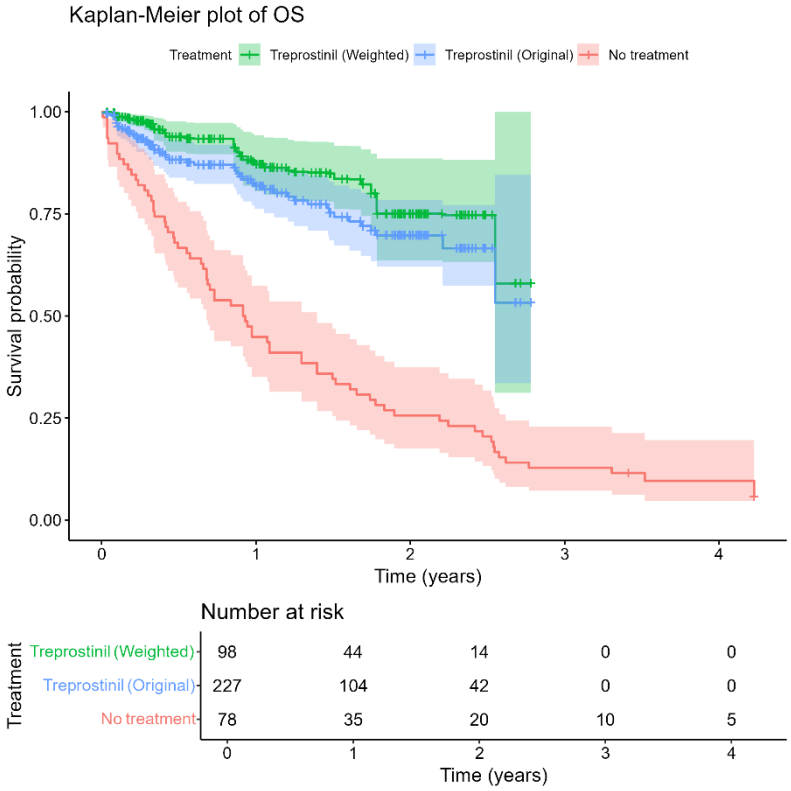


Abbreviations: ITT – intention to treat; OS – overall survival

Sensitivity analysis 4 - Oxygenation

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 34. The population considered from INCREASE was the same as that of the base case analysis population (n=227), including patients from INCREASE and its OLE who were treated with inhaled treprostinil, without patients with CTD or patients with time since diagnosis >2 years, and the covariates included in the MAIC were age, sex, hypertension, 6MWD, DLCO, FEV1, and aetiology (IPF, NSIP, or other). After reweighting to match the Dawes et al. (2022) population and excluding oxygenation as a covariate, the HR of OS was 0.188 (0.111 to 0.316) in the weighted group of patients receiving inhaled treprostinil relative to patients receiving no treatment (Table 13). This is similar to the HR of OS of 0.159 (0.090 to 0.280) when oxygenation is included as a covariate. The HR remained statistically significant in the scenario analysis provided.

Figure 33: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – sensitivity analysis excluding oxygenation covariate



Abbreviations: OS – overall survival

Table 13: Summary statistics OS – sensitivity analysis excluding oxygenation covariate

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=98)	13.31 (13/98)	0.97 (0.97 to 1.19)	1.07 (0.05)	NA (2.55 to NA)	2.32 (0.12)	0.188 (0.111 to 0.316; p<0.001)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.97 to 1.19)	1.07 (0.05)	NA (2.55 to N/A)	2.15 (0.08)	0.276 (0.188 to 0.404; p<0.001)
No treatment (n=78)	92.3 (72/78)	0.88 (0.97 to 1.48)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel of in Figure 35 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 5. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 51.42, which is approximately 22.65% of the total trial population of 227.

Figure 34: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment– sensitivity analysis excluding oxygenation covariate

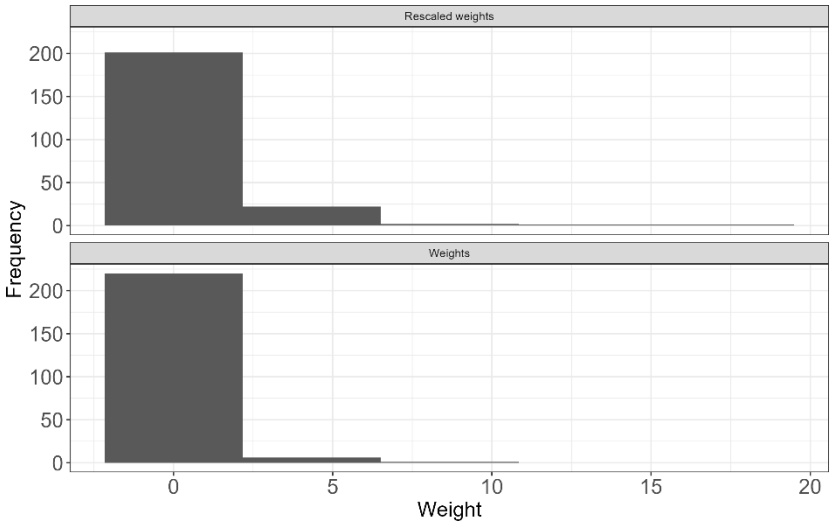


Table 14 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 14: Distribution of effect modifiers at baseline and after matching – sensitivity analysis excluding oxygenation covariate

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.43	0.68
6MWD	260.95	222.0	222.0
DLCO	28.36	26.0	26.0

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
FEV1	66.70	55.0	55.0
Aetiology-IPF	0.33	0.69	0.69
Aetiology-NSIP	0.12	0.09	0.09
Aetiology-other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

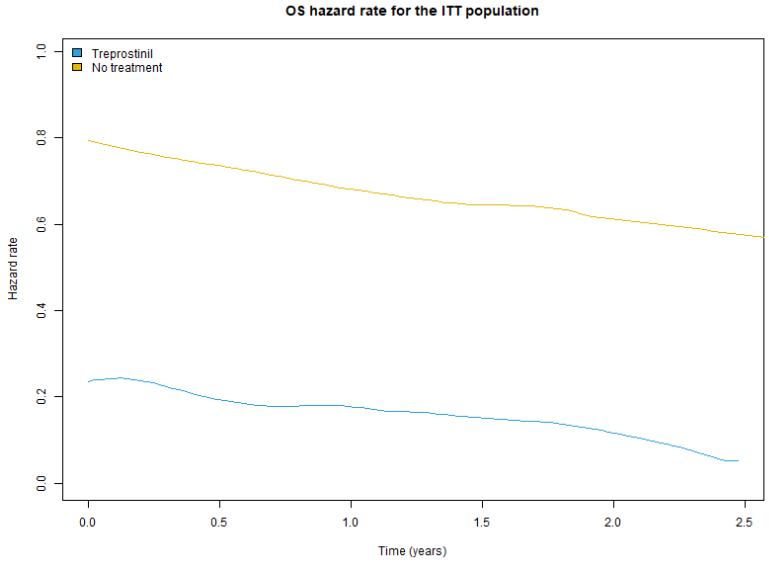
The baseline effect modifiers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 36 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

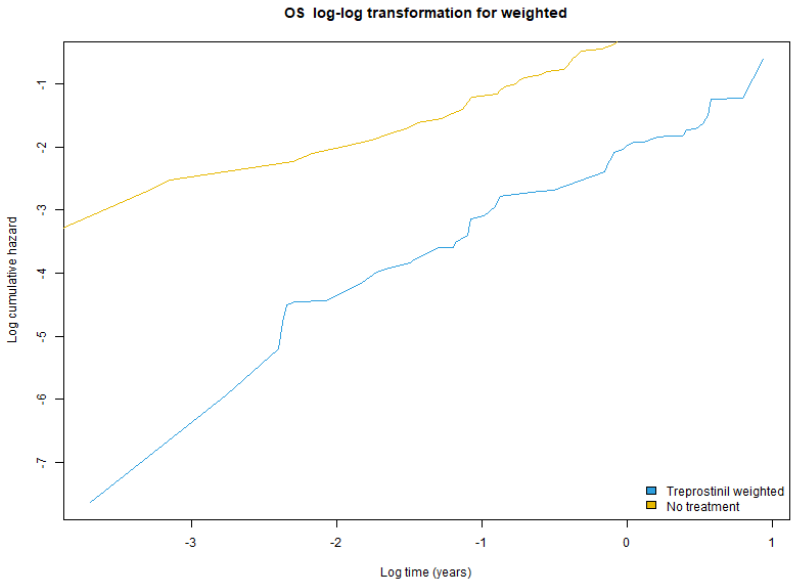
Figure 35: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population – sensitivity analysis excluding oxygenation covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 37 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

Figure 36: Log-log plot of OS in the ITT population – sensitivity analysis excluding oxygenation covariate

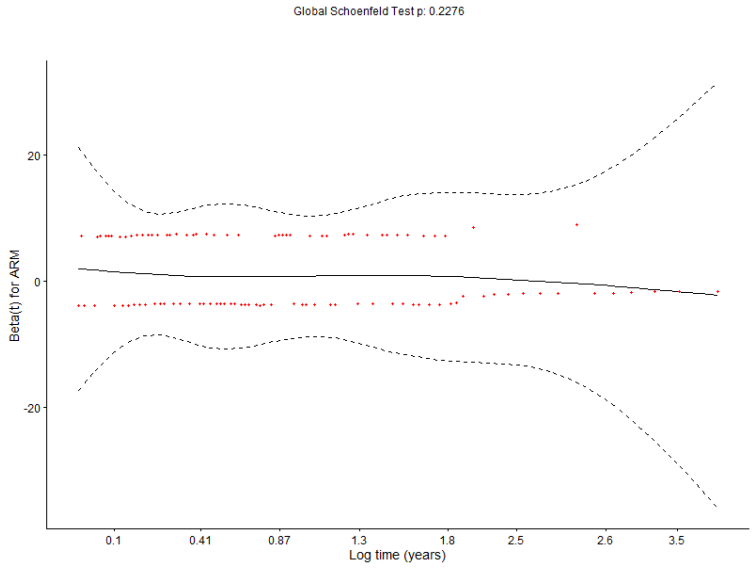


Abbreviations: OS – overall survival

Figure 38 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows non-random, monotonic linear relationship with a zero slope, giving evidence

that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.2276).

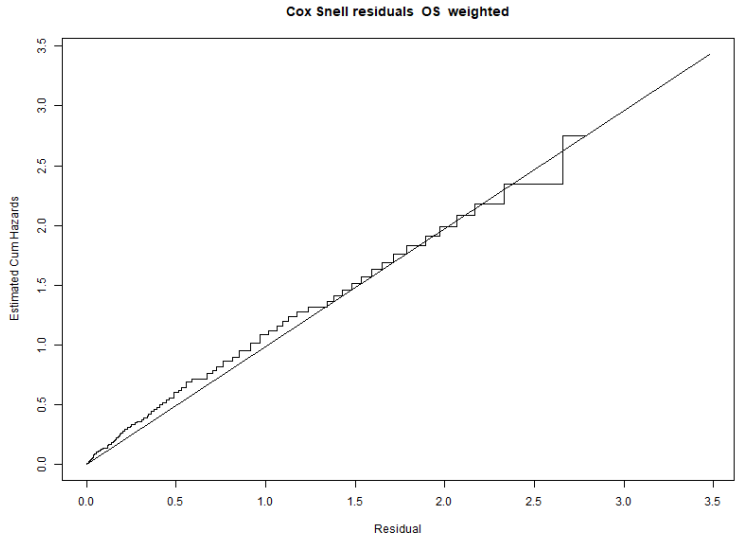
Figure 37: Schoenfeld plot of OS in the ITT population (p=0.2276) – sensitivity analysis excluding oxygenation covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 39 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 38: Cox-Snell residual plot of OS in the ITT population – sensitivity analysis excluding oxygenation covariate

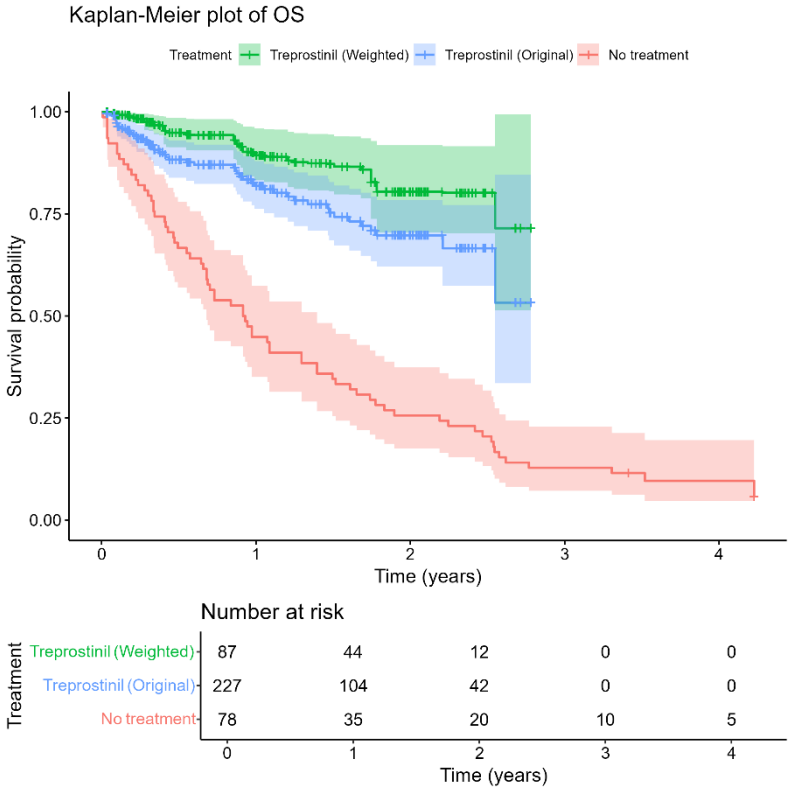


Abbreviations: ITT – intention to treat; OS – overall survival

Sensitivity analysis 5 – 6MWD

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 40. The population considered from INCREASE was the same as that of the base case analysis population (n=227), including patients from INCREASE and its OLE who were treated with inhaled treprostinil, without patients with CTD or patients with time since diagnosis >2 years, and the covariates included in the MAIC were age, sex, hypertension, oxygenation, DLCO, FEV1, and aetiology (IPF, NSIP, or other). After reweighting to match the Dawes et al. (2022) population and excluding 6MWD as a covariate, the HR of OS was 0.145 (0.081 to 0.260) in the weighted group of patients receiving inhaled treprostinil relative to patients receiving no treatment (Table 15). This is similar to the HR of OS of 0.159 (0.090 to 0.280) when 6MWD is included as a covariate. The HR remained statistically significant in the scenario analysis provided.

Figure 39: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – sensitivity analysis excluding 6MWD covariate



Abbreviations: OS – overall survival

Table 15: Summary statistics OS – sensitivity analysis excluding 6MWD covariate

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=87)	10.97 (9.5/86.8)	0.97 (0.96 to 1.19)	1.07 (0.05)	NA (NA to NA)	2.42 (0.11)	0.145 (0.081 to 0.260; p<0.001)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.96 to 1.19)	1.07 (0.05)	NA (2.55 to NA)	2.15 (0.08)	0.276 (0.188 to 0.404; p<0.001)
No treatment (n=78)	92.3 (72/78)	0.88 (0.95 to 1.49)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel of in Figure 41 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 5. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 43.2, which is approximately 19.0% of the total trial population of 227.

Figure 40: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – sensitivity analysis excluding 6MWD covariate

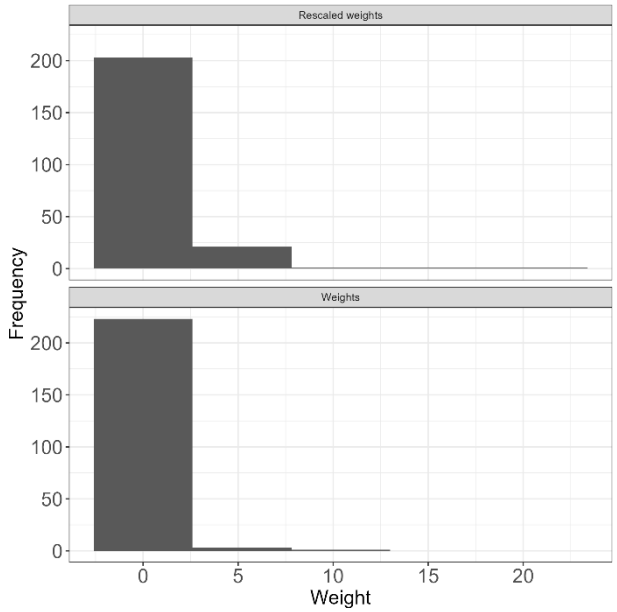


Table 16 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 16: Distribution of effect modifiers at baseline and after matching – sensitivity analysis excluding 6MWD covariate

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.68	0.68
6MWD	260.9	231.8	222.0
DLCO	28.4	26.0	26.0
FEV1	66.7	55.0	55.0
Aetiology-IPF	0.33	0.69	0.69
Aetiology-NSIP	0.12	0.09	0.09
Aetiology-other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

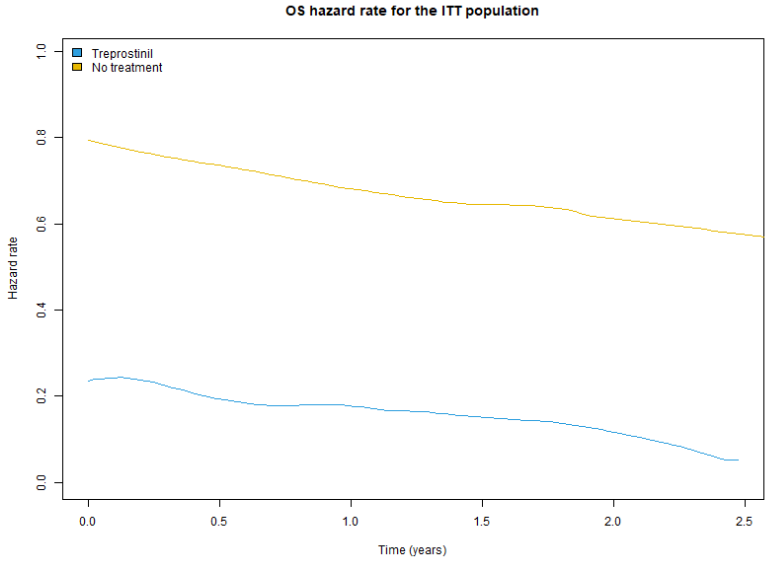
The baseline effect modifers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 42 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

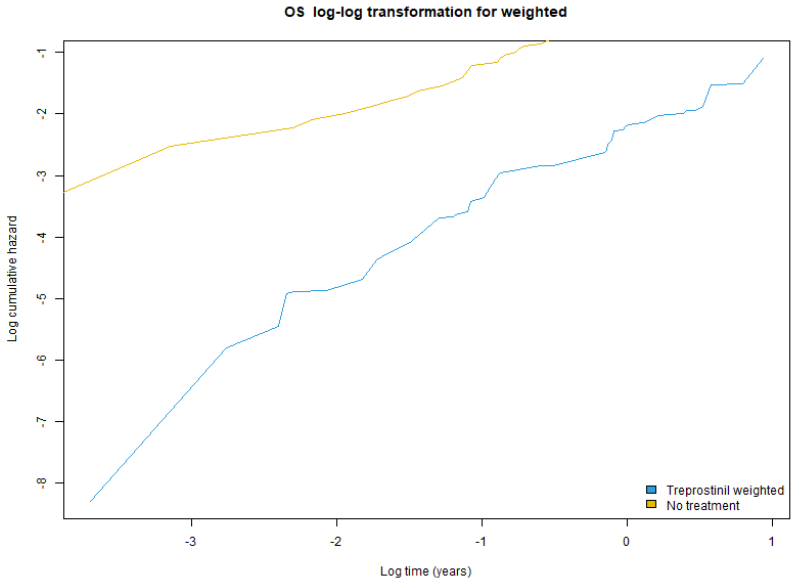
Figure 41: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population – sensitivity analysis excluding 6MWD covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 43 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

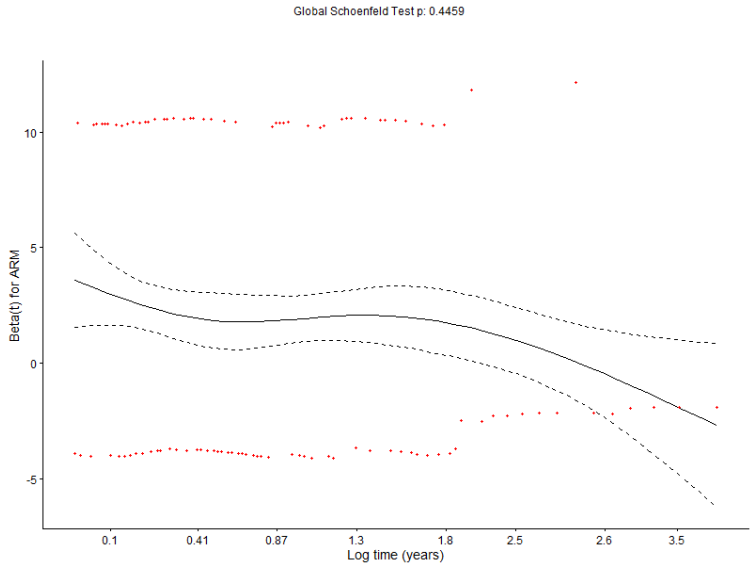
Figure 42: Log-log plot of OS in the ITT population – sensitivity analysis excluding 6MWD covariate



Abbreviations: OS – overall survival

Figure 44 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. Although a non-zero slope is not observed, the residuals show a largely random pattern against time. The relationship between residuals and time is also not statistically significant (p-value=0.4459), therefore when considering the diagnostic results of all tests conducted, there is not sufficient evidence to reject the PH assumption for the treatment covariate.

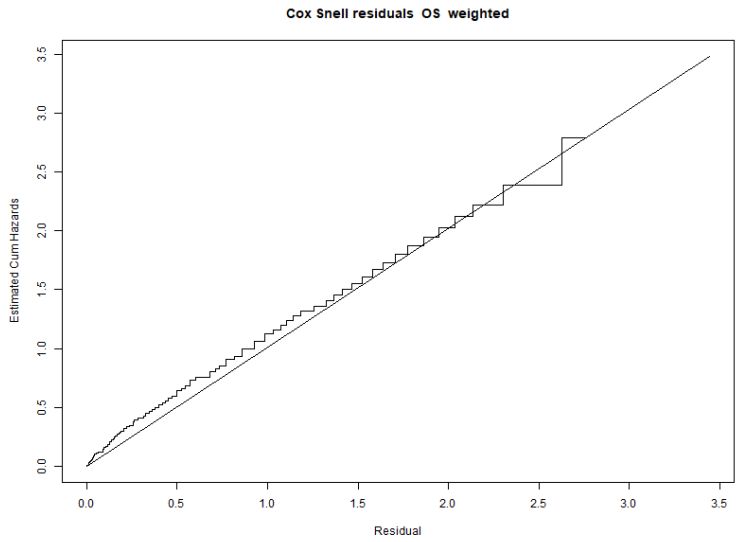
Figure 43: Schoenfeld plot of OS in the ITT population (p=0.4459) – sensitivity analysis excluding 6MWD covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 45 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 44: Cox-Snell residual plot of OS in the ITT population – sensitivity analysis excluding 6MWD covariate

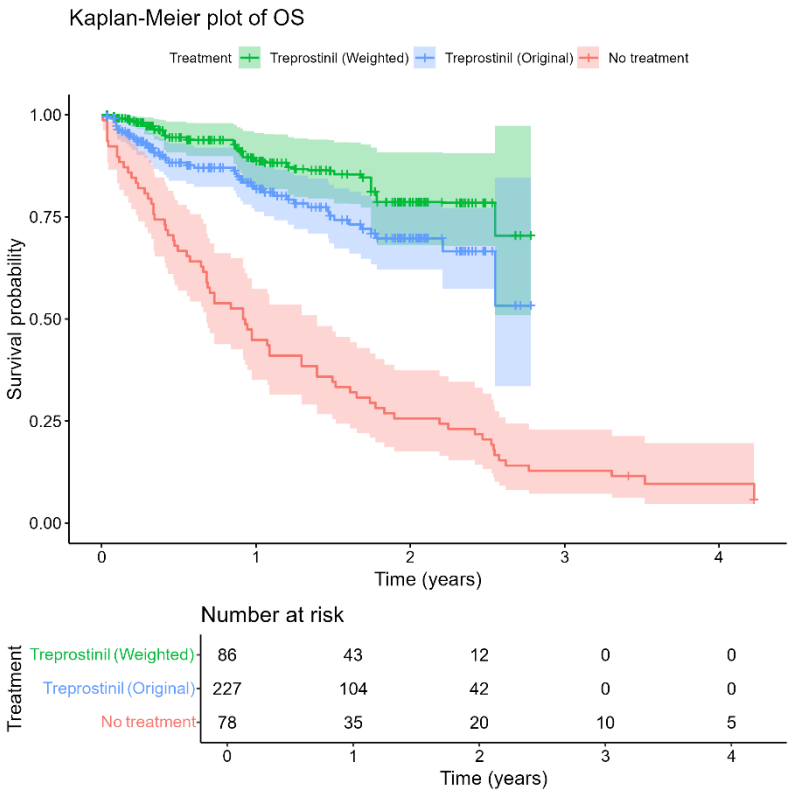


Abbreviations: ITT – intention to treat; OS – overall survival

Sensitivity analysis 6 - DLCO

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 46. The population considered from INCREASE was the same as that of the base case analysis population (n=227), including patients from INCREASE and its OLE who were treated with inhaled treprostinil, without patients with CTD or patients with time since diagnosis >2 years, and the covariates included in the MAIC were age, sex, hypertension, oxygenation, 6MWD, FEV1, and aetiology (IPF, NSIP, or other). After reweighting to match the Dawes et al. (2022) population and excluding DLCO as a covariate, the HR of OS was 0.158 (0.089 to 0.279) in the weighted group of patients receiving inhaled treprostinil relative to patients receiving no treatment (Table 17). This is similar to the HR of OS of 0.159 (0.090 to 0.280) when DLCO is included as a covariate. The HR remained statistically significant in the scenario analysis provided.

Figure 45: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – sensitivity analysis excluding DLCO covariate



Abbreviations: OS – overall survival

Table 17: Summary statistics OS – sensitivity analysis excluding DLCO covariate

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=86.3)	11.73 (10.1/86.3)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (NA to NA)	2.39 (0.11)	0.158 (0.089 to 0.279; p<0.001)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.97 to 1.19)	1.07 (0.05)	NA (2.55 to NA)	2.15 (0.08)	0.276 (0.188 to 0.404; p<0.001)
No treatment (n=78)	92.3 (72/78)	0.88 (0.95 to 1.48)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel of Figure 47 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 10. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 43.8, which is approximately 19.3% of the total trial population of 227.

Figure 46: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – sensitivity analysis excluding DLCO covariate

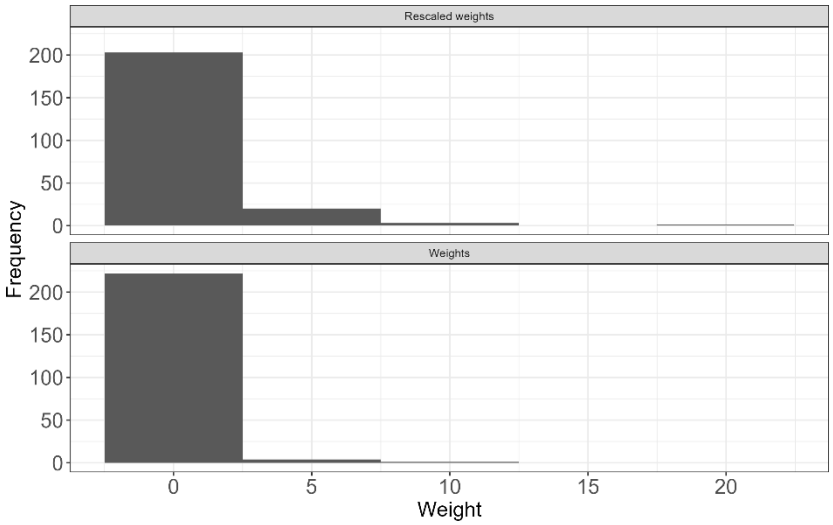


Table 18 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 18: Distribution of effect modifiers at baseline and after matching – sensitivity analysis excluding DLCO covariate

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.68	0.68
6MWD	261.0	222.0	222.0
DLCO	28.4	26.2	26.0

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
FEV1	66.7	55.0	55.0
Aetiology-IPF	0.33	0.69	0.69
Aetiology-NSIP	0.12	0.09	0.09
Aetiology-other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

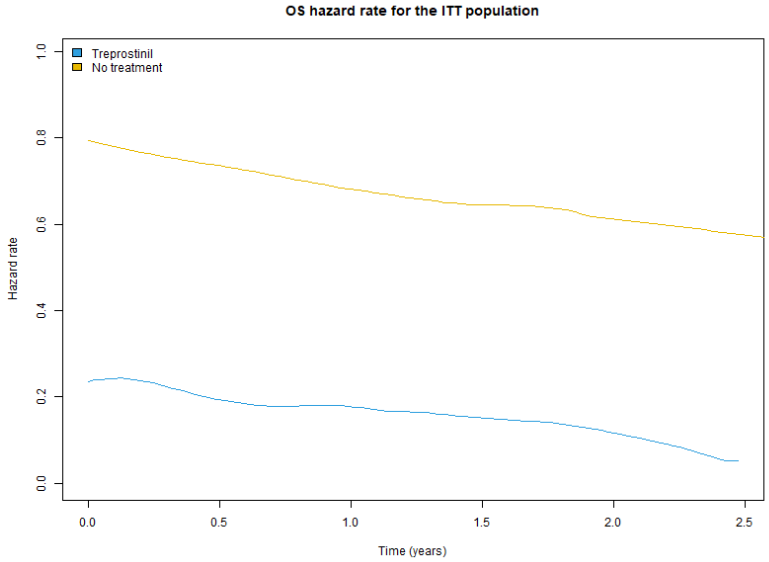
The baseline effect modifiers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 48 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

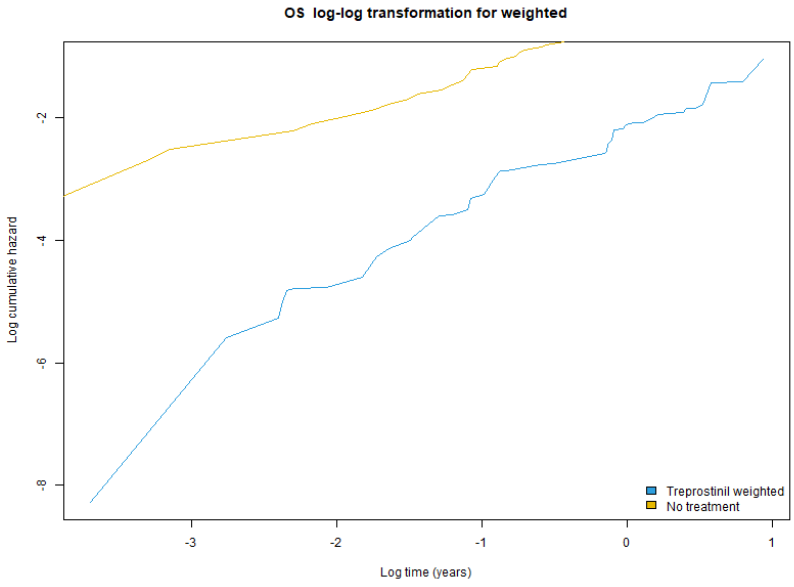
Figure 47: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population – sensitivity analysis excluding DLCO covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 49 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

Figure 48: Log-log plot of OS in the ITT population – sensitivity analysis excluding DLCO covariate

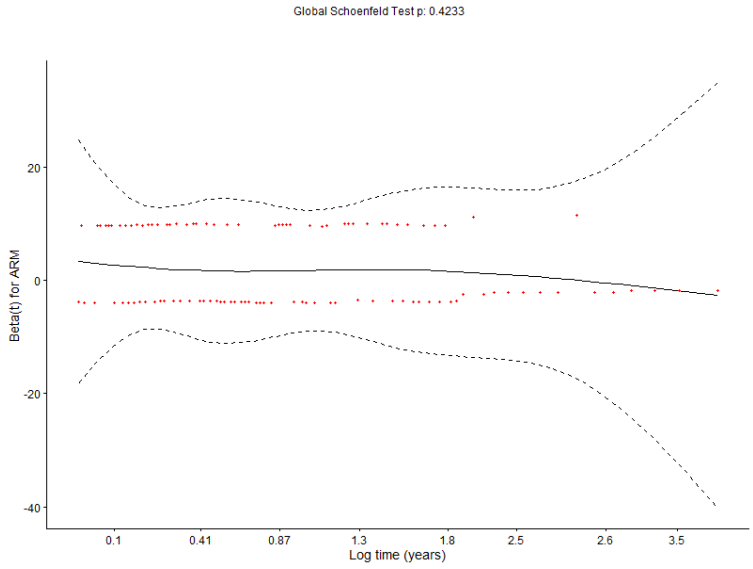


Abbreviations: OS – overall survival

Figure 50 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows non-random, monotonic linear relationship with a zero slope, giving evidence

that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.4233).

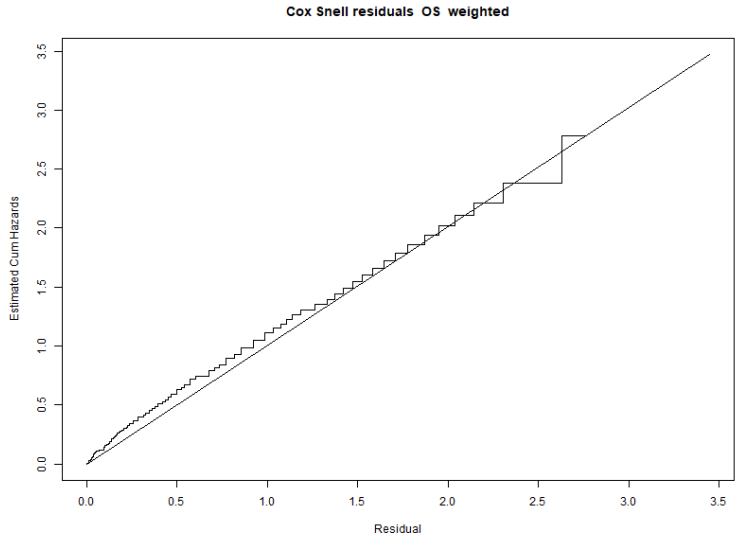
Figure 49: Schoenfeld plot of OS in the ITT population (p=0.4233) – sensitivity analysis excluding DLCO covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 51 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 50: Cox-Snell residual plot of OS in the ITT population – sensitivity analysis excluding DLCO covariate

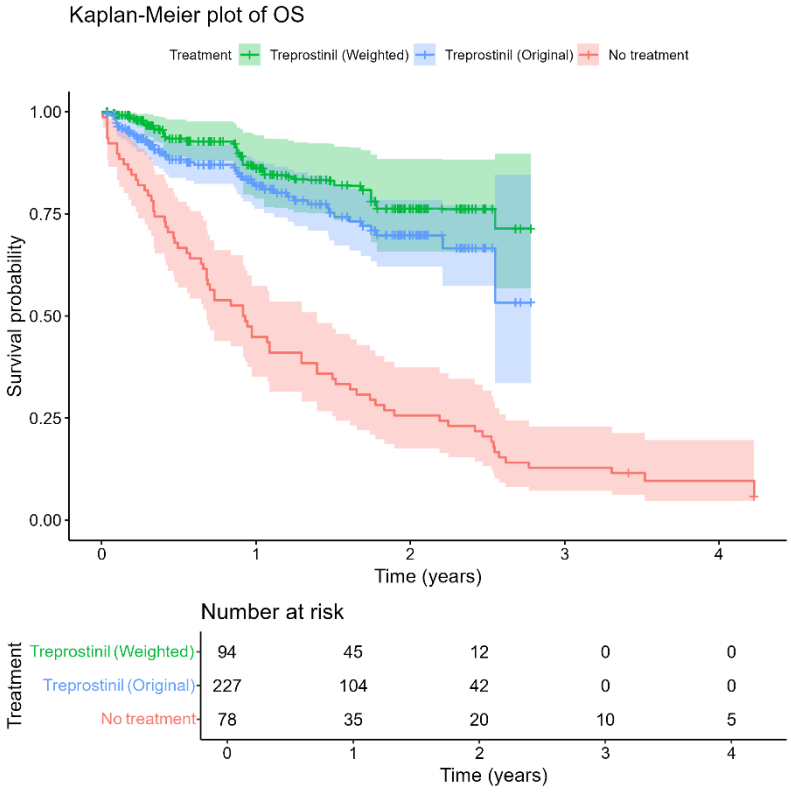


Abbreviations: ITT – intention to treat; OS – overall survival

Sensitivity analysis 7 – FEV1

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 52. The population considered from INCREASE was the same as that in the base case analysis (n=227), including patients from INCREASE and its OLE who were treated with inhaled treprostinil, without patients with CTD or patients with time since diagnosis >2 years, and the covariates included in the MAIC were age, sex, hypertension, oxygenation, 6MWD, DLCO, and aetiology (IPF, NSIP, or other). After reweighting to match the Dawes et al. (2022) population and excluding FEV1 as a covariate, the HR of OS was 0.183 (0.105 to 0.318) in the weighted group of patients receiving inhaled treprostinil relative to patients receiving no treatment (Table 19). This is similar to the HR of OS of 0.159 (0.090 to 0.280) when FEV1 is included as a covariate. The HR remained statistically significant in the scenario analysis provided.

Figure 51: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – sensitivity analysis excluding FEV1 covariate



Abbreviations: OS – overall survival

Table 19: Summary statistics OS – sensitivity analysis excluding FEV1 covariate

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=94)	13.40 (13/94)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (N/A to N/A)	2.34 (0.11)	0.183 (0.105 to 0.318; p<0.001)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (2.55 to N/A)	2.15 (0.08)	0.276 (0.188 to 0.404; p<0.001)
No treatment (n=78)	92.3 (72/78)	0.88 (0.97 to 1.48)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel of Figure 53 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 10. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 53, which is approximately 23.3% of the total trial population of 227, highlighting the difference between trials and increasing uncertainty of the results. The histogram demonstrates a skewed distribution with most of the data points being concentrated on the left side near smaller weight values. No extreme weights were seen within the histogram suggesting that results from the MAIC are reliable.

Figure 52: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – sensitivity analysis excluding FEV1 covariate

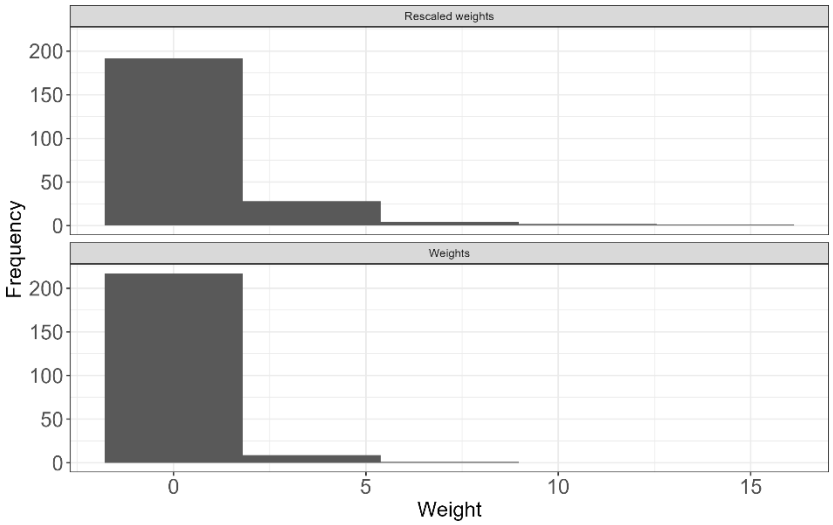


Table 20 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 20: Distribution of effect modifiers at baseline and after matching – sensitivity analysis excluding FEV1 covariate

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.68	0.68
6MWD	261.0	222.0	222.0
DLCO	28.4	26.0	26.0
FEV1	67.0	61.0	55.0
Aetiology-IPF	0.33	0.69	0.69
Aetiology-NSIP	0.33	0.09	0.09
Aetiology-other	0.55	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

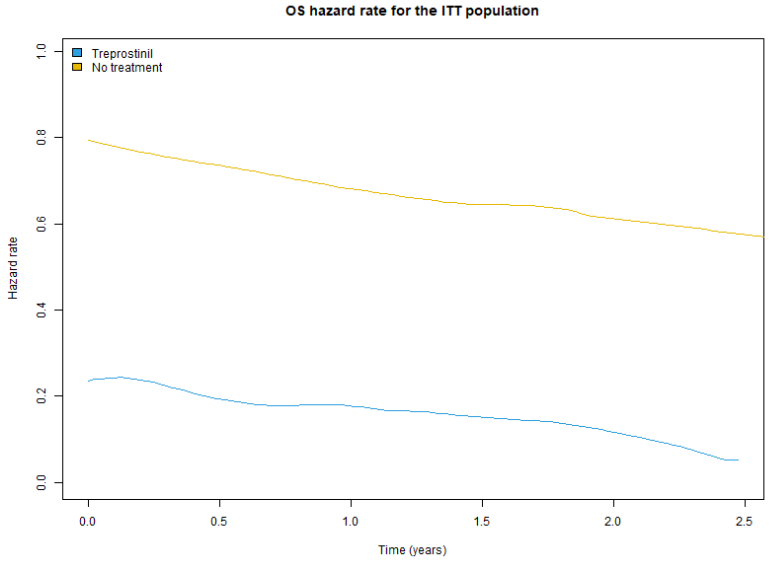
The baseline effect modifiers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 54 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

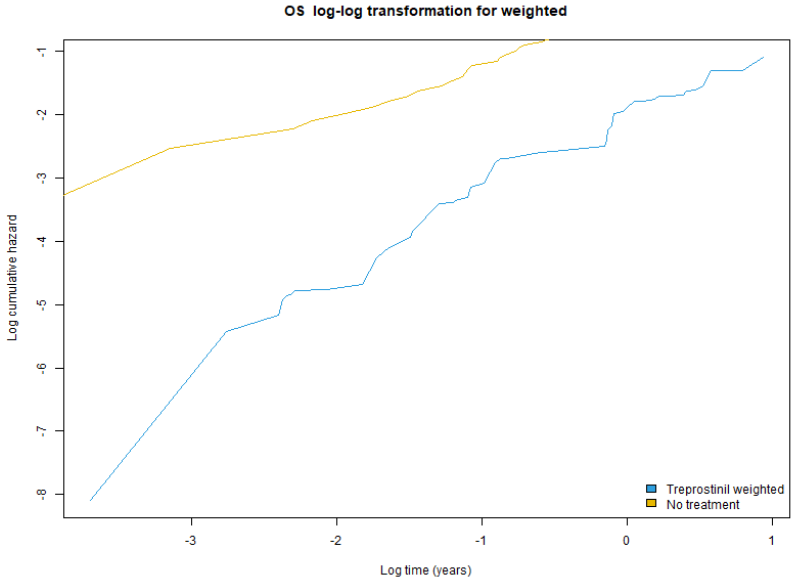
Figure 53: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population– sensitivity analysis excluding FEV1 covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 55 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

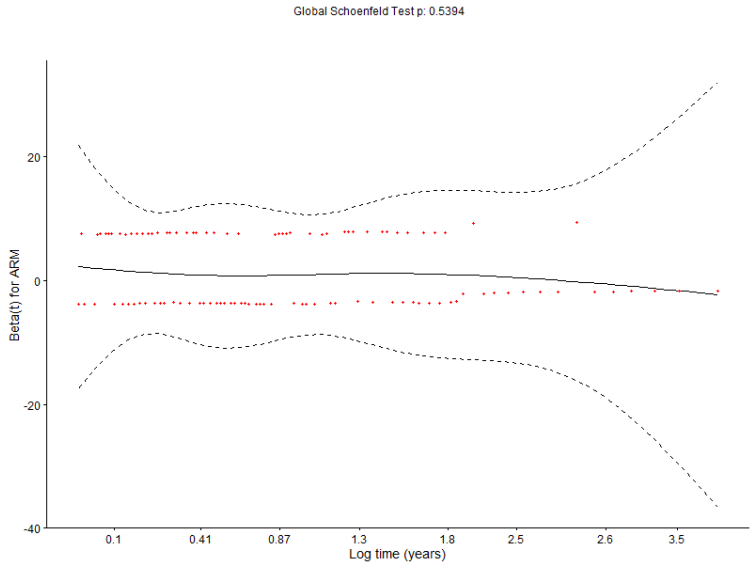
Figure 54: Log-log plot of OS in the ITT population



Abbreviations: OS – overall survival

Figure 56 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows non-random, monotonic linear relationship with a zero slope, giving evidence that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.5394).

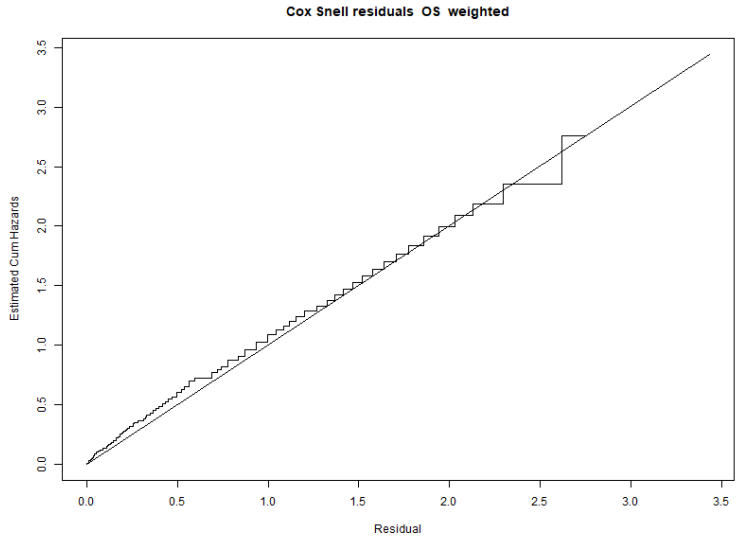
Figure 55: Schoenfeld plot of OS in the ITT population (p=0.5394)



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 57 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 56: Cox-Snell residual plot of OS in the ITT population

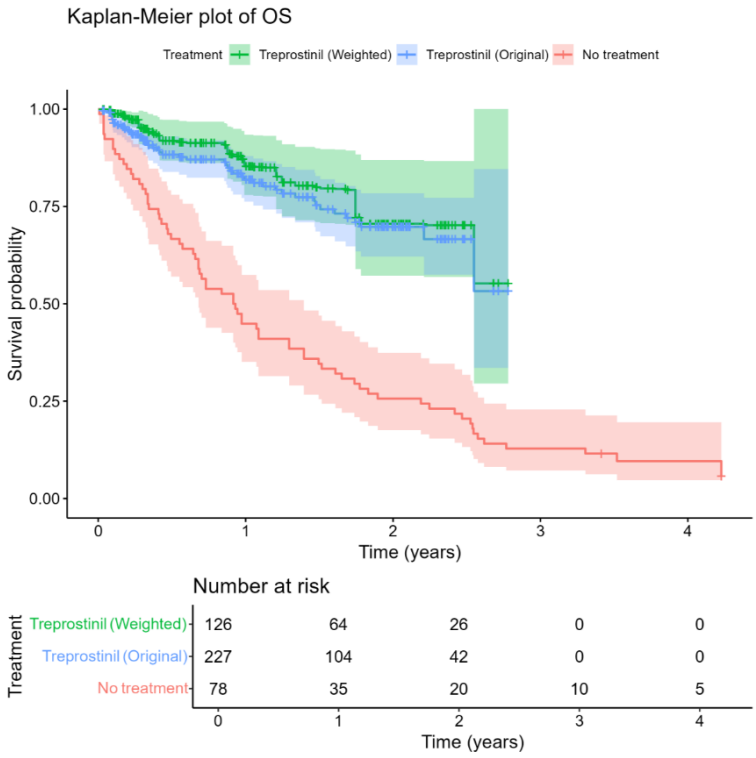


Abbreviations: ITT – intention to treat; OS – overall survival

Sensitivity analysis 8 - Aetiology

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 58. The population considered from INCREASE was the same as the base case analysis (n=227), including patients from INCREASE and its OLE who were treated with inhaled treprostinil, without patients with CTD or patients with time since diagnosis >2 years, and the covariates included in the MAIC were age, sex, hypertension, oxygenation, 6MWD, DLCO and FEV1. After reweighting to match the Dawes et al. (2022) population and excluding aetiology as a covariate, the HR of OS was 0.233 (0.137 to 0.398) in the weighted group of patients receiving inhaled treprostinil relative to patients receiving no treatment (Table 21). This is similar to the HR of OS of 0.159 (0.090 to 0.280) when aetiology is included as a covariate. The HR remained statistically significant in the scenario analysis provided.

Figure 57: KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – sensitivity analysis excluding aetiology covariate



Abbreviations: OS – overall survival

Table 21: Summary statistics OS – sensitivity analysis excluding aetiology covariate

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=126)	18.52 (23.4/126.4)	0.97 (0.96 to 1.18)	1.07 (0.05)	NA (2.55 to NA)	2.24 (0.10)	0.233 (0.137 to 0.398; p<0.001)
Inhaled treprostinil – unweighted (n=227)	20.26 (46/227)	0.97 (0.97 to 1.18)	1.07 (0.05)	NA (2.55 to NA)	2.15 (0.08)	0.276 (0.188 to 0.404; p<0.001)
No treatment (n=78)	92.3 (72/78)	0.88 (0.97 to 1.50)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel of Figure 59 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 4. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 84.5, which is approximately 37.2% of the total trial population of 227.

Figure 58: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – sensitivity analysis excluding aetiology covariate

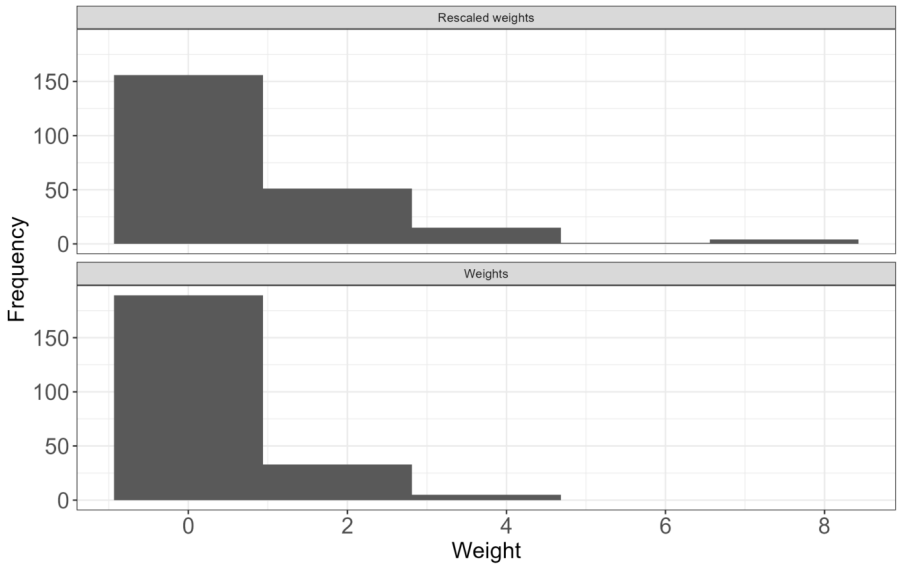


Table 22 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 22: Distribution of effect modifiers at baseline and after matching – sensitivity analysis excluding aetiology covariate

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.68	0.68
6MWD	261.0	22.0	222.0

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
DLCO	28.4	26.0	26.0
FEV1	66.7	55.0	55.0
Aetiology-IPF	0.33	0.30	0.69
Aetiology-NSIP	0.12	0.16	0.09
Aetiology-other	0.55	0.55	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

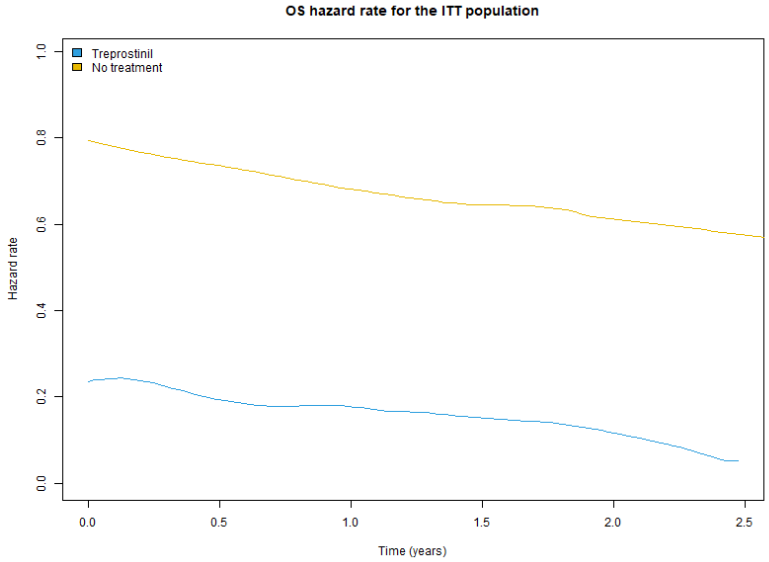
The baseline effect modifers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results.

Assessment of the PH assumption

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 60 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

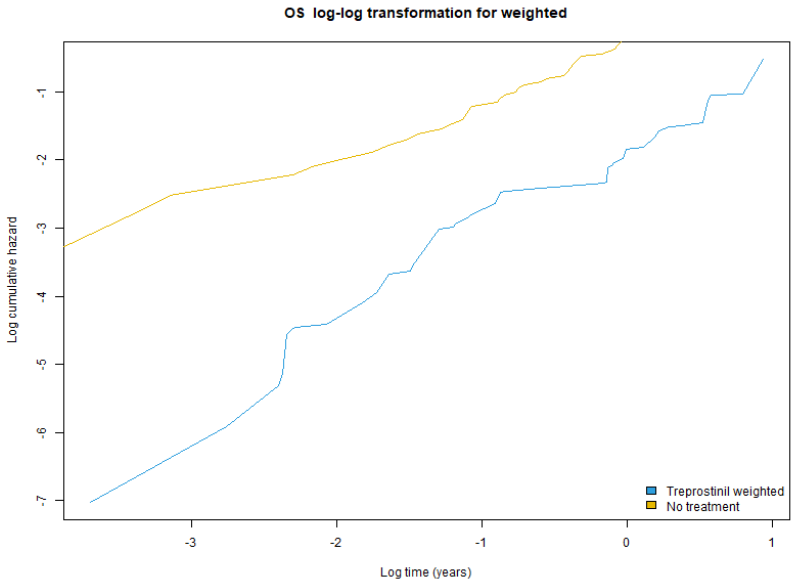
Figure 59: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population – sensitivity analysis excluding aetiology covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 61 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

Figure 60: Log-log plot of OS in the ITT population – sensitivity analysis excluding aetiology covariate

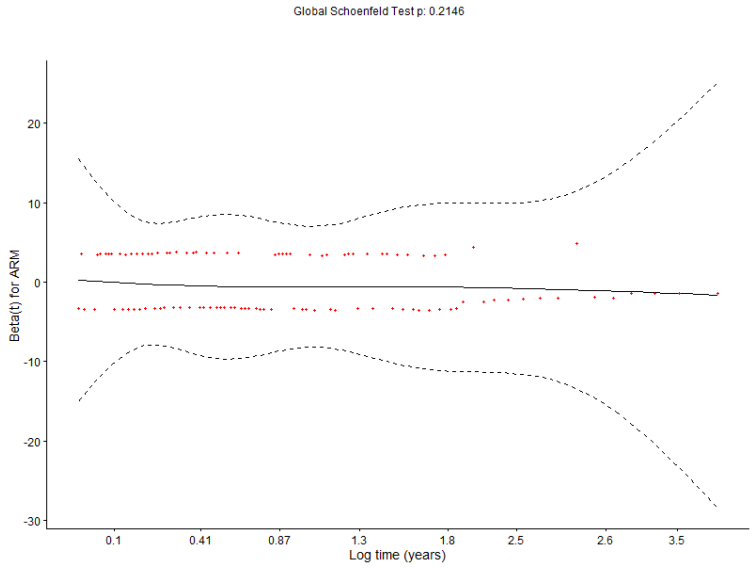


Abbreviations: OS – overall survival

Figure 62 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows non-random, monotonic linear relationship with a zero slope, giving evidence

that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.4248).

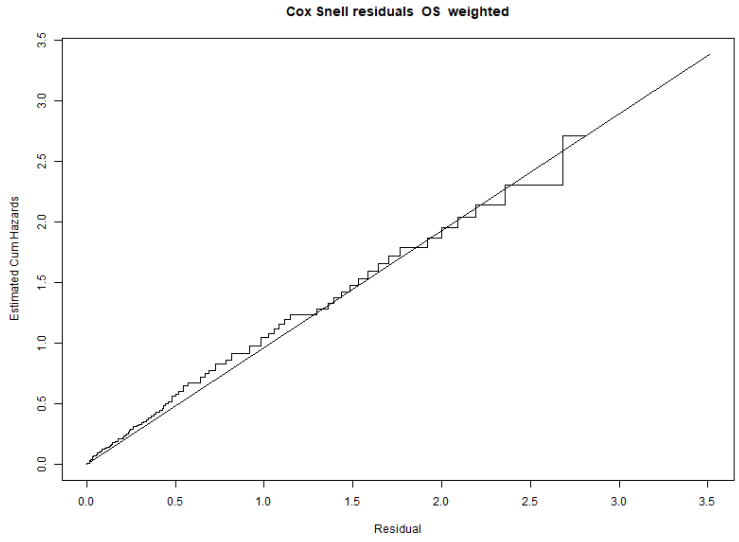
Figure 61: Schoenfeld plot of OS in the ITT population (p=0.4248) – sensitivity analysis excluding aetiology covariate



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 63 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 62: Cox-Snell residual plot of OS in the ITT population – sensitivity analysis excluding aetiology covariate



Abbreviations: ITT – intention to treat; OS – overall survival

A24. Please comment on the difference in overall survival as observed between the Dawes et al. untreated population and the RHC population from the CPRD HES analysis.

The primary known prognostic factor that differs between the Dawes et al. untreated population and the RHC population from the CPRD HES analysis is the age at inclusion in the study. In the Dawes et al. untreated population, the mean age at inclusion is 67.4 (with a standard deviation of 10.3). The age at inclusion in the RHC population from the CPRD HES analysis is comparatively younger, with a mean age of 60 (and standard deviation of 16). Further prognostic factors cannot be compared between studies as equivalent characteristics and their values have not been reported in both studies, such as 6MWD or haemodynamic measures (i.e., PVR scores).

It is important to note that the overall survival curve for the RHC population from the CPRD HES analysis (N=220) is not considered representative of survival rates in patients with PH-ILD in the UK. Feedback received in an advisory board for inhaled treprostinil detailed that only a minority of patients are referred to specialist PH centres for diagnosis of PH-ILD with RHC, due to the lack of an effective treatment.[12] Referral rates differ across the UK but remain low compared to the total population of patients with suspected PH-ILD. It is expected that the introduction of an approved treatment for patients with PH-ILD, such as inhaled treprostinil, will mean that more patients will receive a confirmed diagnosis of PH-ILD via RHC. Furthermore, input received in a clinical validation workshop elaborated that there is a steep decline in survival rates within the first year, and the majority of patients with PH-ILD receiving best supportive care will die by 5 years.[13] Therefore, the higher survival rates reported in the RHC CPRD population are not aligned with observed survival rates in the broader PH-ILD population in the UK.

Of the survival curves presented in the CPRD report, the survival rates in the total combined population of patients with suspected (without RHC) and confirmed (with RHC) PH-ILD in the CPRD HES data are likely more representative of the UK patient population that would receive inhaled treprostinil. This is because all patients with suspected PH-ILD are likely to undergo a RHC to confirm their diagnosis before receiving inhaled treprostinil, in line with the target patient population in the

INCREASE trial and Dawes et al study. However, the Dawes et al. survival curve is considered more reflective and representative of survival rates observed in UK patients with PH-ILD according to clinician feedback.

Notably, the CPRD survival curves are subject to limitations due to missing data, including missing dates of deaths and incomplete cause of death fields. Furthermore, the CPRD data were censored at an arbitrary date in December 2021. Therefore, outcomes were not collected for many prevalent patients after this time point resulting in a flattened KM curve after 36 months.

A25. PRIORITY: Please perform MAICs comparing all people who received treprostinil in INCREASE and INCREASE OLE (n=284), and separately using the company's MAIC population (n=227) to the CPRD HES analysis RHD ILD (n=220) subgroup, matching on age and sex, plus comorbidities if possible. Please also add survival models fitted to the CPRD HES analysis to the economic model

As mentioned in the response above, the CPRD HES data in the RHC PH-ILD subgroup (N=220) are not considered relevant for a MAIC vs patients receiving inhaled treprostinil in INCREASE and INCREASE OLE. The survival rates in the RHC PH-ILD population are much higher than those previously reported in patients with PH-ILD and are not considered representative of real-world outcomes for patients who will receive inhaled treprostinil.

Table 23 presents the variables included in the MAIC for INCREASE versus Dawes et al, and highlights which factors are reported in the CPRD study. This highlights the lack of available data in the CPRD for these key characteristics that are used to phenotype the severity of PH-ILD and a patient's prognosis. The differences in survival rates reported in Dawes et al versus the CPRD RHC population cannot be explained based on the differences in age and sex alone. Therefore, these other prognostic factors are essential to conduct a valid and reliable MAIC. As these data are missing in the CPRD study, we are not able to provide the additional MAIC requested.

Table 23. Variables included in MAIC with Dawes et al versus those reported in the CPRD study

Variable included in MAIC	Dawes et al	CPRD study
Age (years)	✓	✓
Sex (% male)	✓	✓
Hypertension (% with)	✓	× (Arterial hypertension only is reported)
Oxygenation (% receiving)	✓	×
6MWD	✓	×
DLCO	✓	×
FEV1	✓	×
NSIP	✓	×

Abbreviations: 6MWD: 6-Minute Walk Distance; CPRD: Clinical Practice Research Datalink; DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide; FEV1: Forced Expiratory Volume in 1 Second; MAIC: Matching-Adjusted Indirect Comparison; NSIP: Non-Specific Interstitial Pneumonia

A26. Please clarify the difference between the definitions of "clinical worsening" events (figure 9), "disease progression" events (figure 11) and EFS events.

In the INCREASE trial, clinical worsening events included the following criteria:

- Decrease in peak 6MWD >15% from baseline (directly related to the disease at two consecutive visits occurring ≥24 hours apart)
- Hospitalisation due to a cardiopulmonary indication
- Lung transplantation
- Death

Alternatively, disease progression is defined as the occurrence of any of the following events:

- ≥15% or more decline in 6MWD from baseline
- ≥10% or more decline in FVC from baseline

- Acute lung-disease exacerbation
- Cardiopulmonary hospitalisation
- Lung transplantation
- Death

As such, the differences between the two definitions lie in the inclusion of “a ≥10% or more decline in FVC from baseline” and “acute lung-disease exacerbation” in the definition for disease progression.

The definition of disease progression events was used to inform the definition of clinical worsening events for the purposes of the economic model. This is highlighted in Table 14 in the main submission that compares the two definitions and clarifies that all events captured under ‘disease progression’ in the Nathan et al analysis were included in the definition of clinical worsening events in the cost-effectiveness model based on expert feedback.

In comparison, event-free survival in the post-hoc efficacy analysis was defined as the time to first hospitalisation, disease exacerbation, or death.

Table 24 provides an overview of the definition for clinical worsening events used in the cost-effectiveness model compared to the definitions for clinical worsening events in INCREASE, disease progression events in the post hoc analysis of INCREASE and event free survival in the post hoc analysis of INCREASE OLE.

Table 24. Comparison of definitions for clinical worsening events, disease progression events and event free survival

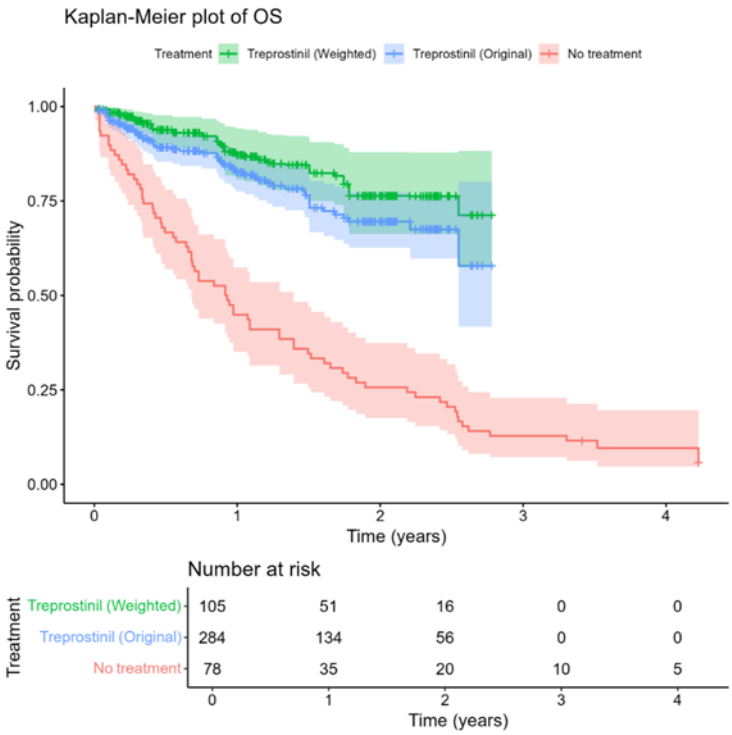
Clinical worsening event definition in CE model	INCREASE clinical worsening events (Waxman 2021[1])	INCREASE disease progression events (Nathan 2022[14])	INCREASE OLE event free survival [15]
Fall in 6MWD of ≥15% from baseline	Included	Included	Not included
Fall in FVC% of ≥10% from baseline	Not included	Included	Not included
Cardiopulmonary hospitalisation	Included	Included	Defined as time to first hospitalisation
Acute lung-disease exacerbation	Not included	Included	Included
Lung transplant	Included	Included	Not included
Death	Included	Included	Included

Abbreviations: CE – cost effectiveness; FVC – Forced vital capacity; 6MWD – six-minute walking distance.

A27. Please re-perform MAIC against the Dawes et al. untreated population using the full population of people who received treprostinil (n=284)

The OS KM data for no treatment, inhaled treprostinil unweighted and inhaled treprostinil weighted to match the untreated population in Dawes et al. (2022) are presented in Figure 64. The population analysed for the inhaled treprostinil arm included patients from INCREASE who were treated with inhaled treprostinil and patients who were treated inhaled treprostinil in the OLE and re-baselined after placebo treatment in INCREASE, without excluding patients with CTD or patients with time since diagnosis >2 years. The unweighted inhaled treprostinil population thus consisted of 284 patients. The covariates included in the MAIC were age, sex, hypertension, oxygenation, 6MWD, DLCO, FEV1, and aetiology (IPF, NSIP and other). The HR of OS for patients treated with inhaled treprostinil was 0.178 (0.106 to 0.300) (Table 25), compared to an OS HR of 0.266 (0.186 to 0.381) for patients treated with inhaled treprostinil versus untreated patients from Dawes et al. (2022). The HR remained statistically significant in the scenario analysis provided.

Figure 63. KM for inhaled treprostinil, weighted treprostinil and no treatment OS in the ITT population – scenario analysis using the full population receiving inhaled treprostinil



Abbreviations: OS – overall survival

Table 25. Summary statistics OS – scenario analysis using the full population receiving inhaled treprostinil (n=284)

Treatment arm (N)	Maturity % – (n/N)	Duration of follow-up (months)		Median (95% CI) - years	Restricted mean (SE) - years	HR compared with no treatment (95% CI; p-value)
		Median (95% CI) - years	Mean (SE) - years			
Inhaled treprostinil – reweighted (n=105.3)	13.30 (14/105.3)	0.99 (1.02 to 1.22)	1.11 (0.05)	NA (NA to NA)	2.35 (0.10)	0.178 (0.106 to 0.300; p<0.001)
Inhaled treprostinil – unweighted (n=284)	20.07 (57/284)	0.99 (1.02 to 1.21)	1.11 (0.05)	NA (2.55 to NA)	2.17 (0.07)	0.266 (0.186 to 0.381; p<0.001)
No treatment (n=78)	92.30 (72/78)	0.88 (0.97 to 1.50)	1.22 (0.12)	0.92 (0.68 to 1.40)	1.37 (0.14)	-

Abbreviations: CI – confidence intervals; SE – standard error

Reweighting the INCREASE and INCREASE OLE studies

Following generation of the logistic propensity score model, weights were generated to match covariate distributions in INCREASE and INCREASE OLE for inhaled treprostinil to no treatment with PDE5i from the Dawes et al (2022) population. The first panel of Figure 65 shows the distribution of weights after rescaling, while the second panel shows the distribution of unscaled weights. The rescaled weights are slightly skewed to the right with the majority of values ranging between 0 and 10. The original weights plot (prior to rescaling) also shows a right-skewed distribution with most data on the lower end (closer to 0), with a long tail extending to higher values. The ESS was calculated to be 50.5, which is approximately 17.8% of the total trial population of 284.

Figure 64: Histogram presenting rescaled weights for inhaled treprostinil vs no treatment – scenario analysis using the full population receiving inhaled treprostinil

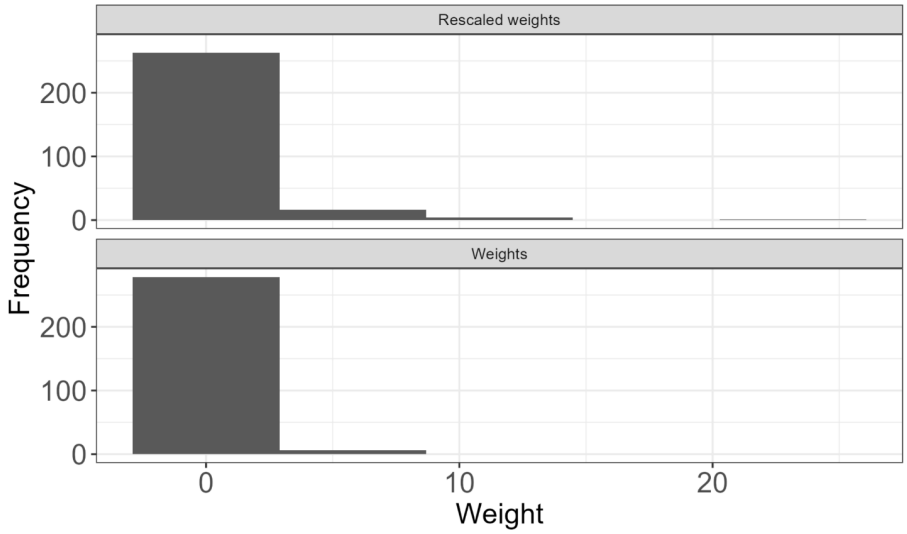


Table 26 below shows the distribution of effect modifiers at baseline before and after they were changed due to reweighting and matching.

Table 26: Distribution of effect modifiers at baseline and after matching – scenario analysis using the full population receiving inhaled treprostinil

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
Age (years)	66.62	67.0	67.0
Sex (male %)	0.52	0.26	0.26
Hypertension	0.48	0.33	0.33
Oxygenation	0.45	0.68	0.68

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)
6MWD	261.0	222.0	222.0
DLCO	28.6	26.0	26.0
FEV1	64.3	55.0	55.0
Aetiology-IPF	0.28	0.69	0.69
Aetiology-NSIP	0.12	0.09	0.09
Aetiology-other	0.60	0.22	0.22

Abbreviations: 6MWD – 6-minute walk distance; DLCO – Diffusing capacity of the lungs for carbon monoxide; FEV1 – Forced expiratory volume in 1 second; IPF – Idiopathic pulmonary fibrosis; NSIP – Non-specific interstitial pneumonia

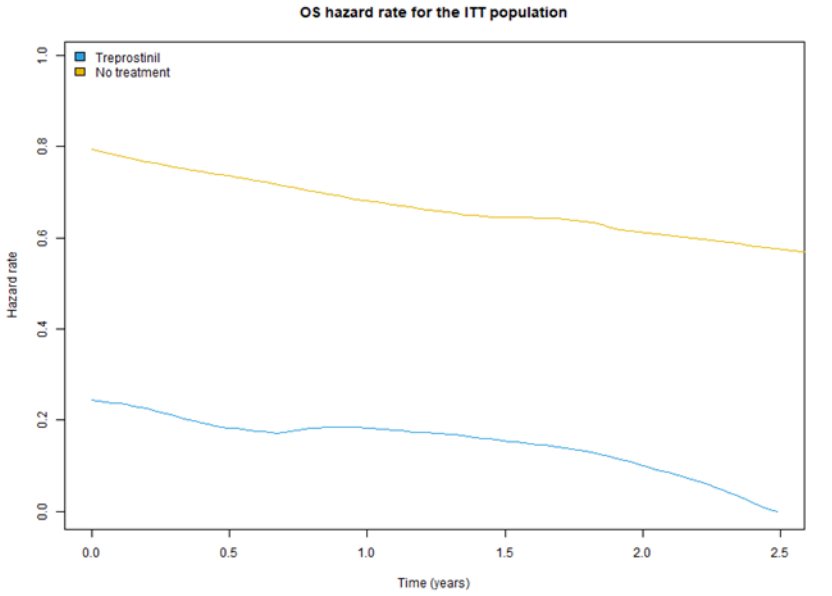
The baseline effect modifiers were generally homogeneous across the INCREASE trials and the patient population treated with no treatment from the Dawes et al. (2022) study.

After applying weights to the INCREASE trial population, most of the baseline characteristics were in a range deemed representative of the PH-ILD patient population. Before matching, baseline characteristics of INCREASE were balanced when compared with those reported in the Dawes et al. study. However, these imbalances are no longer present after matching in the MAIC, indicating good overlap between the IPD and aggregate study which will likely result in stable results.

Assessment of the PH assumptions

To ensure that the PH assumption applies and that a constant HR can describe the difference in OS between inhaled treprostinil and no treatment, the empiric hazards were assessed, and the PH assumptions were tested between inhaled treprostinil and no treatment. Figure 66 presents the hazard rate of OS over time for inhaled treprostinil and no treatment. The hazard rate for no treatment and inhaled treprostinil are parallel and shown to both monotonically decrease over time.

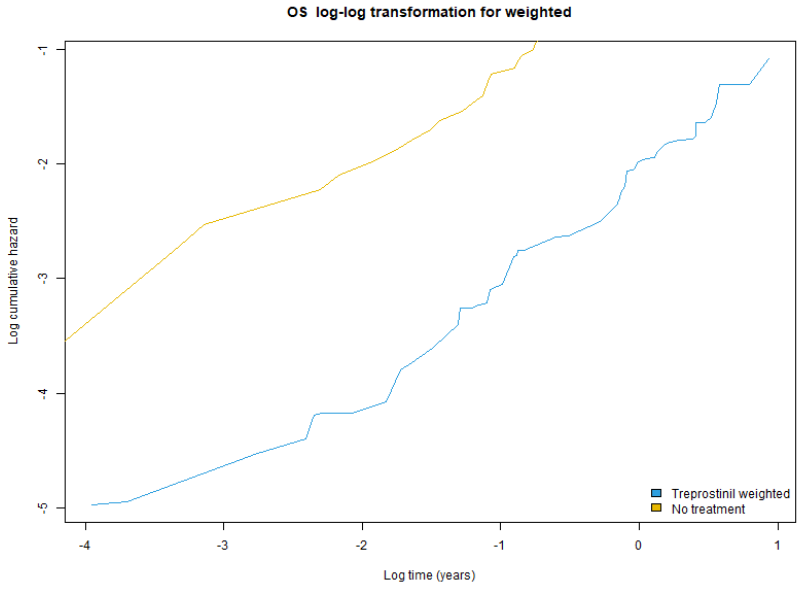
Figure 65: Empiric OS hazard rate for inhaled treprostinil and no treatment in the ITT population – scenario analysis using the full population receiving inhaled treprostinil



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 67 shows the log-log transformation hazards plot for the weighted inhaled treprostinil and no treatment groups, which are characterised by monotonic lines that are relatively parallel and do not cross. This provides evidence that HRs are constant, and the PH assumption does hold.

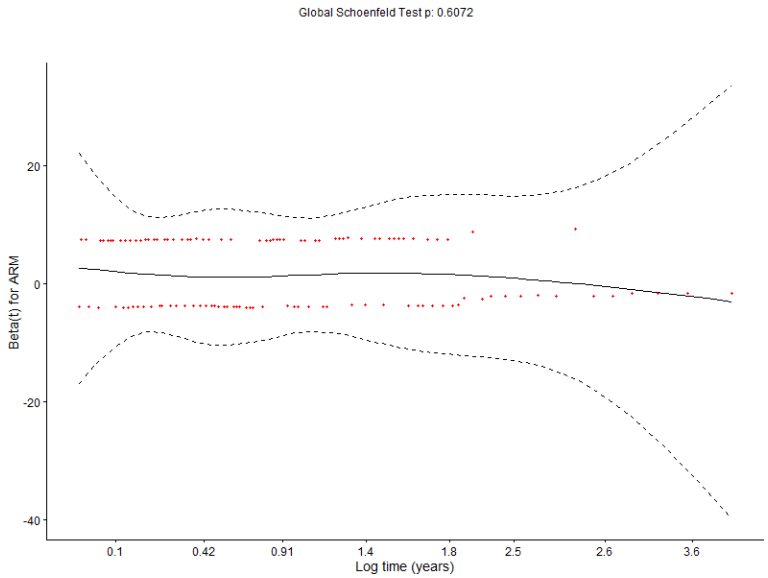
Figure 66: Log-log plot of OS in the ITT population – scenario analysis using the full population receiving inhaled treprostinil



Abbreviations: OS – overall survival

Figure 68 shows the Schoenfeld plot for inhaled treprostinil and no treatment OS. It shows non-random, monotonic linear relationship with a zero slope, giving evidence that the PH assumption holds for the treatment covariate. The PH assumption is further supported by a non-significant relationship between residuals and time (p=0.6072).

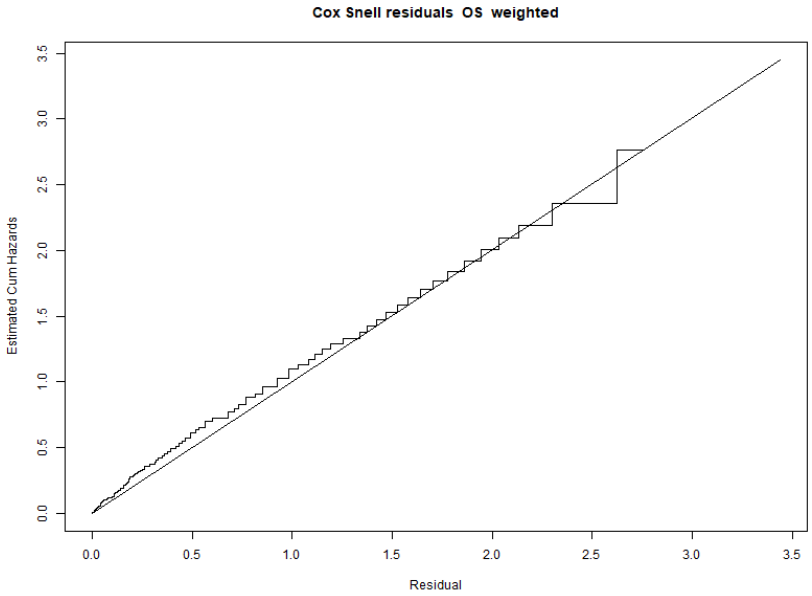
Figure 67: Schoenfeld plot of OS in the ITT population (p=0.6072) – scenario analysis using the full population receiving inhaled treprostinil



Abbreviations: ITT – intention to treat; OS – overall survival

Figure 69 plots the Cox-Snell residuals against the cumulative hazard rate of the Cox-Snell residuals; as the residuals lie on the straight line with zero intercept and unit slope, this provides evidence of no violation of the PH assumption.

Figure 68: Cox-Snell residual plot of OS in the ITT population – scenario analysis using the full population receiving inhaled treprostinil



Abbreviations: ITT – intention to treat; OS – overall survival

Section B: Clarification on cost-effectiveness data

B1. Please complete the table below with all background medications received by more than 1% of patients in INCREASE and INCREASE OLE.

These are provided in Table 2 below.

Table 27. Background medications received by more than 1% patients in INCREASE and INCREASE OLE

Background medication	Inhaled Treprostinil % (n)	BSC % (n)	Required Number of Doses	Per-dose cost
Pirfenidone	11.7% (19)	15.3% (25)	801mg 3 times daily Weekly dose = 801mg x 3 x 7 days = 16,821mg per week	£1.25
Nintedanib	6.7% (11)	11.7% (19)	150mg 2 times daily Weekly dose= 150mg x 2 x 7 days=4,200mg per week	£35.85

B2. Please provide a detailed explanation for the lung transplants observed in some patients receiving treprostinil, considering that no transplants were

reported in the placebo group. Additionally, please clarify whether patients who underwent lung transplants were censored in the overall survival analysis.

There were 2 lung transplants in the inhaled treprostinil group and 0 in the placebo group. This was considered random and does not reflect any treatment difference. An additional analysis with lung transplantation excluded from clinical worsening events was performed and the hazard ratio was smaller than in the analysis with lung transplantation. Patients with lung transplants were not censored in the analysis of overall survival.

B3. Could the company provide further details regarding the parameter titled 'Include off-label PDE5i' as presented in Table 35 (CS, document B), and explain the rationale for its exclusion?

The model parameter 'Include off-label PDE5i' allows the costs of PDE5is to be captured in the model through the related 'Sildenafil treatment cost' inputs on the 'Unit costs' worksheet, covering the cost and dosing of sildenafil and inputs to define proportions of patients who would be incurring the cost of PDE5is in the inhaled treprostinil and BSC arms of the analysis. This option was excluded from the base case analysis on the grounds that patients received PAH therapies, such as PDE5is, were not included in the INCREASE trial and, as outlined in Section 1.3.3.1 of the CS, "[the] effectiveness of PDE5is [...] is reported to be limited and variable, and their off-label use reflects the lack of licensed treatment options for PH-ILD" and that "only a very small proportion of patients with severe PH-ILD may be treated with off-label PAH therapies, such as PDE5is". The option has no effect on clinical parameters or outcomes in the model.

B4. The company stated that adverse event costs were not included in the model, yet costs related to adverse events causing hospitalization appear to be considered. Can the company clarify this discrepancy?

The hospitalisation costs captured in the model are limited to lung disease exacerbations and cardiopulmonary hospitalisations (rows 47 and 48 of the 'Unit costs' worksheet). As these are both components of the clinical worsening composite endpoint that governed CW1 and CW2 partition membership within the model, they

were considered to be indicative of disease progression and therefore distinct from adverse events.

B5. In the company's model, the sums of each column under 'First clinical worsening event distributions' and 'Second clinical worsening event distributions' (columns BN to BY in the 'Intervention trace' and 'Comparator trace' worksheets) appear lower than the corresponding clinical worsening event percentages. Can the company justify using these lower percentages?

The values presented in columns BN to BY of the 'Intervention trace' and 'Comparator trace' sheets represent sums of the half-cycle corrected proportions of the cohort "entering" the CW1 and CW2 partitions multiplied by the proportion of the CW composite attributable to each of its components.

By way of a worked example, for inhaled treprostinil, these values for CW1 are as follows: decrease in 6MWD: 40.0%, decrease in FVC%: 10.0%, cardiopulmonary hospitalisation: 6.7%, acute lung-disease exacerbation: 42.2%, and lung transplant: 1.1%. These proportions are then multiplied by the increase in the proportion of the cohort in each of the CW1 and CW2 partitions in each cycle in which partition membership is increasing. The nature of a partitioned survival model (as distinct from a state transition model) is such that the proportion of the cohort passing through the state cannot be definitively established and the simplifying assumption of the proportion of the cohort that be unequivocally designated as being new to the health partition in each cycle. This approach was conservative from the treprostinil perspective (i.e. it underestimated the total cost of events that were less common in the treprostinil arm).

Given this approach, the total sums presented in columns BN to BY tally with the peak values of patients in the CW1 and CW2 states as presented in columns Q and R of the 'Intervention trace' and 'Comparator trace' sheets.

B6. It appears the unit costs used in the model are from 2021/22. For example, service code 340 in NCCI 2023/24 is £697, while the model uses £195.64. Could the company confirm that all unit costs align with NCCI 2023/24? Please

update the outdated costs accordingly and provide a revised version of the model incorporating these updated pricing.

The value of £195.64 used in the model was calculated as an activity-weighted average of the NCCI 2023/24 Service Code 340 costs based on the number of attendances across all Currency Descriptions falling under the Service Code (https://app.powerbi.com/view?r=eyJrIjoiZGQxYjNkOGUtOTIwMC00N2VjLWEyM2EtYjAzOGMwNWU5ODQ1IiwidCI6IjM3YzM1NGIyLTg1YjAtNDdmNS1iMjIyLTA3YjQ4ZDc3NGVlMyJ9&pageName=ReportSection72fc22d650856c306192). The NCCI h2023/24 data for Service Code 340 are presented in the table below, with the activity-weighted average presented in the total row. An identical approach was adopted for Service Codes 320 and 410.

Department Code	Department Description	Service Code	Service Description	Currency Code	Currency Description	Number of attendances	Cost	National average unit cost	Number of submissions
CL	Consultant Led	340	Respiratory Medicine Service	WF02B	Multiprofessional Non-Admitted Face-to-Face Attendance, First	16,558	£5,625,611	£340	71
NCL	Non Consultant Led	340	Respiratory Medicine Service	WF02B	Multiprofessional Non-Admitted Face-to-Face Attendance, First	2,025	£790,888	£391	23
CL	Consultant Led	340	Respiratory Medicine Service	WF02A	Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	29,031	£9,050,920	£312	73
NCL	Non Consultant Led	340	Respiratory Medicine Service	WF02A	Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up	4,681	£1,287,232	£275	32
CL	Consultant Led	340	Respiratory Medicine Service	WF02D	Multiprofessional Non-Admitted Non-Face-to-Face Attendance, First	2,763	£362,256	£131	44
NCL	Non Consultant Led	340	Respiratory Medicine Service	WF02D	Multiprofessional Non-Admitted Non-Face-to-Face Attendance, First	330	£58,733	£178	6
CL	Consultant Led	340	Respiratory Medicine Service	WF02C	Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up	4,890	£955,649	£195	51
NCL	Non Consultant Led	340	Respiratory Medicine Service	WF02C	Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up	4,423	£589,752	£133	14
CL	Consultant Led	340	Respiratory Medicine Service	WF01B	Non-Admitted Face-to-Face Attendance, First	342,172	£95,190,335	£278	123
NCL	Non Consultant Led	340	Respiratory Medicine Service	WF01B	Non-Admitted Face-to-Face Attendance, First	93,842	£17,212,674	£183	95
CL	Consultant Led	340	Respiratory Medicine Service	WF01A	Non-Admitted Face-to-Face Attendance, Follow-up	555,650	£112,566,033	£203	123
NCL	Non Consultant Led	340	Respiratory Medicine Service	WF01A	Non-Admitted Face-to-Face Attendance, Follow-up	159,745	£24,482,463	£153	93
CL	Consultant Led	340	Respiratory Medicine Service	WF01D	Non-Admitted Non-Face-to-Face Attendance, First	118,662	£19,376,254	£163	111
NCL	Non Consultant Led	340	Respiratory Medicine Service	WF01D	Non-Admitted Non-Face-to-Face Attendance, First	44,698	£4,588,600	£103	73
CL	Consultant Led	340	Respiratory Medicine Service	WF01C	Non-Admitted Non-Face-to-Face Attendance, Follow-up	305,905	£48,259,965	£158	113
NCL	Non Consultant Led	340	Respiratory Medicine Service	WF01C	Non-Admitted Non-Face-to-Face Attendance, Follow-up	119,407	£12,682,090	£106	82
Total						1,804,782	£353,079,456	£196	124

We have now incorporated the NCCI 2023/24 data directly into the model (in the "NHS NCC 2023-24" worksheet) and linked the corresponding input cells to the activity-weighted averages directly.

B7. Please provide further justification for excluding SGRQ at week 108, specifically regarding the statement: "*a lack of statistical significance in the difference in SGRQ between health states at week 108, which supported the exclusion of data from this timepoint*". Additionally, please do the analysis including it.

The number of patients with data available for SQRQ analysis at week 108 was very low, with only 14 patients available to inform the CWF health state utility value, and only 17 patients available to inform the CW1 health state utility value. These low patient numbers were the primary reason for the exclusion of SGRQ data at the week 108 timepoint, with the exclusion further supported by the lack of a significant difference between states. Given the serious nature of the clinical worsening events

that govern the difference between the health states, the lack of any significant difference in the health state utility values at week 108 suggests that the data are not reliable or reflective of the clinical reality. Therefore, an analysis including the SGRQ at week 108 has not been provided.

B8. In the CS, document B, the total number of patients in Table 13 is 280, but Table 7 shows 277 patients with SGRQ data for both arms. Can the company clarify this discrepancy?

Table 7 in the CS included patients with both a baseline and a week-16 SGRQ measurement, whereas Table 13 only required patients to have a week 16 SGRQ measurement. A version of Table 13 aligned with the inclusion criteria for Table 7 is presented below:

Table 28: SGRQ scores – INCREASE 16-week trial

	No event	One event	Two events	Three events	≥ Four events
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGRQ: Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: N, number; SD, standard deviation; SGRQ, Saint George's Respiratory Questionnaire.

B9. There appears to be a discrepancy between sections 3.4.1 and 3.4.6 regarding the inclusion of adverse events in SGRQ. Section 3.4.1 states hospitalization effects are not included, while Section 3.4.6 says they are. Please clarify whether adverse events leading to hospitalization are included for both arms?

Adverse events leading to hospitalisation are not included as separate events in the model. Lung exacerbation and cardiopulmonary hospitalisations are included in the clinical worsening event composite endpoint that forms the basis of each health state in the model.

Serious adverse events reported in the INCREASE trial (e.g., acute respiratory failure) may result from a lung exacerbation and lead to hospitalisation. Therefore, to avoid double counting, adverse events were not included as separate events in the model. In section 3.4.1, it is highlighted that the SGRQ may not fully reflect the

impact of clinical worsening events, such as exacerbations or cardiopulmonary hospitalisations, on patients' HRQoL as patients will not complete the questionnaire in hospital. Therefore, the SGRQ may provide a more conservative perspective of the impact of inhaled treprostinil on HRQoL, given the reduction in clinical worsening events vs patients receiving placebo.

B10. Can the company confirm that the method (General Population, EQ-5D = 0.9508566 + 0.0212126male − 0.0002587age − 0.0000332*age^2) introduced by Ara and Brazier (2010) was used to determine the EQ-5D-3L population norm?

The method used to determine the EQ-5D-3L population norm was that proposed in the 2022 NICE DSU report "Estimating EQ-5D by Age and Sex for the UK" (https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d) and specifically using the values reported in accompanying Excel file "Expected EQ-5D-3L by age and sex and covariance matrices of the models using the HSE 2014 dataset".[16]

We have also incorporated functionality into the model to switch to use the proposed 2010 Ara and Brazier method. The option is included in the drop-down menu titled "Population norm calculation approach" on the "Quality of life" worksheet.

B11. Please clarify the text in section 3.2.3.7 which describes how censoring death events would overestimate the frequency of clinical worsening events.

As death and the other clinical worsening events are competing risks (i.e. death precludes any further clinical worsening events) and death is likely to be preceded by clinical worsening, censoring death would violate the assumption of noninformative censoring. Censoring death events would result in an overestimation of the nonfatal components of the clinical worsening event.

B12. Please clarify the inconsistencies between the list of clinical worsening events in Section 3.2.3.7 and Figure 5. Please confirm whether all clinical worsening items mentioned in Section 3.2.3.7 (e.g., FVC% decline, exacerbation) were originally part of the INCREASE trial definition?

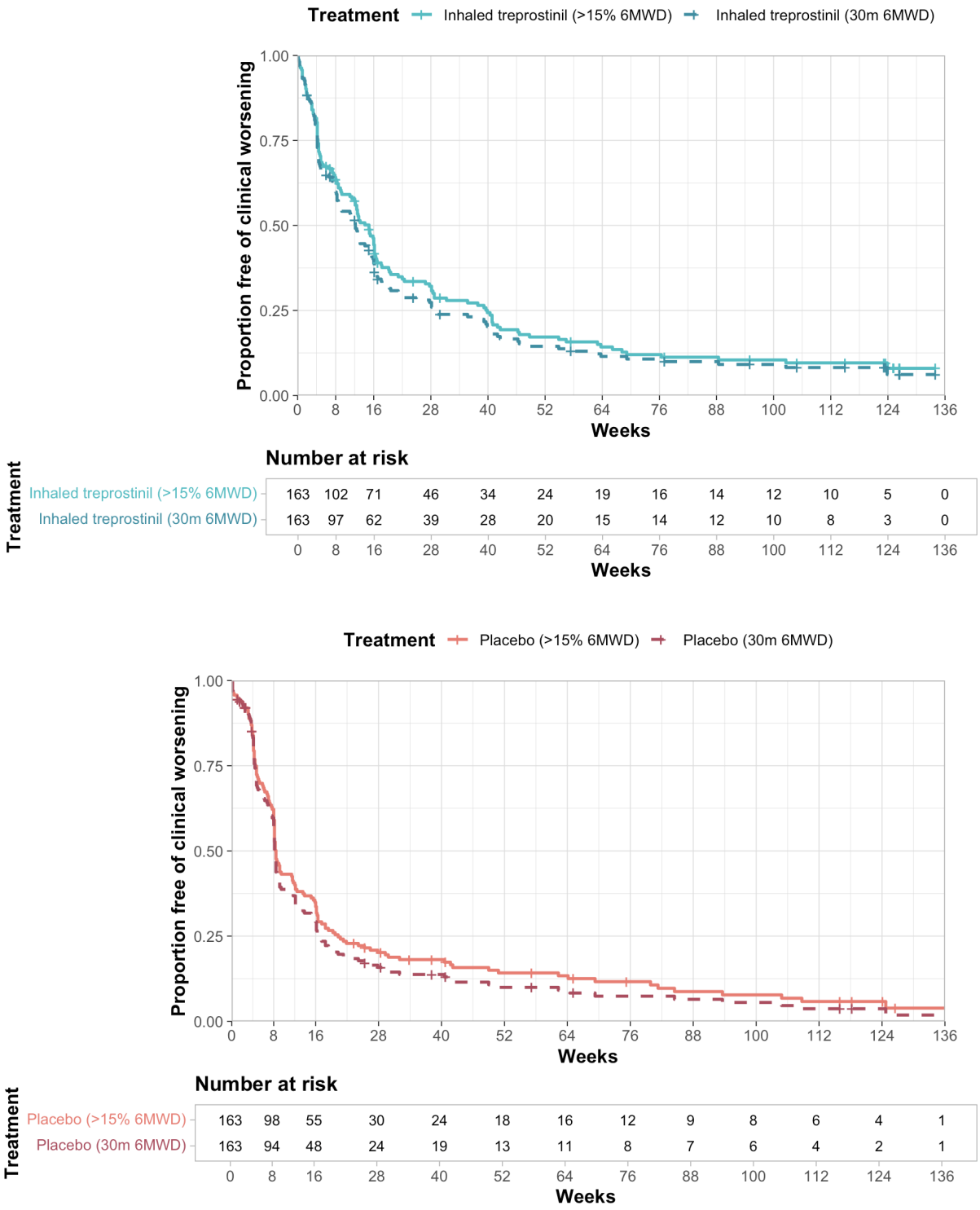
The differences between the clinical worsening events in the original INCREASE publication (Waxman *et al*. 2021) and the model are detailed in Table 14 of the CS, in which it was noted that "Fall in FVC% of ≥10% from baseline" and "Acute lung-

disease exacerbation" were not included in the Waxman *et al.* publication, although both were recorded in the trial. The rationale for their inclusion in the model is detailed in Section 3.2.3.7 of the CS, namely that, during the advisory boards, clinical experts noted that the inclusion of a decrease in FVC% was important to capture the impact of treatment on underlying ILD.

B13. Please can the company provide a revised model with the functionality to apply a 30-meter decrease from baseline in 6MWD as the threshold for clinical worsening?

We have re-run the clinical worsening analyses and derived new parametric models using a 30-meter threshold for decrease from baseline 6MWD rather than a 15% decrease. The model includes these additional model parameters for CW1 and CW2 based on INCREASE alone and the combined INCREASE and INCREASE OLE dataset. The parameters based on the 30-meter decrease endpoint can be utilised by checking the "Use composite with 30m 6MWD" checkbox on the "CW1 Settings" and "CW2 Settings" worksheets. KM curves showing the comparison of the effect on the first clinical worsening event (CW1) are depicted in the figures below.

Figure 69: Kaplan-Meier curves showing the differences between the first clinical worsening composite event based on a 30m decrease in 6MWD in place of a 15% decrease in 6MWD



New parametric models of CW1 have been developed using the composite endpoint with the 30m decrease in 6MWD. The CW1 model fits for the inhaled treprostinil arm

(from INCREASE and INCREASE OLE) are depicted in the figure below (in red) superimposed over the KM curves and 95% confidence intervals (in black). Goodness of fit criteria (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) for the revised inhaled treprostinil CW1 models are presented in the table below.

Figure 70: Parametric model fits for the revised first clinical worsening models based on a clinical worsening composite including 30m decrease in 6MWD in place of a 15% decrease in 6MWD in the inhaled treprostinil arm

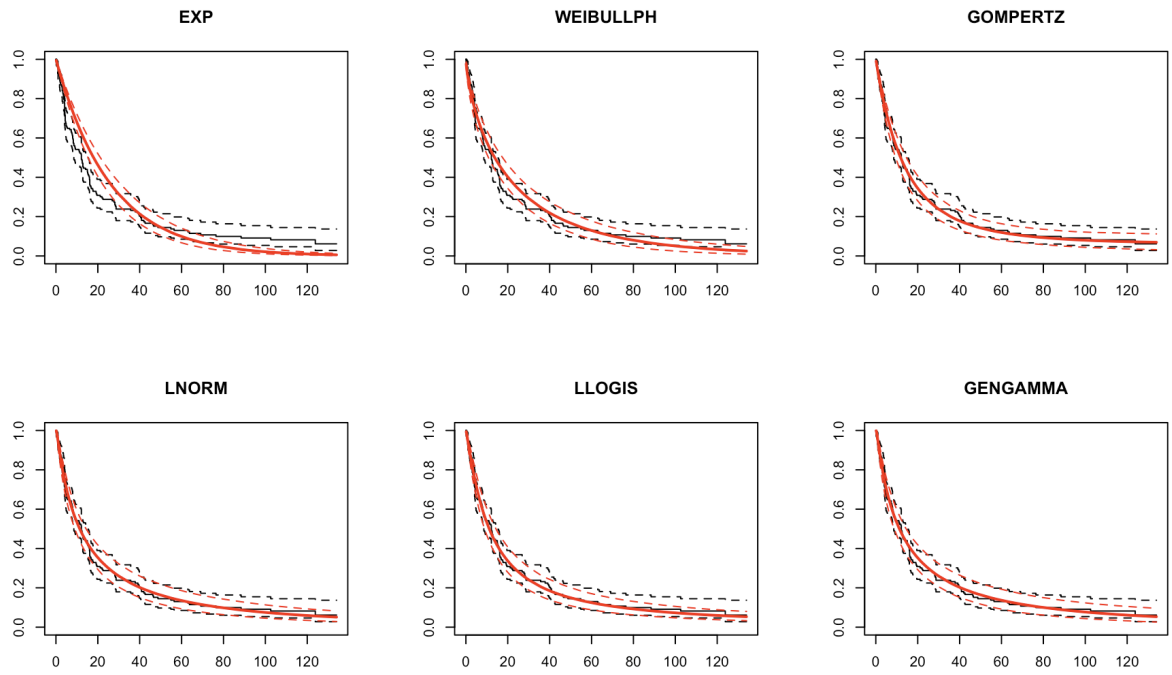


Table 29. Goodness-of-fit criteria for the revised first clinical worsening models based on a clinical worsening composite including 30m decrease in 6MWD in place of a 15% decrease in 6MWD in the inhaled treprostinil arm

Survival distribution	AIC	BIC
Exponential	1212.267	1224.642
Weibull	1187.891	1203.36
Gompertz	1170.689	1186.158
Log-normal	1169.416	1184.885
Log-logistic	**1168.705**	**1184.174**
Generalised gamma	1171.377	1189.94

Bold denotes best model fit by AIC and BIC.

The corresponding model fits for the placebo arm are depicted in the figure below (in red), again superimposed over the KM curves and 95% confidence intervals (in black). Goodness of fit criteria (Akaike Information Criterion and Bayesian Information Criterion) for the revised placebo CW1 models are presented in the table below.3

Figure 71: Parametric model fits for the revised first clinical worsening models based on a clinical worsening composite including 30m decrease in 6MWD in place of a 15% decrease in 6MWD in the placebo arm

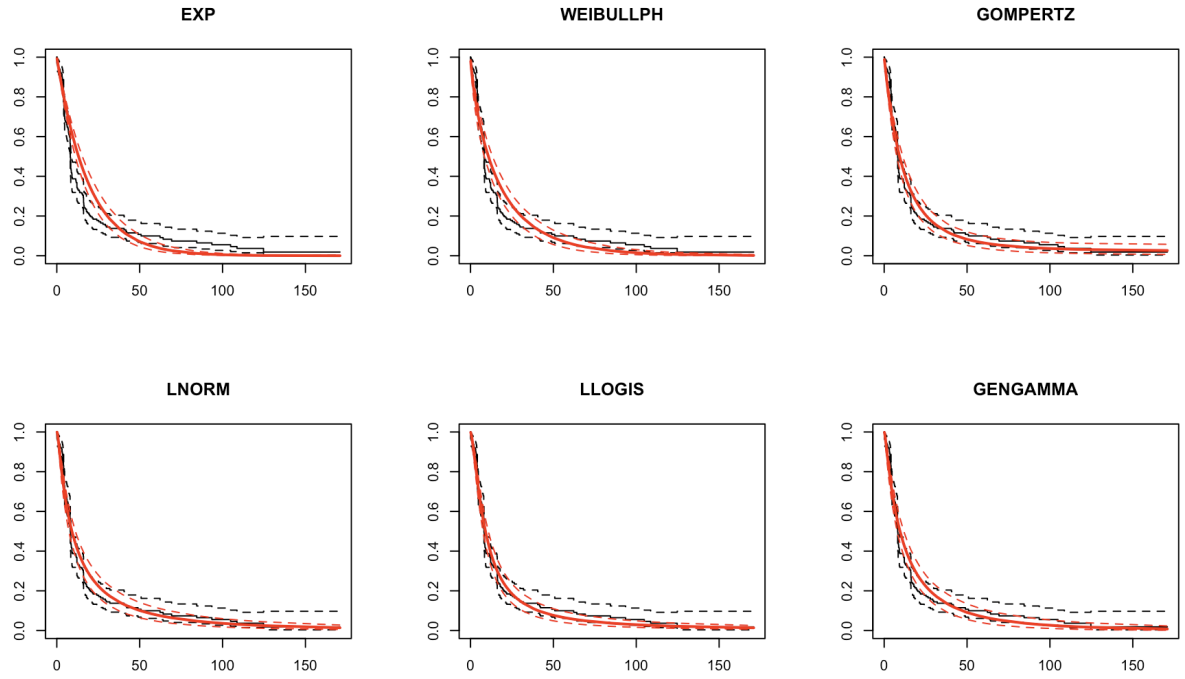


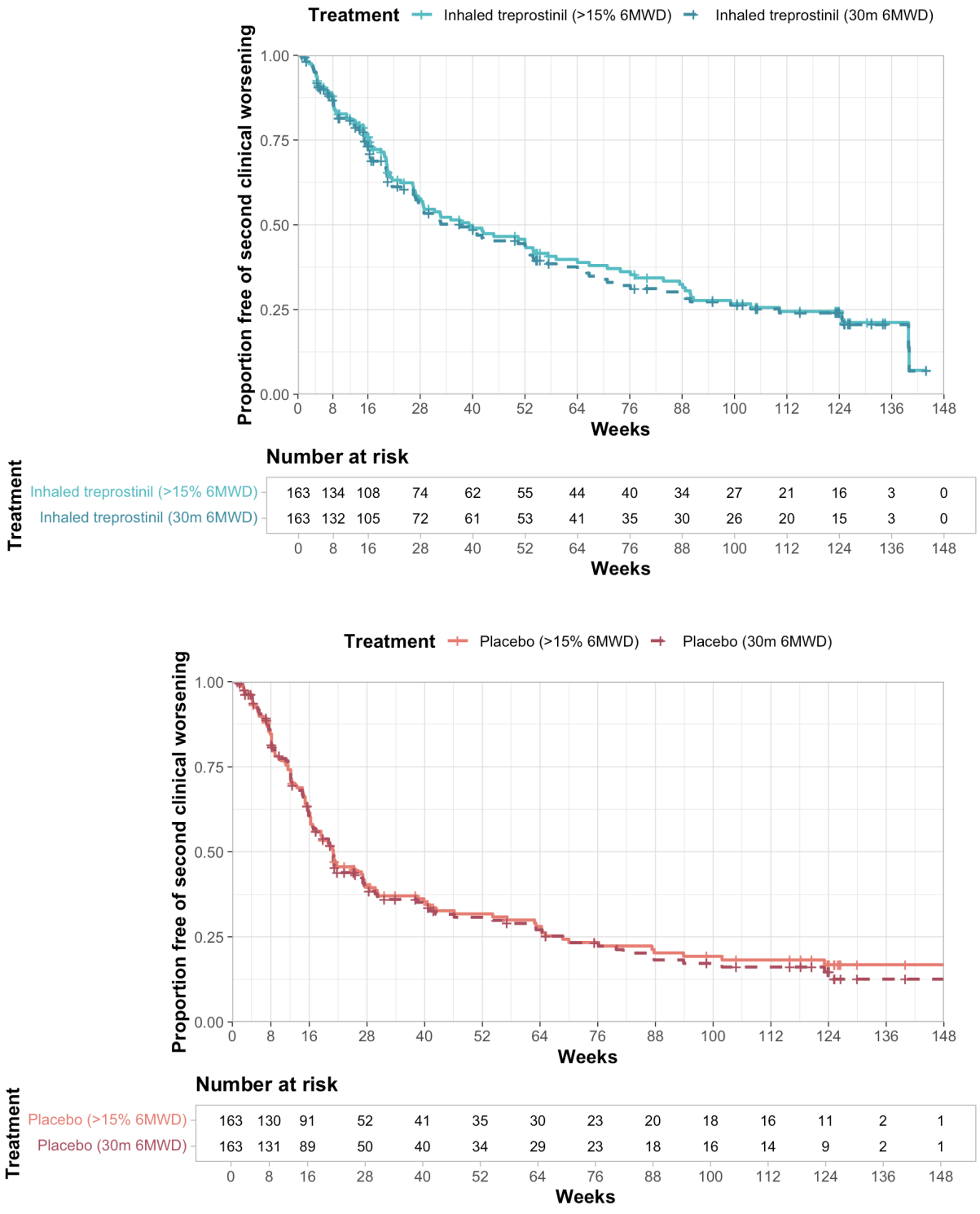
Table 30. Goodness-of-fit criteria for the revised first clinical worsening models based on a clinical worsening composite including 30m decrease in 6MWD in place of a 15% decrease in 6MWD in the placebo arm

Survival distribution	AIC	BIC
Exponential	1181.612	1193.987
Weibull	1169.69	1185.159
Gompertz	1147.377	1162.846
Log-normal	1153.367	1168.836
Log-logistic	**1135.3**	**1150.769**
Generalised gamma	1153.262	1171.824

Bold denotes best model fit by AIC and BIC.

KM curves showing the comparison of the effect on the second clinical worsening event (CW2) are depicted in the figures below.

Figure 72: Kaplan-Meier curves showing the differences between the second clinical worsening composite event based on a 30m decrease in 6MWD in place of a 15% decrease in 6MWD



New parametric models of CW2 have also been developed using the composite endpoint with the 30m decrease in 6MWD. The CW2 model fits for the inhaled treprostinil arm (again from INCREASE and INCREASE OLE) are depicted in the figure below (in red) superimposed over the KM curves and 95% confidence intervals (in black). Goodness of fit criteria (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) for the revised inhaled treprostinil CW2 models are presented in the table below.

Figure 73: Parametric model fits for the revised second clinical worsening models based on a clinical worsening composite including 30m decrease in 6MWD in place of a 15% decrease in 6MWD in the inhaled treprostinil arm

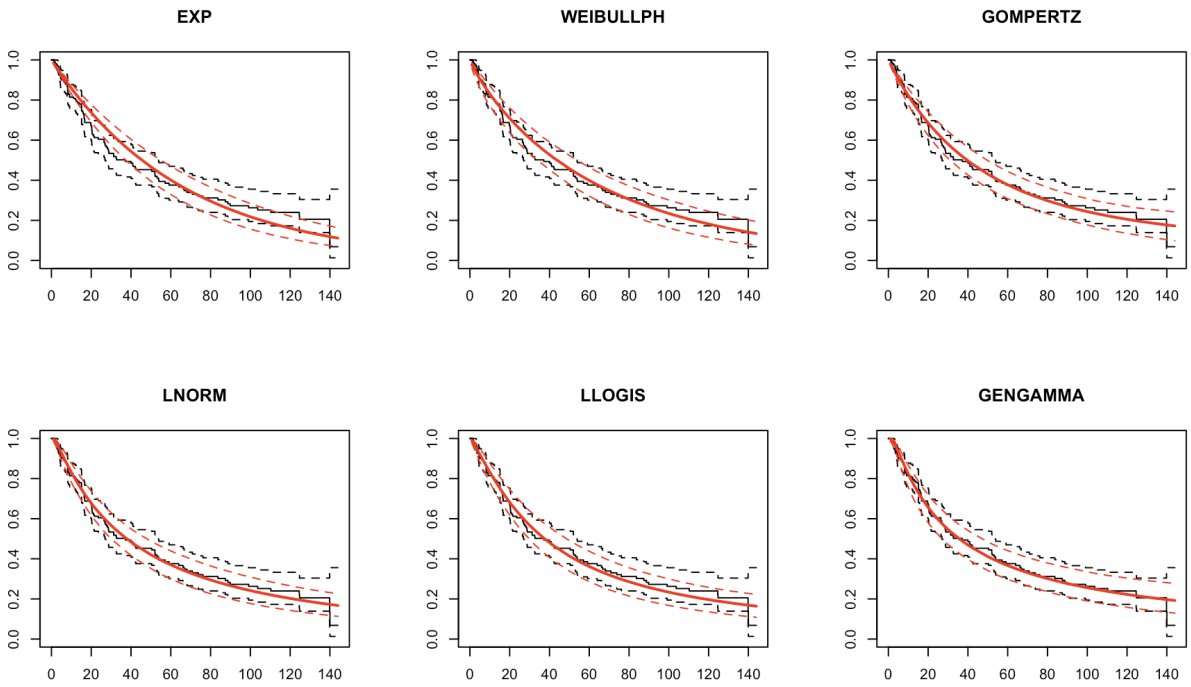


Table 31. Goodness-of-fit criteria for the revised second clinical worsening models based on a clinical worsening composite including 30m decrease in 6MWD in place of a 15% decrease in 6MWD in the inhaled treprostinil arm

Survival distribution	AIC	BIC
Exponential	1084.173	1096.548
Weibull	1083.953	1099.422
Gompertz	1079.744	1095.213
Log-normal	**1070.995**	**1086.464**
Log-logistic	1076.052	1091.521

Survival distribution	AIC	BIC
Generalised gamma	1071.283	1089.846

Bold denotes best model fit by AIC and BIC.

The corresponding model fits for the placebo arm are depicted in the figure below (in red), again superimposed over the KM curves and 95% confidence intervals (in black). Goodness of fit criteria (Akaike Information Criterion and Bayesian Information Criterion) for the revised placebo CW2 models are presented in the table below.

Figure 74: Parametric model fits for the revised second clinical worsening models based on a clinical worsening composite including 30m decrease in 6MWD in place of a 15% decrease in 6MWD in the placebo arm

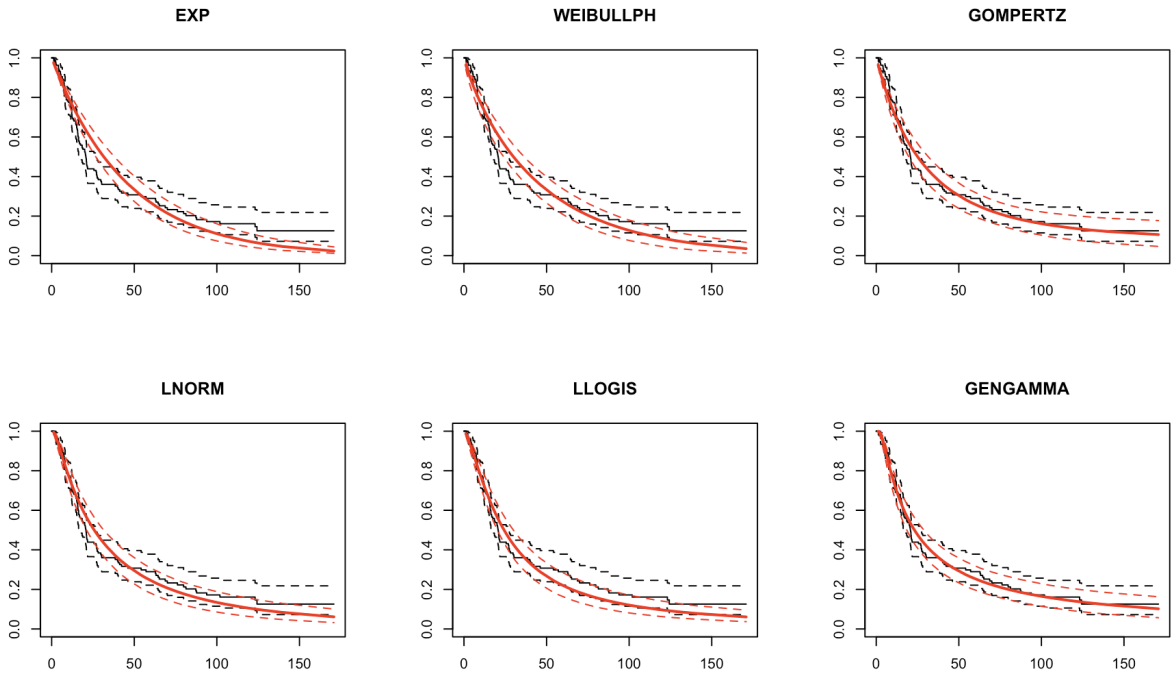


Table 32. Goodness-of-fit criteria for the revised second clinical worsening models based on a clinical worsening composite including 30m decrease in 6MWD in place of a 15% decrease in 6MWD in the placebo arm

Survival distribution	AIC	BIC
Exponential	1133.803	1146.178
Weibull	1133.671	1149.140
Gompertz	1120.092	1135.561
Log-normal	1106.909	1122.378

Survival distribution	AIC	BIC
Log-logistic	1108.839	1124.308
Generalised gamma	**1101.650**	**1120.212**

Bold denotes best model fit by AIC and BIC.

B14. Based on the company's submission, 40 (24.5%) patients in the treprostinil arm and 38 (23.3%) in the placebo arm discontinued study treatment, with AEs being the most frequent reason (9.8% and 8.0%, respectively). Please can the company provide complete information on reasons for treatment discontinuation and consider whether these may introduce bias, particularly regarding their impact on HRQoL?

Further information on the reasons for treatment discontinuation was not collected in the clinical database so unfortunately this cannot be provided. However, it is not expected that treatment discontinuation would introduce bias. The rates of AEs reported across the inhaled treprostinil and placebo arms were comparable in the INCREASE trial. The majority of AEs were mild and therefore were not expected to have a meaningful impact on HRQoL. Therefore, it is not expected that treatment discontinuation would introduce bias.

B15. Based on Table 7, the SGRQ was completed by 143 patients in the treprostinil arm and 134 in the placebo arm, out of a total of 163 patients. Could the company clarify why the questionnaire was not completed by all patients? Additionally, please provide the characteristics of those who did not complete it in both arms. Finally, could the company confirm whether all patients who completed the SGRQ at baseline and subsequently crossed over to the OLE phase also completed the questionnaire at OLE baseline and at week 16?

Table 7 showed that 143 patients in the treprostinil arm and 134 in placebo arm completed the SGRQ questionnaire at both baseline and Week 16 visits. The table footnote indicated "Only subjects with both Baseline and Week 16 SGRQ measure are included." If all patients with all SGRQ measurements are included in the table, there would be 161 patients (2 with missing) in treprostinil arm and 160 patients (3 with missing) in placebo arm with baseline SGRQ measures. The 5 patients with missing SGRQ measures at baseline were due to a protocol compliance issue.

There were less subjects with SGRQ measures at Week 16 because of early terminations.

The characteristics for the patients who did not complete the SGRQ and information on who completed the SGRQ in relation to those who entered the OLE are not available.

B16. PRIORITY: Please clearly describe the data used to inform each OS, CW and TTD population and hazard ratio featured in the economic model (e.g. source, sample size, start of follow-up). If not already included, please add the functionality to model these outcomes for the company's MAIC populations, pre and post-weighting.

We have included subsections pertaining to each source of modelled data in the below. The section headings describe the provenance of the data, and each section contains KM curves annotated with both number at risk and cumulative event tables, which illustrate the number of patients at-risk at the start of follow-up (i.e. the sample size) and the number of patients having experienced an event at the final time point.

Figure 75: Kaplan-Meier for overall survival - BSC "Crossover Analysis" and Inhaled Treprostinil "INCREASE – OLE: Parametric" (INCREASE and INCREASE OLE)

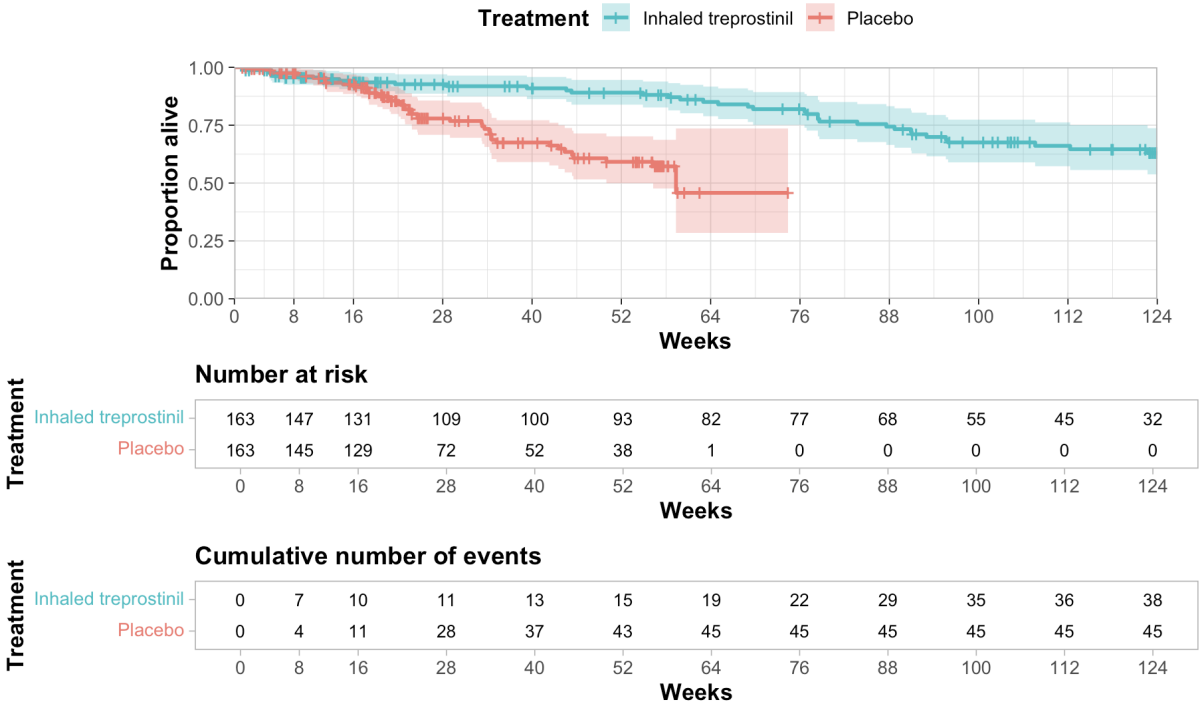


Figure 76: Kaplan-Meier for overall survival - "INCREASE – 16 Week: Parametric" and Inhaled Treprostinil "INCREASE – 16 Week: Parametric" (INCREASE)69

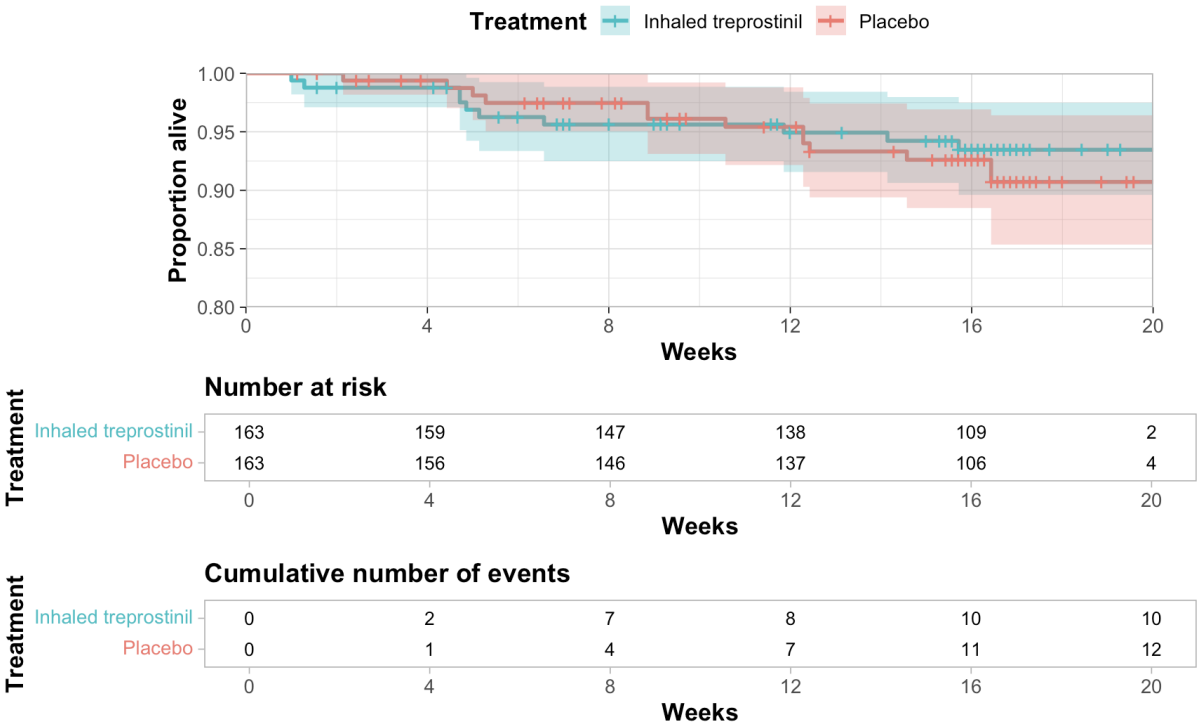
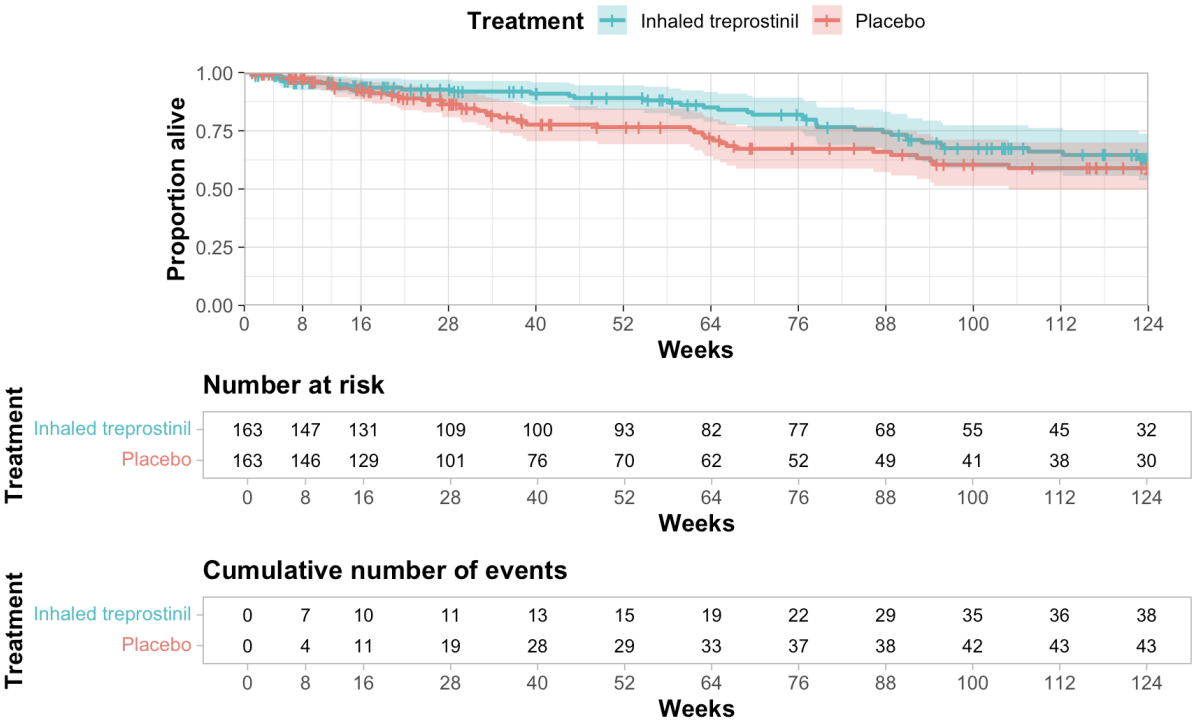
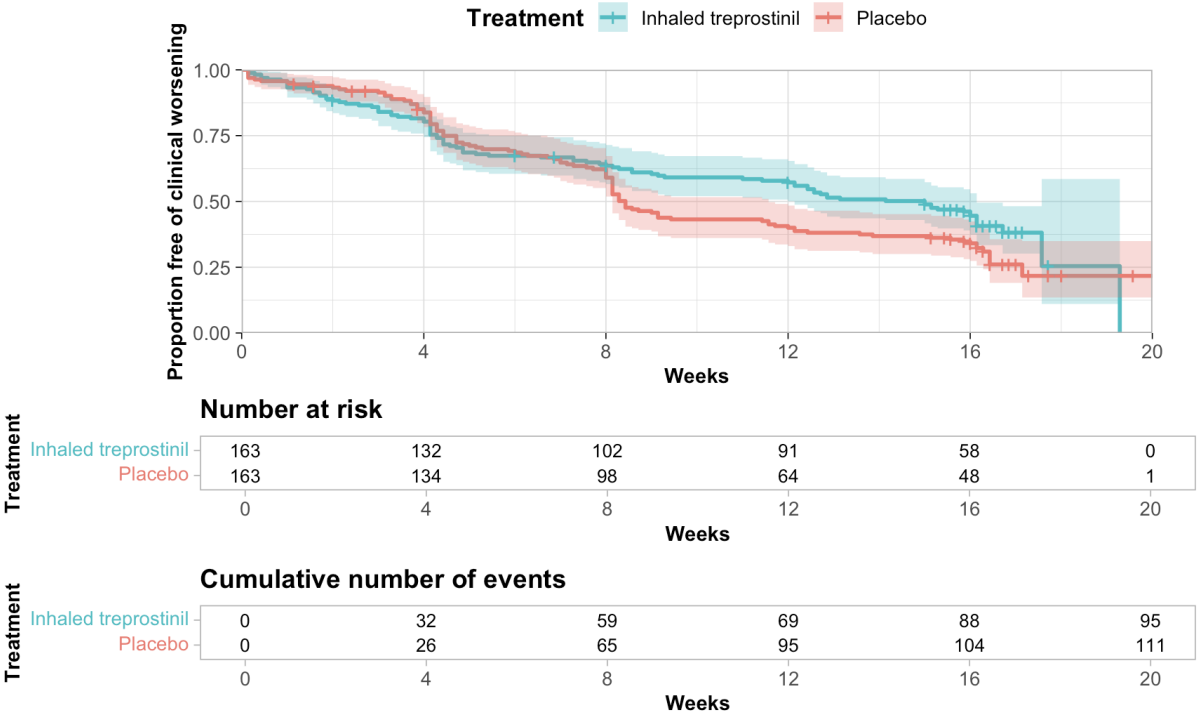


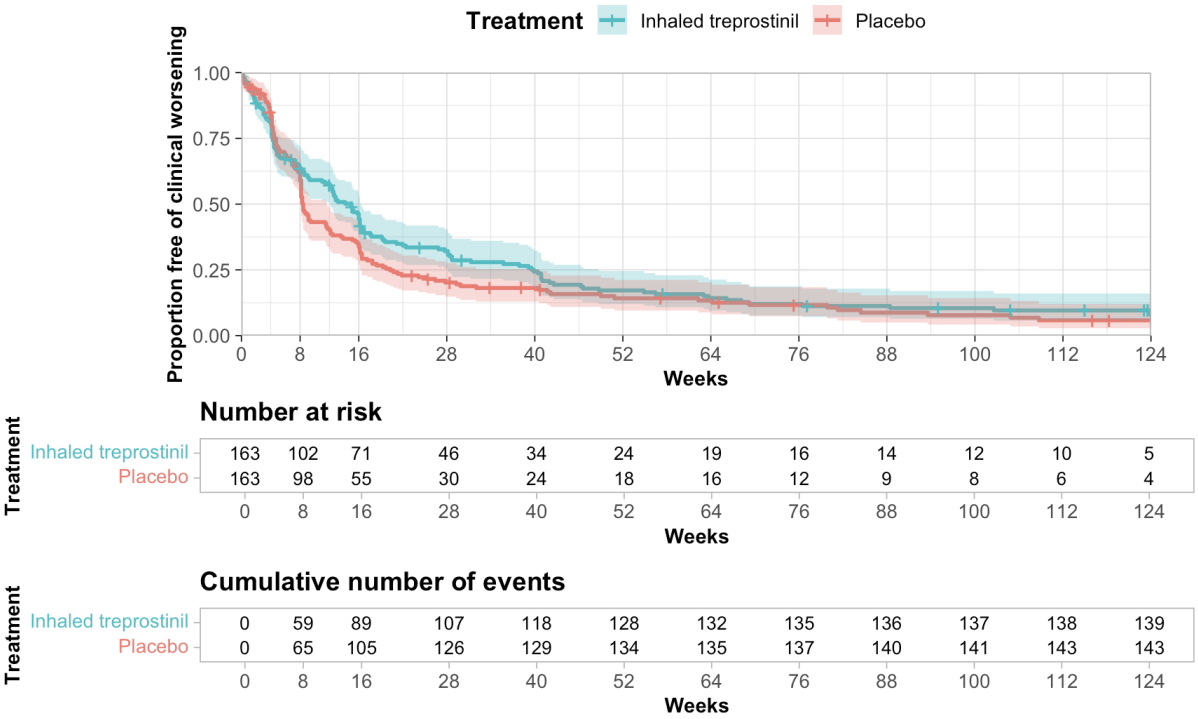
Figure 70: Kaplan-Meier for overall survival - BSC "INCREASE – OLE: Parametric" and Inhaled Treprostinil "INCREASE – OLE: Parametric" (INCREASE and INCREASE OLE)



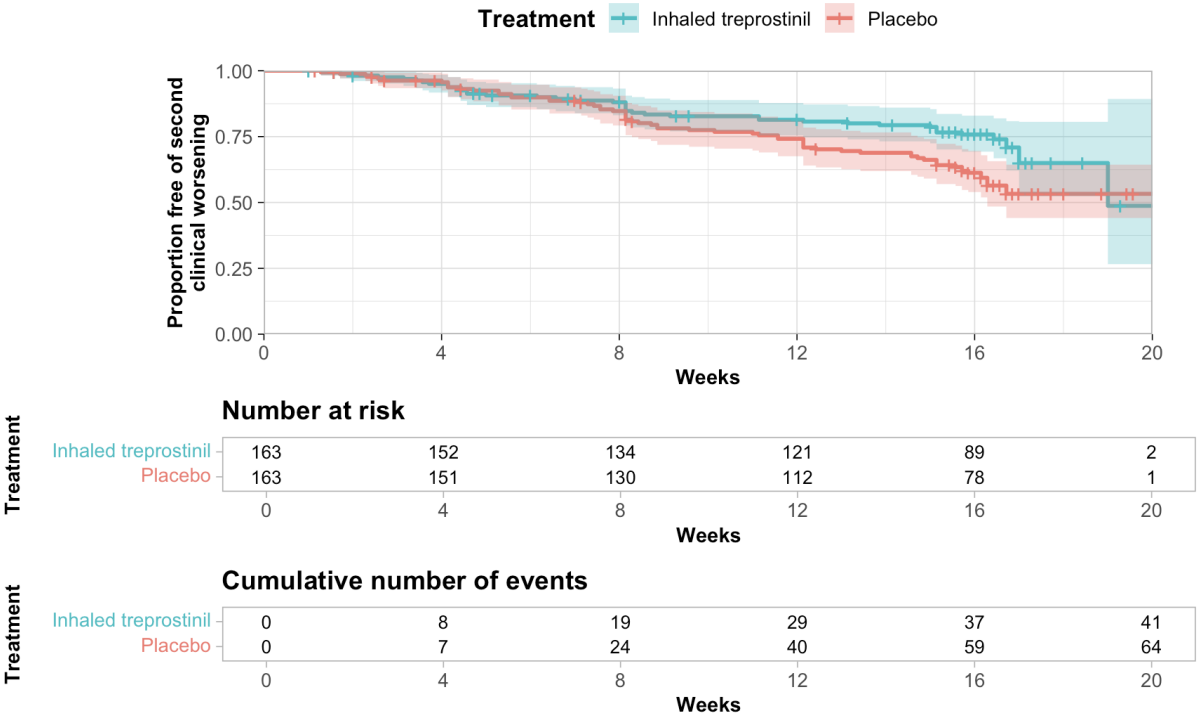
CW1: BSC "INCREASE – 16 Week: Parametric" and Inhaled Treprostinil "INCREASE – 16 Week: Parametric" (INCREASE)



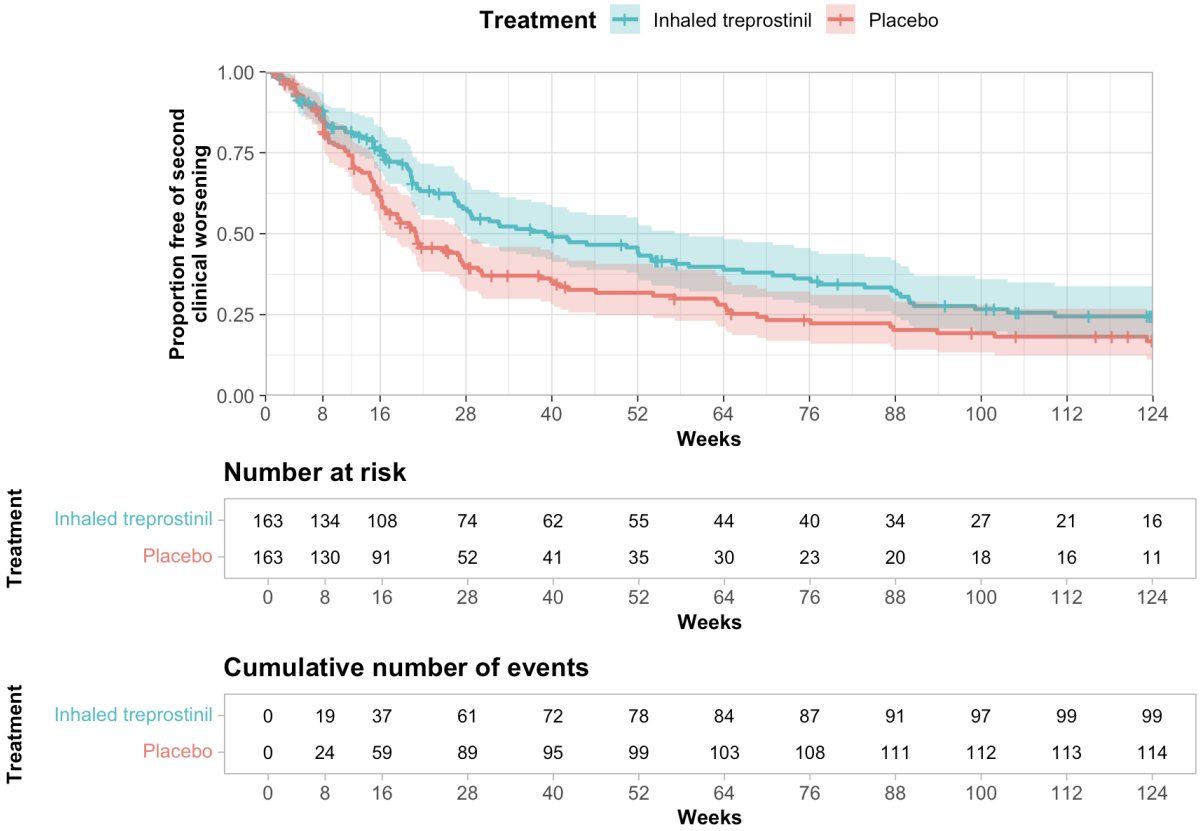
CW1: BSC "INCREASE – OLE: Parametric" and Inhaled Treprostinil "INCREASE – OLE: Parametric" (INCREASE and INCREASE OLE)



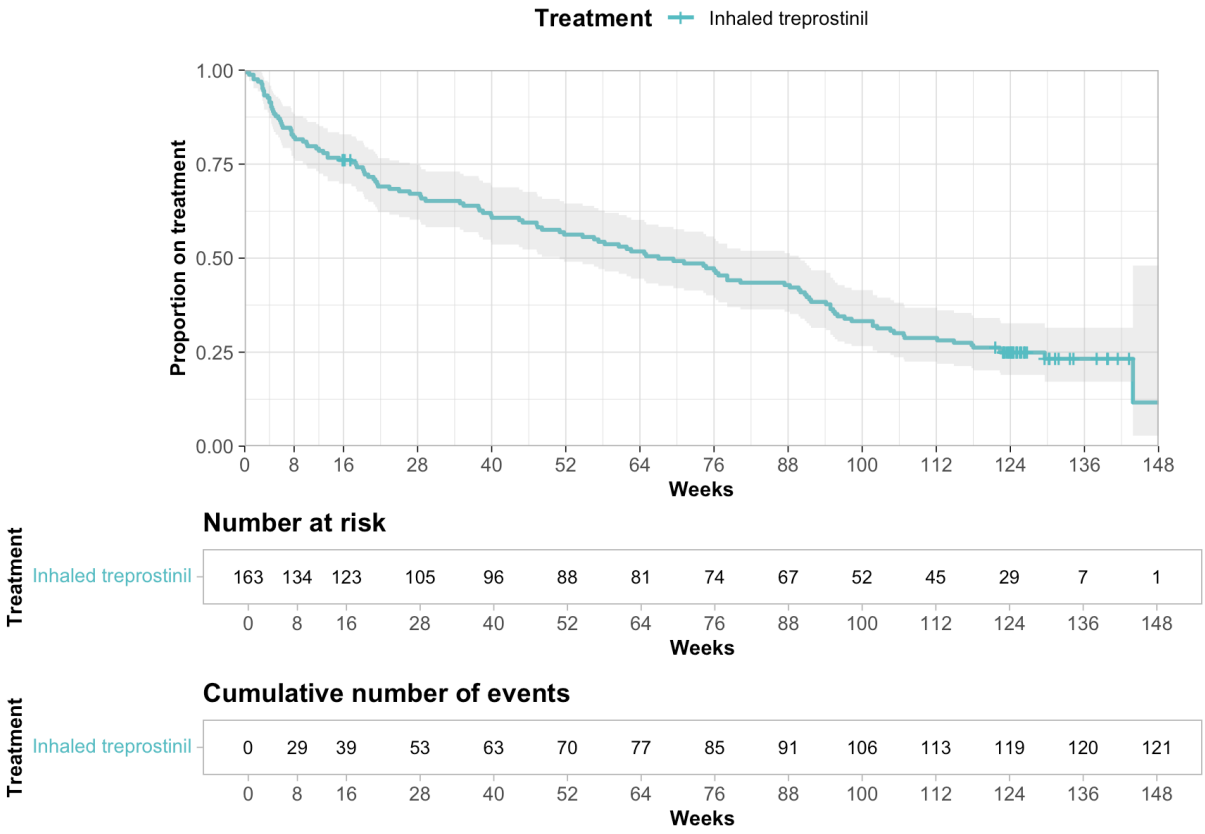
CW2: BSC "INCREASE – 16 Week: Parametric" and Inhaled Treprostinil "INCREASE – 16 Week: Parametric" (INCREASE)



CW2: BSC "INCREASE – OLE: Parametric" and Inhaled Treprostinil "INCREASE – OLE: Parametric" (INCREASE and INCREASE OLE)

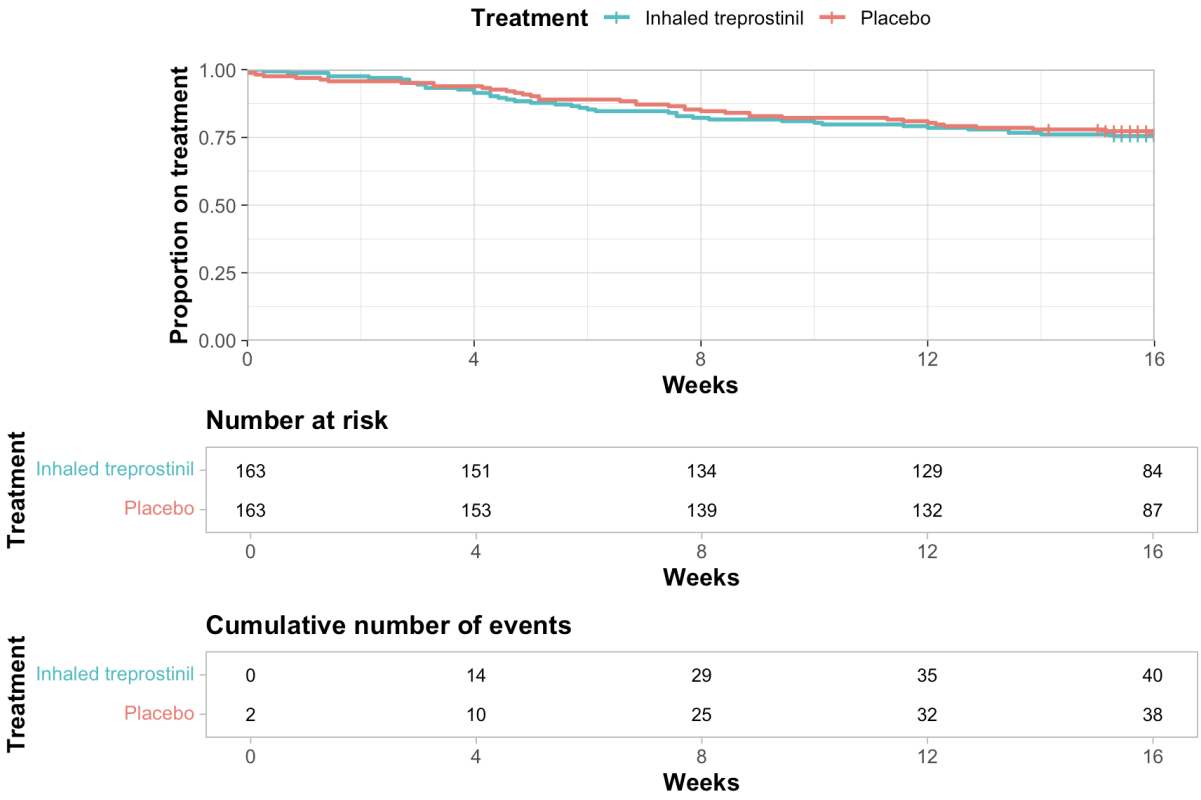


TTD: Inhaled Treprostinil "INCREASE – OLE: Parametric" (INCREASE and INCREASE OLE)



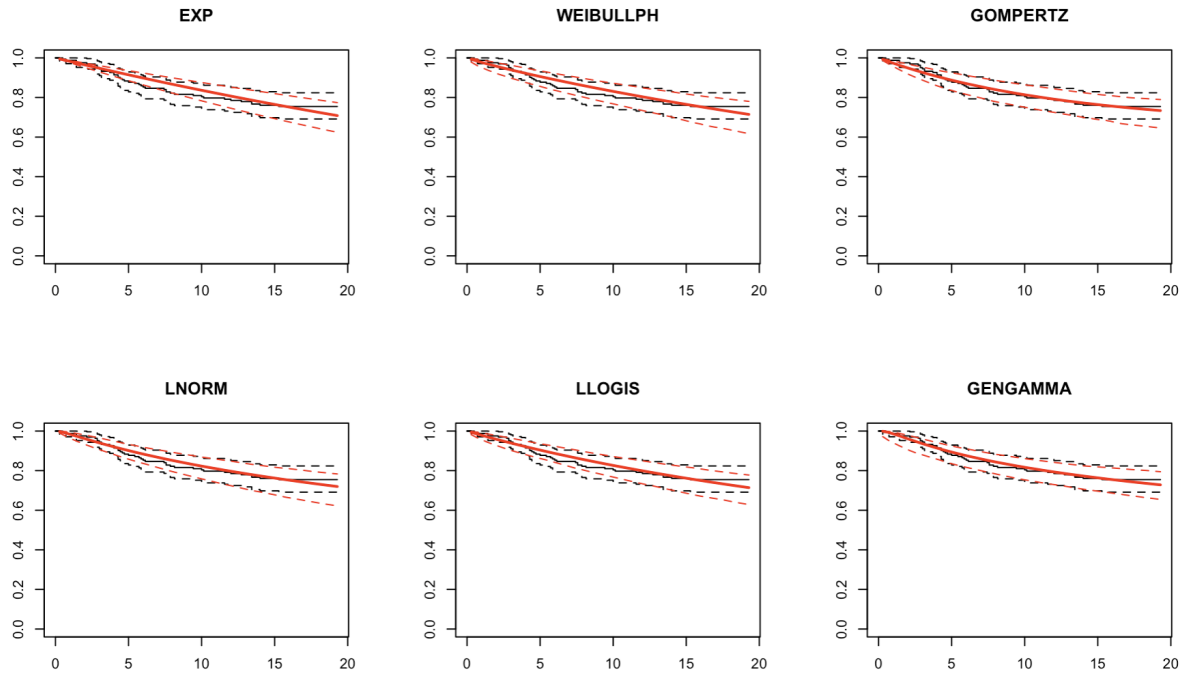
B17. Please fit and implement CW, OS and TTD models fitted only to people who received treprostinil during the randomised period of INCREASE.

The models for OS and CW were already included the submitted cost-utility model; the parameters are included in the INCREASE OS worksheet (range D33:F88) for OS, the INCREASE CW1 worksheet (range D33:F88) for the first clinical worsening event, and the INCREASE CW2 worksheet (range D33:F88) for the second clinical worsening event. A TTD model covering only the randomised period of INCREASE had not been developed at the time of submission as the combined INCREASE and INCREASE OLE data were substantially more mature; however, we have now developed TTD models based exclusively on data from the randomised period of INCREASE. The KM curves showing the proportion of patients remaining on treatment are presented below.



Parametric model fits to the randomised period of INCREASE along with goodness-of-fit criteria are presented below.

Parametric model fits to treatment discontinuation data from the inhaled treprostinil arm during the randomised period of INCREASE



Goodness of fit criteria (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) for the inhaled treprostinil TTD models based on the randomised period of INCREASE are presented in the table below.

Table 33. Goodness-of-fit criteria for the TTD models based on the inhaled treprostinil arm during the randomised period of INCREASE

Survival distribution	AIC	BIC
Exponential	404.0026	**407.0964**
Weibull	405.5656	411.7531
Gompertz	402.5852	408.7727
Log-normal	**401.9576**	408.1451
Log-logistic	404.3758	410.5633
Generalised gamma	402.8795	412.1607

Bold denotes best model fit by the respective goodness-of-fit criterion.

Figure 71. Parametric model fits to treatment discontinuation data from the placebo arm during the randomised period of INCREASE

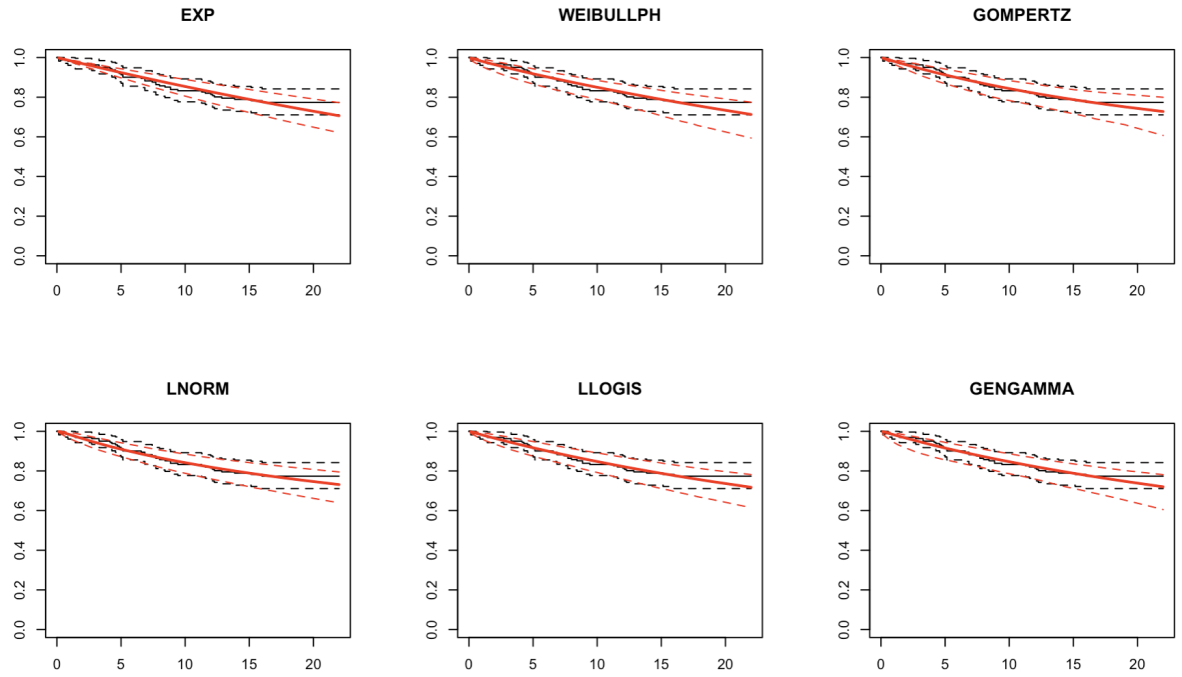


Table 34. Goodness-of-fit criteria for the TTD models based on the placebo arm during the randomised period of INCREASE

Survival distribution	AIC	BIC
Exponential	**372.6044**	**375.6858**
Weibull	374.3806	380.5434
Gompertz	373.9000	380.0629

Survival distribution	AIC	BIC
Log-normal	374.7029	380.8657
Log-logistic	374.0857	380.2485
Generalised gamma	376.1445	385.3887

Bold denotes best model fit by AIC and BIC.

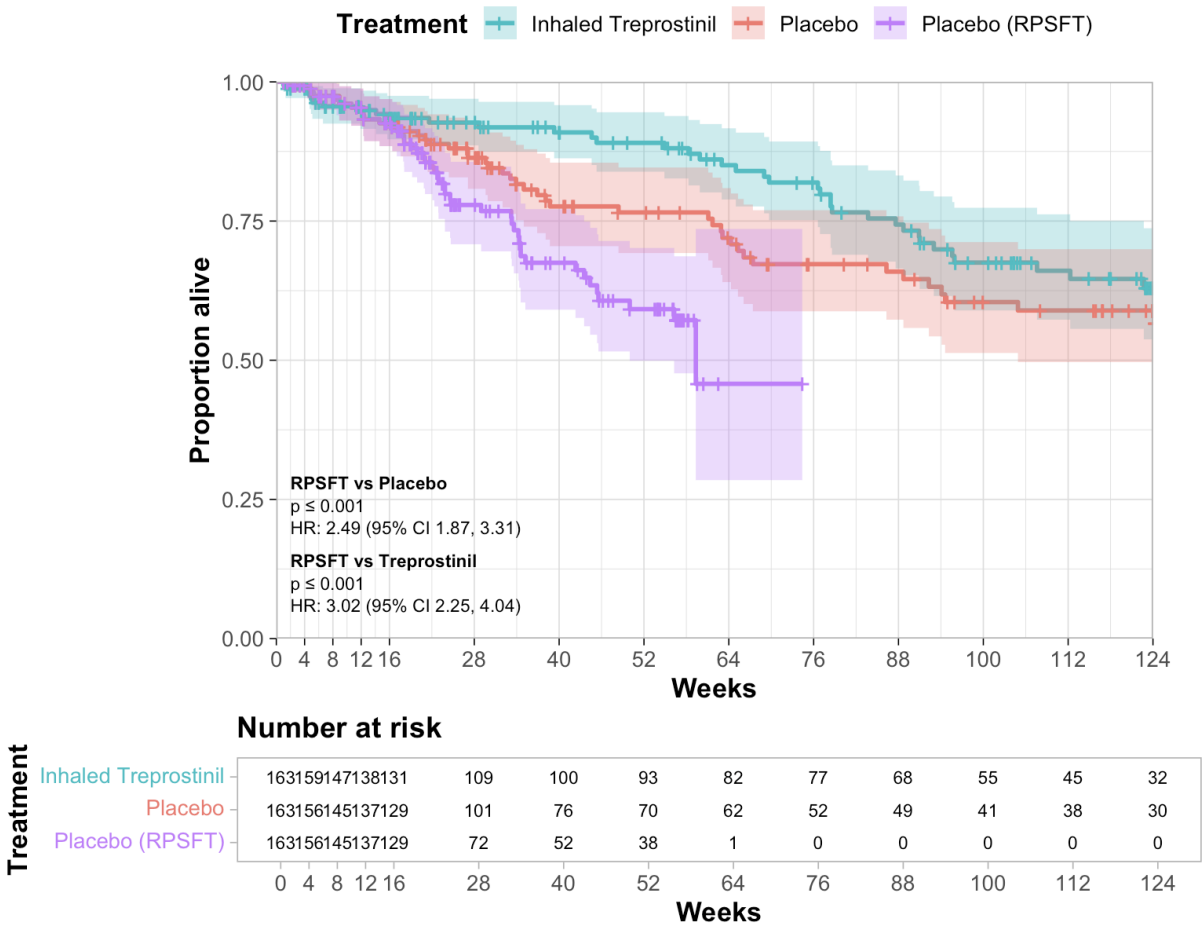
B18. Please confirm what the anticipated stopping rule of treprostinil in real-world use is likely to be. E.g. first or second clinical worsening. Is it possible treprostinil will be given beyond second worsening given the lack of alternative treatments?

Inhaled treprostinil is anticipated to be given until unacceptable toxicity, lung transplant or death. Discontinuation of inhaled treprostinil in the economic model was based on parametric models fitted to Kaplan-Meier estimates of treatment discontinuation as it occurred in INCREASE and INCREASE OLE. The parametric models selected were validated with clinicians who confirmed discontinuations will be driven by toxicity or death.

B19. Please confirm whether any exploration of the uncertainty associated with the wide confidence intervals of the RPSFT adjustment is included in the model or through scenario analyses.

In the CS, uncertainty around the parametric model incorporating the RPSFT adjustment was captured in the probabilistic sensitivity analysis (PSA) around the base case by way of sampling of all OS model parameters using the Cholesky decomposition matrices. The confidence intervals around the RPSFT-adjusted model of the placebo arm are presented in the figure below. We would recommend any further exploration of the uncertainty around the RPSFT adjustment to be captured by using the “User-defined HR” functionality in the “OS settings” worksheet of the model, using an unadjusted hazard ratio derived from the RPSFM-adjusted survival estimates versus inhaled treprostinil (HR=3.018 for RPSFT-adjusted placebo mortality versus placebo; SE=0.149; 95% CI: 2.255–4.039). We would contend that the confidence intervals around the RPSFT hazard ratios reported by Nathan *et al.* already capture the uncertainty arising from baseline and time-varying prognostic factors, which would overlap with the uncertainty captured in the parametric OS model of inhaled treprostinil in the probabilistic sensitivity analysis, thereby potentially overestimating the total uncertainty by double counting. Using the

unadjusted hazard ratio and confidence intervals from the RPSFT-derived survival times would mitigate this effect.



Section C: Textual clarification and additional points

References, Documentation and Searches

C1. Please provide the Cochrane Risk of Bias 2 (RoB 2) assessment for the INCREASE and INCREASE OLE trials, including detailed responses and justifications for each domain assessed.

Please see files attached entitled “RoB2_INCREASE” and “RoB2_INCREASE_OLE”.

C2. Please indicate how many reviewers were involved in data extraction for the company’s systematic literature review (SLR). Additionally, provide a

detailed description of the methods and procedures followed during the data extraction process.

Information from the full-text articles was extracted independently by one reviewer, and the data extraction was independently validated by a second reviewer.

Studies reported in multiple articles (including interim and/or final results) were extracted as a single study.

Information from the included studies was extracted into pre-designed data extraction forms. A standardised data extraction sheet was used and piloted on two studies, which allowed for the resolution of potential ambiguities and differences in the interpretation of findings.

Information from the included studies was extracted into pre-designed data extraction forms. Information extracted included:

- Publication details (author list, title, year of publication, journal, DOI)
- Trial details (study design, duration, arms, arm allocation method, blinding, endpoints, endpoint definitions, and pre-specified times of assessment)
- Patient population details
    - Mean age
    - Sex
    - Ethnicity
    - Time since PH-ILD diagnosis
    - ILD diagnosis (e.g. idiopathic interstitial pneumonia, chronic hypersensitivity pneumonitis, etc.)
    - Idiopathic interstitial pneumonia subcategory (e.g. idiopathic pulmonary fibrosis, Idiopathic nonspecific interstitial pneumonia, etc.)
- Baseline values for all characteristics measured in primary and secondary outcomes
- Intervention, comparator(s) and regimen
- Statistical techniques employed:
    - Approach to handling missing data
- Primary outcomes, with time points of assessment:
    - Change in 6-minute walk distance (6MWD)

- Secondary outcomes, with time points of assessment:
    - Change in plasma concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline
    - Incidence of clinical worsening events, including:
        - Hospitalisation due to a cardiopulmonary indication
        - Decrease in 6MWD >15% from baseline
        - Death (all causes)
        - Lung transplantation
    - Adverse events
    - Exacerbations of underlying lung disease
    - Baseline and change from baseline in pulse oximetry (saturation of peripheral capillary oxygenation [SpO2]) and supplemental oxygen requirement (L/min)
    - Baseline and changes in forced expiratory volume in one second (FEV1)
    - Baseline and changes in total lung capacity (TLC)
    - Baseline and changes in forced vital capacity (FVC%)
    - Baseline and changes in diffusion capacity of the lung for carbon monoxide (DLCO%)
    - Baseline and changes in mean pulmonary arterial pressure and pulmonary blood flow
    - Baseline and changes in quality-of-life scores

C3. For the clinical effectiveness systematic literature review (SLR) reported in Appendix B, please provide lists (full citations) of studies/reports excluded from the SLR with reasons for exclusion; both the 33 reports excluded at full-text screening stage and the further 16 reports judged to not be relevant to the NICE scope (and therefore not listed in tables 5 and 6)

Please see below the table with the 33 reports excluded at full-text screening stage, with full citation and reason for exclusion:

Author, Year	Full citation	Reason for exclusion at FT

Bongiovanni, 2024 (NCT00287716)	Bongiovanni G, Tonutti A, Stainer A, et al. Vasoactive drugs for the treatment of pulmonary hypertension associated with interstitial lung diseases: a systematic review. BMJ Open Respir Res. 2024;11:10.1136/bmjresp-2023. doi:10.1136/bmjresp-2023-002161. PMID:38479818.	Study design
Cottin, 2012 (HYPID study)	Cottin V, Reynaud-Gaubert M, Traclet J, et al. Hemodynamics and response to therapy of pulmonary hypertension in patients with interstitial lung disease: Preliminary results of the “HYPID” prospective study. European Respiratory Journal. Vienna: ERS; 2012.	Intervention
Hage, 2021	Hage R, Gautschi F, Steinack C, Schuurmans MM. Combined pulmonary fibrosis and emphysema (CPFE) clinical features and management. Int J Chron Obstruct Pulmon Dis. 2021;16:167–77. doi:10.2147/COPD.S286360. PMID:33536752.	Study design
Han, 2013	Han MK, Bach DS, Hagan PG, et al. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. Chest. 2013;143:1699–708. doi:10.1378/chest.12-1594. PMID:23732584.	Population
Haynes, 2023	Haynes ZA, Chandel A, King CS. Pulmonary hypertension in interstitial lung disease: updates in disease, diagnosis, and therapeutics. Cells. 2023;12:10.3390/cells12192394.-10.3390/cells12192394. doi:10.3390/cells12192394. PMID:37830608.	Study design
Hong, 2014	Hong IS, Coe HV, Catanzaro LM. Macitentan for the treatment of pulmonary arterial hypertension. Ann Pharmacother. 2014;48:538–47. doi:10.1177/1060028013518900. PMID:24458948.	Population
Jackson, 2010	Jackson RM, Glassberg MK, Ramos CF, et al. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. Lung. 2010;188:115–23. doi:10.1007/s00408-009-9209-8. PMID:20012639.	Population
Kang, 2021	Kang J, Song JW. Effect of sildenafil added to antifibrotic treatment in idiopathic pulmonary fibrosis. Sci Rep. 2021;11:17824–17824. doi:10.1038/s41598-021-97396-z. PMID:34497295.	Population
Kolb, 2018	Kolb M, Raghu G, Wells AU, et al. Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2018;379:1722–31. doi:10.1056/NEJMoa1811737. PMID:30220235.	Population

Le Pavec, 2011	Le Pavec J, Girgis RE, Lechtzin N, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. Arthritis Rheum. 2011;63:2456–64. doi:10.1002/art.30423.	Intervention
Lee, 2020	Lee J, Song JU. The clinical efficacy of pulmonary hypertension-specific agents in idiopathic pulmonary fibrosis: systematic review and meta-analysis of randomized controlled clinical trials. J Korean Med Sci. 2020;35:e48–e48. doi:10.3346/jkms.2020.35.e48.	Study design
Lefèvre, 2013	Lefèvre G, Dauchet L, Hachulla E, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum. 2013;65:2412–23. doi:10.1002/art.38029. PMID:23740572.	Study design
Madden, 2006	Madden BP, Allenby M, Loke T-K, Sheth A. A potential role for sildenafil in the management of pulmonary hypertension in patients with parenchymal lung disease. Vascul Pharmacol. 2006;44:372–6. doi:10.1016/j.vph.2006.01.013.	Population
Madden, 2007	Madden BP, Sheth A, Wilde M, Ong YE. Does sildenafil produce a sustained benefit in patients with pulmonary hypertension associated with parenchymal lung and cardiac disease? Vascul Pharmacol. 2007;47:184–8. doi:10.1016/j.vph.2007.06.003.	Population
Mohamed, 2022	Mohamed M, Mwangi JK, Patolia S. Meta-analysis of the use of inhaled trepostinil in patients with group 3 pulmonary hypertension; what is the evidence? American Journal of Respiratory and Critical Care Medicine. San Francisco, CA: American Thoracic Society; 2022. doi:10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A5633.	Study design
Nathan, 2019	Nathan S, Flaherty K, Raghu G, et al. Open-label dose-escalation data from the randomized, double-blind, placebo-controlled study to assess the safety and efficacy of pulsed, inhaled nitric oxide (iNO) in subjects at risk of pulmonary hypertension associated with pulmonary fibrosis (PH-PF) on long term oxygen therapy. Chest. American College of Chest Physicians; 2019. p. A2273–5. doi:10.1016/j.chest.2019.08.308.	Population
Nathan, 2019	Nathan SD, Flaherty K r., Glassberg Csete MK, et al. A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of pulsed, inhaled nitric oxide (iNO) at a dose of 30 mcg/kg-IBW/hr (iNO 30) in subjects at risk of pulmonary hypertension associated with pulmonary fibrosis (PH-PF) on long term oxygen therapy. American Journal of Respiratory and Critical Care Medicine.	Population

	Dallas, TX: American Thoracic Society; 2019. p. A7354. doi:10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A7354.	
Nathan, 2020	Nathan SD, Flaherty KR, Glassberg MK, et al. A randomized, double-blind, placebo-controlled study of pulsed, inhaled nitric oxide in subjects at risk of pulmonary hypertension associated with pulmonary fibrosis. Chest. 2020;158:637–45. doi:10.1016/j.chest.2020.02.016.	Population
NCT00287716, 2006	NCT00287716. Sildenafil to increase exercise capacity in individuals with idiopathic pulmonary fibrosis and pulmonary hypertension. https://clinicaltrials.gov/show/NCT00287716 [Internet]. 2006	Population
NCT00352482, 2006	NCT00352482. Sildenafil to increase exercise capacity in individuals with idiopathic pulmonary fibrosis and pulmonary hypertension. https://clinicaltrials.gov/show/NCT00352482 [Internet]. 2006	Duplicate (No new results)
NCT00637065, 2008	NCT00637065. Bosentan in pulmonary hypertension in interstitial lung disease treatment study. https://clinicaltrials.gov/show/NCT00637065 [Internet]. 2008	Duplicate (No new results)
NCT01366209, 2011	NCT01366209. Efficacy and safety of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF). https://clinicaltrials.gov/show/NCT01366209 [Internet]. 2011	Population
NCT02138825, 2014	NCT02138825. Efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension (PH) associated with idiopathic interstitial pneumonias (IIP). https://clinicaltrials.gov/show/NCT02138825 [Internet]. 2014	Duplicate (No new results)
NCT02951429, 2016	NCT02951429. Efficacy, safety, and tolerability study of pirfenidone in combination with sildenafil in participants with advanced idiopathic pulmonary fibrosis (IPF) and intermediate or high probability of group 3 pulmonary hypertension. https://clinicaltrials.gov/show/NCT02951429 [Internet]. 2016	Population
Prins, 2017	Prins KW, Duval S, Markowitz J, Pritzker M, Thenappan T. Chronic use of PAH-specific therapy in World Health Organization Group III pulmonary hypertension: a systematic review and meta-analysis. Pulm Circ. 2017;7:145–55. doi:10.1086/690017. PMID:28680574.	Study design
Raghu, 2013 (MUSIC study)	Raghu G, Behr J, Brown KK, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013;158:641–9. doi:10.7326/0003-4819-158-9-201305070-00003. PMID:23648946.	Population

Spikes, 2022 (BREEZE study)	Spikes LA, Bajwa AA, Burger CD, et al. BREEZE: open-label clinical study to evaluate the safety and tolerability of treprostinil inhalation powder as Tyvaso DPI™ in patients with pulmonary arterial hypertension. Pulm Circ. 2022;12:e12063. doi:10.1002/pul2.12063. PMID:35514770.	Population
Steen, 2014	Steen VD. Treatment of pulmonary hypertension in scleroderma patients with restrictive lung disease. Observations from the PHAROS cohort. American Journal of Respiratory and Critical Care Medicine. San Diego, CA: American Thoracic Society; 2014. p. A4789.	Duplicate
Tanaka, 2017	Tanaka Y, Hino M, Gemma A. Potential benefit of bosentan therapy in borderline or less severe pulmonary hypertension secondary to idiopathic pulmonary fibrosis-an interim analysis of results from a prospective, single-center, randomized, parallel-group study. BMC Pulm Med. 2017;17:200–200. doi:10.1186/s12890-017-0523-2. PMID:29237441.	Outcome
West, 2023	West N, Smoot K, Patzlaff N, Miceli M, Waxman A. Plain language summary of the INCREASE study: inhaled treprostinil (Tyvaso) for the treatment of pulmonary hypertension due to interstitial lung disease. Future Cardiol. 2023;19:229–39. doi:10.2217/fca-2022-0108.	Duplicate (No new results)
Zhao, 2022	Zhao N, Chen J, Zhang M, et al. PAH-specific therapy for pulmonary hypertension and interstitial lung disease: a systemic review and meta-analysis. Front Cardiovasc Med. 2022;9:992879–992879. doi:10.3389/fcvm.2022.992879.	Study design
Zhu, 2021	Zhu L, Chung MP, Gagne L, et al. Rituximab versus mycophenolate in the treatment of recalcitrant connective tissue disease-associated interstitial lung disease. ACR Open Rheumatol. 2021;3:3–7. doi:10.1002/acr2.11210.	Population
Zisman, 2010	Zisman D, Dubrock H, King C, et al. Safety and tolerability of inhaled treprostinil with phosphodiesterase-5 inhibitors in patients with pulmonary hypertension due to interstitial lung disease. Eur Respiratory Soc; 2023	Population

Please see below the table with the further 16 reports judged to not be relevant to the NICE scope:

Trial name or ID	Reference	Reason for exclusion
Ahmadi-Simab 2006	Ahmadi-Simab K, Hellmich B, Gross WL. Bosentan for severe pulmonary arterial hypertension related to systemic sclerosis with interstitial lung disease. European Journal of Clinical Investigation. 2006 Sep;36:44-8. DOI: 10.1111/j.1365-2362.2006.01695.x	Intervention/comparator
Chapman 2009	Chapman TH, Wilde M, Sheth A, Madden BP. Sildenafil therapy in secondary pulmonary hypertension: is there benefit in prolonged use?. Vascular pharmacology. 2009 Aug 1;51(2-3):90-. DOI: 10.1016/j.vph.2009.04.002	Intervention/comparator
COMPERA registry; NCT01347216	Hoeper MM, Behr J, Held M, Grunig E, Vizza CD, Vonk-Noordegraaf A, Lange TJ, Claussen M, Grohé C, Klose H, Olsson KM. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. PloS one. 2015 Dec 2;10(12):e0141911. DOI: 10.1371/journal.pone.0141911	Intervention/comparator
Corte 2010	Corte TJ, Gatzoulis MA, Parfitt L, Harries C, Wells AU, Wort SJ. The use of sildenafil to treat pulmonary hypertension associated with interstitial lung disease. Respirology. 2010 Nov;15(8):1226-32. DOI: 10.1111/j.1440-1843.2010.01860.x	Intervention/comparator
Fernandez 2018	Fernandez Romero GA, Marchetti N, Hu A, Vaidy A, Nieves Prado CA, Zhao H, Criner GJ. Efficacy of Oral Antifibrotic Agents in the Management of Combined Pulmonary Fibrosis and Emphysema. InA42. ILD SCIENTIFIC ABSTRACTS: TREATMENT AND ACUTE EXACERBATION 2018 May (pp. A1646-A1646). American Thoracic Society.	Intervention/comparator
Hoeper 2013	Hoeper MM, Halank M, Wilkens H, Günther A, Weimann G, Gebert I, Leuchte HH, Behr J. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. European Respiratory Journal. 2013 Apr 1;41(4):853-60. DOI: 10.1183/09031936.00213911	Intervention/comparator
INSTAGE	Behr J, Kolb M, Song JW, Luppi F, Schinzel B, Stowasser S, Quaresma M, Martinez FJ. Nintedanib and sildenafil in patients with idiopathic pulmonary fibrosis and right heart dysfunction. A prespecified subgroup analysis of a double-blind randomized clinical trial (INSTAGE). American journal of respiratory and critical care medicine. 2019 Dec 15;200(12):1505-12. DOI: 10.1164/rccm.201903-0488OC	Intervention/comparator
Minai 2008	Minai OA, Sahoo D, Chapman JT, Mehta AC. Vaso-active therapy can improve 6-min walk distance in patients with pulmonary hypertension and fibrotic interstitial lung disease. Respiratory medicine. 2008 Jul 1;102(7):1015-20. DOI:	Intervention/comparator
Mittoo 2010	Mittoo S, Jacob T, Craig A, Bshouty Z. Treatment of pulmonary hypertension in patients with connective tissue disease and interstitial lung disease. Canadian respiratory journal. 2010;17(6):282-6. DOI: 10.1016/j.rmed.2008.02.002	Intervention/comparator
NCT00352482	Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest. 2007 Mar 1;131(3):897-9. DOI: 10.1378/chest.06-2101	Intervention/comparator
NCT02036970	Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez FJ, Corte TJ, Keogh AM, Leuchte H, Mogulkoc N, Ulrich S. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. The Lancet Respiratory Medicine. 2019 Sep 1;7(9):780-90. DOI: 10.1016/S2213-2600(19)30250-4	Intervention/comparator
NCT02126943; OPUS and NCT03197688; OrPHeUS	Sahay S, Channick R, Chin K, McLaughlin V, Agron P, Ong R, Wetherill G, Kim NH. Macitentan in pulmonary hypertension (PH) due to chronic lung disease: real-world evidence from OPUS/OrPHeUS. The Journal of Heart and Lung Transplantation. 2021 Apr 1;40(4):S105-6. DOI: 10.1016/j.healun.2021.01.342	Intervention/comparator
Su 2018	Su P, Hsu C. Evaluation of the Prognostic Factor and the Treatment Efficacy of Inhaled Iloprost in Patients with Group 3 Pulmonary Hypertension. The Journal of Heart and Lung	Intervention/comparator

	Transplantation. 2018 Apr 1;37(4):S493. DOI: 10.1016/j.healun.2018.01.1287	
Tahara 2019	Tahara M, Oda K, Yamasaki K, Yatera K. Temporal Echocardiographic Assessment of Pulmonary Hypertension in Patients with Idiopathic Pulmonary Fibrosis Treated with Nintedanib, Pirfenidone and Other Agents. InC71. PULMONARY HYPERTENSION 2019 May (pp. A5501-A5501). American Thoracic Society. DOI: 10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A5501	Intervention/comparator
Venkat 2024	Ramanan SV, Kumar A, Parikh R. USING DOBUTAMINE AS A BRIDGE TO INHALED TREPROSTINIL IN SEVERE PULMONARY HYPERTENSION DUE TO INTERSTITIAL LUNG DISEASE. CHEST. 2024 Oct 1;166(4):A5768.	Intervention/comparator
Zimmermann 2014	Zimmermann GS, von Wulffen W, Huppmann P, Meis T, Ihle F, Geiseler J, Leuchte HH, Tufman A, Behr J, Neurohr C. Haemodynamic changes in pulmonary hypertension in patients with interstitial lung disease treated with PDE-5 inhibitors. Respirology. 2014 Jul;19(5):700-6. DOI: 10.1111/resp.12294	Intervention/comparator

C4. Please provide the following two documents referenced in the company submission, which appear to be missing from the reference pack:

- **62. Ferrer International. Inhaled treprostinil stakeholder workshop. Data on file 2024.**
- **85. Ferrer International. Clinical validation workshop of the cost-effectiveness model assumptions for inhaled treprostinil in PH-ILD indication 2025.**

These references can be found in the clarification response reference pack provided with this document.

C5. Two documents supplied as PDFs in the reference pack have different titles from those in the reference list of the main submission document. Please provide the correct documents for the references below:

- **97. Barker E, Moss J, Dymond A, Harper S, Green W. The ad hoc analysis of INCREASE and INCREASE OLE trials to inform a cost-effectiveness analysis model by york health economics consortium (YHEC) [data on file]. 2024 (the document in the reference pack named ’97. Ferrer International 2024.pdf' is in fact: ‘Economic Analysis of Inhaled Treprostinil in Pulmonary Hypertension Associated with Interstitial Lung Disease Cost-Effectiveness**

Analysis and Budget Impact Analysis – Technical Report. By Sam Harper, Amy Dymond and Will Green').

- **114. Ferrer International. Characterization of the epidemiology and burden of Pulmonary Hypertension WHO Group 3 in France: a retrospective study from the French National Hospital-Discharge database (PMSI). 2023. (The document in the reference pack named: '114. Ferrer international 20230517_Alira Health_Ferrer RWE Study.pdf' is in fact: 'Characterization of the epidemiology, treatment patterns and burden of Pulmonary Hypertension Group 1 and 3 in France, Germany and the UK: a real-word evidence study. Study protocol final v2.0.')**

These references can be found in the clarification response reference pack provided with this document.

C6. Please provide full citations for the records not retrieved due to full text not being available for all SLRs, as indicated in the PRISMA diagrams:

- **7 reports in the clinical effectiveness SLR (Appendix B, Figure 1)**
- **1 report in the cost-effectiveness / costs SLR (Appendix E, Figure13)**
- **3 reports in the health-related quality of life (HRQoL) SLR (Appendix F, Figure 15)**

Full citations for the seven records not retrieved due to full text not being available for the clinical effectiveness SLR:

1. Harder EM, Waxman AB. Clinical trials in group 3 pulmonary hypertension. Curr Opin Pulm Med. 2020;26:391–6. doi:10.1097/MCP.0000000000000694. PMID:32657833.
2. Behr J, Nathan SD, Wuyts WA, et al. Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021;9:85–95. doi:10.1016/S2213-2600(20)30356-8.

3. Shioleno AM, Ruopp NF. Group 3 pulmonary hypertension: a review of diagnostics and clinical trials. Clin Chest Med. 2021;42:59–70. doi:10.1016/j.ccm.2020.11.006. PMID:33541617.
4. Behr J, Nathan SD. Pulmonary hypertension in interstitial lung disease: screening, diagnosis and treatment. Curr Opin Pulm Med. 2021;27:396–404. doi:10.1097/MCP.0000000000000790. PMID:34127619.
5. Tomassetti S, Ruy JH, Gurioli C, et al. The effect of anticoagulant therapy for idiopathic pulmonary fibrosis in real life practice. Sarcoidosis Vasc Diffuse Lung Dis. 2013;30:121–7. PMID:24071883.
6. Bharani A, Mathew V, Sahu A, Lunia B. The efficacy and tolerability of sildenafil in patients with moderate-to-severe pulmonary hypertension. Indian Heart J. 2003;55:55–9.
7. Raghu G, Behr J, Brown KK, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013;158:641–9. doi:10.7326/0003-4819-158-9-201305070-00003. PMID:23648946.

Full citation for the record not retrieved due to full text not being available for the cost-effectiveness / costs SLR:

1. Maqhuzu PN, Schwarzkopf L, Markart P, et al. Costs of pharmacological and non-pharmacological interventions in interstitial lung disease management in Germany. Respiration. 2022;101:1015–23. doi:10.1159/000526575. PMID:36302347.

Full citations for the three records not retrieved due to full text not being available for the health-related quality of life (HRQoL) SLR:

1. Sheth JS, Belloli E, Salisbury M, et al. Prevalence of pulmonary hypertension in newly diagnosed patients with idiopathic pulmonary fibrosis (IPF) enrolled in the IPF-PRO registry. American Journal of Respiratory and Critical Care Medicine. American Thoracic Society; 2017. p. A1546. doi:10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A1546.
2. Dore M, Provencher S, Poirier P, et al. Validity of the modified dyspnea index for the French-Canadian population. J Nurs Meas. 2021;29:121–39. doi:10.1891/JNM-D-19-00042. PMID:33593990.

3. Polomis D, Runo JR, Meyer KC. Pulmonary hypertension in interstitial lung disease. Curr Opin Pulm Med. 2008;14:462–9. doi:10.1097/MCP.0b013e3283043e30. PMID:18664977.

C7. Please explain why, for the clinical effectiveness SLR, the numbers in the PRISMA diagram do not align with the numbers in the search strategy table for the Cochrane search. In Appendix B.1.1 Table 3, the number of records identified is given as 299 but in Appendix B.1.2 Figure 1 it is given as 622.

There appears to have been an error during the upload of records into the screening tool. Specifically, 622 records from line #1 were uploaded instead of the 299 records identified in the final search (line #13). To verify accuracy, we re-ran the Cochrane search on 10 June 2025, using the following strategy:

#	Search terms	Records (10 June 2025)
#1	MeSH descriptor: [Idiopathic Pulmonary Fibrosis] explode all trees	609
#2	(idiopathic pulmonary fibrosis):ti,ab,kw	1734
#3	(interstitial pneumoniti*):ti,ab,kw	275
#4	(interstitial lung disease*):ti,ab,kw	2355
#5	(diffuse parenchymal lung diseas*):ti,ab,kw	40
#6	(connective tissue disease):ti,ab,kw	2540
#7	(combined pulmonary fibrosis and emphysema):ti,ab,kw	23
#8	#1 OR #2 OR #3 OR #4 OR #5 OR (#6 AND #4) OR #7	3772
#9	MeSH descriptor: [Hypertension, Pulmonary] explode all trees	1705
#10	(pulmonary):ti,ab,kw	68321
#11	(hypertension):ti,ab,kw	77498
#12	#9 OR (#10 AND #11)	6532
#13	#8 AND #12	298
#14	#13 NOT #1 with Publication Year to 2024, with Cochrane Library publication date to Dec 2024, in Trials	243

Among the 243 additional records identified, no new studies met the inclusion criteria for the clinical SLR that had not already been included from other sources.

C8. In relation to the clinical effectiveness SLR, main submission document 2.1 states "*The search identified 45 relevant reports after duplicate removal and screening, yielding 35 studies in total. Of these, 19 of the studies are relevant to the decision problem, as they report on inhaled treprostinil or best supportive care (BSC).*" However, Appendix B1.2 reports "*In total, the SLR identified 45 publications reporting on 35 studies. Of these studies, only 20*

***were considered relevant to the decision problem specified in the final scope (Table 5).*" Please explain the discrepancy.**

The number of studies considered relevant to the decision problem specified in the final scope stated in the SLR is correct.

The number of studies relevant to the decision problem stated in Section 2.1 of the main submission is incorrect. The text in Section 2.1 of the main submission should align with the text reported in Appendix B1.2 and state *"The search identified 45 relevant reports after duplicate removal and screening, yielding 35 studies in total. Of these, 20 of the studies are relevant to the decision problem, as they report on inhaled treprostinil or best supportive care (BSC)."*

C9. For all SLRs (reported in Appendices B, E, F and G), the population inclusion criterion is adults with PH-ILD (Appendices Tables 4, 11, 15 and 20). How were eligibility decisions made regarding studies in a broader or mixed population (for example WHO Group 3 PH which could include PH-ILD alongside other disease subtypes)?

A pragmatic approach was taken to determine eligibility for studies involving broader or mixed populations, in order to preserve focus on the PH-ILD population while maximising inclusion of relevant evidence. Studies were included if it was clear that the majority of participants had PH-ILD, based on the reported diagnostic characteristics of the study population. Specifically, inclusion was supported when ILD subtypes typically associated with PH-ILD were the predominant diagnoses, such as idiopathic pulmonary fibrosis (IPF), connective tissue disease-associated ILD (CTD-ILD), combined pulmonary fibrosis and emphysema (CPFE), or other fibrosing idiopathic interstitial pneumonias (e.g., NSIP). Conversely, studies were excluded if the population was too heterogeneous (e.g., inclusion of significant proportions of patients with COPD, sarcoidosis, or other non-ILD causes of PH), and where no disaggregated data for the PH-ILD subgroup were available.

C10. For the cost-effectiveness, HRQoL and costs/healthcare resource use SLRs reported in Appendices E, F and G, the search strategies and inclusion criteria focus on the narrow population of adults with PH-ILD, in line with the NICE scope. Does the company believe that a model structure for a broader population, such as WHO Group 3 PH, any PH or any ILD, would differ

significantly from that for PH-ILD specifically? If so, please explain the reasons behind this.

Yes, based on the literature we might expect broader models to differ structurally from a PH-ILD model. A model of all WHO Group 3 PH patients would include PH due to ILD and COPD, OSA, combined emphysema–fibrosis, and others. Models in this patient group may also be anticipated to include underlying lung-disease events (e.g., COPD or sleep-apnoea exacerbations and the need for long-term oxygen or non-invasive ventilation). Furthermore, prognosis in WHO Group 3 PH tracks PAH-style risk markers more closely than raw FVC and a model of the entire group may require PH risk strata within FVC bands to more accurately model disease progression in the broader group.

PH-ILD is a distinct condition associated with poor prognosis and worse outcomes versus PH or ILD alone. Therefore, a unique model structure was required for inhaled treprostinil versus those that have been developed to assess treatments in PAH or ILD.

Modelling any PH (with or without ILD) would remove the ILD dimension from the model leaving a model in which costly PAH therapies would be likely to dominate costs. Previous PAH models have been developed based primarily on PAH risk strata (low, low-intermediate, intermediate-high, and high), as validated in PAH registries and recommended by the European Society of Cardiology and the European Respiratory Society, because of the established prognostic relevance for survival. [17]

Conversely, modelling any ILD (with or without PH) would remove the PH dimension from the model and would likely require the cardiopulmonary exacerbation element of the clinical worsening composite to be changed or removed, while potentially necessitating the inclusion of progression to the progressive fibrosing ILD (PF-ILD) phenotype and long-term oxygen. Previous ILD-only models have been structured using exclusively 10%-point FVC bands [18] or, for instance, with idiopathic pulmonary fibrosis (IPF) and IPF-progression states, which omit any PH-specific events from the model structure.[19]

C11. For the cost-effectiveness, HRQoL and costs/healthcare resource use SLRs reported in Appendices E, F and G, please provide full details of the electronic database search strategies (original and update searches) to include numbers of results in the tables.

Full details of the original and update search strategies, including the number of results retrieved at each stage, are not available. However, a summary of the total number of records identified and screened for each SLR search is provided below:

SLR		Search Period			Database	Records Identified	D
Cost-Effectiveness and Cost/ HCRU		Inception – 16 Jan 2024			PubMed	40	
		Embase	72	1	111		
	Jan 2024 – 22 Jan 2025 (Update)	PubMed	5				
		Embase	10	0	15		
HRQoL		Inception – 16 Jan 2024			PubMed	251	
		Embase	74	4	321		
	Jan 2024 – 14 Feb 2025 (Update)	PubMed	21				
		Embase	18	2	37		

C12. Typo: In the formula below (CS, section 3.4.2), the value '0.001' should be corrected to '0.0001'.

$$\boldsymbol{EQ-5D-3L = 0.9617 - (0.0013 \times SGRQ) - 0.001 \times SGRQ^2 + 0.0231 \times \%male}$$

Thank you for noting this error. The main submission has been updated.

C13. Can the company clarify the inconsistencies in values for certain parameters (e.g. death, lung transplant) between Table 6 and Figure 10 in CS Document B for both arms?

Table 6 presents a summary and analysis of the number of clinical worsening events in the INCREASE ITT population. These data show patients who experienced their first clinical worsening event and shows a singular value for each patient. Figure 10 however, presents every disease progression event, with singular patients potentially contributing multiple disease progression events to these data. Further clarity on the differences in definitions between clinical worsening and disease progression events is provided in response to question A26.

References

1. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *New England Journal of Medicine*. 2021/01/28/ 2021;384(4):325-334. doi:10.1056/NEJMoa2008470
2. Hadda V, Guleria R. Antifibrotic drugs for idiopathic pulmonary fibrosis: What we should know? 152doi:10.4103/ijmr.IJMR_90_20
3. Parikh R, O'Sullivan DM, Farber HW. The PH-ILD Detection tool: External validation and use in patients with ILD. *Pulmonary Circulation*. 2023;13(3):e12273. doi:https://doi.org/10.1002/pul2.12273
4. Celli B, Tetzlaff K, Criner G, et al. The 6-Minute-Walk Distance Test as a Chronic Obstructive Pulmonary Disease Stratification Tool. Insights from the COPD Biomarker Qualification Consortium. *American Journal of Respiratory and Critical Care Medicine*. 2016;194(12):1483-1493. doi:10.1164/rccm.201508-1653OC
5. Olsson KM, Hoeper MM, Pausch C, et al. Pulmonary vascular resistance predicts mortality in patients with pulmonary hypertension associated with interstitial lung disease: results from the COMPERA registry. *Eur Respir J*. Aug 2021;58(2)doi:10.1183/13993003.01483-2021
6. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *European heart journal*. 2022;43(38):3618-3731.
7. Ferrer. NICE engagement meeting. Data on file. 2024. . 2024.
8. United Therapeutics Corporation. A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease - INCREASE CSR. 2020.
9. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Long-term inhaled treprostinil for pulmonary hypertension due to interstitial lung disease: INCREASE open-label extension study. *European Respiratory Journal*. 2023/06// 2023;61(6):2202414. doi:10.1183/13993003.02414-2022

10. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching (Available from http://www.nicedsu.org.uk) (2014).
11. Connock M, Auguste P, Capelle A, Hénaine A-M, Obadia J-F, Armoiry X. Potential impact on cost-effectiveness estimates of using immature survival data: a case study based on transcatheter edge-to-edge repair (TEER) used for patients with severe mitral regurgitation at high surgical risk. *BMJ Open*. 2023;13(3):e060423. doi:10.1136/bmjopen-2021-060423
12. Ferrer International. Managing the challenges for Group 3 PH in the UK – Is the NHS ready? Advisory Board for Inhaled Treprostinil 2025.
13. Ferrer International. Clinical validation workshop of the cost-effectiveness model assumptions for inhaled treprostinil in PH-ILD indication 2025.
14. Nathan SD, Waxman A, Rajagopal S, et al. Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study. *The Lancet Respiratory Medicine*. 2021;9(11):1266-1274.
15. Nathan S, Argula R, Rajagopal S, et al. Inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease: event-free survival in INCREASE study open-label extension. *European Respiratory Journal*. 2022;60(suppl 66):2133. doi:10.1183/13993003.congress-2022.2133
16. Hernández Alava M, Pudney S, Wailoo A. *Estimating EQ-5D by age and sex for the UK*. 2022. *NICE DSU Report*. 2022/07/08/. Accessed 2025/01/22/. https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d
17. McLaughlin VV, Sitbon O, Chin KM, et al. Initial combination therapy with macitentan and tadalafil in patients with pulmonary arterial hypertension, with and without cardiac comorbidities. *European Journal of Heart Failure*. 2024;26(11):2379-2391. doi:https://doi.org/10.1002/ejhf.3319
18. Dempsey TM, Thao V, Moriarty JP, Borah BJ, Limper AH. Cost-effectiveness of the anti-fibrotics for the treatment of idiopathic pulmonary fibrosis in the United States. *BMC Pulmonary Medicine*. 2022/01/10 2022;22(1):18. doi:10.1186/s12890-021-01811-0
19. Loveman E, Copley VR, Colquitt J, et al. The clinical effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation. *Health Technol Assess*. 2015/03/12 2015;19(20)doi:10.3310/hta19200

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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2. Name of organisation	Action for Pulmonary Fibrosis
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	APF is a national UK charity. We bring people together to drive change so more people affected by pulmonary fibrosis (or lung scarring) can live well for longer. People living with lung scarring, their loved ones and the professionals caring for them are at the heart of everything we do. We provide expert support, information, education, help a growing network of support groups and raise awareness of pulmonary fibrosis. We collaborate to drive change that improves health and care and we provide vital resources to researchers, bringing hope for new and future treatments for this devastating disease. The vast majority of our funding comes from donations from our supporters. We also receive a small amount of grant funding from charitable organisations, as well as a small percentage of income from the pharmaceutical industry either for policy/involvement consultation, or as grants where industry has no influence on work.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	No

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Patient surveys (I Wish It Was Cancer report) and regular focus groups with the community; review of the European patient work in this area: doi: 10.1002/pul2.12405**

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Those living with pulmonary fibrosis face a debilitating terminal diagnosis. A large proportion of this group will also have PH-ILD. The largest issues faced include accurate diagnosis, a lack of treatment options, and access to supportive services. PH-ILD patients face long journey to diagnosis, with many unable to access diagnostic tests (see other answers for details). There are a number issues faced by people living with PH-ILD, including shortness of breath, fatigue, cough, dizziness, syncope (reported by patients as feeling faint), edema (reported by patients as swelling), and palpitations. They also face limitation on physical function, leading to them being unable to perform daily activities. This is linked to the symptoms above (such as being too out of breath to perform these tasks). It has a significant effect on their emotional and psychological wellbeing, including social isolation; anxiety; and depression. There is a significant lack of action around a holistic approach to PH-ILD care. There is a postcode lottery for accessing supportive services.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	**There are no effective treatment option available for this group currently.**
8. Is there an unmet need for patients with this condition?	**The lack of satisfactory treatments, poorer prognosis, and decreased survival has led to the recognition of a high unmet medical need in PH-ILD. There is an urgent need for a new treatment, especially one which could have a transformative effect on this group.** **We expect that there is an underestimation of the prevalence of PH-ILD within the NHS. We believe that the reason for this underdiagnosis is limited access to diagnostic tests or PH specialist centres. The main confirmatory diagnosis for PH-ILD is through right heart catheterisation (RHC). This test is only co-located for some ILD centres, and equally many clinicians do not see a huge benefit of putting the patient through it if there are few treatment options or the patients is unable or unwilling to travel to a PH centre. An abstract from the recent American Thoracic Society conference demonstrated that an audit of one ILD specialist service saw less than 25% of those with intermediate or high probability were referred for right RHC. Therefore this medicine could have an even bigger impact if approved.**

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**This medicine is seen as a significant benefit by patients as there are currently no effective options for treatment. It has the potential to significantly improve their quality of life.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	They are required to use this treatment 4 times daily, which is a burden on patients. However, given the nature of the disease and lack of other options available, this is still seen to be a welcome addition.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	ILD patients with suspected PH who are being treated in a centre with access to RHC are the most likely to access the drug. Many developed ILD specialist centres still do not have easy access to this essential diagnostic tool. In IPF, those from more socially deprived groups are less likely to benefit, and have significantly worse outcomes than those in the least socially deprived areas. This is the same for those living closer to respiratory centres versus further away.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No equity of access to RHC and thus diagnosis Limitation of access through specialist ILD or PH centres.

Other issues

13. Are there any other issues that you would like the committee to consider?	Shared care necessary between ILD and PH centres. The OneVoiceILD pathway will bring an enhanced amount of specialist care to new prescribing ILD centres which will bring high quality ILD care closer to home for patients. The Clinical Reference Group for Specialised Respiratory is currently writing a new Service Specification for ILD services to reflect this model.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There are currently no effective treatments for PH-ILD patients • PH-ILD patients face significant burdens in access to diagnosis and support services • There is not currently equity of access to diagnostics for PH-ILD leading to inequities of care • Patients would benefit enormously from having access to this treatment. •

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of Respiratory Nurses (ARNS)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Respiratory Nurses (ARNS) is a nursing forum to champion the specialty respiratory nursing community, promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of respiratory nursing care. The organisation is funded by subscriptions from members and further support from the following companies: Boehringer Ingelheim, Astrazeneca, Chiesi, GSK and Trudell Medical UK.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To treat ILD-associated Pulmonary Hypertension and improve exercise capacity
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A relevant systematic review suggests a minimal clinically important difference for change in 6-minute walk test distance of adults may be 14.0-30.5 metres (Bohannon and Crouch, 2016)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There is currently no licensed treatment for ILD-associated pulmonary hypertension available in the UK.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Supportive measures only (eg oxygen, non-pharmacological symptom management)
9a. Are any clinical guidelines used in the	2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS).

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care, as yet, is not well defined. However, at a recent ILD regional professional meeting, a Pulmonary Hypertension specialist was present and he described how discussions have begun on how access to Treprostinil might potentially be managed by existing services (eg ILD and PH specialist centres)
9c. What impact would the technology have on the current pathway of care?	Referral to a Pulmonary Hypertension specialist centre is likely to be needed for diagnosis and/or treatment, which will impact workload, including diagnostic testing, MDT capacity, prescribing and specialist nursing support. This will also impact patients/carers in terms of travel etc.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No- this will represent a completely new treatment option.
10a. How does healthcare resource use differ between the technology and current care?	Current care is supportive only. The new treatment will impact healthcare resource through increased diagnostic testing, referrals to specialist centres and associated MDT meetings, prescribing and any associated monitoring or nursing/pharmacist support needed.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Likely to be specialist centres (ILD and/or PH)
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As above.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, potentially. Symptoms associated with Pulmonary Hypertension include increased breathlessness, reduced exercise capacity, reduced quality of life and poorer prognosis. In the trials, Treprostinil impacted exercise capacity, as demonstrated by an increase in 6MWT distance. It did not demonstrate an impact on quality of life, as indicated by the St George's Respiratory Questionnaire. It is not clear whether symptoms such as breathlessness were impacted. Longitudinal data is needed to indicate impact on prognosis.
11a. Do you expect the technology to increase length of life more than current care?	Treprostinil is expected to lengthen time to clinical worsening, although longitudinal data is not yet available.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Potentially, although the clinical trial was limited as it only used one health-related quality of life measure (St George's Respiratory Questionnaire) which did not demonstrate a difference between treatment groups. Other patient-reported measures (eg generic quality of life measures, symptom-specific measures assessing breathlessness etc or other disease-specific measures) would be useful to understand this further, as would qualitative data.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I do not know.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical	As the current comparator is supportive care, this treatment will be more difficult for both patients and healthcare professionals. In terms of practical implications, needing to use a nebuliser up to four times daily is a significant lifestyle change for patients, the impact of which will need to be balanced against the benefits of the medication. This regime is likely to be impractical for more frail, vulnerable or isolated patients. Follow up visits to specialist centres, if required, will also be challenging.

requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As ILDs are frequently progressive and prognosis often poor, quality of life is a key consideration and stopping the medication, in collaboration with the patient, if quality of life is negatively impacted by side effects etc is likely to be appropriate.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Potentially clinical outcomes, such as symptom improvement, may not be captured. Impact on emotional wellbeing may also not be captured.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	See below.
16a. Is the technology a 'step-change' in the management of the condition?	Treprostinil represents a 'step-change' in that it will be the only drug licensed to treat ILD-related PH, however, the impact of the drug in clinical trials is modest, longitudinal data is not yet available and the outcome measures were limited, meaning the impact on patients' symptom burden, function and quality of life is not clear.

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, there is an unmet need for effective, licensed treatments of ILD-associated PH.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The clinical trial report that the most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhoea. Adverse events led to withdrawal of Treprostinil in 47/163 participants and placebo in 38/163 participants. It is unclear how significantly these adverse effects impacted patients' quality of life as there is no corresponding qualitative data or associated patient-reported outcome measures.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, I believe so. The diagnostic process for ILD and ILD-related PH is similar to the US, as are potential concomitant therapies such as Nintedanib and Pirfenidone.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	In my view, the most important outcomes are quality of life, symptom burden, function and survival. These were not adequately measured in the trials, which had limited patient-reported outcome measures and no qualitative data.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical	Not that I am aware of.

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	To my knowledge, no real-world data is available.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	As mentioned previously, the medication regime may be more difficult in practical terms for more frail, vulnerable or isolated patients. If access to a Pulmonary Hypertension Specialist Centre is needed for diagnosis/prescribing, this will limit patients who find travel difficult/impossible.
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• There is an unmet need for effective, licensed treatments of ILD-associated PH. • Specialist ILD and PH centres will need significant support to develop an appropriate care pathway for the use of Treprostinil which is practical and equitable. • Further data is needed on patient-centred outcomes, such as symptom burden and function. • Longitudinal and real-world data is also needed. • The dosing regime used in the trials will place a significant burden on patients.

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Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted] [redacted]
2. Name of organisation	British Thoracic Society
3. Job title or position	[redacted] [redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Society is the professional membership Society for healthcare professionals working in respiratory. It is a charity whose funding comes from membership income, conference income and journal publication.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	**Main aim of treatment for PH** – to slow progression of disease, improve overall function / ability to complete activities to improve overall quality of life (Measured with PH specific QOL tool). The main aim in this group of patients is to improve QOL. There is no trial currently that has shown improved survival in this group with PH therapy. This could be a therapeutic option for those patients with ILD and associated pulmonary hypertension. The treatment aims to increase exercise tolerance, improve overall function/ability to complete activities and therefore improve overall quality of life. There is evidence of achievement of this aim in the INCREASE trial to suggest that Treprostinil can offer symptomatic benefit in terms of increase in exercise tolerance and therefore QOL. *Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med 2021; 384: 325–34*
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Clinically significant treatment response – increased 6MW distance, patient reports of better symptom control of breathlessness, better haemodynamic state as measured with ECHO and decrease NTpro-BNP bio marker. Improvement in RV function is very important and can be measured biochemically or using imaging such as echo or MRI.There is lack of clear evidence as to which PROM we should use in this cohort and that is an important research question going forward. Improvement in functional class is also important to assess and would translate into a very important meaningful outcome. Improved haemodynamic state (ECHO and right heart catheterisation to establish cardiac index, cardiac output, right atrial pressure, pulmonary arterial pressure and pulmonary vascular resistance)

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an urgent unmet need for patients here. This is a condition which leads to death and there is no licensed therapy for it. Currently there is the option for some patients to perhaps benefit from a PDE5i treatment but this has not been validated in prospective clinical trials. Therfore there is no UK recognised therapy available for these patients. The iNcrease trial has shown promise of using inhaled Treprostinil in patients with ILD-PH. This offers the hope that there is some potential treatment options and indeed has opened up the research areas for the se patients. No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. The prognosis for this subgroup of ILD patients is poor despite the use of antifibrotic medication.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There is no licensed therapy for these patients in the UK. Therefore there is often only palliative approaches available. In those patients that we feel have a pulmonary vascular phenotype with an elevated pulmonary vascular resistance (>4Wood units) then under special conditions and monitoring we can offer therapy. This is usually a PDE5i (sildenafil) since the STEP trial suggested some QOL benefit. Some other retrospective studies have suggested some benefit too. However there is no real benefit from other agents currently used in the UK to treat PAH and indeed some can be harmful (Riociguat / Ambrisentan). These agents should only be administered by specialist centres. No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease (group 3 pulmonary hypertension). These patients are often treated with systemic pulmonary vasodilators, which are currently approved only for treatment of group 1 pulmonary hypertension.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	**Guidelines in place** – National Commissioning policies & ESC guidelines 2022 No therapies available for treatment.

9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**Clear patient pathway in place** - Variance – treatment is tailored on an individual patient basis, according to clinical evaluation of condition, functional class, and haemodynamic state to guide appropriate treatment options. No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. This treatment is therefore not offered in routine clinical practice and there is no pathway of care.
9c. What impact would the technology have on the current pathway of care?	This would be the first licensed therapy in this field and would potentially allow improved QOL. This is drug therefore represents a potentially beneficial option to this cohort of patients with an especially poor prognosis and would a novel pathway of care prior to initiation in clinical practice.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**The use of inhaled prostacyclin is not new and has been used in PAH patients with nebulisd iloprost. However this is better nebuliser technology and has reduced frequency. This has been used in PAH cenres and so this is why the PH centres need to be the leaders here in patient care.** **Technology use** – in specialist centres with the correct depth of knowledge to safely evaluate the treatment compliance and effects The definition and diagnosis of pulmonary hypertension can only be made on RHC (right heart catheter), centres will have to be able to offer this option at the point of diagnosis and therefore enable patient eligibility for treatment. RHCs are a secondary care diagnostic intervention and not provided in all secondary care centres. Given one of the potential outcome measures noted above includes • haemodynamic assessment (e.g. cardiac index, cardiac output, right atrial pressure, pulmonary arterial pressure and pulmonary vascular resistance) which will require a RHC – this suggests that monitoring and therefore further prescription will also be within the remit of secondary care.
10a. How does healthcare resource use differ between the technology and current care?	There are currently no recognised agents for treatment of this group of patients. This would allow a therapy for patients that otherwise have no therapeutic options.

	Given the current evidence, a RHC will be required to assess the patient for eligibility for this treatment. Patients are not routinely referred for this investigation in clinical care as there are no therapeutic options. The inhaler device could be easily assimilated into current care pathways as could be administered by the patient at home.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This should only be used in specialist centres. PH centres as the main support centres although the volume may preclude that. This is because the PH centres are well versed in using prostacyclin agents and a right heart catheterisation is required for diagnosis. Secondary care for the initial assessment as required a RHC, and management thereafter could be directed by the ILD team who are also in a secondary care setting.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	**Investment** – Adding to current homecare delivery services, staff training in use & administration of the drug and machinery – contractual agreement for long term care of equipment e.g – nebuliser machine and supply of ancillaries to patient, patient & staff guidance for use information. • Additional role of current homecare delivery services and input from pharmacy team, • staff training in use & administration of the drug • equipment e.g. – nebuliser machine and supply of ancillaries to patient • patient & staff guidance for use information
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Meaningful benefits – better QOL for patients – control of symptoms & slowing progression of disease. The evidence from the clinical trials is that this will have a meaningful impact in exercise tolerance for the patients and it has less burden than some of the previous inhaled prostacyclin therapy. There is no current clinical therapy available in this area. This subset of patients (i.e. those with both ILD and PH) have a limited life expectancy. Treprostinil offers some improvement to QOL in terms of increased exercise tolerance as suggested by the INCREASE trial, which although was

	positive in terms of reaching its primary end point (improved exercise tolerance), was limited by its short duration of 16 weeks. A further 52-week trial is currently on going. *Steven D Nathan, Jurgen Behr, Vincent Cottin, Lisa Lancaster, Peter Smith, CQ Deng, Natalie Pearce, Heidi Bell, Leigh Peterson, Kevin R Flaherty - Study design and rationale for the TETON phase 3, randomised, controlled clinical trials of inhaled treprostinil in the treatment of idiopathic pulmonary fibrosis: BMJ Open Respiratory Research 2022;9:e001310.*
11a. Do you expect the technology to increase length of life more than current care?	There is no survival benefit that has been shown in this area but currently we have absolutely no treatment options that will improve QOL or exercise tolerance. Therefore this can only be a good thing for these patients. Survival in this population in my opinion is a secondary importance vs improved QOL. The INCREASE trial has been further reviewed to attempt to clarify whether there is any mortality benefit of Treprostinil. *Nathan SD, Johri S, Joly JM, King CS, Raina A, McEvoy CA, Lee D, Shen E, Smith P, Deng C, Waxman AB. Survival analysis from the INCREASE study in PH-ILD: evaluating the impact of treatment crossover on overall mortality. Thorax. 2024 Mar 15;79(4):301-306. doi: 10.1136/thorax-2023-220821. PMID: 37979971; PMCID: PMC10958253.* This further sub analysis has suggested it can offer benefit in terms of both FVC (forced vital capacity) and mortality. *Nathan SD, Waxman A, Rajagopal S, Case A, Johri S, DuBrock H, De La Zerda DJ, Sahay S, King C, Melendres-Groves L, Smith P, Shen E, Edwards LD, Nelsen A, Tapson VF. Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study. Lancet Respir Med. 2021 Nov;9(11):1266-1274. doi: 10.1016/S2213-2600(21)00165-X. Epub 2021 Jun 29. PMID: 34214475.*
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes – we would expect an improvement although this does have to be weighed up with the administration and make up and time taken of the drug and nebuliser. Again as mentioned before it is not clear which PROM is best to use in this area. See Q11 above

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This should be used for patients with PH-ILD who have been diagnosed as such by a PH specialist centre. This may change with time but at the outset this should be the plan.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There is no current care – it will be more difficult but only because there is no acceptable care otherwise. There is a certain degree of patient dexterity and acceptability that will be required here for patients. It also requires specialist nurse and pharmacist input for the management and monitoring of these patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	A close follow up here is essential. Like the current management of some patients with PDE5i – if there is no improvement or deterioration after 3 months the PDE5i is stopped. The same policy should be applied to this technology although maybe after 6 months. Compliance monitoring is essential here too – it may be cumbersome but offers a therapeutic option for the first time. But we need to know that patients are taking it before we say it is not working. I think this should be assessed by the use of routine clinical PH follow up – 6 min walk test, QOL, FC.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – this is an inhaled therapy which demonstrates efficacy in patients with an untreatable condition. The approach of local administration to the lung via inhaled route has been efficacious in PAH and so it is nice to see this work in Gp3 disease. This is drug represents a potentially beneficial option to this cohort of patients with an especially poor prognosis. There is a further larger and longer study ongoing which aims to provide further clarification in this area.
16a. Is the technology a 'step-change' in the management of the condition?	Yes – absolutely. Currently there is no treatment – this offers a definite improvement. I would describe this as a step change simply because for the first time we have treatment that shows efficacy in this group of patients.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – it allows the first evidence based therapeutic option to be made available for this group of patients.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects of prostanoids should not be underestimated. However the local administration reduces this and allows reduced systemic absorption. This will hopefully attempt to mitigate as much as possible side effects. Further large studies are ongoing.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	The patient cohort in the Increase trial does reflect a similar group of patients that are seen in the Uk. So I believe the findings are relevant.
18a. If not, how could the results be extrapolated to the UK setting?	A novel pathway would need to be established.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcome in this group was improved exercise tolerance. This was seen with the 6 minute walk test.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	In PAH trials the use of 6MWD has been validated against outcomes but the PH-ILD is a unique population. This needs further study.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that we are aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no

20. How do data on real-world experience compare with the trial data?	Long term extension has continued to show benefit although not so clear in the patients that crossed over form the placebo group. There is a TETON study looking at the use of Treprostinil in IPF and the effect on FVC but this is not a PH specific study..

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	nil
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• First evidence based therapy in ILD-PH • Needs careful evaluation and management by specialist PH centres initially • Should be available for consideration of therapy in the UK • Needs development of a well managed clinical pathway with integration between ILD and PH teams • • No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. • This is drug therefore represents a potentially beneficial option to this cohort of patients with an especially poor prognosis. There is a further larger and longer study ongoing which aims to provide further clarification in this area.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NHS England (specialised commissioning)
3. Job title or position	[redacted]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? Yes Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing)? No An expert in treating the condition for which NICE is considering this technology? No An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England is responsible for a portfolio of around 150 specialised services, including treatments for rare cancers, genetic disorders, and complex medical conditions. From 1 April 2025, the commissioning of many of these services was delegated to Integrated Care Boards (ICBs) although the funding for high cost drugs used by these services remains with NHS England. Specialised services are important for supporting patients with rare and complex conditions, delivering cutting-edge care and fostering innovation within the NHS.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	No
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No. There are no licensed treatments for this indication. Pathway of care will vary depending on access/referral to specialist centres.
8. What impact would the technology have on the current pathway of care?	Availability of the technology is expected to change the pathway of care and result in an increase in referrals to specialised services for ILD and pulmonary hypertension. Clinical leads for these services have started to discuss with NHS England how services will need to develop to increase capacity and ensure appropriate access to treatment, noting that patients with PH/ILD are typically older and more frail so favouring a more local/network approach. Home treatment/homecare supply would be beneficial and could be considered for inclusion in the existing national homecare framework for the supply of medicines in pulmonary hypertension.

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Not routinely commissioned by NHS England so not currently funded in the NHS.
10. Will the technology be used (or is it already	NA

used) in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Treprostinil will be the first licensed treatment for this indication and expected to have a significant impact on use of resources. Clinical leads for these services have started to discuss with NHS England how services will need to develop to increase capacity and ensure appropriate access to treatment, noting that patients with PH/ILD are typically older and more frail so favouring a more local/network approach. Home treatment/homecare supply would be beneficial and could be considered for inclusion in the existing national homecare framework for the supply of medicines in pulmonary hypertension.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Initiated within specialised services with ongoing prescribing/supply through secondary care utilising hub/spoke model or 'shared care' to increase capacity and ensure care closer to the patient
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	TBC. Ongoing discussion regarding increasing capacity within specialised services
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	TBC
11. What is the outcome of any evaluations or audits of the use of the technology?	NA

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Affected group of patients expected to be older and more frail than those already managed within PH and ILD services so important to ensure equitable access to care for those living distant from specialised services.
12b. Consider whether these issues are different from issues with current care and why.	This technology is the first licensed treatment for the indication so may expose equality issues

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Monday 15 September.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating pulmonary hypertension with interstitial lung disease and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor David G Kiely
2. Name of organisation	Sheffield Teaching Hospitals NHS FT
3. Job title or position	Director of Sheffield Pulmonary Vascular Disease Unit
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with pulmonary hypertension with interstitial lung disease? ☒ A specialist in the clinical evidence base for pulmonary hypertension with interstitial lung disease or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for pulmonary hypertension with interstitial lung disease? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve how a patient feels, functions or survives.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in exercise capacity of at least 30m compared to placebo and a 30% reduction in clinical worsening events.
10. In your view, is there an unmet need for patients and healthcare professionals in pulmonary hypertension with interstitial lung disease?	Yes.
11. How is pulmonary hypertension with interstitial lung disease currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	• Patients being considered for PH treatment are assessed in one of 7 adult and one children's nationally designated PH referral centres. • Current commissioning policies for the treatment of PH have been under review since 2019, including a proposed new treatment algorithm. The 2022 ESC/ERS guidelines (Humbert M *et al., Eur Resp J* 2022) provide updated guidance along with the 7th World Symposium on Pulmonary Hypertension (Shlobin O *et al., Eur Resp J* 2024) with respect to the treatment of ILD-PH. • Current UK practice is to systematically assess i) patients with unexplained PH ii) patients with lung disease where patients may have co-existing PAH or CTEPH, iii) patients with lung disease where PH is considered severe, and iv) where patients with ILD are being considered for lung transplantation. • Assessments for PH, when PH treatments are being considered, should ideally be performed out-with exacerbations and following optimisation of the underlying lung disease. • In patients with lung disease (ILD) where PAH, CTEPH and other causes of PH are excluded (such as co-existing left heart disease) patients are classified as either i) severe PH (defined haemodynamically as mPAP> 20, PAWP≤15mmHg and PVR>5WU) and non-severe PH with (PVR≤5WU).

	• For those who have haemodynamically severe disease (PVR>5WU) selected patients may be considered for off label treatment with oral sildenafil. • If a patient is considered for sildenafil, doses typically of 25mg tds, 50mg tds, 75mg tds or 100mg tds may be considered. My approach would be to try 25mg tds and if tolerated up-titrate to 50mgtds and a maximum of 75mg tds, depending on tolerability and treatment response.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• The technology, namely inhaled Treprostinil, is the first study to demonstrate efficacy in patients with ILD-PH in a prospective phase 3 study, meeting the primary end-point of the study, namely an improvement in exercise capacity. • I would expect the treatment to be provided in a specialist clinic. In the first instance at a nationally designated PH centre, working in partnership with a specialist ILD clinic. Over time and depending on the experience of the ILD centre I would expect treatment to be initiated and followed up in an ILD specialist centre. • Based on current estimates of patients likely to have PH-ILD and be eligible for treatment there would need to be additional infrastructure provided at PH referral centres. This would include i) staff to assess patients, train patients in administration of drug and provide support to patients, ii) additional access to diagnostics such as imaging, exercise testing and right heart catheterisation and iii) MDT discussion to ensure that only suitable patients are commenced on treatment. Over time I would expect the delivery of this therapy to be from an ILD specialist clinic with links to a PH referral centre so this would need to be considered in medium term plans.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care?	• My expectation, based on my experience of treating patients with PAH, would be that an improvement in exercise capacity (seen with the technology under review) would translate into an improvement in life expectancy, compared to current care. • Being able to exercise is a surrogate for how a patient functions. If a patient has improvements in function one would expect that this would translate into

• Do you expect the technology to increase health-related quality of life more than current care?	improvements in HRQoL, if the side effects and administration of treatment were not overly burdensome.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• In my opinion, and data is relatively limited to support this, I would expect i) patients with ILD-PH who are in the terminal phase of their illness with significant frailty ii) those with combined pulmonary fibrosis and emphysema (CPFE) where extent of emphysema exceeds ILD and iii) those with multiple comorbidities including multiple risk factors for left heart disease, would be less likely to benefit. • In my opinion, and data is relatively limited to support this, I would expect those with i) a higher PVR >4 WU if the aim is to improve exercise capacity, ii) those with no additional comorbidities with the exception of hypertension alone and iii) those with an underlying connective tissue disease, who may be more likely to have a co-existing pulmonary vasculopathy, would be most likely to benefit.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	• Nebulised delivery of drugs has been established as a treatment for PH for over 20 years and PH centres are well versed in its delivery. • Compared to oral therapies it is more complex to deliver but compared to intravenous therapies it is less complex. In PH-ILD current treatment is either no therapy or compassionate treatment with oral therapy so treating patients would be more complex for patients and HCPs. • Challenges associated with the delivery of nebulised therapies include i) time to train patients in its administration, ii) long term concordance with treatment, impacted by iii) time taken for patients to administer treatment, clean and transport equipment, iv) side effects and tolerability (eg cough) of therapy • Monitoring response to therapy in ILD-PH would be similar to patients with PAH and CTEPH. However, symptomatic and functional assessment in ILD-PH is also impacted by the patients' underlying lung disease. This may necessitate more detailed pulmonary vascular assessments of right ventricular function or pulmonary heamodynamics, if there is diagnostic

	doubt regarding response to treatment, particularly if this is used to define whether to continue with or stop the intervention.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	• In patients with PAH and CTEPH current assessments include a measure of i) symptoms (including WHO FC, frequency of syncope and symptoms of right heart failure), ii) measure of exercise capacity (eg 6MWT, ISWT and less frequently CPET), iii) right ventricular function (eg NT-proBNP and or echocardiography and or CMR iv) pulmonary haemodynamic assessment (PVR, mPAP, RA, CI, SVI, pulmonary artery saturation) and HRQL (eg emPHasis-10 or CAMPHOR). Approach based on individual patient with a preference for non-invasive over invasive assessments. • As in PAH and CTEPH I would expect that the treating physician would make a decision with the patient on whether to continue with therapy. • In patients with ILD-PH, who are declining despite treatment with no benefit from initial therapy introduction, particularly where there are characteristics suggesting that patients are less likely to respond on the basis of their initial assessment, my current recommendation, is that these patients would stop therapy. • For patients who have had an initial improvement or period of stability on the background of previous decline, my current recommendation would be to continue with therapy even if the patient should subsequently deteriorate, with the caveat that if the patient finds the treatment intrusive or side effects undesirable I would currently recommend a review of treatment and discussion regarding treatment cessation • At diagnosis, I would currently recommend a multimodality systematic assessment including clinical assessment, WHO FC, identification of symptoms of interest eg syncope and right heart failure, measure of exercise capacity, lung function (spirometry and DLco), blood testing including immunology testing, recent CT imaging <6 months or repeat if recent decline, right heart catheterisation and MDT discussion to identify patients potentially suitable for inhaled treprostinil; with patient selection informed by Phase 3 trial entry criteria and MDT discussion, including with the patient.

	• For follow-up, I would suggest mandating i) symptomatic assessment, WHO functional class, presence or absence of syncope, ii) exercise test and iii) assessment of RV function with NTproBNP as a minimum at baseline and FU (+3-6 months and at least yearly), with performance of repeat imaging (echocardiography of MRI) or pulmonary haemodynamics where there is diagnostic doubt and further testing will impact on treatment decisions.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	• This is not an area of my expertise, however, I am aware that there is a relative paucity of data with respect to validated PROMs in ILD to allow for an assessment of the impact on HRQL and a subsequent QALY calculation.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	• Given this is the first treatment to improve exercise capacity in patients with ILD-PH it does represent in my opinion a "step change" in the treatment of ILD-PH. It is the first treatment I am aware of in patients with ILD (UIP) that has been demonstrated to result in an improvement in measures of exercise capacity • Given the poor prognosis of patients with ILD-PH (median survival <2 years in patients evaluated in UK PH-audit) an improvement with treatment represents a very significant achievement, particularly given the multiple negative studies in this area previously.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	• Frequency of administration, time taken to administer and side effects such as cough and the complexity of initial dose titration may be challenging for some patients with ILD-PH. These have the potential to impact overall HRQL.
20. Do the clinical trials on the technology reflect current UK clinical practice?	• Enrolment of patients in the Phase 3 study are broadly representative of patients that we see in our clinical practice in the UK. They could be extrapolated to the UK setting recognising that a not insignificant proportion

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	of patients with PH-ILD would not have met the inclusion criteria; in particular the 6MWT minimal distance would have excluded patients with more severe disease (both ILD and PH) and those with co-existing mobility issues. • Being able to demonstrate improvements in how a patient feels, functions or survives is important. This study demonstrates functional improvements (the study was powered for 6MWT) but does not demonstrate improvements in how a patient feels or survives. However, being able to demonstrate an improvement in the primary end-point of 6MWT with an intervention in patients with ILD-PH is a significant achievement, with a clinically relevant change in walking distance in those receiving active drug. Of improvements in secondary endpoints, an improvement in clinical worsening is also an important clinically relevant achievement, particularly given the short duration of the study. An improvement in NTrpBNP suggests an impact on pulmonary vascular status. • It is difficult to extrapolate these measures to long term outcomes given that relative paucity of data for these metrics as surrogate measures of outcome in ILD-PH. However, clinical worsening events are a strong predictor of mortality events in patients with PAH and one may extrapolate that this may also be the case in ILD-PH. • I am not aware of any adverse events in the literature that have come to light subsequent to the study.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	• There are a number of studies on-going with different preparations of Treprostinil that may provide additional evidence of the effect of this therapy in patients with ILD-PH. In addition, the recently presented TETON study has demonstrated beneficial effects in patients with ILD with respect to improvements in FVC and also provides additional information on adverse events and tolerability in patients with ILD.(Nathan S et al, European Respiratory Society Meeting, Barcelona, Sept 2024)
22. How do data on real-world experience compare with the trial data?	• I have no personal experience of using inhaled Treprostinil. My understanding from colleagues in the PH community is that the real world efficacy is in keeping with the clinical study findings.

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	• Patients may have disabilities that limit their exercise capacity. Therefore, if criteria are established that rely on exercise capacity over a threshold to access treatment or an initial improvement in exercise capacity to allow continued use of therapy, then safeguards would need to be in place to ensure that such patients were not excluded.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Group 3 pulmonary hypertension in the setting of interstitial lung disease (ILD-PH) is an area of high unmet need, with a very poor prognosis, significantly worse than most forms of cancer and cardiac disease
Currently in the United Kingdom, there are no licensed therapies available for the treatment of ILD-PH
Inhaled treprostinil is the first therapy to demonstrate a clinically significant improvement in exercise capacity in people with ILD-PH in a Phase 3 clinical study and improvements in secondary end points assessing clinical worsening and right ventricular function
Data on long term efficacy of ILD-PH are limited, although the Phase 3 study suggests improvements in clinical worsening events (a surrogate marker of mortality in other forms of PH) and sustainability of effect in the open label extension study
The introduction of inhaled treprostinil as a treatment for ILD-PH would require additional infrastructure support to allow equitable delivery of this treatment in the UK

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with pulmonary hypertension with interstitial lung disease or caring for a patient with pulmonary hypertension with interstitial lung disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with pulmonary hypertension with interstitial lung disease

Table 1 About you, pulmonary hypertension with interstitial lung disease, current treatments and equality

1. Your name	Dr Iain Armstrong
2. Are you (please tick all that apply)	☐ A patient with pulmonary hypertension with interstitial lung disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with pulmonary hypertension with interstitial lung disease? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Pulmonary Hypertension Association UK (PHA UK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I am drawing on 30 years of experience treating

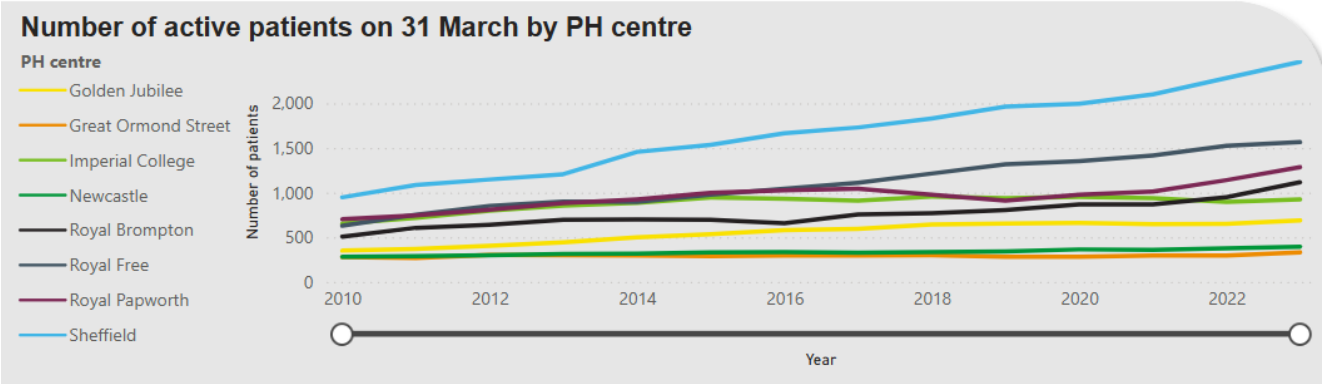
	people with PH and PH-ILD as a Consultant Nurse, and on 30 years as Chairman of the Pulmonary Hypertension Association – working with thousands of patients and caregivers affected by these diseases. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with pulmonary hypertension with interstitial lung disease? **If you are a carer (for someone with pulmonary hypertension with interstitial lung disease) please share your experience of caring for them**	I have over 30 years of experience of caring for people with PH and PH-ILD, as a Consultant Nurse at the Sheffield Pulmonary Vascular Disease Unit and as Chairman of the Pulmonary Hypertension Association (PHA UK). This time has given me in-depth knowledge of the lived experiences of this population and includes formal research undertaken by the PHA UK, conducted as recently as this year. I have treated or spoken with hundreds of people living with PH-ILD during these three decades, as well as their loved ones. This has included people in other parts of Europe and worldwide through collaborative work with other patient groups internationally.
7a. What do you think of the current treatments and care available for pulmonary hypertension with interstitial lung disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a) Patients living with PH-ILD are exceptionally challenged and there is very little effective treatment available for this population, who are classified as group 3. Currently available treatments (approved for groups 1 and 4) are not commissioned for this type of PH. As such, PH-ILD is a patient population that is currently without any effective licensed therapy. Many of these patients require oxygen therapy, some 24/7, which presents additional challenges and restrictions. PHA UK research, conducted in 2025, involved in-depth interviews with 19 people living with PH-ILD. The majority reported issues with fragmented management and disconnected care, expressing concern and frustration over which specialist team was leading.

	These people all reported a huge burden of symptoms, living restricted lives with little or no effective treatment. Analysis of this study is still ongoing, but it has clearly shown us that despite slight nuances, people living with PH-ILD have similar challenges and unmet needs as those with PH in association with other conditions such as CHD and CTD. They are desperate for a care pathway that will increase their quality of life. This might include drug therapies as well. A 2023 PHA UK survey showed 52% of people with PH rate overall improvement in quality of life as what matters to them most from treatment (sample size 859). In the same survey conducted in 2016 (sample size 563), this figure was 56%. Whilst this research was completed mainly with those in groups one and four, we would extrapolate that it would be equally important to group three due to their high symptom burden. There is a clear and urgent unmet need for effective therapies for people living with PH-ILD. Many of the existing drug therapies used in ILD and chronic disease carry a high side effect profile that impacts on their lived experiences. It is accepted clinically that the ILD service in the UK is inconsistent and dysfunctional when compared to a specialist service like PH. b) To my knowledge, the views expressed above align with others who work in the field of PH-ILD, and with those with lived experience (patients and caregivers).

8. If there are disadvantages for patients of current NHS treatments for pulmonary hypertension with interstitial lung disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Whilst not a targeted therapy, patients prescribed oxygen therapy describe the huge restrictions the logistical challenges places on their lives. This includes the limited supply/bulk of oxygen equipment that make it difficult to leave the house, travel by air or go on international holidays. Plus, the visible equipment carries stigma. Because of the way oxygen therapy is delivered in the UK via the NHS, geographically patients experience differing levels of satisfaction. There is no current structure or care pathway for patients living with PH-ILD in the UK.
9a. If there are advantages of inhaled treprostinil over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does inhaled treprostinil help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	There is a current lack of data around the impact of this drug on aspects such as quality of life, improvement in work, education, etc, so it is difficult to comment on this. A clinical endpoint of walk distance for example, does not provide insight into this. This question is very difficult for a patient to answer, as they would not have knowledge of this drug.
10. If there are disadvantages of inhaled treprostinil over current treatments on the NHS please describe these.	There are significant challenges for effective implementation of inhaled treprostinil. Accurate diagnosis, phenotyping and appropriate expert follow-up to measure efficacy of treatment will need careful consideration as this group of patients currently fall outside the remit of the PH expert centres.

For example, are there any risks with inhaled treprostinil? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I recognise capacity issues at both the PH and ILD specialist centres. I also recognise that given the frail, co-morbid nature of the population in question, and in line with the transformation agenda within specialist respiratory medicine that care would ideally be delivered close to home. Because we do not know the number of patients that would be prescribed this drug, specialist centres may be so stretched that it damages the service provided to patients using more established therapies. This patient group, because of their often-high burden of symptoms and oxygen demands, travelling long distances for care can be highly problematic. Due to uncoordinated care in the NHS, hospital transport, for example, often prevents patients accessing the care they need.
11. Are there any groups of patients who might benefit more from inhaled treprostinil or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The preparation of inhaled medication may be difficult for those with dexterity issues caused, for example, by Raynaud's or Systemic Scleroderma. Again, a patient would find it very difficult to provide a meaningful answer to this. I and my organisation (PHA UK) have been involved in a number of conferences and congresses over the last 18 months where there is not consensus amongst the clinical community in the use of the treatment of PH-ILD with this drug.
12. Are there any potential equality issues that should be taken into account when considering pulmonary hypertension with interstitial lung disease and inhaled treprostinil? Please explain if you think any groups of people with this condition are particularly disadvantage	I have no concerns with regards to equality issues specifically about this drug. However, there are wider issues around equality when it comes to engagement in healthcare. The burden of symptoms / level of disability PH-ILD patients experience makes accessing services problematic.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	In adult PH services across the UK, drugs are funded within the national commissioning policy – but infrastructure is not (this is left to individual Trusts). The majority of the diagnostic eligibility work involved with the delivery of this technology will fall to frontline staff in PH services, not simply those writing the prescription. There is a lack of clarity around where the ongoing management of these patients will sit. I feel strongly that given capacity issues with group one and four patients at specialist centres, group three must be regarded as an entirely separate cohort and managed in addition to current services. ECONOMIC ANALYSIS: The cost of delivering this technology needs to be considered from the perspective of infrastructure and capacity as well as the cost of the therapy itself. PH centres managing group one and four patients may already be working at capacity – the graph below is taken from the most recent National Audit of Pulmonary Hypertension and shows how the numbers of managed patients continues to rise.



I am positive about this novel treatment option and the need for it to be commissioned, but the above points do need to be considered. We must protect the present core work of the specialist PH service and imagination needs to be brought in when considering whether these patients could be managed in a more local ILD setting.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Patients with PH-ILD carry a huge burden of symptoms which impact lived experience, health-related quality of life and longevity
- There are very limited treatments available for this patient population, particularly in comparison to other types of PH
- Inhaled treprostinil has the potential to address an unmet treatment need in this population – if data can show an impact on lived experience, health-related quality of life and longevity
- It is vital that consideration is given to how and where patients on this therapy would be managed, both initially and long-term – bearing in mind the difficulty for this patient group to travel long distances frequently.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with pulmonary hypertension with interstitial lung disease or caring for a patient with pulmonary hypertension with interstitial lung disease. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Monday 15 September.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with pulmonary hypertension with interstitial lung disease

Table 1 About you, pulmonary hypertension with interstitial lung disease, current treatments and equality

1. Your name	Steve Jones
2. Are you (please tick all that apply)	☐ A patient with pulmonary hypertension with interstitial lung disease? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with pulmonary hypertension with interstitial lung disease? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): Former IPF patient and patient advocate who has supported many people living with PH-ILD researched impact of PF-ILD on patients.
3. Name of your nominating organisation	Action for Pulmonary Fibrosis
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing a patient expert statement
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience

	☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I have been an active (volunteer) patient advocate for people living with pulmonary fibrosis (including PH-ILD) since my lung transplant in 2016. I am currently Patient President of APF and a board member of the European Pulmonary Fibrosis Federation. I have known and supported many people living with PH-ILD and have organised focus groups with PH-ILD patients in UK and Europe, published research on the PH-ILD Patient journey. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with pulmonary hypertension with interstitial lung disease? **If you are a carer (for someone with pulmonary hypertension with interstitial lung disease) please share your experience of caring for them2024)**	Pulmonary fibrosis (fibrotic ILD) is a devastating disease with a life expectancy of 3-6 years, worse than most common cancers. It affects over 70,000 people in the UK and over time, patients become increasingly breathless, find it difficult to walk-up stairs or do day-to-day tasks. They become dependent on supplementary oxygen, housebound and eventually die from respiratory failure or a related cause. A significant proportion of PF patients also suffer from a debilitating cough and fatigue. The disease also impacts on the mental health of the patient and their families, who also 'live with the disease'. These symptoms – shortness of breath (dyspnea), cough and fatigue are also the main symptoms reported by PH-ILD patients*. The impact of developing PH on top interstitial lung disease (PH-ILD), to the patient, is to exacerbate existing symptoms of PF and speed up the progression of the disease. Sadly, the life expectancy of people with PH-ILD is much worse than those with PF alone. PH-ILD is a cruel and aggressive disease. People with severe PH-ILD may live for less than a year after diagnosis. PH-ILD is one of the deadliest pulmonary conditions.

	* *Piccari et al (2024). doi/10.1002/pul2.12405*
7a. What do you think of the current treatments and care available for pulmonary hypertension with interstitial lung disease on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	(a) There are currently no treatments available for PH-ILD, over and above the two antifibrotic drugs (pirfenidone and nintedanib), which have been made available to PF patients over the last 5-10 years. These drugs can be effective in slowing progression, but they can have challenging side effects (for example, nausea, diarrhoea, susceptibility to sunlight), causing some patients to give up treatment. Those PH-ILD patients with PF caused by connective tissue disease (for example, CTD-ILD, RA-ILD) may be given immune-suppressive medicines although the efficacy of these has not been proven in RCTs. Other treatments which PH-ILD and PF patients can both receive (though access can be difficult), include: cough therapies, pulmonary rehabilitation, psychological support (not easily available) and supplementary oxygen. These therapies can be effective in improving quality of life for all PF and PH-ILD patients. But patients can often find it difficult to access them. (b). My views accurately reflect the majority view of the hundreds of PF patients and scores of PH-ILD patients I have met over the last decade or more.
8. If there are disadvantages for patients of current NHS treatments for pulmonary hypertension with interstitial lung disease (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There are currently no treatments available under the NHS for PH-ILD (over end above those for any PF patients), so there are no disadvantages to report. At some centres, Sildenafil (a PDE5 inhibitor) may occasionally be prescribed, off label, but the drug has side effects and must be carefully monitored at an expert centre.
9a. If there are advantages of inhaled treprostinil over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does inhaled treprostinil help to overcome or address any of the listed disadvantages of current**	Inhaled Treprostinil has been shown in the RCT published in 2021 and the results of the open-label extension, published in 2023 to: • significantly improve exercise capacity, as measured by the 6-minute walk test • reduce the risk of experiencing events like hospitalisation, death, and worsening of 6MWD. In a post-hoc analysis, patients were also shown to have significantly improved their lung function (as measured by Forced Vital Capacity (FVC)).* * *Nathan S, et al (2021) Lancet Respiratory Medicine.*

treatment that you have described in question 8? If so, please describe these	All of these benefits would lead to significant improvements in the patient's quality of life and ability for self-care enabling them to live a more normal life for longer. They would also impact positively on patients' families and their ability to work and lead a normal life. The most significant benefit of the treatment is improved exercise capacity (as indicated by 6MWD).
10. If there are disadvantages of inhaled treprostinil over current treatments on the NHS please describe these. For example, are there any risks with inhaled treprostinil? If you are concerned about any potential side effects you have heard about, please describe them and explain why	**The side effects and risks of inhaled Treprostinil would seem acceptable to most PH-ILD patients**. The results of the RCT (Waxman et al, 2021) show that there are significantly fewer serious adverse events in the active cohort compared to the placebo (47 v 38 sae). And while 28.8% of participants in the active arm withdrew from the trial due to adverse effects, this was not very much higher than placebo (28,8% of patients on the active arm compared to 23.3% on placebo). The main side effects experienced by people in the active group were cough, headache and dizziness, while the placebo group reported more adverse events linked to breathless. Most PF patients are not accustomed to inhaling medicines but, in my experience, the mechanism of administering a drug does not seem to discourage people from taking part in clinical trials, if the perceived benefits of the new drug are positive. I think the same would be the case here. ☐
11. Are there any groups of patients who might benefit more from inhaled treprostinil or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The group of patients who would benefit most from inhaled treprostinil are those who are diagnosed with moderate or severe PH. Such patients are most likely to experience rapid progression in symptoms (breathlessness, cough and fatigue) as their disease progresses and are most likely to have a short life expectancy. If the PH of these patients can be slowed by taking inhaled Treprostinil they should be able to enjoy a better quality of life for longer and live longer.
12. Are there any potential equality issues that should be taken into account when considering pulmonary hypertension with interstitial lung disease and inhaled	

treprostinil? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	An RHC is required to confirm a diagnosis of PH-ILD and to assess the severity of the condition but RHC is currently only available in a limited number of centres. Many ILD specialist centres do not have easy access to RHC so many patients who would benefit from inhaled Treprostinil will not to be able to get it. There is a need to develop RHC capacity in other hospitals, especially ILD Centres. People living in remote areas, away from RHC centres will find it most difficult to access RHC, along with people from socially deprived groups who may find the cost and effort involved in getting to an RHC centre may be prohibitive.
13. Are there any other issues that you would like the committee to consider?	There is currently no treatment available for PH-ILD on the NHS. Patients with PH-ILD have a very poor prognosis and little hope. Inhaled treprostinal has been available in the USA for a few years. British patients often take part in American webinars and ask why it's not available yet over here? This treatment would have an enormous impact on the lives of people living with this deadly disease.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- PH-ILD is one of the deadliest pulmonary conditions, with a life expectancy worse than most common cancers .
- There is currently no treatment available for this condition on the NHS leaving patients with little hope.
- Making Inhaled Treprostinil available to patients, especially those with moderate or severe PH-ILD, would improve their exercise capacity and enable them to enjoy an improved quality of life for longer and increase their life expectancy.
- There is a shortage of centres able to do RHCs to diagnose and assess the severity of PH-ILD. Without more centres able to do this there will be problems of equity in accessing the new treatment.
- Click or tap here to enter text.
- Click or tap here to enter text.

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External Assessment Group (EAG) Report

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease [ID6459]

Produced by	Centre for Evidence and Implementation Science, University of Birmingham
Authors	Amin Mehrabian, Research Fellow, University of Birmingham Mehdi Yousefi, Research Fellow, University of Birmingham Anna Brown, Information Specialist, University of Birmingham Roger Thompson, Senior Clinical Lecturer, University of Sheffield April Coombe, Information Specialist, University of Birmingham Daniel Gallacher, Assistant Professor, University of Birmingham
Correspondence to	Dr Daniel Gallacher; d.c.gallacher@bham.ac.uk
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Declared competing interests of the authors

KB has received speaker fees from Janssen.

RT is a site sub-investigator for clinical trials sponsored by Merck, Sharp and Dohme UK.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Daniel Gallacher led the project and conducted the review of the statistical analysis.
Amin Mehrabian conducted the review of the clinical evidence.
Mehdi Yousefi conducted the review of the cost-effectiveness evidence.
Anna Brown and April Coombe conducted the review of the literature search.
Roger Thompson provided expert input and reviewed the final report.

Copyright statement

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Table of Abbreviations

Abbreviation	Definition
6MWD	6-minute walk distance
6MWT	Six-minute walk test
AE	Adverse event
AF	Adjustment factor
BIC	Bayesian Information Criterion
BNF	British National Formulary
BNP	Brain natriuretic peptide
BSA	Body surface area
BSC	Best supportive care
CEM	Cost-effectiveness model
CI	Confidence interval
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPET	Cardiopulmonary exercise testing
CPFE	Combined pulmonary fibrosis and emphysema
CPI	Composite physiologic index
CT	Computed tomography
CW	Clinical worsening
CW1	First clinical worsening event
CWF	Clinical worsening-free
CW≥2	Two or more clinical worsening events
DLCO	Diffusing capacity of the lungs for carbon monoxide
DPLD	Diffuse parenchymal lung disease
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
EQ-5D	EuroQol 5-Dimensions questionnaire
ERA	Endothelin receptor antagonist
ESC/ERS	European Society of Cardiology/European Respiratory Society
FC	Functional class
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity

FVC% pred	Forced vital capacity percentage predicted
GLM	Generalized linear model
HCRU	Healthcare resource utilisation
HP	Hypersensitivity pneumonitis
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IM	Intramuscular
INCREASE	INCREASE clinical trial
IPD	Individual participant data
IPF	Idiopathic pulmonary fibrosis
IQR	Interquartile range
ITT	Intent-to-treat
IV	Intravenous
JBI	Joanna Briggs Institute
KM	Kaplan-Meier
LOCF	Last Observation Carried Forward
LS	Least squares
LTOT	Long-term oxygen therapy
MCID	Minimal clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
MID	Minimal important difference
MMRM	Mixed-model repeat-measurement
mPAP	Mean pulmonary arterial pressure
NA	Not applicable
NCC	National Cost Collection
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NSIP	Non-specific interstitial pneumonia
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label extension
OS	Overall survival

PAH	Pulmonary arterial hypertension
PAS	Patient Access Scheme
PCWP	Pulmonary capillary wedge pressure
PDE5i	Phosphodiesterase Type 5 Inhibitor
PFT	Pulmonary function test
PFTs	Pulmonary function tests
PH	Pulmonary Hypertension
PH-ILD	Pulmonary Hypertension associated with Interstitial Lung Disease
PROs	Patient-reported outcomes
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVR	Pulmonary vascular resistance
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RHC	Right heart catheterisation
ROBIS	Risk of bias assessment tool for systematic reviews
RPSFT	Rank-preserving structural failure time
RV	Right ventricle
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SGRQ	Saint George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TLC	Total lung capacity
TTD	Time to treatment discontinuation
VOP	Voice of the Patient
WHO	World Health Organization
WU	Wood units

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

Table 1 contains an overview of the EAG key issues.

Table 1: Overview of EAG key issues

ID6459	Summary of issue	Impact on results	Report sections
Key issue 1	Choice of comparator: Are PDE5is a relevant comparator?	Unknown	2.2.2
Key issue 2	Concerns around implementation and impact of inhaled treprostinil.	Unknown	2.2.4
Key issue 3	Crossover adjustment for the INCREASE comparator arm	Large	3.3.2.1
Key issue 4	Uncertain efficacy of best supportive care	Large	3.3, 3.5
Key issue 5	Choice of extrapolation for inhaled treprostinil overall survival	Large	4.2.2.2, 4.2.5.3
Key issue 6	Approach to extrapolation for inhaled treprostinil time to treatment discontinuation	Medium	4.2.2.3, 4.2.5.4
Key issue 7	Inappropriate choice of utility values and analysis of health-related quality of life data.	Small	4.2.6.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the choice of adjustment for the comparator arm of INCREASE, the extrapolation for inhaled treprostinil overall survival, and for inhaled treprostinil time-to-treatment discontinuation (TTD).

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing survival and time spent in superior health states

Overall, the technology is modelled to affect costs by:

- Having a higher acquisition cost than current care.
- Incurring longer follow-up costs due to extended survival time.

The modelling assumptions that have the greatest effect on the ICER are:

- The choice of extrapolation for inhaled treprostinil OS
- The choice of hazard ratio for modelling BSC OS
- The approach to modelling TTD for inhaled treprostinil

1.3 EAG's key issues

Issue 1: Choice of comparator: Are PDE5is a relevant comparator?

Report section	2.2.2
Description of issue and why the EAG has identified it as important	The company has excluded a group of treatments known as PDE5 inhibitors (PDE5i). These treatments are given to some patients, with the proportion varying considerably across centres, with expert estimates ranging from 8% to 60%. The EAG considers PDE5is are likely to be a relevant comparator.
What alternative approach has the EAG suggested?	The EAG has not been able to adapt the economic model to compare to PDE5is.
What is the expected effect on the cost-effectiveness estimates?	It is unknown whether inhaled treprostinil would be more or less cost-effective against PDE5is than against best supportive care. PDE5is will likely have increased both costs and efficacy compared to the currently modelled comparator.
Could any additional evidence or analyses be provided to resolve this key issue?	If the committee consider the PDE5is are a relevant comparator, then the company should be able to incorporate information from Dawes et al. through a MAIC analysis to provide a helpful comparison.

Issue 2: Concerns around implementation and impact of inhaled treprostinil.

Report section	2.2.4
Description of issue and why the EAG has identified it as important	The EAG understands that at present, some people with suspected or confirmed PH-ILD may not be referred to, or may be referred and discharged from, specialist centres, for reasons such as their disease is not severe enough, and a lack of treatment options. The availability of inhaled treprostinil would transform care for PH-ILD, with specialist centres likely managing greater volumes of patients, possibly requiring expansion. Furthermore, inhaled treprostinil treatment will likely require disease confirmation through right-heart catheterisation or other clear diagnostic criteria. The availability of inhaled treprostinil may cause an increase in the number of people undergoing RHC and shift the baseline characteristics of the treated population to be on average, less severely ill than the current population.
What alternative approach has the EAG suggested?	The EAG has not been able to explore alternative scenarios, but the committee may wish to consider the challenges and costs of implementing inhaled treprostinil and RHC.
What is the expected effect on the cost-effectiveness estimates?	Implementation costs would increase the total costs associated with inhaled treprostinil, whilst it is unclear what impact treating a younger and earlier diagnosed population would have on the cost-effectiveness.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could present exploratory analyses which capture the costs associated with the implementation of inhaled treprostinil.

Issue 3: Crossover adjustment for INCREASE comparator arm

Report section	3.3.2.1
Description of issue and why the EAG has identified it as important	The company applies a rank-preserving structural failure time (RPSFT) adjustment to the open-label extension (OLE) of INCREASE, to account for the fact that all people entering the OLE received inhaled treprostinil. The EAG does not consider that the assumption of a common treatment effect is supported by the data, nor that the magnitude of the RPSFT adjustment holds any face validity.
What alternative approach has the EAG suggested?	The EAG prefers to apply no adjustment, as it is unclear whether any benefit was received by switching, and explores the impact of applying an alternative adjustment (inverse probability of censoring weighting (IPCW)).
What is the expected effect on the cost-effectiveness estimates?	This has a large effect on the life-years for the control arm, varying the relative efficacy of inhaled treprostinil. (ICER = £65,919)
Could any additional evidence or analyses be provided to resolve this key issue?	No

Issue 4: Uncertain efficacy of best supportive care

Report section	3.3, 3.5
Description of issue and why the EAG has identified it as important	The company presents analyses comparing inhaled treprostinil to the control arm of INCREASE, and an indirect comparison to the untreated arm from Dawes et al. The company have not implemented a comparison to other potential sources, including a CPRD study commissioned by the company; however, there are concerns about the classification of patients in this source.
What alternative approach has the EAG suggested?	The EAG is content with a comparison of data based on the randomisation within INCREASE. A naïve comparison of INCREASE to the CPRD study is the only way to explore using this alternative source, as the company did not complete a MAIC matching to the CPRD dataset.
What is the expected effect on the cost-effectiveness estimates?	A naïve comparison of Kaplan-Meier plots suggests that inhaled treprostinil is dominated by the RHC population of the CPRD study.
Could any additional evidence or analyses be provided to resolve this key issue?	The company could implement a MAIC adjusting for age and sex differences between the two sources, however no further covariates were available to be matched on.

Issue 5: Choice of extrapolation for inhaled treprostinil overall survival

Report section	4.2.2.2, 4.2.5.3
Description of issue and why the EAG has identified it as important	The company selected a Weibull extrapolation, which is the model with the most optimistic predictions from models which capture an increasing hazard rate.
What alternative approach has the EAG suggested?	The EAG selected a generalised gamma extrapolation for the EAG base case, which also models an increasing hazard rate, and explored the impact of using a Gompertz model, which is the only other model with an increasing hazard rate.
What is the expected effect on the cost-effectiveness estimates?	Using either the generalised gamma (ICER = £36,308) or Gompertz models causes a large increase in the ICER, compared to the Weibull model.
Could any additional evidence or analyses be provided to resolve this key issue?	Longer follow-up from INCREASE would inform the long-term efficacy on survival and other outcomes which could serve as potential surrogates for overall survival.

Issue 6: Approach to extrapolation for inhaled treprostinil time to treatment discontinuation

Report section	4.2.2.3, 4.2.5.4
Description of issue and why the EAG has identified it as important	Within the observed follow-up, a comparison of time to discontinuation (TTD) for treprostinil and second clinical worsening (CW2) suggests that people remain on treatment beyond CW2. However, in the company's extrapolations into the future, TTD is shorter than CW2. The EAG considers there is no rationale for this change, and so the company's model is likely to be underestimating the true duration of treatment with inhaled treprostinil.
What alternative approach has the EAG suggested?	The EAG adds a constraint to the modelling of TTD so that it cannot fall below the extrapolation for CW2.
What is the expected effect on the cost-effectiveness estimates?	This has a moderate effect on the cost-effectiveness analysis (ICER = £33,952)
Could any additional evidence or analyses be provided to resolve this key issue?	An extended follow-up, or the establishment of a clear stopping rule, could reduce the uncertainty around this aspect of modelling.

Issue 7: Inappropriate choice of utility values and analysis of health-related quality of life data.

Report section	4.2.6.1
Description of issue and why the EAG has identified it as important	No EQ-5D data was collected in INCREASE. Hence the company rely on mapping data from the St George's respiratory questionnaire. The company prefers to use utility values from a univariate analysis, however, the EAG considers this prone to bias.
What alternative approach has the EAG suggested?	The EAG prefers to use utility values obtained from a generalised linear model analysis.
What is the expected effect on the cost-effectiveness estimates?	Moderate (ICER = £30,455)
Could any additional evidence or analyses be provided to resolve this key issue?	Additional research capturing the quality of life using EQ-5D could reduce uncertainty.

1.4 Secondary issues identified by the EAG

The EAG has identified several secondary issues, which have a reduced impact on the cost-effectiveness results.

Issue 8: Potential for bias from difference in definition of clinical worsening used across clinical and cost-effectiveness sections

Report section	3.3.2.4, 4.2.2.1
Description of issue and why the EAG has identified it as important	The company's definitions for clinical worsening in the cost-effectiveness section adds two additional types of events, compared to the definition of clinical worsening as defined in the INCREASE trial. These are: acute lung disease exacerbation and decrease in FVC of ≥ 10% from baseline.
What alternative approach has the EAG suggested?	The EAG has compared the Kaplan-Meier functions for these outcomes and considers the potential for bias and impact on the ICER to be small.
What is the expected effect on the cost-effectiveness estimates?	Small (not explored in cost-effectiveness)
Could any additional evidence or analyses be provided to resolve this issue?	The company could implement economic analyses using an identical definition of clinical worsening as the INCREASE trial protocol.

Issue 9: Choice of extrapolation for first clinical worsening (CW1)

Report section	4.2.5.1
Description of issue and why the EAG has identified it as important	The company selects two separate types of parametric model to extrapolate CW1 data for inhaled treprostinil and BSC. The EAG is concerned the choice of models may be influenced by the differing lengths of follow-up and could be a source of bias.
What alternative approach has the EAG suggested?	The EAG uses log-logistic extrapolations for both arms.
What is the expected effect on the cost-effectiveness estimates?	Small for inhaled treprostinil (ICER = £27,854) and BSC (ICER = £28,251)
Could any additional evidence or analyses be provided to resolve this issue?	No

Issue 10: Inappropriate application of discounting in first year of the model

Report section	4.2.2.4
Description of issue and why the EAG has identified it as important	The company apply discounting on a weekly basis, beginning from the start of the model time horizon. The EAG understands discounting rates should be applied from after one year has passed within the model.
What alternative approach has the EAG suggested?	The EAG does not apply discounting within the first year of the economic model.
What is the expected effect on the cost-effectiveness estimates?	Small. (ICER = £27,960)
Could any additional evidence or analyses be provided to resolve this issue?	No.

Issue 11: Inaccuracies in dosing and costing assumptions for background medications

Report section	4.2.7.1
Description of issue and why the EAG has identified it as important	The EAG noted discrepancies in the pack sizes, dosing and prices used by the company for pirfenidone and nintedanib. These overestimate costs for BSC.
What alternative approach has the EAG suggested?	The EAG uses pricing and pack sizes using eMIT prices and corrects the dosing error for nintedanib.
What is the expected effect on the cost-effectiveness estimates?	Small. (ICER = £27,682)
Could any additional evidence or analyses be provided to resolve this issue?	No.

Issue 12: Underestimation and simplification of ongoing resource use and costs

Report section	4.2.7.3
Description of issue and why the EAG has identified it as important	The company's choice of inputs for representing resource use appears to underestimate use compared to data included in the company's CPRD report.
What alternative approach has the EAG suggested?	The EAG prefers to use the CPRD as the source for a range of inputs to represent NHS resource use for people with PH-ILD.
What is the expected effect on the cost-effectiveness estimates?	Small. (ICER = £29,565)
Could any additional evidence or analyses be provided to resolve this issue?	No.

Issue 13: Costs relating to lung transplant

Report section	4.2.7.2
Description of issue and why the EAG has identified it as important	The company does not include costs relating to lung transplant, though a small number of people do receive lung transplants in the INCREASE study, the efficacy of which is included for overall survival.
What alternative approach has the EAG suggested?	The EAG includes costs of lung transplant for the small proportion of people who received them within the INCREASE study.
What is the expected effect on the cost-effectiveness estimates?	Small. (ICER = £28,572)
Could any additional evidence or analyses be provided to resolve this issue?	No.

1.5 Company's modelling errors identified by the EAG

The EAG's review did not identify any major modelling errors in the company's economic model. However, two minor technical issues were noted:

First, a computational error occurs when certain survival distributions are selected for inhaled treprostinil overall survival (OS) while applying the hazard ratio (HR) for BSC. Specifically, the model produces a #NUM! error due to the use of the function –LN(0), located in column R (H(t)) of the OS calculation worksheet.

Second, in incorporating lung transplant costs, the model does not correctly calculate the total cost based on the known proportion of patients receiving a transplant (2 out of 163). The correct undiscounted cost should be approximately £960, calculated as (2/163) × £78,316 (unit cost of transplant). While there is a discrepancy in the implemented value, the EAG confirms that the resulting impact on the ICER is negligible.

Third, according to the NICE Reference Case 2023 (Section 6.2.11), decision-making modifiers (such as the severity modifier) are based on value judgments and factors beyond QALYs, and therefore should not be directly included in the QALY estimate. However, in the company's base case analyses, the severity modifier was applied by multiplying the total QALYs by the modifier in both arms of the model. This approach is incorrect and may lead to a misinterpretation of the true QALY gains, as it embeds the modifier directly into the QALY calculation rather than applying it separately in the decision-making process.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 demonstrates the individual and combined impact of the EAG's changes from the company's base case analysis.

Table 2: Summary of EAG's preferred assumptions and ICER pairwise v BSC (deterministic)

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case	[redacted]	[redacted]	£28,000
Change 1: OS inhaled treprostinil gen gamma	[redacted]	[redacted]	£36,308
Change 2: OS BSC using ITT HR	[redacted]	[redacted]	£65,919
Change 3: CW1 inhaled treprostinil log-logistic	[redacted]	[redacted]	£27,854
Change 4: CW1 BSC log-logistic	[redacted]	[redacted]	£28,251
Change 5: TTD inhaled treprostinil not below CW2	[redacted]	[redacted]	£33,952
Change 6: No discounting in year 1	[redacted]	[redacted]	£27,960
Change 7: Utility values from GLM	[redacted]	[redacted]	£30,455
Change 8: Dosing/pricing change for nintedanib/pirfenidone	[redacted]	[redacted]	£27,682
Change 9: Resource use changes	[redacted]	[redacted]	£29,565
Change 10: Include lung transplant costs	[redacted]	[redacted]	£28,572
EAG's preferred base-case deterministic	[redacted]	[redacted]	£122,475
EAG's preferred base-case probabilistic	[redacted]	[redacted]	£109,402

1.7 Outline of confidential comparator or subsequent treatment prices

The EAG report includes a separate cPAS appendix, which applies confidential pricing for at least one other treatment that is included in the economic model.

2 Background

The purpose of this appraisal is to evaluate the clinical and cost effectiveness of inhaled treprostinil within its anticipated marketing authorisation for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD). At the time of this appraisal, inhaled treprostinil does not yet have marketing authorisation for any indication in the UK. The expected date of Medicines and Healthcare products Regulatory Agency (MHRA) approval is currently unknown.

2.1 Critique of the company's description of underlying health problem

2.1.1 Condition, incidence and prognosis

Pulmonary hypertension (PH) associated with lung disease and/or hypoxia classified as World Health Organization (WHO) Group 3 is characterised by elevated pulmonary arterial pressure and vascular resistance, typically resulting from chronic lung diseases such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD).[1] Group 3 PH arises due to impaired oxygen exchange caused by these conditions. It often indicates more advanced disease and is associated with poorer outcomes. Unlike other PH groups, treatment focuses on managing the underlying lung disease and improving oxygenation, as PH-specific therapies are generally less effective.[2-4]

ILD refers to a group of disorders that cause progressive scarring of the lung interstitium, the tissue surrounding the air sacs. This fibrosis impairs oxygen transfer, leading to symptoms like breathlessness, dry cough, and fatigue. Causes of ILD include autoimmune diseases, environmental exposures, medications, or unknown factors, as in idiopathic pulmonary fibrosis (IPF). As ILD progresses, chronic hypoxia, fibrosis and inflammation can lead to vascular remodelling, resulting in pulmonary hypertension, placing patients in WHO Group 3, which significantly worsens prognosis and quality of life.[4, 5]

PH-ILD yearly prevalence and incidence rate (Incidence rate per 10,000 person years (95% CI)) in 2019 were reported as 0.36 (0.33 – 0.38) and 0.19 (0.18-0.21), respectively.[6]

Estimates of the prevalence of PH-ILD vary and may be as high as 86%, depending on the type of ILD and disease severity. Patients with PH-ILD experience reduced exercise capacity, increased oxygen needs, lower quality of life, and earlier death compared to those with ILD or PH alone. In idiopathic pulmonary fibrosis (IPF), mean pulmonary arterial pressure (mPAP)≥25 mmHg is seen in 8–15% at diagnosis, 30–50% in advanced stages, and over 60% in end-stage disease.

In PH-ILD, prognosis worsens in people with severe PH (PVR >5 Wood units), particularly in those with IPF.[1, 7] Right ventricular dysfunction, elevated N-terminal pro B-type natriuretic peptide (NT-proBNP), reduced six-minute walk distance (6MWD), greater oxygen dependency, and WHO functional class III/IV are all associated with higher mortality.[7] This submission focuses on patients PH-ILD (WHO Group 3 PH), diagnosed via right heart catheterization (RHC) as part of the PH-ILD pathway.[4, 8, 9]

2.1.2 Diagnosis

Group 3 PH is suspected in patients with ILD based on their NT-proBNP levels and/or echocardiogram results, or if they are experiencing worsening breathlessness or have high oxygen requirements. Other key diagnostic indicators are diffusing capacity of the lungs for carbon monoxide (DLCO) tests, indicating poor gas transfer; computed tomography (CT) scans showing pulmonary artery dilation or echocardiograms showing a high probability of PH.[10-12]

Right heart catheterisation (RHC) is considered the gold standard for diagnosing pulmonary hypertension (PH), as outlined in the 2022 ESC/ERS clinical guidelines. RHC is recommended when results will guide treatment, severe PH is suspected, or patients are being evaluated for lung transplantation or lung volume reduction surgery. PH is classified as severe if pulmonary vascular resistance (PVR) exceeds 5 Wood units (WU); otherwise, it is considered non-severe.[4]

According to EAG clinical experts, echocardiography is useful for identifying suspected cases based on symptoms, but confirmation with RHC is essential.

This is particularly important in the PH-ILD population, who are often older and/or have underlying connective tissue disease and are therefore at increased risk of left heart disease, which can complicate diagnosis.

2.2 Critique of the company's overview of current service provision

2.2.1 Group 3 PH management

The management of Group 3 PH, which includes PH associated with chronic lung diseases and/or hypoxia, focuses on optimising the underlying pulmonary condition. This may involve the use of antifibrotic, parenteral cytotoxic, biological and chemotherapeutic agents, as well as plasmapheresis and intravenous immunoglobulins.[13]

PDE5 inhibitors, such as sildenafil and tadalafil, are orally administered agents that enhance the nitric oxide–cGMP pathway by inhibiting cGMP degradation (meaning they help relax blood vessels in the lungs by boosting a natural chemical that widens them and improves blood flow). Sildenafil, approved at 20 mg three times daily, has demonstrated benefits in exercise capacity, symptoms, and haemodynamics in several PAH trials, with mostly mild vasodilatory side effects.[14-16] Tadalafil, taken once daily at doses up to 40 mg, has shown similar efficacy and tolerability in PAH patients.[17] Although registry data indicate that PDE5is are used in some patients with PH associated with interstitial lung disease (PH-ILD, WHO Group 3),[18-20] there are no direct RCTs evaluating their safety or efficacy in this population. Due to the lack of robust evidence, current guidelines do not support a firm recommendation for or against their use in PH-ILD, and referral to a PH centre for individualized management is advised.[21, 22]

For PH-ILD, systemic vasodilators such as endothelin receptor antagonists and soluble guanylate cyclase stimulators like riociguat are not recommended due to adverse outcomes, including increased risk of clinical worsening and mortality.[23-25] Similarly, large trials of sildenafil have shown no significant benefit in this population.[26, 27]

Conventional therapies such as anticoagulants, diuretics, and calcium channel blockers are generally not indicated in Group 3 PH unless other comorbidities

justify their use.[28-30] The use of systemic pulmonary vasodilators is particularly challenging in this group due to the risk of worsening ventilation-perfusion mismatch and their inconsistent efficacy.[31, 32] Prostacyclins are currently considered only for Group 1 (pulmonary arterial hypertension) and Group 4 (pulmonary hypertension due to chronic thromboembolic disease). Their broader use is limited by complex administration requirements and frequent adverse effects, such as low blood pressure (hypotension), headache, jaw and leg pain, nausea, diarrhoea, and dizziness.[33, 34]

Given the significant impact of even non-severe PH on symptoms, quality of life, and survival, eligible patients should be referred for lung transplantation evaluation. For those with severe PH and/or right ventricular dysfunction, or where treatment decisions are uncertain, referral to a PH centre is essential to guide individualized therapy and potential inclusion in clinical trials.

2.2.2 Treatment pathway

The EAG clinical experts noted that in certain cases, patients may be referred to a PH centre, where treatment with PDE5i might be considered. However, the evidence supporting their use remains limited due to a lack of robust clinical data. Despite this, their inclusion in the treatment pathway is justified by the fact that some patients within NHS care continue to receive these therapies.

The company has indicated that those taking treatment decisions may consider underlying ILD, with inhaled treprostinil potentially used either as monotherapy or in conjunction with other therapies. Background treatments such as pirfenidone or nintedanib have been reported; however, analyses regarding the efficacy of inhaled treprostinil in combination with these or other concomitant therapies were not performed due to small patient numbers.

The EAG's proposed positioning of inhaled treprostinil within the NHS treatment landscape is shown in Figure 1. The EAG's clinical expert commented that tests patients take or require in the NHS may be more complicated. They noted that "p*atients with PH and CTD-ILD are often referred from Rheumatology clinics or joint Respiratory-Rheumatology clinics. CTD patients have annual screening for PH with echo and lung function tests but this wouldn't be the case for other ILD*

patients. Patients with idiopathic interstitial pneumonia (IIPs) could be under the ILD centre or respiratory specialist for some time before PH is suspected or investigated. The transplant referral part is missing".

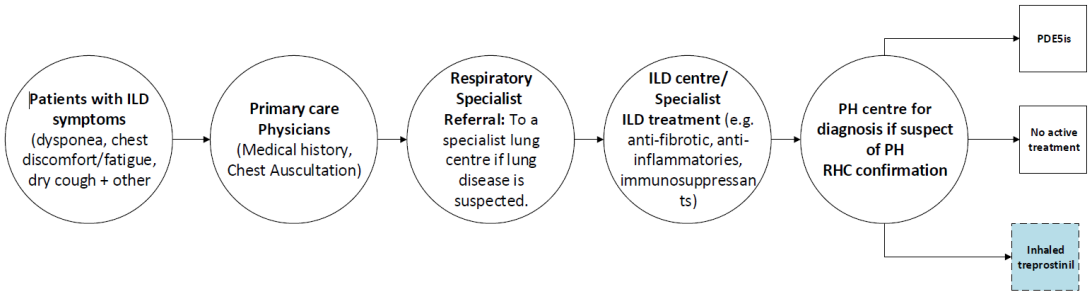


Figure 1: Proposed place of inhaled treprostinil in the PH-ILD diagnosis and treatment pathway (adapted from the company's figure 3)

Abbreviations: ILD: Interstitial lung disease; PDE5i: Phosphodiesterase-5 inhibitors; PH: Pulmonary hypertension.

2.2.3 Inhaled treprostinil administration challenges

Inhaled treprostinil is a type of medication called a prostacyclin analogue. It works by widening the blood vessels (vasodilation) and helping to prevent blood platelets from sticking together (inhibiting platelet aggregation). After it's taken, it reaches its highest level in the blood within about 7 to 15 minutes. Most of the drug in the bloodstream is bound to proteins (about 91%), which affects how it moves through and acts in the body.

Inhaled treprostinil is for inhalation via nebulisation and is designed for exclusive use with its nebuliser. Its safety and effectiveness with other nebulising systems are not established. Patients should be trained and supervised when starting treatment to ensure proper dosing and inhalation technique. The inhaled treprostinil nebuliser is an ultrasonic, pulsed-delivery device that must be prepared daily, with inhalation sessions programmed individually.

The company state that the inhalation solutions/dry powders cannot be used with other inhalation systems. The inhalation formulations, whether as solutions or dry powders, are not interchangeable with alternative inhalation delivery systems. Caution has been advised regarding the potential for symptomatic hypotension in

individuals with reduced systemic arterial pressure, as well as the risks of bleeding, acute bronchospasm, and airway hyperresponsiveness.[35] Inhaled treprostinil may cause systemic hypotension, especially in patients with low blood pressure, and monitoring is recommended during dose adjustments.

The potential for dosing errors, particularly in the context of patient-dependent administration, raises concern, as even minor deviations may precipitate life-threatening hypotension or rebound pulmonary hypertension. Additional challenges include the probability of inconsistent instruction by healthcare providers, the need for specific inhalation techniques distinct from other devices, and the overall burden placed on patients managing complex regimens. Practical demands such as mastering breathing techniques, adhering to treatment frequency, and managing daily preparation, assembly, and cleaning of the device may be perceived as overwhelming. These factors underscore the importance of coordinated, up-to-date communication and support across the care team to ensure safe titration, monitoring, and mitigation of adverse effects.[36]

These limitations have prompted ongoing research efforts aimed at refining delivery mechanisms and developing more practical, orally administered alternatives.[37] For patients with advanced disease, unresponsive to medical therapy, lung transplantation may be pursued, while early integration of palliative care remains essential to address symptom burden and support quality of life.[33, 34]

2.2.4 Role of RHC in the diagnostic and treatment pathway

A panel of eight clinical experts, as referenced by the company, highlighted persistent challenges in diagnosing PH-ILD: primarily due to limited referrals of people with ILD to PH centres. This is driven by the lack of licensed treatments and logistical barriers. As a result, referrals typically occur only when severe PH (PVR ≥5 WU) is suspected, leaving many patients undiagnosed or managed solely within ILD services. RHC, the gold standard for diagnosis, is reserved for those cases where there is a strong clinical suspicion, further limiting early detection. Regional variation in referral rates and differences in ILD subtypes, such as higher referral for connective tissue disease (CTD-ILD) and lower for

combined pulmonary fibrosis and emphysema (CPFE), also contribute to inconsistent access to PH assessment.

This late diagnosis pattern is reflected in CPRD/HES data, where most patients (N=1,561) were not RHC-confirmed and showed poor survival in contrast to those who had RHC. In contrast, both the CPRD/HES subgroups and Dawes et al. (2022) suggest better outcomes in patients who underwent RHC, though the reasons for this are unclear. The EAG experts confirmed that NHS patients generally experience higher mortality than those shown in the CPRD/HES RHC-confirmed dataset. This is likely due to RHC acting as a proxy for better access to care and services and possibly a more interventionist approach.

The EAG assumes that if RHC were used more routinely as part of NHS practice to diagnose PH in lung disease, it may lead to earlier diagnoses and consequently, identification of patients at a younger age. This may result in more life-years gained and potentially improved quality of life. However, there is limited evidence directly examining the impact of RHC on the age at diagnosis and, by extension, on the average fitness and mortality of the subsequent population.

Furthermore, RHC is a standard and essential prerequisite for cardiac and lung transplantation[4, 38, 39] and has routinely been used for transplant-eligible patients. The EAG's clinical expert noted: "*Nearly all patients with PH or lung disease will undergo RHC prior to or as part of their transplant assessment. Some patients with congenital heart disease may not routinely require RHC. Only a proportion of PH patients are referred for transplant; age is a key consideration, and while there is no strict threshold, referred patients are typically under 65*". In conclusion, although the evidence is uncertain, the EAG cannot reject the assumption that younger and fitter patients are likely to have received RHC within NHS care due to various clinical considerations, including transplant eligibility. However, due to limitations in the available evidence, the EAG cannot confirm the impact of these assumptions.

2.3 Critique of the company's definition of decision problem

The EAG's comments on the company's decision problem are in Table 3. Given the limited treatment options, in line with NICE and EAG clinical experts, the exclusion of PDE5i as a potential comparator is a concern.

Table 3: Summary of decision problem

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with a confirmed diagnosis of pulmonary hypertension with interstitial lung disease.	Adult with a confirmed diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD WHO Group 3)	Inhaled treprostinil is anticipated to be indicated specifically for PH-ILD, within WHO Group 3.	Slightly deviated from NICE's decision problem. The company's recommendation is in line with the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension[4] and in line with anticipated indication for MHRA marketing authorisation The EAG agrees with the company.
Intervention	Inhaled treprostinil	As per NICE final scope	N/A	In line with NICE decision problem.
Comparator(s)	• Established clinical management without inhaled treprostinil • Phosphodiesterase 5 inhibitors (PDE5is): sildenafil and tadalafil	Established clinical management, without inhaled treprostinil (best supportive care)	European guidelines state that PDE5is (such as sildenafil and tadalafil) may be considered on a case-by-case basis in patients with severe PH-ILD (defined in the guidelines as patients with a PVR ≥5 WU).[4] The use of PDE5is in patients with non-severe PH-ILD is not recommended. These recommendations are	Narrower than NICE decision problem. For the severe disease, the EAG's clinical advisor noted that excluding PDE5i may be challenging due to limited treatment alternatives. However, patients with mild PH-lung disease are not currently referred to PH centres. They noted that usage varies widely across

			based on conflicting and limited evidence. Additionally, expert clinical insights from the UK advisory board indicated that PDE5is are only used in a small percentage of very severe PH-ILD patients (in the absence of any licensed treatment), with low expectations of effectiveness and are not considered standard of care in the overall patient population.[40] This is supported by results from the UK-based epidemiological study (commissioned by Ferrer), which reported that only 8% of patients with PH-ILD received PDE5is (sildenafil or tadalafil).[41] As such, PDE5is are not considered to be relevant comparators.	centres (up to 60%) likely reflecting this gap. Similarly, a UK real-world study by the company found at least 8% of PH-ILD patients received PDE5i.[41] It also reports that 14-18% of PH Group 3 patients and 13-21% of PH-ILD patients had received PAH therapies. The EAG concurs with the comparators recommended by NICE.
Outcomes	The outcome measures to be considered include: • exercise capacity (for example 6-minute walk distance – 6MWD) and other measures of physical function	The outcome measures to be considered in the company submission are: • exercise capacity • time to clinical worsening • hospitalisations	The following outcomes were not assessed in the trial: • transplant-free survival	Narrower than NICE's decision problem, the EAG agrees with the company's listed outcomes given the low rate of transplant in this population.

	• time to clinical worsening • hospitalisations • overall survival • lung function • breathlessness • haemodynamic assessment (for example cardiac index, cardiac output, right atrial pressure, pulmonary arterial pressure and pulmonary vascular resistance) • fatigue • transplant-free survival • adverse effects of treatment • health-related quality of life	• overall survival • lung function • breathlessness • haemodynamic assessment • fatigue • adverse effects of treatment • health-related quality of life		
Subgroups	If the evidence allows, the following subgroups will be considered: Different types of interstitial lung disease, for example idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, idiopathic interstitial pneumonia, sarcoidosis, hypersensitivity pneumonitis	A subgroup analysis of patients with PH-ILD, excluding those with combined pulmonary fibrosis and emphysema CPFE) is considered	Considering the number of patients in the trial and the number of different types of interstitial lung disease (ILD) (>200), it was not feasible to conduct further subgroup analyses	Narrower than NICE. The number of subgroups raises concerns about statistical power. The EAG agrees with the company's justification for focusing on certain predefined subgroups.

Special considerations including issues related to equity or equality	NA	NA	NA	EAG clinical experts highlighted recognised concerns regarding long travel distances to PH centres and the potential inequities arising from socioeconomic barriers to access. While many patients travel over 50 miles to reach a specialist centre, the majority still prefer specialist care over local non-specialist services. However, challenges related to poor physical health and financial constraints remain significant. If PH centres are required to deliver inhaled treprostinil, expansion in their number or capacity may be necessary, potentially straining existing resources and affecting access for other PH patient groups. The requirement for RHC before treprostinil administration, further adds to the complexity of treatment delivery.

Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; EAG, Evidence Assessment Group; ESC/ERS Guidelines, European Society of Cardiology/European Respiratory Society Guidelines; MHRA, Medicines and Healthcare products Regulatory Agency; NA, not applicable; NICE, National Institute for Health and Care Excellence; PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; RHC, right heart catheterisation.

3 Clinical effectiveness

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR), reported in CS Appendix B, to identify published studies on PH-ILD treatments. CS section 2.1 and Appendix B.1 suggest that evidence from RCTs and observational studies was sought; however, the eligibility criteria (Appendix B.1.2, Table 4) also included single-arm and non-randomised trials.

3.1.1 Systematic literature review methodology

A summary of the EAG's quality assessment of the company's SLR using the modified risk of bias assessment tool for systematic reviews (ROBIS)[42] is presented in Table 4. The full EAG assessment using the modified ROBIS is in the EAG Appendix, section 7.1. Overall, the EAG found the company's SLR to have a high risk of bias.

Table 4: Summary of the EAG's critique of the company SLR

Method step	Section(s) of CS of relevance	EAG overall assessment
Eligibility criteria	CS, appendix B, section B.1.2	High concern
Searches and selection of studies	CS, appendix B, section B.1.1	High concern
Data extraction and risk of bias assessment	CS, appendix B, sections B.1.2, B.3	Some concerns
Evidence synthesis	CS, appendix B, sections B.1.2, B.1.3	Some concerns

Eligibility criteria

The comparator arm was broadly defined, with limited detail provided, which may affect the clarity of comparisons. Some studies, including those involving elderly or frail populations with missing data, were excluded based on criteria that were not explicitly defined in advance. Additionally, the approach to identifying conference abstracts was not clearly determined, which may have

influenced the completeness of the evidence base, particularly given the limited availability of observational data.

Searches and selection

The search strategy lacked clarity in scope and may not have fully captured relevant evidence, particularly from earlier conference abstracts, non-randomised or single-arm trials, or broader PH populations. Trial registries, a key source recommended by the Cochrane Handbook for systematic reviews of interventions,[43] were not considered, and some methodological steps like citation searching were not clearly reported. An upload error resulting in the wrong set of Cochrane CENTRAL results being screened further undermines confidence in the search and selection processes.

Data extraction and risk of bias assessment

Only limited information was provided on data collection, extraction, and study results, with no justification for narrowing included studies. The use of the JBI checklist may have underestimated bias due to its lack of depth compared to Cochrane's recommendations.

Evidence synthesis

Some referenced datasets in the main submission were not used for the MAIC analysis. 3 of 35 included studies were incorporated and analysed, despite broader evidence being identified. Sensitivity analyses lacked detail, and the Cochrane RoB tool for the systematic reviews was not used.

3.2 Critique of the methods of the trials of the technology of interest

The company used data from the INCREASE trial, a phase 3, multicentre, randomised controlled trial with a 16-week follow-up period. After this initial phase, eligible patients were enrolled into a single-arm, open-label extension (OLE) study. Patients who had previously received placebo were crossed over to receive inhaled treprostinil for an additional 108 weeks. Taken

together, the INCREASE RCT and OLE phases spanned approximately 124 weeks.

Short trial duration and high dropout rate: The 16-week trial duration is relatively short for assessing and interpreting INCREASE RCT outcomes. 21% of participants discontinued before week 16, exceeding the anticipated dropout rate and potentially reducing statistical power. Only a small proportion of participants completed long-term follow-up (OLE study), with varied follow-up durations. In the OLE study, no imputation was used to account for early discontinuations, which may have included patients with clinical deterioration.

Risk of bias: Clinical worsening and exacerbations were investigator-reported without independent adjudication, introducing subjectivity. Unblinded investigators were involved in participant selection and exclusion, which may have introduced selection bias. The open-label extension (OLE) was single-arm and unblinded, with sponsor-defined outcomes that were inconsistently applied. Sponsor encouragement for participants to remain in the trial despite discontinuation may have affected autonomy and introduced bias.

Generalisability: Differences in demographics, smoking history, disease profile, and treatment use suggest that the INCREASE trial population may not fully reflect real-world clinical settings, potentially limiting broader interpretations.

3.2.1 Trial design

The EAG's summary of the key features of INCREASE RCT and its OLE, based on the company' submitted information, are summarised in Table 5.

Table 5: Summary of INCREASE RCT and OLE trials

Method step	Summary of the approach used	Section(s) of CS of relevance or other sources

Trial design and location	The INCREASE study (NCT02630316) was a phase 3, multicentre, randomised, double-blind, placebo-controlled, 16-week, parallel-group trial conducted at 119 sites across the US and Puerto Rico. The INCREASE OLE study (NCT02633293) was a phase 3, multicentre, open-label extension with a single group assignment, conducted at 92 sites in the US and Puerto Rico.	CS appendix J
Method of randomisation	Randomization based on a 1:1 ratio was conducted using permuted blocks and stratified by baseline 6-minute walk distance (≤350 m vs. >350 m), facilitated through an interactive web-response system. The OLE had an open-label structure.	CS doc B section 2.3; CS appendix J
Eligibility criteria	Adults aged 18 or older with WHO Group 3 PH associated with ILD or CPFE were eligible if CT imaging within six months confirmed diffuse parenchymal lung disease. RHC within the past year had to show PVR >3 WU, PCWP ≤15 mmHg, and PAPm ≥25 mmHg. A baseline 6MWD of at least 100 metres and a stable dose of any chronic lung medication for at least 30 days were also required. Final inclusion was contingent on the investigator's discretion. Beyond meeting clinical criteria, patients had to be deemed suitable in the investigator's opinion. The investigator's role and decision-making have been considered in both inclusion and exclusion criteria. Additional exclusions applied to those with prior intolerance to or inefficacy of prostacyclins, recent use of PAH therapies (within 60 days), or left-sided heart disease unless due solely to right heart strain. Patients were also excluded if they required >10 L/min of oxygen at rest, had recent exacerbations or infections (within 30 days), or were using inhaled tobacco or marijuana, or had a significant history of drug abuse. Eligibility for the OLE was limited to patients who had either remained on the study drug and completed all scheduled visits during INCREASE, discontinued due to clinical worsening but fulfilled visit requirements, or were still enrolled when the sponsor ended the study. Exclusion applied to those with serious or life-threatening AEs, the investigator's judgment, protocol deviations, or behaviours deemed likely	CS appendix J; Waxman et al. (2021)[44]

	to compromise data integrity, as well as those who initiated infused prostacyclin therapy for more than 29 days.	
Treatment regimens	Treprostinil inhalation solution (0.6 mg/ml) was administered via ultrasonic nebulizer at 6 µg per breath, starting at 3 breaths (18 µg) four times daily, with in-clinic initiation and 1-hour observation. The dose was titrated by 1 breath every 3 days to a target of 9–12 breaths (54–72 µg) per session, totalling 216–288 µg daily, tailored to individual tolerance; in the INCREASE trial, patients reached 12 breaths per session, while in the OLE phase, dosing was re-initiated at 3 breaths with a maximum of 15. The company reminded investigators that patients starting treprostinil should be trained and closely supervised in using the nebuliser. They added that elderly patients should be cautious due to increased risks of organ impairment and drug interactions. One 2.9 ml ampoule was regarded as covering.	CS appendix J; Waxman et al. (2021)[44]
Measured outcomes	The INCREASE trial's primary endpoint was change in peak 6MWD from baseline to Week 16. Secondary endpoints included changes in NT-proBNP, 6MWD at peak/trough treprostinil levels (Weeks 12 and 15), and time to clinical worsening defined by hospitalization, >15% 6MWD decline, lung transplant, or death. No prespecified outcomes were considered for the OLE phase. The OLE study has aimed to provide observational data on long-term safety and efficacy in an open setting.	CS appendix J; Waxman et al. (2021)[44]
Statistical analysis	To detect a 30-metre difference in peak 6-minute walk distance between treprostinil and placebo groups at week 16, 314 patients were randomised, accounting for a 15% dropout rate. The primary efficacy analysis used mixed-model repeated-measures methods, with baseline walk distance as a covariate. Sensitivity analysis employed multiple imputation. In the OLE phase, analyses were performed on the safety population, with descriptive statistics summarizing results. New adverse events were tabulated, and time to exacerbation of lung disease, cardiopulmonary hospitalization, and death were analysed using the Kaplan–Meier	CS doc B section 2.4; Waxman et al. (2021)[44]

	method and log-rank test. Hazard ratios were obtained using a Cox regression model.

Abbreviations: 6MWD, six-minute walk distance; AE, adverse event; CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; FVC, forced vital capacity; IQR, interquartile range; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro–B-type natriuretic peptide; OLE, open-label extension; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SD, standard deviation; WU, Wood units.

The 350-metre baseline 6MWD threshold used for randomisation was sourced from COPD literature and has been shown to inversely correlate with risk of hospitalisation and mortality in PH-ILD (clarification question A4). Stratifying solely by this cut-off may overlook other relevant factors such as pulmonary function (FVC, DLCO), age, sex, extent of fibrosis, and biomarkers like NT-proBNP. While the company justified this approach based on the small sample size (clarification question A4), the EAG believes some of these prognostic variables could have been incorporated, raising concerns about the adequacy of risk stratification.

Table 6 presents the EAG's summary of the company's stated key endpoints for the INCREASE trial based on submitted information.

Table 6: EAG summary of the company's stated key endpoints for (INCREASE RCT and OLE) based on submitted information

Objectives	Endpoint Description	Assessment	Chosen Assessment Time Points	Incorporated into Economic Analyses
Primary Endpoint	Change in peak 6MWD from baseline	6MWT conducted 10–60 minutes post-dose	Baseline, weeks 4, 8, 12, 16, or early discontinuation; Week 20, 28, then every 12 weeks up to week 124	Not incorporated

Secondary and exploratory Endpoints	Change in peak 6MWD, plasma NT-proBNP levels, and trough 6MWD; Time to clinical worsening; time to exacerbation	Trough 6MWD at least 4 hours after dose, and at least 24 hours before week 16 test Time to Clinical Worsening from randomisation until hospitalisation (cardiopulmonary), ≥15% drop in 6MWD (confirmed at 2 visits ≥24h apart), death (any cause), or lung transplantation	Baseline to week 4, 8,12, 15, 16, 64, 124	Incorporated
Exploratory PROs	Quality of life	SGRQ	Baseline to week 16, 64 and 124	Incorporated
Safety	AE, SAE, and hospitalization	Vital signs, labs, ECG, PFTs, oxygenation, AE	From informed consent to study termination or week 124	Partially incorporated

Abbreviations: 6MWD, six-minute walk distance; 6MWT, six-minute walk test; AE, adverse event; ECG, electrocardiogram; NT-proBNP, N-terminal pro b-type natriuretic peptide; OLE, open-label extension; PFTs, pulmonary function tests; PROs, patient-reported outcomes; SAE, serious adverse event; SGRQ, St. George's Respiratory Questionnaire.

INCREASE trial

Eligibility assessments were conducted by investigators before randomisation. In the INCREASE trial, 29.4% (136/462) of patients were not enrolled by investigators before randomisation. Although re-evaluation for eligibility was permitted (CSR INCREASE, p. 56), the proportion of such cases was not reported. The company did not provide details on these excluded patients, but general reasons (per clarification question A2) included failure to meet criteria, screening period exceeding 30 days, consent withdrawal, adverse events, death, or disease progression.

Following eligibility confirmation, 326 participants were selected and enrolled between February 3, 2017, and August 30, 2019. Although a 15% dropout

rate was anticipated, higher premature discontinuation rates were observed: 24.5% in the treprostinil group and 23.3% in the placebo group. Reasons included adverse events (9.8% vs. 8.0%), progressive disease (3.7% vs. 6.1%), death (3.7% vs. 3.1%), withdrawal by subject (4.3% vs. 5.5%), protocol violations (1.8% vs. 0.0%), and other causes (1.2% vs. 0.6%). Ultimately, 20.2% of treprostinil and 21.5% of placebo participants did not complete the final assessment, exceeding the expected 15% dropout rate and potentially affecting the study's statistical robustness and interpretability. To preserve statistical power, participants were encouraged to complete assessments through week 16, though no further details on the nature of this encouragement were provided. This approach may introduce potential bias.

INCREASE OLE

At week 16, 130 treprostinil and 128 placebo patients completed the trial, though 8.5% and 5.5%, respectively, did not enter the open-label extension (OLE) phase, with no justifications reported. Two additional patients, initially excluded due to labelling discrepancies, were subsequently included.

The selection process for the OLE phase and involvement of unblinded personnel may have introduced bias. Of the 242 participants enrolled, only 70 (28.9%) completed the planned 108-week treatment, which marked the final data cut. Per protocol, the study was discontinued by the sponsor following FDA approval of inhaled treprostinil for PH-ILD. At termination, all participants had been enrolled for at least 60 weeks, and those who had completed or were still active at Week 108 were assessed for eligibility under the external Continued Access Plan. Scheduled visits were infrequent and inconsistently applied (e.g., at weeks 20, 28, and every 12 weeks thereafter). Clinical worsening was not assessed, and key endpoints such as HRQoL and NT-proBNP were measured only at weeks 64 and 124 or at early termination. Dosing in the OLE was individualized based on tolerability and clinical response. By study end, 80.6% reached at least 9 breaths (suggested optimal dose) four times daily, though 20% did not exceed this dose and [redacted]%

reached 15 breaths. It is unclear why [redacted]% exceeded 15 breaths. The maximum recommended dose is 12 breaths per session, four sessions daily (CS, doc B, Table 2). While flexible dosing reflects clinical practice, frequent adjustments due to adverse events and intolerance (CSR OLE Listing 16.2.6.1) may have introduced variability and complicated interpretation of treatment effects.

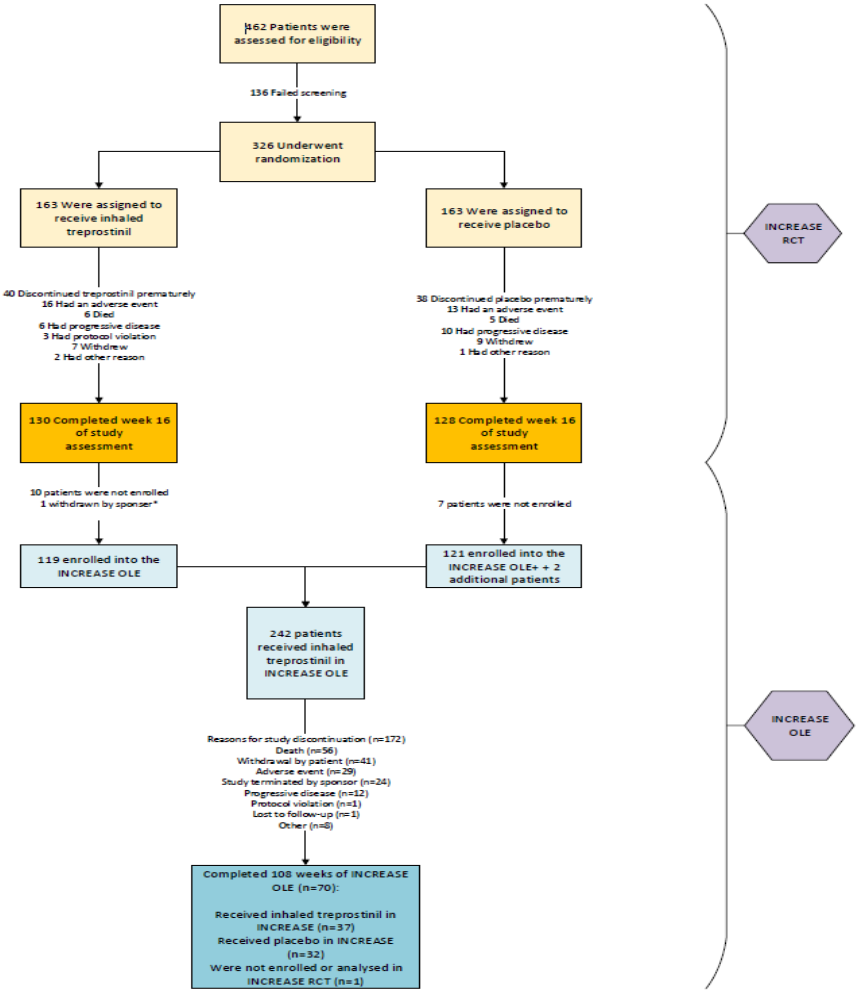


Figure 2: Screening, randomisation, and follow-up for INCREASE RCT and OLE[44, 45]

Protocol deviations

[redacted]% ([redacted]/326) of subjects in the randomized phase had at least one major protocol deviation, compared to [redacted]% ([redacted]/242) in the OLE phase (CSR INCREASE, p. 304; CSR OLE, p. 572), with the total number of subjects with any protocol deviation declining from [redacted] to [redacted]. The difference between [redacted] and [redacted] subjects with at least one major deviation (such as misrandomisation/ stratifications, study drug-compliance etc.) should be noted. Precisely, [redacted] deviations deemed major in INCREASE were reclassified as non-major in the unblinded OLE phase, an approach potentially influenced by prior trial experiences. While the risk of bias may be unclear, this shift raises questions about adherence and protocol rigour in real-world settings, where treatment complexity and patient diversity may further challenge compliance.

Among participants who received treprostinil, the reduction in the proportion with major protocol deviations, from [redacted]% in the randomized phase to [redacted]% in the unblinded OLE, may reflect the impact of unblinded investigators, assessors, and participants during the OLE phase.

In response to clarification question A3, it was confirmed that one patient with a baseline 6MWD of 30 metres was included, representing a protocol deviation. This may raise considerations regarding overall protocol compliance and adherence.

3.2.2 Risk of bias for the INCREASE and INCREASE OLE trials

The INCREASE study was appraised using the JBI checklist for RCTs (CS, Appendix B.3), based on the primary publication, and judged to have low risk of bias. While JBI is user-friendly and broadly applicable, it lacks the specificity and transparency of RoB 2, particularly for RCTs.[46] In response to clarification question C1, the company provided RoB 2 assessments for INCREASE and INCREASE OLE, rated as low risk and some concerns, respectively. These have been replicated in the Appendix 7.2. The EAG judged INCREASE to be with some concerns, and OLE with a high risk of bias.

The INCREASE showed baseline imbalances without statistical adjustment and included several post hoc outcomes. The OLE lacked a published protocol, had high attrition (only 29% completed 108 weeks), and followed a single-arm, open-label design, introducing risks of selection and performance bias. There is a potential risk of bias due to the involvement of unblinded investigators for patient enrolment, leading to the exclusion of 136 patients out of 462 screened patients (29.4% screening failure). But the extent of this is unclear, as the company has not provided the granular details (clarification question A2).

In the INCREASE trial, outcome assessors appear to have been blinded for prespecified endpoints outlined in the protocol. However, the post hoc analysis of modified clinical worsening (referred to as disease progression) may have introduced a degree of measurement uncertainty. Acute exacerbations were determined locally without centralized adjudication, which could have affected the consistency of event reporting.

In the OLE phase, clinical worsening was not a prespecified outcome and was not documented in the clinical study report. Nonetheless, it was included in the cost-effectiveness modelling without details on its measurement, raising concerns about potential bias and the reliability of this outcome.

Additionally, overall survival, event-free survival, and time to discontinuation were not prespecified and were analysed post hoc.

Eligibility for the OLE was based on prior participation rather than predefined clinical thresholds, with inclusion criteria allowing patients who had completed scheduled visits or discontinued due to clinical worsening. Exclusions were partly discretionary, relying on the investigator's judgment without clearly defined criteria. This eligibility framework raises concerns about consistency, selectivity, and the interpretability of long-term outcomes.

3.2.3 Source of real-world evidence for the inhaled treprostinil

3.2.3.1 CPRD-HES

One source of real-world evidence (RWE) is from the Clinical Practice Research Datalink (CPRD) linked with Hospital Episode Statistics (HES) data of group 3 PH-ILD patients. This study is a comprehensive UK database integrating primary care and hospital data, to evaluate the prevalence, incidence, baseline characteristics, hospitalizations, mortality, and economic burden of pulmonary hypertension (PH).[41]

Between January 2017 and December 2019, 38,242 patients with at least one inpatient or two outpatient PH visits were identified. To focus on PH due to lung disease (World Health Organization Group 3), 10,888 patients with diagnoses linked to other PH causes (Group 2 [left heart disease], Group 4 [chronic thromboembolic PH], and Group 5 [miscellaneous causes]) were excluded. Some patients had one or more recorded diagnoses. Among these excluded patients, 10,215 had Group 2 conditions, 1,284 had Group 5, 175 had Group 4, and 1,093 had other PH-related diagnoses.

Ultimately, 8,855 patients met the criteria for Group 3 PH. Real-world outcomes and disease burden were assessed in the incident population, comprising 6,690 Group 3 PH and 1,561 PH with interstitial lung disease (PH-ILD) patients. Among PH-ILD patients, only 220 underwent right heart catheterization prior to diagnosis, while 1,341 did not. Outcomes for people with RHC, were more optimistic than expected, with the EAG's clinical experts hypothesizing potential misclassification.

3.2.3.2 Dawes et al. (2022)

A second source, Dawes et al. (2022), was identified in the company's SLR as a comparator study (CS, doc B, section 2.1) and later used in a matching-adjusted indirect comparison (MAIC) (CS, doc B, section 2.10). This

retrospective cohort study from the Royal Brompton Hospital, UK (2000–2021), evaluated survival in ILD-PH patients using a Bayesian approach.

Of 932 ILD patients screened, 128 with confirmed ILD-PH were included. Exclusions were due to absence of RHC (n=473), echocardiography (n=397), spirometry (n=214), or presence of connective tissue disease. Included patients had RHC-confirmed severe ILD-PH (mPAP ≥35 mm Hg or ≥25 mm Hg with low cardiac index).

The study's retrospective design introduces potential for residual confounding and selection bias. Measurement limitations include the use of tools not fully validated for ILD-PH (e.g., Composite Physiologic Index [CPI], emPHasis-10), and selective use of RHC may limit generalisability. For instance, emphysema can falsely preserve forced vital capacity (FVC) values, while pulmonary hypertension may lower diffusing capacity of the lungs for carbon monoxide (DLCO), potentially distorting disease severity assessments. Moreover, CPI has not been validated outside idiopathic pulmonary fibrosis, and emPHasis-10 was developed for pulmonary arterial hypertension, not ILD-PH. Invasive follow-up with RHC was applied cautiously to minimise procedural risk, which may have further influenced the completeness of outcome data.

Only 20% of IPF patients were male (15 of 74), whereas male predominance is typically observed, as noted by EAG clinical experts. The exclusion of connective tissue disease patients further limits generalisability to NHS clinical practice.

During the final stages of the EAG critique, an 'in print' paper by Yogeswaran et al. was identified that could not be incorporated into the EAG report, but may be a useful source to inform on efficacy of PDE5i. Titled "Hemodynamics and Phosphodiesterase-5 Inhibitor Treatment Associated with Survival in ILD-PH: A PVRI GoDeep Meta-Registry Analysis", due to be published in the American Journal of Respiratory and Critical Care Medicine, the study discusses the association between PDE5i use and survival in ILD-PH

patients, highlighting potential benefits of PDE5i monotherapy or combination with inhaled prostacyclin analogues across different subgroups. (https://doi.org/10.1164/rccm.202412-2371OC)

3.2.4 Critique of patient characteristics

Table 7: Comparison of baseline characteristics for inhaled treprostinil arm, placebo arm, UK real world evidence and Dawes et al. (2022)

		INCREASE inhaled treprostinil (N = 163)	INCREASE placebo (N = 163)	UK RW CPRD-HES patients with RHC diagnosis (N=220)[41]	UK RW CPRD-HES patients with/without RHC (N=1,561)[41]	Dawes et al. (2022)[47] treated with PDE5i (N=50)	Dawes et al. (2022)[47] not treated with PDE5i (N=78)
Female sex (%)		52.1%	41.7%	75%	62%	58%	74%
Age (years)	Mean (SD)	65.6 [redacted]	67.4 [redacted]	60 (16)	71 (15)	64.8 (12.1)	67.4 (10.3)
	Median	[redacted]	[redacted]	64	74	NR	NR
	≥ 65 years old	60.7%	70.8%	49%	73%	NR	NR
White ethnic group (%)		68.7%	77.3%	84%	82%	NR	NR
Never smoked tobacco (%)		0	0.6%	27%	28%	NR	NR
Cause of lung disease (%)	IIP	39.9%	49.7%	NR	41%	NR	NR
	CTD	24.5%	19.6%	NR	34.5%	0	0
	IPF	22.7%	33.7%	NR	45.6%	40%	59.2%
	HP	6.1%	5.5%	NR	NR	20%	9%
	NSIP	12.9%	9.8%	NR	NR	10%	8.9%
Background and concomitant therapies (%)	None	81.6%	73%	NR	NR	NR	NR
	Pirfenidone only	11.7%	15.3%	NR	NR	16%	10.3%

		INCREASE inhaled treprostinil (N = 163)	INCREASE placebo (N = 163)	UK RW CPRD-HES patients with RHC diagnosis (N=220)[41]	UK RW CPRD-HES patients with/without RHC (N=1,561)[41]	Dawes et al. (2022)[47] treated with PDE5i (N=50)	Dawes et al. (2022)[47] not treated with PDE5i (N=78)
	Nintedanib only	6.7%	11.7%	NR	NR	14%	2.6%
	PDE5i	0	0	NR	8%	NA	NA
	PAH therapies	0	0	NR	13-21%	14%*	11.5%*
6MWD (meters)	Mean (SD)	254.1 ([redacted])	265.1 ([redacted])	NR	NR	258 (92)	222 (93)
PVR (WU units)	Median	5.57	5.06	NR	NR	6.7	6.0
PAPm (mmHg)	Median	35.0	35.0	NR	NR	38.0	35.0
PCWP (mmHg)	Mean (SD)	10.1 ([redacted])	9.6 ([redacted])	NR	NR	11 (5)	10 (4)
FEV1 % Predicted	Median	63.0	63.0	NR	NR	59.0	55.0
FVC % Predicted	Median	60.0	61.0	NR	NR	57.0	52.0
DLCO % Predicted	Median	29.0	26.0	NR	NR	25.0	26.0

Abbreviations: 6MWD, 6-Minute Walk Distance; CPRD-HES, Clinical Practice Research Datalink – Hospital Episode Statistics; CTD, Connective Tissue Disease; DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; FEV1, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; HP, Hypersensitivity Pneumonitis; IIP, Idiopathic Interstitial Pneumonia; IPF, Idiopathic Pulmonary Fibrosis; NSIP, Non-Specific Interstitial Pneumonia; PAPm, Mean Pulmonary Arterial Pressure; PCWP,

	INCREASE inhaled treprostinil (N = 163)	INCREASE placebo (N = 163)	UK RW CPRD-HES patients with RHC diagnosis (N=220)[41]	UK RW CPRD-HES patients with/without RHC (N=1,561)[41]	Dawes et al. (2022)[47] treated with PDE5i (N=50)	Dawes et al. (2022)[47] not treated with PDE5i (N=78)

Pulmonary Capillary Wedge Pressure; PDE5i, Phosphodiesterase Type 5 Inhibitor; PVR, Pulmonary Vascular Resistance; SD, Standard Deviation.

*Endothelin receptor antagonist

The INCREASE trial did not have any UK-based centres. Although no UK patients were enrolled, the company argues that the study population is broadly generalisable to NHS practice, citing similarities in age and background antifibrotic therapy as supporting evidence.

Age, sex and ethnicity

The CPRD/HES real-world population differed notably from the INCREASE trial, with a higher proportion of white, older and female patients. The EAG's clinical expert confirmed that NHS patients referred to PH centres tend to be older and more often female. The placebo arm of INCREASE had slightly higher mean and median ages than the treprostinil arm and included a greater proportion of males and a higher share of individuals aged 65 or older. According to the EAG clinical expert, "*sex balance will be altered by differences in the proportions of causes of the ILD, for example, CTD-ILD is found predominantly in females (>70%) while IPF is predominantly found in male patients. CTD patients may have ILD diagnosed when younger than IPF, which tends to be diagnosed more often over the age of 60*".

In terms of ethnicity, although both trial arms had lower representation of white patients compared to CPRD/HES, the treprostinil group had the lowest proportion overall.

Smoking

In response to clarification question A7, the company reported that 0% and 0.6% of patients in the treprostinil and placebo groups, respectively, were never smokers. In contrast, 27% of patients in the CPRD cohort were never smokers. This notable discrepancy may limit the generalisability of the trial findings to real-world populations.

Aetiology

The INCREASE trial arms show imbalances in lung disease aetiology between placebo and treprostinil, and also imbalances in relation to the CPRD-HES real-world cohort. Idiopathic pulmonary fibrosis (IPF), seem to be underrepresented in the treprostinil arm (22.7%) versus the CPRD (45.6%). Conversely, connective tissue disease-associated ILD (CTD-ILD) was more

common in the treprostinil group (24.5%) than in the placebo (19.6%) and was underrepresented in CPRD (34.5%). IPF and IIP were both higher in the placebo group than in the treprostinil group. To support the observed differences between the INCREASE trial population and NHS patients, the EAG's clinical expert highlighted findings from an unpublished UK-based study, which reported a higher proportion of patients with connective tissue disease (CTD) and combined pulmonary fibrosis and emphysema (CPFE) in the treprostinil intervention arm compared to the placebo arm.

Pulmonary arterial pressure

In the CS, section 1.3.3.1, the company defines the PH as a mPAP >20 mmHg, PVR >2 Wood units (WU), and PCWP <15 mmHg. In the INCREASE trial, patients were enrolled with mPAP >25 mmHg and PVR >3 WU (originally >4 WU, later amended), with PCWP <15 mmHg (CS, Section 2.3.1.1). The median PVR values in the treprostinil and placebo arms were 5.57 and 5.06 WU, respectively. The EAG's clinical expert noted that in patients receiving PDE5 inhibitors, median PVR values tend to exceed 6 WU which would be classified as severe PH according to ERS/ESC guidelines (PVR >5 WU), in contrast to the INCREASE trial population. Additionally, in the UK, right ventricular function will be assessed, but it was not clear to the EAG if this was assessed within the INCREASE trial on the information made available.

Concomitant treatments

Although inhaled treprostinil is not intended to replace ILD treatments (CS, doc B, section 1.3.3), the INCREASE trial excluded patients on pulmonary arterial hypertension (PAH) approved therapies, limiting its generalisability to real-world settings where such treatments are common. The CPRD source reports that 14-18% of PH Group 3 patients and 13-21% of PH-ILD patients had received PAH therapies. No concomitant therapies were reported for the trial patients (clarification question A7). The efficacy of treprostinil in the real world is potentially thus uncertain due to potential interaction with other treatments. Additionally, in response to clarification question A1, the company

did not provide post-hoc analyses on background treatments, citing these were prevented due to the small number of people receiving background medications, but that they did not expect any interaction due to differing mechanisms of action.

6MWD

Patients who were unable to walk at least 100 metres during the six-minute walk test (6MWD < 100 m) were deemed ineligible for trial participation or treatment with treprostinil (see eligibility criteria in Section 3.2.1) and were excluded. The EAG's clinical expert highlighted that "*Excluding patients who cannot walk that distance presents a challenge when applying the trial findings to real-world clinical practice. It would be difficult to limit treatment only to those capable of walking more than 100 metres.*"

Dawes et al. (2022)

Dawes et al. included more females and a higher proportion of IPF patients, especially in the non-PDE5i group, while INCREASE had more patients with CTD and IIP. Use of antifibrotics and PAH therapies was more common in Dawes et al., suggesting a more heterogeneous treatment landscape. Functional and haemodynamic parameters (e.g., 6MWD, PVR, DLCO) were broadly comparable, though Dawes et al. showed slightly worse lung function and higher PVR.

EAG summary:

Compared to the INCREASE trial, the CPRD/HES real-world cohort included more older, white, and female patients, with lower smoking rates and greater comorbidity burden. Differences in disease aetiology, treatment exposure, and restricted concomitant therapies in the trial may limit generalisability. The EAG's expert noted that patients in the NHS practice often present with higher PVR values than those observed in the INCREASE trial. Additionally, the trial excluded patients unable to walk at least 100 metres during the six-minute

walk test, which may further limit applicability to routine clinical settings, where such patients are commonly encountered.

3.3 Critique of the results of the trials of the technology of interest

The trial was of short duration, and discontinuation rates exceeded those anticipated in the protocol. Additionally, pulmonary function tests (PFT) and exacerbation of underlying lung disease events were not centrally adjudicated, which may introduce bias and inconsistency, potentially affecting the robustness and reliability of the findings. Some events are post-hoc and exploratory.

In this section the EAG summarises and comments on results for both the trial and OLE periods of INCREASE.

3.3.1 Primary outcome: 6-minute walk distance

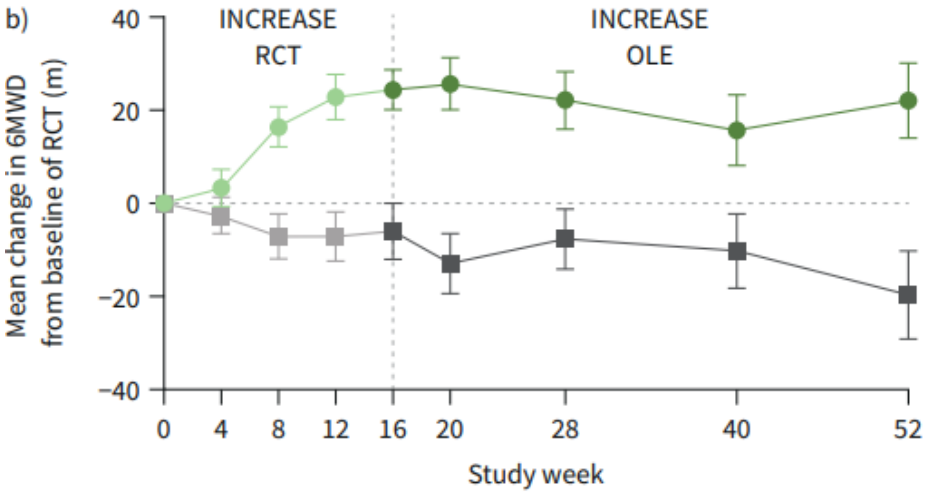
The primary endpoint of the INCREASE RCT was the change in 6-minute walk distance (6MWD) from baseline to week 16. Change in 6MWD was later evaluated as a secondary objective in the OLE phase.

The INCREASE trial prespecified a standard deviation of 75 metres in 6MWD to detect a 30-metre difference with 90% power (n=266), but 68 premature discontinuations (33 treprostinil, 35 placebo) from the 326 recruited, resulted in 258 completions; meaning the final sample remained below target, resulting in a slightly underpowered analysis.

The imputation strategy (assigning 0 metres for subsequent measurements of patients who died, clinically worsened, or were too unwell) may have introduced systematic bias, particularly given the higher clinical worsening rate in the placebo group (33.1% vs. 22.7%), likely depressing placebo averages and amplifying the apparent treatment effect in favour of treprostinil. Additionally, the use of ‘Last Observation Carried Forward’ (LOCF) for other missing data, which tends to underestimate deterioration, may have further

biased results and introduced analytical inconsistencies affecting the reliability of conclusions.

The EAG presents the most relevant representation of this outcome, using mean change from baseline instead of absolute score, the latter of which is more prone to bias from non-random missing data. Figure 3 shows how treprostinil patients gained a benefit which was sustained into the early stages of the OLE. Meanwhile, patients randomised to placebo demonstrated a gradual decline which continued into the OLE phase despite switching to treprostinil at week 16. Figure 4 shows a longer follow-up from INCREASE OLE. Note, in this plot, the baseline is the start of the OLE period, not the start of the trial period, as in Figure 3. Week 4 of Figure 4 corresponds to Week 20 of Figure 3. Figure 4 suggests both arms show an equal decline in 6MWD across the extended OLE period; however, uncertainty is higher due to the smaller number of people contributing information, the lowest sample size being [redacted] for the original placebo group at week 96 of the OLE.



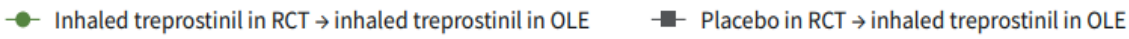


Figure 3: Change in baseline 6-minute walking distance from INCREASE (CS Figure 12b)

[redacted]

Figure 4: Mean change from baseline in 6MWD (metres) by visit (CSR OLE Figure 14.2.1)

Table 8 shows the results of the analysis at week 16, where a mixed model for repeated measures (MMRM) was fitted with baseline score, treatment, week and treatment/week interaction term fixed effects, with a random effect for each participant and unstructured variance-covariance matrix. The EAG notes a considerable difference between the mean change in baseline for treprostinil and the least-squares estimate from the MMRM model ([redacted]vs 21.1), with a similar magnitude of difference for the placebo arm ([redacted]vs -10.0).

Table 8: Summary of 6MWD (metres) by visit sourced from INCREASE and INCREASE OLE CSR tables 11-3 and 11-4.

Visit	Metric	Change from baseline (Treprostinil)	Change from baseline (Placebo)
Week 16	N	163	163
	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
Hodges-Lehmann estimator (week 16)			[redacted]
Mixed model repeated measurement analysis (ITT Population)			31.12 [95% CI, 16.85, 45.39; p-value<0.0001)

In the OLE phase, patients initially randomised to treprostinil maintained a positive change from baseline through Week 52 (mean: [redacted]; median: [redacted]). However, by week 64, a notable decline was observed (mean: [redacted]; median: [redacted]), with further deterioration by Week 124 (mean: [redacted]; median: [redacted]). Treprostinil may not maintain 6MWD benefits in the long term. The former placebo group (transitioned to treprostinil post-week 16) that received treprostinil in the OLE phase also showed a [redacted] median change of [redacted] at Week 124.

EAG summary:

Treprostinil appears to offer only marginal clinical benefit in 6MWD.[44] The modest effect size, broad confidence intervals, and similar rate of decline in 6MWD in the OLE raise questions about its long-term clinical value.

3.3.2 Secondary and extrapolatory outcomes

3.3.2.1 Time to death and overall survival

Figure 5 shows the OS data from the start of the INCREASE randomised period and including follow-up into the OLE. The EAG considers the OS data

immature, with the median OS not reached. A small benefit appears in favour of people who were randomised to treprostinil, but this occurs beyond 16 weeks when all participants are now receiving treprostinil.

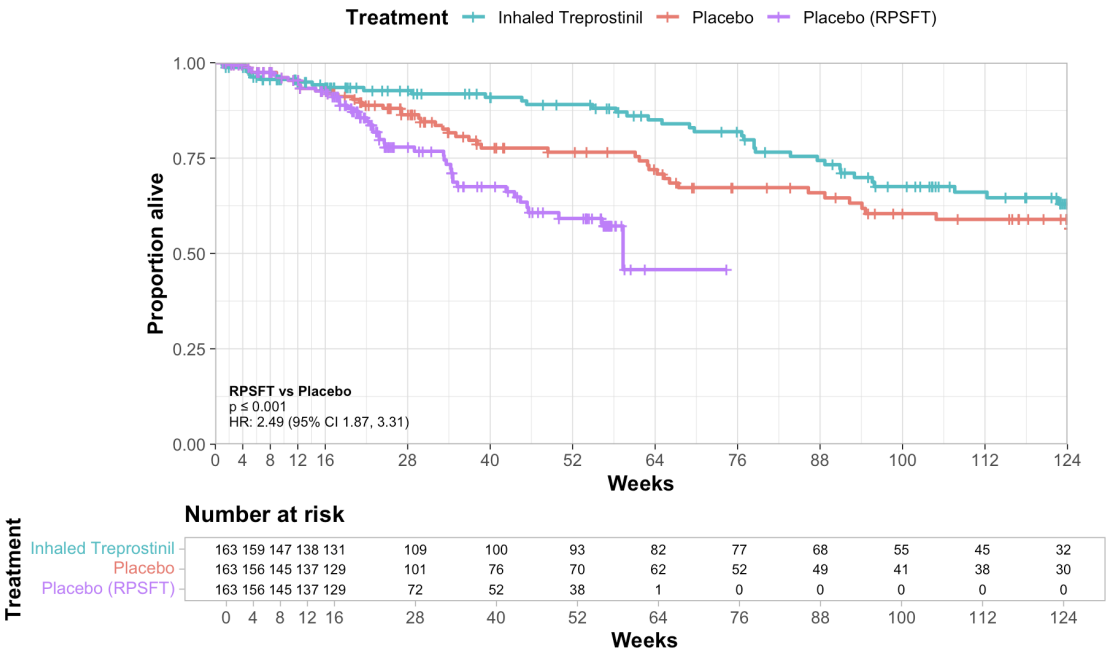


Figure 5: Kaplan-Meier plot of overall survival from INCREASE RCT and the OLE

The company reported that a comparison of OS outcomes from INCREASE OLE was biased due to the switching to treprostinil that occurred for people originally randomised to placebo. The company proposed the Rank Preserving Structural Failure Time (RPSFT) model to estimate overall survival (OS), removing any potential benefit of treatment crossover to predict counter-factual survival times as if patients had not received treprostinil. The RPSFT model assumes a constant treatment effect regardless of timing or duration, which may not hold in PH-ILD, where early initiation and dose escalation of inhaled treprostinil appear influential.[48-50] Former placebo-treated patients who initiated treprostinil with delay may have had reduced functional responses, as noted in the peer-reviewed publication of INCREASE.[49] The

EAG considers that the subsequent results do not show a clear benefit of treprostinil to people who switched from placebo, across the outcomes presented, and it is unclear whether a survival benefit requires adjusting.

RPSFT treats the treatment effect as constant and time invariant, regardless of when it starts or how long it lasts. The model does not consider dose up-titration events and the possibility that higher dosages may confer additional benefits beyond those observed at lower doses.[49] As a result, the estimates derived using the RPSFT method may not be realistic.[48, 49] While RPSFT leverages randomization to circumvent the need for modelling confounders, its estimated hazard ratio (HR 0.26) diverges markedly from both the intention-to-treat (ITT) analysis (HR 0.71, p = 0.1227) and the Kaplan-Meier estimates for time to death (see Figure 5). It is also considerably higher than hazard ratios for other time-to-event outcomes. This discrepancy raises concerns that the RPSFT model lacks face validity. In response to clarification question A18, the company confirmed that no covariate adjustments or re-censoring were applied, citing that all patients became eligible for switching. They declined to provide a hazard ratio or acceleration factor to report the magnitude of the RPSFT adjustment, arguing that all placebo patients switched to treprostinil. The EAG does not agree, as not all patients enrolled into the OLE and there is the potential for some selection bias. The EAG considers that a scenario with re-censoring would be important in this case, as recommended by NICE TSD 16.[50] The EAG requested a comparison of the adjusted and unadjusted survival times to explore the magnitude of the adjustment, such as a hazard ratio of the observed and counterfactual event times. The company provided only a Kaplan-Meier plot showing the impact of the RPSFTM adjustment (clarification A18).

An alternative method of adjusting, the Inverse Probability of Censoring Weights (IPCW) method, provides a more plausible estimate of potential switching benefit, though it requires an assumption of accounting for all confounding variables. IPCW censors people who switch therapies, and re-

weights those who don't, ensuring the original distribution of baseline covariates is preserved to produce an unbiased estimate of efficacy. The EAG considers that the covariates included in the IPCW adjustment were comprehensive.[49] A limitation of the IPCW approach is that there remains only a few people who did not switch to treprostinil, and so estimates coming from the weighted analysis may be unreliable and biased. Consequently, the company prefers the RPSFT model and considers IPCW inappropriate (clarification question A17). This position contrasts with the earlier company-sponsored publications,[49] which judged both to be appropriate under different assumptions. A visual comparison of the hazard ratios of the approaches is shown in Figure 6. The EAG requested a Kaplan-Meier plot of the IPCW, and also an exploration of a third method of adjusting for crossover (2-stage adjustment); however, the company declined to provide these analyses (clarification A17) as they consider the 2-stage adjustment not appropriate for this scenario.

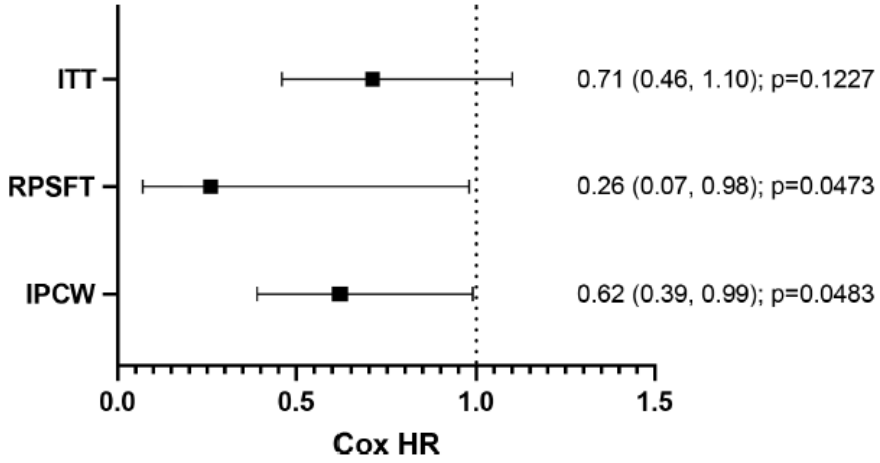


Figure 6: Estimates of overall survival HR. (sourced from Nathan et al. (2024)[49])

EAG's summary:

The EAG rejects the RPSFT adjustment on plausibility grounds. The IPCW adjustment is more plausible but is subject to weaknesses and potential for

bias, and so the EAG preference is to use the ITT analysis due to uncertainty whether a clinically meaningful benefit was obtained from switching.

3.3.2.2 Event-free survival

For this outcome, events were defined as death, exacerbation of underlying disease, or hospitalisation.[51] A post hoc analysis reported a hazard ratio of 0.73 (95% CI: 0.54–0.99; p = 0.0454) for patients previously treated with inhaled treprostinil versus placebo (CS, doc B, section 2.6.2.2) with both groups receiving treprostinil without any adjustment for treatment switching. This analysis only used data from the OLE period and ignored follow-up from the randomised period. This outcome and analysis were of a post-hoc nature and should be treated with caution. It is also complicated by the fact that the data informing this outcome begins follow-up at the OLE stage and does not account for events or differences during the 16-week randomised period.

Moreover, patients who responded well may have been more likely to continue treatment, while those with adverse events (AEs) or poorer outcomes may have discontinued. It is unclear whether disease exacerbations overlapped with treatment discontinuations (AEs, lack of efficacy, patient choice, etc.), which are not necessarily equivalent, adding further ambiguity to the interpretation.

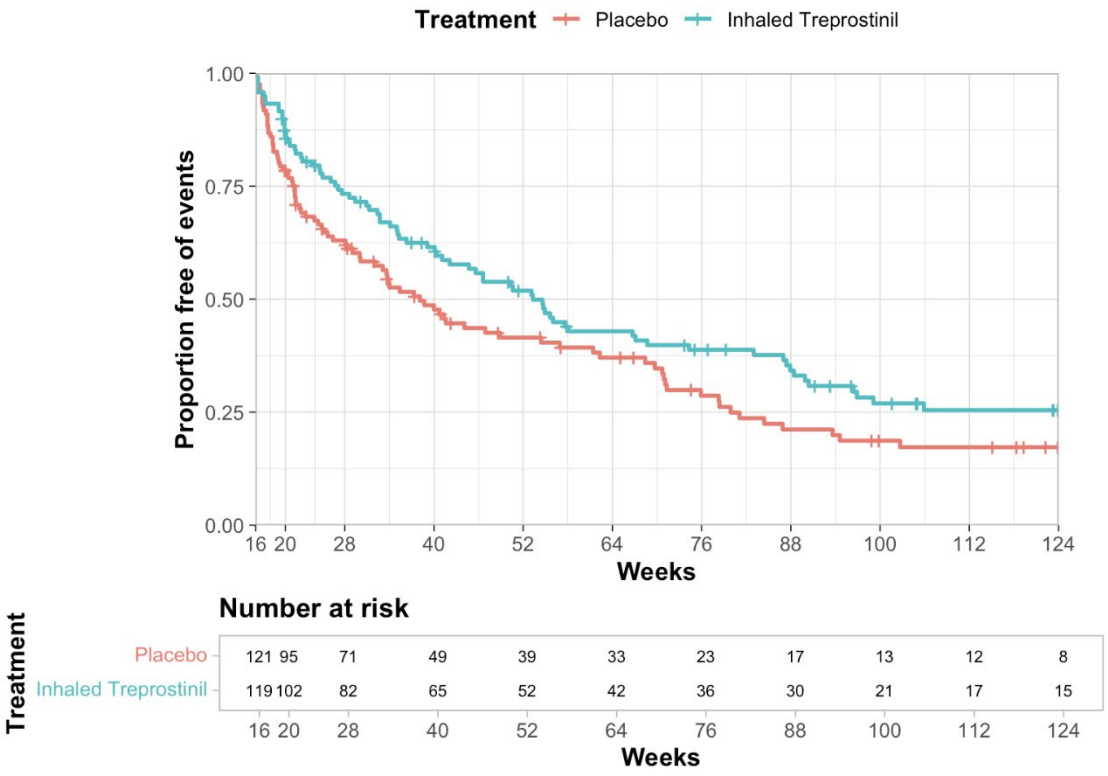


Figure 7: Kaplan-Meier plot of event-free survival in INCREASE-OLE in patients previously treated with treprostinil or placebo (copied from clarification question A10 response provided by the company)

EAG summary:

This post hoc analysis of event-free survival showed a small benefit to people who originally received treprostinil versus those who received it for the first time entering the OLE.

3.3.2.3 Clinical worsening

In the INCREASE trial, clinical worsening (CW) was defined as the first occurrence of one of four events: a ≥15% decline in 6MWD, cardiopulmonary hospitalization, lung transplantation, or death. The majority of patients reached this endpoint through either a decline in 6MWD (accounting for 35% of events in the treprostinil arm and 48% in the placebo arm) or hospitalization (49% and 44%, respectively). However, patients remained at risk for further

deterioration, which was not captured under the CW definition. Individuals who experienced multiple qualifying events were counted only once.

Events such as acute exacerbations and forced vital capacity (FVC) declines as potential indicators of clinical worsening were classified as safety outcomes and therefore not accounted for in the CW definition, which may have obscured the broader extent of disease instability. At the time of protocol development, harmful effects of treprostinil in patients had not been anticipated - an oversight that, in retrospect, may have contributed to treatment-related risks.[52]

By the end of the 16-week evaluation, the median time to CW was similar between groups ([redacted] weeks for treprostinil vs. [redacted] weeks for placebo), with a hazard ratio of 0.61 (p = 0.041) and a wide confidence interval (0.40–0.92), suggesting a modest effect size and statistical uncertainty. The EAG presents graphical representation of the CW outcome, which uses data from the trial and OLE periods of INCREASE (see Figure 8).

Table 9: Summary and analysis of number of clinical worsening events in INCREASE – ITT Population (n=326)

Occurrence of clinical worsening, n (%)	**INCREASE by 16 weeks**	
	CS doc B, table 6 Inhaled treprostinil (n=163) clinical worsening events	**CS doc B, table 6 Placebo (n=163) clinical worsening events**
Any event	37 (22.7)	54 (33.1)
Hospitalisation for cardiopulmonary indication	18 (11.0)	24 (14.7)
Decrease in 6MWD of >15% from baseline	13 (8.0)	26 (16.0)
Death from any cause	4 (2.5)	4 (2.5)
Lung transplantation	2 (1.2)	0

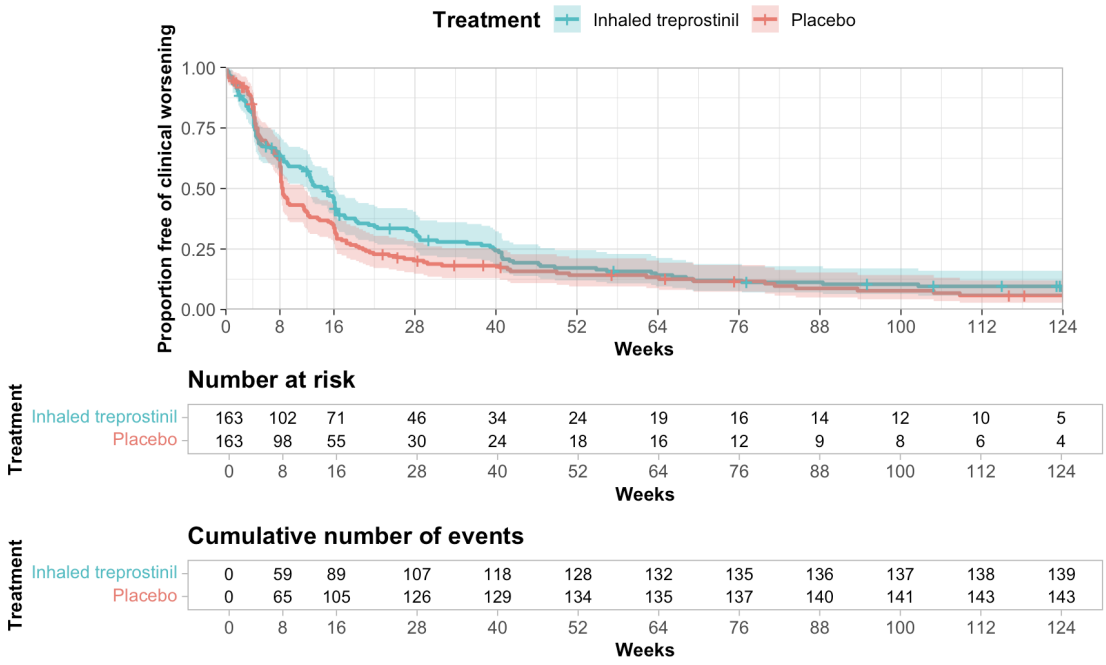


Figure 8: Time to clinical worsening from INCREASE trial and OLE.

Of the patients who experienced clinical worsening in the INCREASE trial period, 57.4% (31 out of 54) from the placebo group and 40.5% (15 out of 37) from the treprostinil group proceeded to the OLE (clarification question A12). It is possible that some individuals in the treprostinil arm may have perceived limited additional benefit from continued participation or may have encountered factors (such as tolerability concerns or personal circumstances) that influenced their decision not to continue.

3.3.2.4 Disease progression

Disease progression was defined in a post-hoc exploratory analysis publication[44] as at least one of the following:

- ≥15% decline in 6-minute walk distance
- exacerbation of underlying lung disease
- cardiopulmonary hospitalization

- lung transplantation
- ≥10% decline in forced vital capacity
- Death

Table 10: Number of disease progression events by treatment arms in the INCREASE RCT (copied from Table 2 of Nathan et al. 2021 by 16 weeks follow-up)

Event	Total number of events		Among subjects who had 1 event		Among subjects who had >1 event	
	Treprostinil (n = 89)	Placebo (n = 109)	Treprostinil (n = 54)	Placebo (n = 51)	Treprostinil (n = 35)	Placebo (n = 58)
Decline in 6MWD > 15%	45	64	21	19	24	45
Exacerbation	48	72	11	15	37	57
Decline in FVC > 10%	19	33	10	13	9	20
Cardiopulmonary hospitalization	23	33	6	4	17	29
Lung transplantation	2	1	1	0	1	1
Death	10	12	5	0	5	12
Total	147	215	54	51	93	164

Abbreviation: 6MWD, 6-minute walk distance; FVC, forced vital capacity.

Patients treated with treprostinil experienced fewer multiple progression events compared to placebo (35 vs. 58; p value 0.005). The treatment was associated with a reduced risk of second events (hazard ratio [HR] 0.53; p value 0.003) and a delayed time to progression. There was no statistically significant difference in mortality between the two groups. And relatively wide confidence intervals, marginal statistical significance, and potential for increased type I error due to multiple comparisons (with no adjustments for multiplicity) may introduce some uncertainty regarding the robustness of the results in relation to the other outcomes.

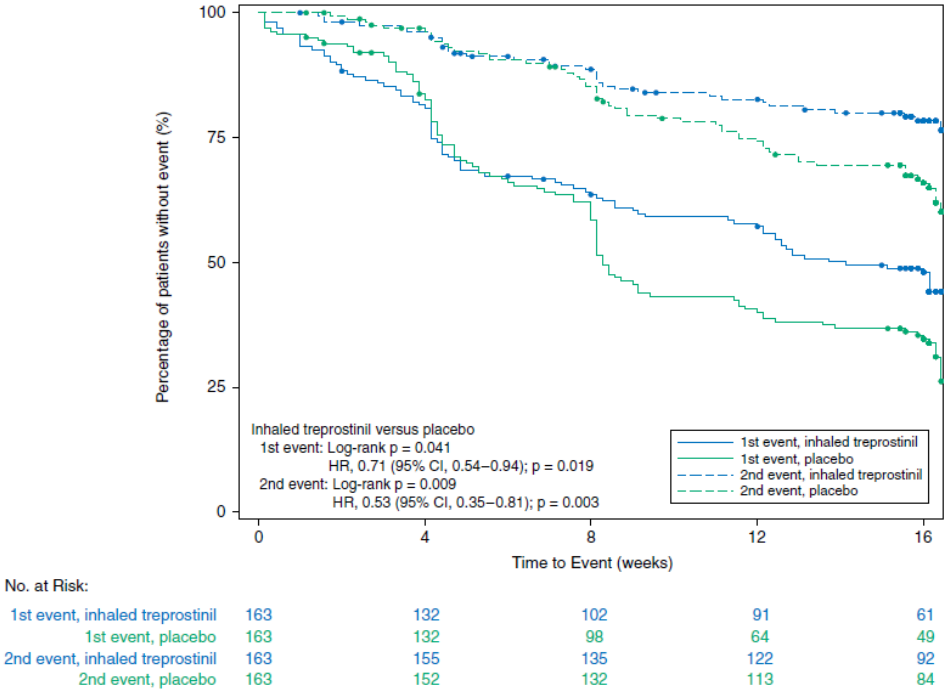
Several limitations of this study warrant careful consideration. The main limitation of disease progression as an outcome measure lies in the post hoc

and exploratory structure and potential risk of bias. This endpoint was retrospectively derived by incorporating two additional safety-related criteria, acute exacerbation and FVC deterioration, after the INCREASE RCT trial.

Acute exacerbations were determined solely by local site investigators without centralized adjudication. This lack of standardized oversight coincided with an unexpectedly high rate of exacerbations across both study arms, particularly in the placebo group. This pattern suggests that patients with more advanced disease may have been more readily labelled as experiencing an exacerbation in response to any clinical decline, regardless of whether formal diagnostic criteria were fully met.[44, 53]

The relatively short study duration, coupled with a 21% premature discontinuation rate before week 16, further limits the robustness of the conclusions. Follow-up PFT was conducted only twice (at Week 8 and Week 16), restricting the ability to confirm the FVC component of disease progression with sufficient granularity.[53]

The definition of disease progression matched the definition of clinical worsening used by the company in the cost-effectiveness modelling.



No. at Risk:

1st event, inhaled treprostinil	163	132	102	91	61
1st event, placebo	163	132	98	64	49
2nd event, inhaled treprostinil	163	155	135	122	92
2nd event, placebo	163	152	132	113	84

Figure 9: Kaplan–Meier estimates of time to first and second disease progression in the INCREASE RCT (≤16 Weeks): inhaled treprostinil vs. placebo (copied from company Figure 11)

EAG summary:

The post hoc design and modified endpoint introduce potential bias in assessing disease progression. Lack of centralized adjudication and short follow-up raise concerns about the accuracy of exacerbation and FVC assessments. High discontinuation rates and limited PFT data further weaken the robustness of the study's conclusions.

3.3.2.5 N-terminal pro B-type natriuretic peptide

Plasma NT-proBNP (N-terminal pro B-type natriuretic peptide) concentration is a biomarker associated with changes in right heart morphology and function (Waxman et al. (2021) trial protocol, page 101).[44]

According to Table 11-4 of the CSR for the INCREASE OLE, the median change in NT-proBNP levels from baseline to Week 16 was reported as

[redacted] pg/mL in the treprostinil arm and [redacted] pg/mL in the placebo arm. At the first post-crossover assessment during the OLE phase (Week 64), the corresponding median changes were [redacted] pg/mL and [redacted] pg/mL, respectively. By the final data cutoff at Week 124, the median changes had reached [redacted] pg/mL for the treprostinil group and [redacted] pg/mL for the placebo group.

Table 11: Median Change in NT-proBNP levels from baseline

Timepoint (Week)	Treprostinil pg/mL (min,max)	Placebo pg/mL (min,max)
16	[redacted]	[redacted]
64	[redacted]	[redacted]
124	[redacted]	[redacted]

Abbreviations: NT-proBNP, N-terminal pro B-type natriuretic peptide; pg/mL, picograms per millilitre.

Formal statistical analyses were not undertaken to assess changes from baseline during the OLE phase.

The observed breadth of minimum-to-maximum ranges may reflect considerable variability and the potential presence of outliers.

Compared to the placebo group, which exhibits variability, the treprostinil group appears to exhibit [redacted]; the persistently wide range may be indicative of substantial underlying heterogeneity in patient responses.

EAG summary:

Taken together, these observations highlight the necessity for prudent interpretation, particularly in light of the absence of inferential statistical testing and the potential influence of survivor bias at later timepoints.

3.3.2.6 Pulmonary function test (PFT) results

The parameters assessed during the pulmonary function test (PFT) encompassed the following:

- Forced Expiratory Volume in 1 second (FEV_1)
- Forced Vital Capacity (FVC)
- Total Lung Capacity (TLC)
- Diffusing Capacity of the Lung for Carbon Monoxide (DLCO)

DLCO, FVC, and FEV_1 are absolute measures of lung function, reflecting gas transfer, lung volume, and airflow, respectively. Their % predicted values adjust for age, sex, height, and ethnicity, enabling clinical interpretation by indicating the degree of impairment and aiding diagnosis. The % predicted compares the patient's PFT to an expected reference value derived from healthy individuals of the same age, sex, height, and ethnicity.

Table 12: Pulmonary function test results by visit - Overall OLE patients (N = 242) (sourced from CSR OLE Table 14.3.3.6)

		Week 12	Week 48	Week 108
FVC (L) change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]	[redacted]
FVC % predicted change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]	[redacted]
DLCO (mL/min/mmHg) change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]

		Week 12	Week 48	Week 108
	(min, max)			
DLCO % predicted (%) change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]	[redacted]
FEV1 (L) change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]	[redacted]
FEV1 % predicted (%) change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median (min, max)	[redacted]	[redacted]	[redacted]

Abbreviations: DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; SD, Standard Deviation; TLC, Total Lung Capacity.

Table 13: Pulmonary function test results by visit - Treprostinil (N=119) and placebo (N=121) OLE patients (sourced from CSR OLE Table 14.3.3.6)

		Week 12		Week 48		Week 108	
		Treprostinil	**Placebo**	**Treprostinil**	**Placebo**	**Treprostinil**	**Placebo**
FVC (L) change from baseline	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (min,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Week 12		Week 48		Week 108	
		Treprostinil	**Placebo**	**Treprostinil**	**Placebo**	**Treprostinil**	**Placebo**
	max)						
FVC % predicted change from baseline	Mean (SD)	[redacted]					
	Median (min, max)	[redacted]					
DLCO (mL/min/mmHg) change from baseline	Mean (SD)	[redacted]					
	Median (min, max)	[redacted]					
DLCO % predicted (%) change from baseline	Mean (SD)	[redacted]					
	Median (min, max)	[redacted]					

		Week 12		Week 48		Week 108	
		Treprostinil	Placebo	Treprostinil	Placebo	Treprostinil	Placebo
FEV1 (L) change from baseline	Mean (SD)	[redacted]					
	Median (min, max)	[redacted]					
FEV1 % predicted (%) change from baseline	Mean (SD)	[redacted]					
	Median (min, max)	[redacted]					

Abbreviations: DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; SD, Standard Deviation; TLC, Total Lung Capacity.

Table 12 presents a summary of longitudinal changes in key pulmonary function parameters (FVC, DLCO, FEV1) over 108 weeks of follow-up within the OLE. The mean changes across all pulmonary function test (PFT) outcomes appear modest; however, the presence of considerable variability, as reflected by the large standard deviations, is noted.

The observed minimum-to-maximum ranges are particularly striking and may suggest that a subset of individuals experienced marked declines in pulmonary function. A modest increase in FVC% predicted was noted at

Week 48 ([redacted]%), followed by a decrease by Week 108 ([redacted]%). DLCO% predicted remained largely stable across all assessed timepoints, although the interpretation is subject to uncertainty due to the considerable standard deviations observed. Similarly, FEV1 % predicted shows a stable median value ([redacted]%) throughout, though the wide range (from [redacted]% to [redacted]%) further underscores the extent of inter-individual variability.

It is possible that the relatively infrequent measurement intervals (e.g., at Weeks 12, 48, and 108) may have limited the ability to detect more nuanced or dynamic changes in lung function over time.

EAG Summary

Taken together, while median values at the group level of the OLE do not indicate a clear trend toward improvement, the pronounced variability among individuals and the absence of consistent directional changes across parameters raise questions regarding the capacity of inhaled treprostinil to stabilize pulmonary function.

3.3.2.7 Health-related quality of life (HRQoL)

The company has used the St. George's Respiratory Questionnaire (SGRQ) to inform the HRQoL outcome. The SGRQ is a tool used to measure health-related quality of life in patients with diseases affecting airway function. The tool measures the frequency and severity of symptoms, physical limitations, and psycho-social function. The SGRQ scores range from 0 to 100. The negative values indicate an improvement, as lower scores on the SGRQ represent better health status. The minimum clinically important difference (MCID) is 4 points.[45]

The results provided in Table 14 show the mean change from baseline at different visits for patients receiving inhaled treprostinil and placebo.

Table 14: SGRQ mean change from baseline

	INCREASE (mean change from baseline) (SD)[44]	INCREASE OLE (mean change from week 16) (SD)[45]

Visit	Inhaled Treprostinil (N=163)	Placebo (N=163)	Received Inhaled Treprostinil in RCT (N=119)	Received Placebo in RCT (N=121)
Baseline	_	_	NA	NA
Week 16	-1.25 (10.99)	-0.18 (10.72)	_	_
LS Mean Difference (SE) and (95% CI)	-1.18 (1.25)	(-3.63, 1.28)	NA	NA
Week 64	NA	NA	0.8 (11.3)	1.3 (12.5)
Week 124	NA	NA	1.7 (13.0)	-3.2 (12.0)

Abbreviations: OLE, open-label extension; NA, not applicable; RCT, randomised controlled trial; SD, standard deviations.

At Week 16, no statistically or clinically meaningful difference was demonstrated to support a treatment-related improvement with inhaled treprostinil. Given the modest magnitude of change (just over one unit) and the considerable variability observed, any interpretation should be approached with caution.

Throughout the OLE phase, mean changes from Week 16 remained minimal across both groups, with no consistent indication of sustained improvement or decline in the measured outcome. The substantial inter-individual variability, as reflected by large standard deviations, combined with the absence of formal statistical comparisons, further limits the interpretability of these findings.

EAG summary:

No statistically significant differences are observable between inhaled treprostinil and placebo using the SGRQ. The high degree of variability and the lack of inferential statistical analysis limit the robustness of any conclusions.

3.3.3 Subgroup analyses

In the context of the INCREASE study, subgroup analyses were conducted for the primary efficacy endpoint (change in 6MWD) at Week 16. However, it is noted that no adjustments for multiplicity or control of Type I error were applied in these analyses. As acknowledged in the sponsor's documentation (CS, Appendices, Figure 8 notes), the results derived from these subgroup explorations are not intended to support definitive conclusions regarding treatment effects. In the absence of appropriate statistical adjustments, the potential for false-positive results cannot be excluded.

Furthermore, the imputation strategy employed for handling missing 6MWD data warrants careful scrutiny. Specifically, assignment of a value of zero to clinically worsened individuals and the last observation carried forward (LOCF) method introduces a risk of systematic bias, particularly in light of the higher investigator-reported clinical worsening events for the placebo. The imputation methodology may have inadvertently amplified perceived treatment effects in favour of inhaled treprostinil and, as a result, may have compromised the robustness of the efficacy conclusions.

Additionally, the relatively short follow-up period and the substantial proportion of early discontinuations (reported as 21%) further constrain the interpretive value of the subgroup analyses. These factors collectively limit the reliability and generalisability of the findings and underscore the need for cautious interpretation.

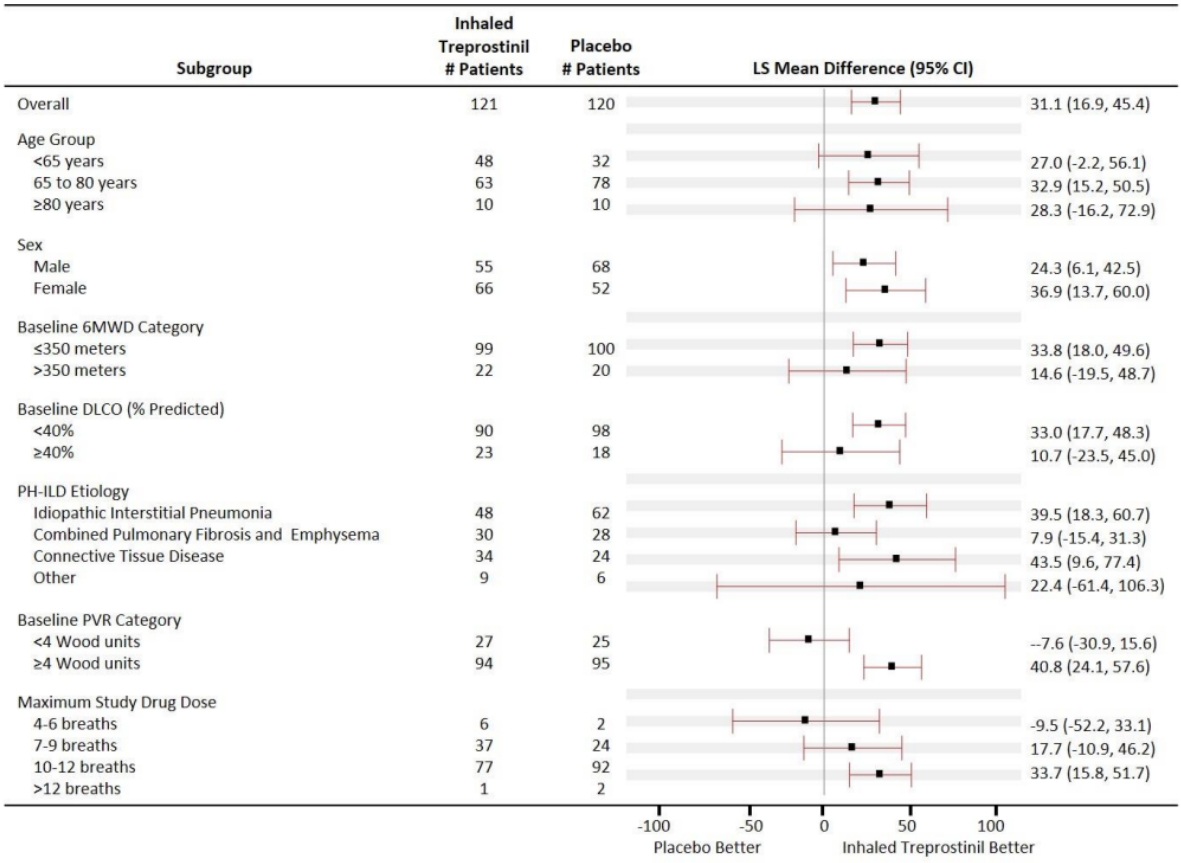


Figure 10: Forest plot on subgroup analyses of peak 6MWD (metres) at Week 16 (replicated from CS, appendices, Figure 8)

Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; ILD, interstitial lung disease; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

3.3.4 Overview of safety outcomes

3.3.4.1 Treatment discontinuations

Patients who transitioned to the OLE phase from the INCREASE trial had a median exposure duration of 62.1 weeks (≈approximately 14.29 months) to inhaled treprostinil. Specifically, patients with previous inhaled treprostinil had a median exposure of 77.3 weeks (≈17.79 months), while those from the previous placebo group had a median exposure of 47.0 weeks (≈10.82 months). The reduced exposure time in the placebo group, in addition to allocation to the control arm, is likely due to higher discontinuation rates,

particularly due to adverse events leading to discontinuation (28.1% in placebo vs. 16.8% in treprostinil).[45]

Table 15: Number of subjects who discontinued study drug early

Trial name	INCREASE (CSR INCREASE page 57)		INCREASE OLE (CSR INCREASE OLE page 38)		
Treatment arm	Inhaled treprostinil (%)	Placebo (%)	Inhaled treprostinil (%)	Placebo (%)	Overall[a] (%)
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by subject	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study terminated by sponsor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSR, clinical study report; NR, not reported.

[a]One subject was inadvertently enrolled in OLE following premature discontinuation of the study drug in the RCT phase due to a treatment-related adverse event. The subject was removed from OLE before study drug administration. Therefore, while we have 243 enrolled patients, 242 patients received the inhaled treprostinil in the OLE phase.

The interpretability of the 16-week INCREASE trial findings is inherently constrained by the limited duration of follow-up. During the OLE phase, where both arms received the same intervention, discontinuation rates reached as high as [redacted]%, a figure that warrants careful consideration. The predominant reasons for discontinuation across the study population included

[redacted].

3.3.4.2 Hospitalisation

According to Table 14.2.3.2 of the CSR INCREASE study, no patients in the inhaled treprostinil arm and one patient ([redacted]%) in the placebo arm experienced three or more hospitalisations. However, this proportion appeared to increase notably during the OLE phase, with [redacted] patients ([redacted]%) experiencing three or more hospitalisations, as reported in CSR OLE Table 14.3.4.6. The median duration of hospitalisation during the INCREASE study was [redacted] days for both treatment groups, with maximum durations of [redacted] and [redacted] days for inhaled treprostinil and placebo, respectively. In contrast, the OLE phase reported a median hospitalisation duration of [redacted] days, with a maximum of [redacted] days.

The median time to first hospitalisation during the OLE phase was [redacted] weeks (range: [redacted] to [redacted] weeks), suggesting a wide-ranging period where people were at risk of first hospitalisation. These findings may raise considerations regarding patient safety. Given that hospitalisation events may occur as late as [redacted] weeks, a longer follow-up period than that implemented may have been preferable to more fully assess long-term safety and risks to patient well-being. This consideration is further underscored by the progressive nature of the underlying disease, which inherently carries a risk of late complications.

Figure 11: Kaplan-Meier Plot of time to hospitalisation OLE phase (CSR OLE, Figure 14.3.2)

An upward trend in cardiopulmonary-related hospitalisations was observed from the INCREASE study to the OLE phase. While [redacted] patients experienced

three or more hospitalisations during the RCT phase, a total of [redacted] such cases were reported in the OLE phase. Furthermore, the duration of hospitalisations demonstrated a tendency to increase over time, with longer stays noted during the OLE phase compared to the RCT period.

Table 16: Cardiopulmonary hospitalisations

Trial name	INCREASE (CSR INCREASE Table 14.2.3.2)		INCREASE OLE (CSR INCREASE OLE Table 14.3.4.6)		
Treatment arm	Inhaled treprostinil N=163 (%)	Placebo N=163 (%)	Inhaled treprostinil N=119 (%)	Placebo N=121 (%)	Overall N=242 (%)
Total hospitalisations related to cardiopulmonary indications during the study					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration (in days) of hospitalisations due to cardiopulmonary indications during study					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3.4.3 Treatment-emergent adverse events (TEAE)

While the incidence of serious adverse events (SAEs) appeared comparable between the inhaled treprostinil and placebo groups during the INCREASE trial, a notable increase in such events was observed during the OLE phase.

Table 17: Overall summary of adverse events

	INCREASE (CSR INCREASE Table 14.3.1.1)	INCREASE OLE (CSR OLE Table 14.3.1.1)

	Inhaled treprostinil N=163 (%)	Placebo N=163 (%)	Overall N=242 (%)
Subjects with at least 1 AE	93.3	91.4	94.6
Subjects with at least one SAE	23.3	25.8	55
Subjects with at least one AE leading to withdrawal	[redacted]	[redacted]	22.3
Subjects with at least one AE leading to death	[redacted]	[redacted]	[redacted]

Based on Table 12-3 of the CSR for the OLE and INCREASE RCT, both the total number of AEs leading to death ([redacted] in OLE vs. [redacted] in inhaled treprostinil and [redacted] in placebo) and the proportion of patients experiencing at least one such event ([redacted]% in OLE vs. [redacted]% and [redacted]% in inhaled treprostinil and placebo, respectively) are notably higher in the OLE, where all patients received relatively long-term inhaled treprostinil. This contrast with the smaller, shorter INCREASE trial raises concerns about long-term safety.

A summary of events provided by the company in the CSR doc, classified by the organ class, is shown below.

Table 18: Summary of TEAEs

	INCREASE (CSR INCREASE Tables 14.3.1.3, 14.3.1.2, and Waxman et al. 2021)[44]		INCREASE OLE (CSR OLE Tables 14.3.1.3, 14.3.1.2 and Waxman et al. 2023)[45]
	Inhaled treprostinil N=163 (%)	Placebo N=163 (%)	Overall N=242 (%)
Any Event	93.3	91.4	94.6
Cough	43.6	33.1	26.9
Dyspnoea	25.2	31.3	26.0

Headache	27.6	19.6	18.6
Diarrhoea	13.5	11.7	15.3
Dizziness	18.4	14.1	14.9
Infections and infestations	[redacted]	[redacted]	[redacted]
Nausea	15.3	16.0	13.2
Fatigue	14.1	14.1	13.2
Acute respiratory failure	[redacted]	[redacted]	12.4
Back pain	[redacted]	[redacted]	10.7
Productive cough	[redacted]	[redacted]	10.3
Chest pain	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]	[redacted]

Following section 12.2.3.2 of the CSR, AEs deemed potentially attributable to inhaled treprostinil were reported with consistency across both RCT and its OLE phase. The most frequently observed events during the RCT and OLE phases, respectively, included cough ([redacted]), headache ([redacted]), and dyspnoea ([redacted]). These occurrences were broadly aligned with the established pharmacodynamic profile for prostacyclin and the inhalation administration route (CSR OLE, p. 63).

Additional AEs such as dizziness ([redacted]), throat irritation ([redacted]), and diarrhoea ([redacted]) were reported at rates exceeding the 10% threshold exclusively during the RCT phase and were not among the most frequently cited events in the OLE. It is noteworthy that within the OLE, a higher incidence of AEs was reported among individuals who initiated prostacyclin therapy following a transition from placebo, in contrast to those who continued treatment with inhaled treprostinil. This observation may suggest a potential modulatory effect of prior treatment exposure (CSR OLE, p. 63). The duration

of exposure, dosage, and treatment history may have contributed to the overall safety profile of inhaled treprostinil.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The company provided a MAIC, with weighted participant data from INCREASE to match the baseline characteristics of a publication by Dawes et al. which has been summarised in section 3.2.3.2. Despite the EAG's request (clarification A25), the company did not implement a MAIC against the CPRD dataset, summarised in section 3.2.3.1, which could have been matched on age and sex variables.

3.5 Critique of the indirect comparison or multiple treatment comparison

The MAIC analysis undertaken by the company matched data of people treated with inhaled treprostinil from INCREASE and INCREASE OLE to the population of the untreated group from Dawes et al.[47] The only outcome presented was overall survival.

The covariates included in the analysis are shown in Table 19. Two additional important covariates were identified (BMI and smoking history) as having prognostic or effect-modifying status but were deemed to have insufficient data for inclusion. The EAG notes these were not reported by Dawes et al., so the extent of bias from these variables is unclear. The company removed people with a time since diagnosis of >2 years, and people with CTD from the starting analysis set of INCREASE. The former was based on an assumption that people in Dawes et al. have had a time since diagnosis of 0 years. The EAG was not able to verify whether this was a reasonable assumption to make and noted that it is a potential source of bias to the MAIC. The EAG

notes that in the reporting of Dawes et al. there is potential misclassification of males and females, due to inconsistent reporting over which group is larger (Table S3 vs Table S1).

Table 19: Covariates included in MAIC

Effect modifier	Original distribution in INCREASE (before matching)	Weighted INCREASE distribution (after matching)	Reported distribution in Dawes *et al.* (2022)[47]
Age (years)	68.36	67.0	67.0
Sex (male %)	0.59	0.26	0.26
Hypertension	0.50	0.33	0.33
Oxygenation	0.46	0.68	0.68
6MWD	261.0	222.0	222.0
DLCO	28.4	26.0	26.0
FEV1	67.0	55.0	55.0
IPF	0.33	0.69	0.69
NSIP	0.12	0.090	0.090
Other	0.55	0.22	0.22

The company also implemented the MAIC using outcomes for only people originally randomised to inhaled treprostinil, alongside some sensitivity analyses. A comparison of outcomes is shown in Table 20. Whilst the estimate of relative effect varied, all analyses suggested a clear benefit associated with the INCREASE population. It remains uncertain whether this can be attributed to inhaled treprostinil.

Table 20: Overall survival hazard ratios from MAIC analyses

Analysis	Overall Survival Hazard Ratio (95% Confidence Interval)
Unweighted naïve comparison	0.28 (0.19, 0.40)
Company Original MAIC	0.16 (0.09, 0.28)
Inhaled treprostinil arm only	0.16 (0.06, 0.41)

The EAG requested that the company repeat the MAIC analysis using information from the placebo arm of INCREASE to investigate whether the effect size might be attributable to remaining underlying differences in the populations rather than treatment with inhaled treprostinil. However, the company declined to perform this analysis (clarification A19) due to immature follow-up of people receiving placebo, considering to only use data from the INCREASE randomised period (16 weeks).

EAG summary:

The EAG is concerned about the impact of unadjustable differences between the populations of INCREASE and Dawes et al., which may bias the results. It is not possible to determine whether the effect size is due to receiving inhaled treprostinil or underlying unadjusted differences between the populations in the two studies.

3.6 Additional work on clinical effectiveness done by the EAG

The EAG undertook some targeted searching to check for any additional studies including useful data on the comparator of interest (established clinical management or PDE5is). Details of the searches can be found in Appendix 0. The EAG also checked the lists of studies excluded from the company's clinical SLR at full text screening stage or judged to not be relevant to the scope (clarification response C3), those excluded at full text were unavailable (clarification response C6) and there were nine publications on BSC included in the SLR which were not examined further listed in CS Appendix B Table 5.

3.7 Conclusions of the clinical-effectiveness section

The INCREASE trial faced notable methodological limitations, including a 29.4% screening failure rate, high early discontinuation (21% before week 16), and limited follow-up. The sponsor did not enrol all patients into the OLE, which was limited by unblinded assessments, high attrition (only 29% completed 108 weeks), and inconsistent visit schedules. Inhaled treprostinil appears to offer at least short-term benefit to patients; however, the benefit to people switching to inhaled treprostinil appears considerably less, and the impact on overall survival remains unclear.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

4.1 Critique of the review of cost-effectiveness evidence

The company undertook SLRs to identify published cost-effectiveness studies, HRQoL data and cost and healthcare resource data in patients with PH-ILD. These are reported in CS Appendices E, F and G, respectively. Searches for the cost-effectiveness and costs/healthcare resource use SLRs were undertaken together.

4.1.1 Eligibility criteria

The population considered for all SLRs is adults with Group 3 PH-ILD (CS Appendices Tables 11,15 and 20), which aligns with the NICE scope. However, studies involving broader or mixed populations, such as those with pulmonary hypertension (PH) Group 3, which includes PH-ILD as well as PH associated with other lung diseases, may still offer relevant insights. In response to clarification question C9, the company described their approach regarding eligibility of studies in broader or mixed populations. However, these "pragmatic" inclusion/exclusion criteria were not specified *a priori,* and it is difficult to ascertain whether they were systematically and consistently applied.

4.1.2 Searches

The searches were originally conducted in January 2024, then updated in January 2025 (cost-effectiveness and costs SLRs) or February 2025 (HRQoL SLR). PubMed and Embase were searched, as well as recent proceedings of three relevant conferences. Reference lists of included studies and relevant systematic reviews were also checked (CS Appendices E.1.1, E.1.2, F.1.1,

F.1.2 and G.1.1). For comprehensiveness, the EAG recommends searching additional economics-specific and grey literature sources, such as INAHTA's HTA database, the Cost Effectiveness Analysis (CEA) Registry from Tuft's Medical Center and RePEC (via EconPapers).

Full details of the bibliographic database search strategies, including the number of results retrieved at each stage were not provided, and the company did not provide any additional information in response to clarification question C11. The EAG is therefore unable to ascertain whether the same search strategy was run for both the original and update searches, how duplicates between the two searches were removed and whether date limits were applied to the update searches. Additionally, the numbers of results retrieved from Embase for the HRQoL searches (CS Appendix F.1.3, Figures 15 and 16) are surprisingly low compared to the PubMed results and the date coverage of the Embase database used is not stated. This introduces further doubt as to the reliability of the search methodology and reporting, which does not adhere to PRISMA-S recommendations.[54]

The text in Appendices E.1.1, F.1.1 and G.1.1 states that "search strategies were developed using search terms related to PH-ILD and including subject indexing terms, and free text search terms in the title, abstract and keyword fields". However, in the PubMed and Embase search strategies (Appendices Tables 9, 10, 13, 14, 18 and 19), only title and abstract fields are searched for the free text disease terms, not the keyword field which would have increased the sensitivity of the search. A reasonable selection of search terms for PH-ILD are used, though some are missing, including the acronym "PH-ILD" and "fibrosing alveolitis" as a free text term.

Appendices E.1.1 and G.1.1 state "The population search terms were then combined with a published study type filter from the Canada's Drug Agency (CDA) for economic evaluations and models", and this is the case for the PubMed search (Tables 9 and 18). However, the Embase search (Tables 10

and 19) uses a search filter unknown to the EAG, which is less comprehensive than the CDA filter, with a focus on costs, so that useful terms for economic models are missing.

The EAG ran searches in PubMed and Embase with date limits since the company's last searches, in order to check for any new, relevant publications. Details of the search strategies can be found in appendices (section 7.4). No additional studies were identified. Despite the limitations of the company's searches, the EAG considers it unlikely that any published cost-effectiveness analyses or economic models specific to the PH-ILD population were missed.

4.2 Critique of the submitted economic evaluation

The EAG reviewed the company's economic evaluation model to assess alignment with NICE standards. The company constructed a de novo cost-utility model to evaluate the cost-effectiveness of inhaled treprostinil compared with BSC. This evaluation was based on the INCREASE and INCREASE OLE clinical trial populations. The licensing criteria, and the decision problem are outlined in the submission. The EAG provided a summary of the model structure and critically appraised the clinical evidence (e.g., efficacy, treatment pathway, and mortality) and economic evidence (e.g., drug costs, health state resource use and costs, and utility values). The EAG critiqued the methods and inputs used in the analysis.

4.2.1 NICE reference case checklist

The EAG undertook an evaluation of the company's submission against the NICE reference case. Findings are summarised in the Table 21.

Table 21: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The model captures patient health effects.
Perspective on costs	NHS and Personal Social Services	The base-case NHS and PSS perspective aligns with NICE requirements. The exclusion of lung transplant costs in the base case is problematic, as they are part of the clinical worsening definition, potentially underestimating costs. Lack of UK-specific resource use data (relying on French data) reduces generalisability.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The cost-utility analysis with incremental analysis meets NICE requirements.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The 30-year lifetime horizon aligns with NICE's requirement to capture all relevant costs and outcomes.
Synthesis of evidence on health effects	Based on systematic review	The company use evidence from INCREASE and also provide scenario analysis which uses information from a MAIC analysis comparing INCREASE data to a published RWE study by Dawes et al.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	QALYs are appropriately used, but the reliance on SGRQ mapped to EQ-5D-3L deviates from NICE's preference for direct EQ-5D data.
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	Patient-reported SGRQ scores meet NICE's requirement for patient-reported data. However, the absence of carer-reported data

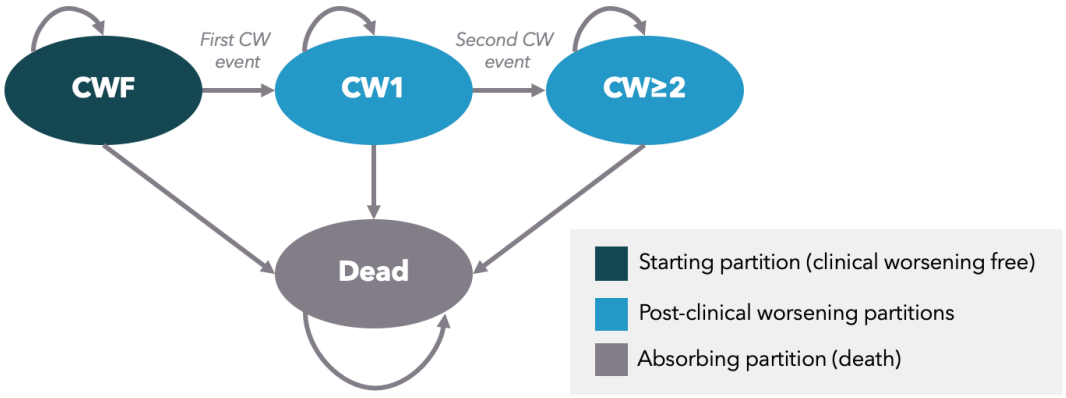
Element of health technology assessment	Reference case	EAG comment on company's submission
		lacks justification, as carer burden may be relevant for PH-ILD.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The Freemantle algorithm),[55] uses a UK IPF population, reasonably representative of the UK, and age/sex adjustments align with NICE's requirement for UK population norms. The choice of Freemantle over Starkie is justified due to IPF's closer clinical relevance to PH-ILD.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	The model adheres to NICE's equity principle by applying equal QALY weights.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Most costs align with NHS and PSS resources, using standard UK sources. However, the exclusion of lung transplant costs in the base case, despite their inclusion in the clinical worsening definition, risks underestimating costs. Reliance on French RWE data for resource use reduces UK relevance, and the lack of UK-specific PH-ILD resource use data is a limitation.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The discount rate is based on 3.5% per annum.

Abbreviations: PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome; IPF, Idiopathic pulmonary fibrosis.

4.2.2 Model structure

The company constructed a de novo partitioned survival model (PSM) in Microsoft Excel® to evaluate the cost-effectiveness of inhaled treprostinil compared to best supportive care (BSC) for patients with PH-ILD. The model

was structured with four distinct health states: (1) clinical worsening-free (CWF), (2) first clinical worsening event (CW1), (3) two or more clinical worsening events (CW≥2), and (4) death (see Figure 12).



Key: CWF, clinical worsening-free; CW, Clinical worsening.
Note: Arrows indicate permitted transitions; no backward movement is allowed between health states.

Figure 12: Model schematic (obtain from CS, document B, section 3.2.3)

The model simulates a cohort of PH-ILD patients beginning in the CWF state and transitioning over time based on time-to-event data from the INCREASE trial and INCREASE OLE study. The model assumes irreversible progression, where patients cannot transition back to earlier states. The company stated that this mirrors the disease trajectory in PH-ILD and is a common assumption in health economic models, particularly in oncology. The company asserted that the structure was considered conservative as it does not explicitly model clinical improvement, such as the 6MWD gains observed in the INCREASE trial. Instead, such benefits are indirectly captured through increased time spent in better health states (CWF) and associated quality-of-life (QoL) improvements.

The EAG notes that the patient population is heterogeneous at the starting point of the model, as time to diagnosis and number of previous worsening events varies. Hence it is possible that one individual may be healthier after two worsening events than another may be at baseline.

4.2.2.1 Definition of Clinical Worsening

Clinical worsening is a composite endpoint, defined by the occurrence of any of the following:

- Decrease in 6MWD of ≥15% from baseline
- Decrease in FVC% of ≥10% from baseline
- Cardiopulmonary hospitalisation
- Acute lung-disease exacerbation
- Lung transplant
- Death

The company stated that, the definition of clinical worsening was based on the secondary outcome measure in the INCREASE trial. However, the company adapted the definition used in the Waxman 2021[44] trial to align with Nathan (2022)[52] post hoc analysis and expert consensus, including exacerbation and FVC decline to better reflect clinical relevance in ILD. Death is retained as a CW event to appropriately model competing risks and avoid overestimation in survival analysis.

The company stated that, while lung transplant is included in the CW definition, its cost is excluded from the base-case analysis due to its extremely low relevance in the UK (e.g., <1% in the INCREASE trial; rare in PH-ILD patients aged >65).

EAG comment

EAG concern: Potential bias and uncertainty due to modified definition of clinical worsening in economic model

Company's Approach: The company adapted the definition of clinical worsening used in the INCREASE trial by incorporating additional

components (specifically, ≥10% decline in FVC% and acute lung-disease exacerbation) based on post hoc analysis (Nathan et al., 2022)[52] and expert input. These additions were not part of the original Waxman 2021[44] trial definition, although such events were recorded. (see section 3.3.2.3 and 3.3.2.4) This adapted definition was used to inform the economic model, matching the definition of “disease progression”.

EAG’s critiques and rationale: The inclusion of additional events not prespecified in the trial protocol as clinical worsening events introduces potential bias and structural uncertainty into the model. While clinical expert input supports the relevance of FVC decline and exacerbation, post hoc modifications to composite endpoints can affect the internal validity and comparability of outcomes. It is unclear whether these changes systematically influence the frequency of events or alter treatment effects, particularly as the original trial was not powered or designed using this broader definition. Furthermore, the inclusion of death in both CW and OS modelling raises concerns about potential double-counting or inappropriate handling of competing risks.

EAG Solution: The EAG recommends that scenario analyses be conducted comparing model outcomes using both the original INCREASE trial definition (Waxman et al., 2021)[44] and the broader definition used in the model. However, the EAG does not currently have access to the necessary disaggregated trial data to conduct this analysis. Therefore, the company is encouraged to explore this sensitivity within its own modelling to test the robustness of outcomes to alternative definitions.

4.2.2.2 Modelling Time-to-Events

Parametric models (fitted to KM data) estimate:

- Time to first CW (informing CW1 state).

- Time to second CW (informing CW≥2 state).
- Time to death (all-cause mortality).

These determine the distribution of patients across health states over the lifetime horizon.

The company stated that, while patients may experience multiple worsening events, the model includes only two CW states (CW1 and CW≥2). This decision was guided by (i) limited data on third/fourth CW events and (ii) analysis showing no significant differences in QoL (SGRQ scores) between patients experiencing two vs. more than two events. This supported the exclusion of a third CW health state, although additional hospitalisation costs are included in CW≥2 to reflect potential resource use beyond the second event.

4.2.2.3 Discontinuation

Discontinuation of inhaled treprostinil is modelled using parametric survival models based on Kaplan–Meier (KM) data from the clinical trials. It affects only the drug cost component of the model.

EAG comment

Concern title: Underestimation of treatment duration due to inappropriate modelling of TTD

Company's Approach: The company modelled discontinuation of inhaled treprostinil using parametric survival models based on Kaplan–Meier (KM) data from the clinical trials. This discontinuation affects only the drug cost

component of the model. Specifically, the model assumes a generalised gamma distribution for TTD, derived from the INCREASE–OLE study data.

EAG's Critiques, Assumptions, and Justification: The company's TTD modelling approach appears to underestimate the proportion of patients who remain on treatment. Based on the company's OS model, OS reaches zero at cycle 1566 (year 30). Over this timeframe, the average proportion of surviving patients on treatment, calculated using the company's assumptions as (1 – [OS – TTD]/OS), results in 7.40%.

However, data from the INCREASE–OLE study suggest a higher rate of treatment persistence among surviving patients. Of 242 patients in the Safety Population, 173 (71.2%) discontinued the study early. After excluding 56 deaths, this implies that 117 of 186 surviving patients discontinued for other reasons, leading to a treatment continuation rate of approximately 37% ([1 – (117/186)]). This figure does not exclude the 24 patients (9.9%) who discontinued due to sponsor termination, whom the EAG believes would likely have continued treatment under real-world conditions.

Additionally, as discussed in section 4.2.5, the TTD KM curve closely aligns with the clinical worsening 2 (CW2) KM curve. The lack of crossing of these curves within the observed period indicates that TTD assumptions falling below CW2 (or lower than CW1) in the extrapolated period may be inconsistent with trial evidence. Therefore, unconstrained extrapolation of TTD beyond observed data may lead to implausibly low treatment duration estimates and, as a result, underestimated drug costs.

EAG Solution:

Base case: The EAG used the company's chosen "INCREASE–OLE: Parametric" generalised gamma model but applied a constraint that TTD should not fall below the CW2 curve.

Scenario analysis: The same generalised gamma model was used, but with a further constraint ensuring that the proportion of surviving patients on treatment remains at or above 37%.

4.2.2.4 Cycle length, time horizon, and discount rate

A weekly cycle length was adopted to allow the model to sensitively capture the possibility of multiple events in short timeframes, enhancing accuracy. A half-cycle correction is applied to minimize temporal bias in state transitions.

The model uses a lifetime horizon of 30 years, consistent with the NICE reference case, ensuring all health outcomes and costs are captured. A shorter time horizon is available when replicating the within-trial analysis based on KM data from the 16-week INCREASE study.
A discount rate of 3.5% for costs and benefits is applied to the model.

EAG comment

EAG Concern: Applying discounting in the first year due to the use of a per-cycle (weekly) discount rate

Company's Approach: The company applied a per-cycle discount rate to calculate discount factors in their economic model. The cycle length is 7 days, and the discounting is applied at the end of each cycle.

EAG comments: According to NICE reference case (2023), Section 4.5.1,[56] cost-effectiveness results should reflect the present value of costs and benefits over the analysis time horizon. The reference case specifically states: "*For the reference case, costs and health effects should be discounted at the same rate of 3.5% per year.*"

The EAG considers that using a per-cycle discount rate deviates from the guideline as it splits the annual discount rate into smaller time intervals (7 days). This applies discounting from a much earlier point in the model than an annual approach.

EAG's Solution:

Base-case: The EAG recommended revising the model to use a per-year discount rate of 3.5% as specified in NICE guidelines. This ensures that both costs and health effects are appropriately discounted over the time horizon, maintaining consistency with the reference case and improving the accuracy of the cost-effectiveness results.

4.2.2.5 Perspective

The company stated that, the model adopts the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS). It includes functionality to explore a societal perspective (e.g., lost productivity), but this is not used in the base-case analysis.

4.2.3 Population

The company defines its target population as adults aged ≥18 years with a confirmed diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD), classified under WHO group 3. The population included in the economic model closely mirrors that of the INCREASE clinical trial. The INCREASE trial was a 16-week, multicentre, double-blind, randomised, placebo-controlled Phase 3 study that enrolled 326 patients, who were assigned to receive either inhaled treprostinil or placebo. It serves as the primary source of clinical effectiveness evidence. The INCREASE study was conducted at 119 sites across the United States and Puerto Rico. Key baseline characteristics are directly derived from the INCREASE trial (see Table 22).

Table 22: Baseline characteristics in the cost-effectiveness model based on the INCREASE study (obtain from CS, document B, section 3.2.1)

Variable	All participants (N=326)
Age, mean (range)	66.45 years (26–90)
Percentage male, % (number)	53.0 (173)
Percentage of patients with CPFE, % (number)	25.2 (82)
Percentage of patients with a PVR >5 Wood units, % (number)	54.0 (176)
Percentage of patients with a PVR >5 Wood units and without CPFE, % (number)	39.6 (129)
Abbreviations: CPFE, Combined pulmonary fibrosis and emphysema; PVR, Pulmonary vascular resistance.	

The company emphasizes that the modelled cohort reflects the heterogeneity observed in the INCREASE study, including varying forms of ILD (e.g., idiopathic interstitial pneumonia, CPFE, and connective tissue disease) and differing levels of disease severity, as indicated by metrics such as six-minute walk distance (6MWD), pulmonary vascular resistance (PVR), and NT-proBNP levels.

Although no UK patients were enrolled, the company argues that the UK clinical experts considered the study population to be broadly generalisable to patients seen in NHS clinical practice. The company stated similarities in baseline demographic characteristics (such as age) and in the use of background antifibrotic therapy, support this assertion, thereby justifying its adoption in the economic model.

4.2.4 Interventions and comparators

4.2.4.1 Intervention: Inhaled treprostinil

The intervention evaluated in the company's economic model is inhaled treprostinil, a prostacyclin analogue, administered via an ultrasonic, pulsed-delivery nebuliser. In the INCREASE trial, participants received inhaled

treprostinil at a target dose of 9 to 12 breaths per session, four times daily. Some participants in the INCREASE OLE trial escalated to 15 breaths per session. However, in the model, the cost of the intervention is not dose-dependent, as all patients are assumed to require one single-use ampule per day. Each ampule is loaded into the nebuliser independently of the number of breaths delivered, and any residual medication is discarded at the end of each day. Therefore, the company stated that the treatment cost remains fixed regardless of within-trial dose escalation.

4.2.4.2 Comparator: Best Supportive Care (BSC)

The company stated that, in line with the NICE scope and European treatment guidelines, the company selected BSC as the comparator in the economic model. This reflects the comparator arm of the INCREASE trial, in which patients received placebo alongside standard background treatments for interstitial lung disease (ILD). The company asserted that, at the time of model development, there was no NICE-approved pharmacological treatment specifically indicated for PH-ILD in the UK, and no such therapies were available in clinical practice. BSC in the model is assumed to comprise standard ILD management without the addition of inhaled treprostinil.

EAG comment

EAG concern: Potential uncertainty from exclusion of PDE5 inhibitors as a comparator

Company's approach: The company compares inhaled treprostinil to established clinical management (BSC), excluding off-label use of pulmonary vasodilators such as PDE5 inhibitors (PDE5is). This decision aligns with the INCREASE trial design (which did not include patients on PDE5is), clinical expert input, and UK epidemiological data showing limited PDE5i use (8% of PH-ILD patients, Ferrer-commissioned study). The company notes that

PDE5is are not considered standard of care due to conflicting evidence and their limited use in non-severe PH-ILD, as reflected in ERS/ESC guidelines.

EAG's critiques and rationale: While the exclusion of PDE5is from the base case is broadly justified given the trial population and guideline recommendations, uncertainty remains due to variation in real-world use across UK specialist centres. Some clinical advisers reported PDE5i use in up to 60% of referred patients, though this likely reflects selection bias and centre-specific practices. Additionally, the 8% usage estimate from CPRD may be an underestimate due to limitations in coding and missing data on prescriptions issued by PH centres.

Given the NICE scope includes PDE5is as a potential comparator, their exclusion introduces some uncertainty. However, the EAG acknowledges that any comparison would be reliant on MAIC or similar methodology due to a lack of direct evidence.

EAG solution: While the EAG cannot currently include PDE5is as a comparator due to data limitations, the company could consider exploring this through a subgroup analysis of the INCREASE trial (if a subset of patients with characteristics similar to those who typically receive PDE5is in UK practice (e.g., PVR ≥5 WU) can be identified. These could then be used in a MAIC analysis to match to population of Dawes et al. who received PDE5is, or other more recently published studies. This may provide indicative insight into how inhaled treprostinil compares with PDE5is in relevant clinical subpopulations and help assess the robustness of excluding PDE5is from the economic evaluation.

4.2.5 Treatment effectiveness and extrapolation

The company extrapolated four time-to-event outcomes to use in the model: overall survival, time to first clinical worsening, time to second clinical

worsening and time to treatment discontinuation (TTD). The company state that the hazard rates were not proportional across arms for any of the outcomes due to crossing of the KM functions and so independent models were fitted to each arm. No further supporting information of non-proportional hazard e.g. hazard plots or log-log plots were provided, aside from a log-log plot for OS, hence the EAG consider it possible that survival models assuming proportionality may be beneficial for modelling OS and other time-to-event outcomes given the unequal length of follow-up across arms, however these models were not made available by the company. The two clinical worsening outcomes have a much smaller effect on the cost-effectiveness outcomes than OS and TTD.

4.2.5.1 First Clinical Worsening

For inhaled treprostinil, the company use data for people randomised to the inhaled treprostinil arm of INCREASE and use their follow-up from the trial and OLE period. The company fitted a standard set of parametric survival models, and selected the log-normal extrapolation. The log-normal has the best statistical fit, though is very similar to the log-logistic model in terms of fit and predictions.

For BSC, the company use data from the placebo arm of the first 16 weeks of INCREASE. The company select the exponential model as it is among the best statistically fitting models. The company's experts stated that they expected all patients to experience a CW1 event within three years, where the exponential extrapolation predicts <1% of people remaining free of CW1 at 1.26 years.

There is a potential for bias in the model selection coming from the differing lengths of follow-up from the two arms. The EAG considers that if models were fitted to the 16-week follow-up of the inhaled treprostinil arm, then it is possible the exponential model may be among the best-fitting models. The longer follow-up of inhaled treprostinil has shown a decreasing hazard rate in

the tail, which may emerge if longer follow-up were available for BSC. The EAG prefers to use a log-logistic model for both arms which is among the best fitting models for both arms and is consistent with guidance from Technical Support Document 14 which suggests using models of the same type.[57]

Table 23: First Clinical Worsening Model Predictions

	Year 2 prediction inhaled treprostinil	**Year 3 prediction inhaled treprostinil**	**Year 2 prediction BSC**	**Year 3 prediction BSC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]

* indicates company preference; ◇indicates EAG preference

Note that extrapolations for CW1 were restricted so that they could not exceed the relevant extrapolation of CW2.

The EAG requested that the company explore the impact of using an alternative definition of clinical worsening, where a decrease of 30m in 6MWD was used instead of a 15% decrease, however this had only a small effect on the outcomes for both arms (clarification B13).

4.2.5.2 Second Clinical Worsening

For inhaled treprostinil, as for first clinical worsening, the company use data for people randomised to the inhaled treprostinil arm of INCREASE and use their follow-up from the trial and OLE period. For BSC, the company again use data from the placebo arm of the first 16 weeks of INCREASE.

For both arms, the company select the log-normal extrapolation as it was the best statistical fit for the inhaled treprostinil arm and among the best fitting models for the placebo arm, and the extrapolations for both arms were deemed plausible by the company's clinical experts.

Table 24: Second and beyond Clinical Worsening Model Predictions

	Year 3 prediction inhaled treprostinil	**Year 5 prediction inhaled treprostinil**	**Year 3 prediction BSC**	**Year 5 prediction BSC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]◇	[redacted]◇	[redacted]◇	[redacted]◇
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]

* indicates company preference; ◇ indicates EAG preference

Overall, the EAG considers the company's approach to modelling CW2 reasonable and makes no changes to the EAG base case, as the choice of curve has little influence on the cost-effectiveness outcomes. There are

however some concerns. Firstly, the differing lengths of follow-up may bias the model fits, i.e. trends of a declining hazard rate in the inhaled treprostinil arm may have emerged in the placebo group, similar to CW1.

Furthermore, the EAG requested that the company produce a plot of time to second clinical worsening for people who had a first clinical worsening. Whilst the groups are no longer randomised, the graph does not show a clear benefit of continued inhaled treprostinil therapy beyond the first clinical worsening (Figure 13). When comparing the QALYs accrued from each health state, the company's choice of models suggests a similar magnitude of benefit of inhaled treprostinil is achieved in the pre-CW1 health state, and the post-CW1/pre-CW2 health state.

Note that extrapolations for CW2 were restricted so that they could not exceed the relevant extrapolation of OS.

Figure 13: Time to second clinical worsening event for people who had a first clinical worsening event (from Clarification Response A13)

4.2.5.3 Overall Survival

For the OS of inhaled treprostinil, in their base case, the company fit parametric models to the population from INCREASE who were originally randomised to inhaled treprostinil and includes their OLE follow-up.

The EAG accepts the choice of population for inhaled treprostinil, but considers that the company's preferred extrapolation is too optimistic. The EAG considers that the KM function displays an increasing hazard rate (see clarification response, which is only captured by three models: Weibull, Gompertz and generalised gamma. The company's preferred model is the Weibull. However, from Figure 20 of the CS, this extrapolation is very similar to the exponential, which assumes a constant hazard rate. Hence, the Weibull model is capturing only a small increase in the hazard rate over time. Furthermore, when comparing the company's selection of models to inform the health state occupancy (Table 26), it is clear that the majority of benefit is accrued in the post-CW2 health state. Given that time on treatment aligns closely with CW2, the EAG considers it implausible that the benefit of inhaled treprostinil will be greatest in this health state when the majority of people have stopped receiving inhaled treprostinil.

The EAG considers the Gompertz and generalised gamma models are the two models which best capture the increasing hazard rate, though none of them represent the observed period very well, and the company could explore more flexible models, such as restricted cubic splines to improve the fit. The EAG base case uses the generalised gamma, but the EAG explores the effect of using the Gompertz in a scenario analysis. This approach was approved plausible by the EAG's clinical expert.

Table 25: Overall survival predictions for inhaled treprostinil

	Year 5 prediction inhaled treprostinil	Year 10 prediction inhaled treprostinil	Year 15 prediction inhaled treprostinil
~~Exponential~~	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
~~Log-normal~~	[redacted]	[redacted]	[redacted]
~~Log-logistic~~	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]◇	[redacted]◇	[redacted]◇

* indicates company preference; ◇ indicates EAG preference

Table 26: Discounted QALYs by health state and arm for Company

	Company inhaled treprostinil	Company BSC	Difference
No Worsening	[redacted]	[redacted]	[redacted]
After first worsening	[redacted]	[redacted]	[redacted]
After second worsening	[redacted]	[redacted]	[redacted]

For the modelling of BSC, the company uses the trial and OLE follow-up with the RPSFTM adjustment applied. As a scenario analysis, the company explored extrapolating using the 16-week follow-up for inhaled treprostinil and BSC.

The company model appeared to have the option to use extrapolations fitted to the ITT OLE data for the BSC arm; however, this option was not populated with any parameters within the model.

Of models fitted to the RPSFTM-adjusted data, the company select the Weibull model as it is among the models with the best statistical fit and is also consistent with their choice of extrapolation for modelling BSC.

Having already described doubts around the RPSFTM adjustment (section 3.3.2.1), the EAG preference is to use the ITT OLE data due to uncertainty whether any OS benefit was obtained by switching. Due to the company's failure to implement alternative approaches, the EAG is reliant on an approach that uses the ITT hazard ratio, assuming proportional hazards, and applies this to the EAG's preferred extrapolation for inhaled treprostinil OS. The EAG also explores the impact of applying the hazard ratio from the IPCW adjustment.

Table 27: Overall survival predictions for BSC

	Year 5 Prediction BSC	Year 10 Prediction BSC	Year 15 Prediction BSC
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]
ITT HR applied to inhaled treprostinil Gen Gamma	[redacted]	[redacted]	[redacted]
IPCW HR applied to inhaled treprostinil Gen Gamma	[redacted]	[redacted]	[redacted]

* indicates company preference; ◇ indicates EAG preference

The EAG prefers to use the trial and OLE follow-up for people randomised placebo without any adjustment applied, but also explores applying the hazard ratio associated with the IPCW adjustment to the extrapolation for inhaled treprostinil.

	EAG inhaled treprostinil	EAG BSC	Difference
No Worsening	[redacted]	[redacted]	[redacted]
After first worsening	[redacted]	[redacted]	[redacted]
After second worsening	[redacted]	[redacted]	[redacted]

4.2.5.4 Time to treatment discontinuation

The modelling of time-to-treatment discontinuation (TTD) is only relevant to the inhaled treprostinil arm, as the BSC arm are not receiving any active treatment.

The EAG has produced a plot which shows the observed follow-up for each of the time-to-event outcomes for people receiving inhaled treprostinil. It is clear that CW2 and TTD are similar to each other, however, in the extrapolated models, the extrapolation for TTD falls below CW2 (Figure 14).

Figure 14: Relationship of time-to-event outcomes for company's modelling of inhaled treprostinil

4.2.6 Health-related quality of life (HRQoL)

The company adopted a structured approach to incorporating HRQoL within its cost-effectiveness model (CEM). The company stated that, recognising the limited availability of disease-specific HRQoL data, a combination of clinical trial data, literature-based mapping algorithms, and expert input was utilised to inform the model's utility inputs.

4.2.6.1 Data sources and rationale for selection

HRQoL data were sourced primarily from the INCREASE trial and its open-label extension (OLE). In both studies, HRQoL was measured using the Saint George's Respiratory Questionnaire (SGRQ). No EQ-5D data were collected directly. Given the absence of validated instruments specifically for PH-ILD with available mapping algorithms to EQ-5D, the SGRQ was considered the most appropriate proxy, based on clinical expert consensus and precedent in similar respiratory conditions. Regarding assessment of HRQoL during the trial the company stated "*patients treated with inhaled treprostinil reported lower scores (i.e., better health) across all domain scores of the SGRQ (symptoms, activities, and impacts). However, the differences between the inhaled treprostinil and placebo arms were not statistically significant, meaning the difference could be due to chance and further research is required to demonstrate the impact of inhaled treprostinil on QoL."* A targeted literature review followed by a systematic literature review (SLR) confirmed a paucity of published HRQoL data specific to PH-ILD, further justifying the use of trial-derived SGRQ scores. The available HRQoL options are listed in Table 28, with the base-case choice indicated in bold and underlined.

Table 28: All available options for HRQoL

Source options	Mapping algorithm	Type of utility
Options for HRQoL		
• INCREASE 16-week univariate SGRQ • **INCREASE OLE univariate SGRQ** • INCREASE OLE GLM	• Starkie 2011 • **Freemantle 2015**	• **Treatment-independent SGRQ** • Treatment-dependent SGRQ • Treatment-independent SGRQ

Key: GLM, generalized linear model; OLE, open-label extension; SGRQ, Saint George's Respiratory Questionnaire.

Note: Base-case analysis selected settings are underlined and in **bold**

The base-case analysis used univariate, treatment-independent SGRQ values derived from the INCREASE OLE study at week 48. These were mapped to EQ-5D utilities using the Freemantle algorithm and adjusted accordingly. Due to the lack of treatment-dependent HRQoL data for best supportive care (BSC), values for BSC were assumed to be equivalent to those for inhaled treprostinil across all health states. SGRQ data were stratified by clinical worsening (CW) health states: clinical worsening free (CWF), one event (CW1), and two or more events (CW≥2) (see Table 29).

Table 29. Base-case analysis HRQoL inputs

Health states	Inhaled treprostinil			BSC		
	SGRQ	EQ-5D	AF	SGRQ	EQ-5D	AF
Clinical worsening free (CWF)	[redacted]					
Clinical worsening one (CW1)	[redacted]					
Clinical worsening two (CW≥2)	[redacted]					

Key: AF, adjustment factor; CW, clinical worsening; CWF, clinical worsening-free; SGRQ, Saint George's Respiratory Questionnaire.

Note: Given the lack of treatment-dependent HRQoL data for best supportive care from INCREASE OLE, it was assumed to be the same as inhaled treprostinil

The company stated that data from week 108 of the INCREASE OLE were excluded due to high levels of missing data and lack of statistical significance in observed differences.

The company reported that patients receiving inhaled treprostinil had lower (indicating better health) scores across all SGRQ domains: symptoms, activities, and impacts. However, the differences between the inhaled treprostinil and placebo groups were not statistically significant, suggesting the observed effects may be due to chance. Further research is needed to establish the treatment's impact on quality of life.

To explore robustness, the company also conducted a multivariate regression analysis using a generalised linear mixed model (GLM) with a beta distribution and logit link. This regression incorporated baseline SGRQ, age, and gender, accounting for repeated measures per participant. The resulting coefficients produced time- and treatment-independent SGRQ estimates by health state. These estimates were also mapped to EQ-5D using both Freemantle and Starkie algorithms. However, the company stated that the regression-based estimates demonstrated smaller differences between health states than the univariate analysis.

Table 30: Outcome from the regression analysis

	Freemantle 2015			Starkie 2015		
	SGRQ	**EQ-5D**	**AF**	**SGRQ**	**EQ-5D**	**AF**
Clinical worsening free	[redacted]					
Clinical worsening one	[redacted]					
Clinical worsening two	[redacted]					

Key: AF, Adjustment factor; SGRQ, Saint George's Respiratory Questionnaire.

The company stated that, following discussion at an April 2025 advisory board, the univariate analysis was retained in the base case on the grounds of clinical plausibility.

EAG comments:

EAG Concern: Univariate analysis risks bias, overestimating HRQoL benefits without addressing selection bias.

Company's Approach: The company selected univariate analysis of INCREASE OLE treatment-independent SGRQ data as the base case, using the Freemantle (2015) algorithm to map SGRQ to EQ-5D-3L utilities. The company stated that this choice was justified by larger HRQoL differences between health states, deemed clinically plausible by experts, and consistency with trial time-to-event data.

EAG's critiques, assumptions, and justification: The EAG criticised the univariate approach for several reasons:

1. Failure to address selection bias: Univariate analysis does not adjust for selection bias, unlike the multivariate GLM, which accounts for covariates (age, sex, baseline SGRQ) and repeated measures.
2. Overstated HRQoL differences: Univariate analysis exaggerates health state differences, potentially inflating cost-effectiveness outcomes, while GLM's conservative estimates align with non-significant trial findings.
3. Lack of statistical rigor: Univariate reliance on descriptive statistics overlooks complex HRQoL relationships, unlike the GLM's regression modelling.
4. Subjective expert reliance: The preference for univariate analysis is based on expert opinion regarding clinical plausibility, without quantitative validation through sensitivity analyses. This subjectivity introduces uncertainty, especially given the trial's statistical findings.
5. Small sample sizes: The INCREASE OLE's small sample sizes (e.g., N=[redacted] for CWF in the inhaled treprostinil arm) reduces estimate reliability, making the GLM's statistical adjustments more robust.

Assumption: The EAG assumes that the multivariate GLM better handles bias and small sample sizes, ensuring reliable HRQoL estimates.

EAG Solution:

Base-Case Analysis: The EAG recommended the multivariate GLM approach (CWF: [redacted], CW1: [redacted], CW≥2: [redacted]) as the preferred base case for estimating HRQoL in the cost-effectiveness model.

Scenario Analysis: To explore uncertainty, the following scenario analyses are recommended:

1. Univariate Analysis: Use the company's univariate approach (CWF: [redacted], CW1: [redacted], CW≥2: [redacted]) to assess the impact of larger HRQoL differences on model outcomes.
2. Starkie Algorithm: Apply the Starkie (2011) algorithm to map SGRQ to EQ-5D-3L, evaluating the effect of a less relevant disease population (e.g., CWF: [redacted], CW1: [redacted], CW≥2: [redacted]).

EAG Concern: Uncertainties in HRQoL measurement tool (SGRQ) and missing long-term data for PH-ILD.

Company's Approach: The company estimated health state utility values by mapping SGRQ total scores to EQ-5D utilities, using data from INCREASE and OLE at the last follow-up of 16-weeks and week 48, respectively. The company stated that the SGRQ, though not validated for PH-ILD, was used due to the lack of alternatives. Week 108 data were excluded due to small sample sizes (e.g., N=[redacted] for CWF) and non-significant differences (p=[redacted]). The company acknowledges potential utility overestimation from SGRQ during exacerbations but frames it as conservative for inhaled treprostinil.

EAG's critiques, assumptions, and justification: The EAG criticised the univariate approach for several reasons:

1. Unvalidated SGRQ in PH-ILD: The SGRQ's lack of validation in PH-ILD introduces measurement uncertainty. While no better alternatives exist, downplaying this limitation risks inaccurate utility estimates, particularly for severe health states.

2. Utility overestimation: As mentioned by the company, the SGRQ may overestimate utilities by not capturing HRQoL during exacerbations, potentially skewing cost-effectiveness outcomes, despite being framed as conservative.
3. Lack of long-term data: Excluding week 108 data due to small sample sizes and missing data limits the model's ability to capture long-term HRQoL impacts, critical for chronic PH-ILD.
4. Unavailability of specific Instruments: The ongoing PHA UK study (March 2025) on EmPHasis-10, potentially more specific to PH-ILD, is unavailable, leaving a gap in disease-specific HRQoL measurement.
5. Reliance on univariate analysis: The univariate approach, despite expert support, fails to adjust for selection bias or small sample sizes (e.g., N=[redacted] for CWF in INCREASE OLE), increasing uncertainty compared to the multivariate GLM.

Assumption: Robust HRQoL estimation requires validated instruments and long-term data to minimize uncertainty and capture chronic disease progression accurately.

EAG Solution:

To address the uncertainty surrounding HRQoL measurement in PH-ILD, the EAG adopts a pragmatic interim solution:

Short-Term (current decision-making): The EAG recommends using the multivariate GLM as the base case (Same recommendation as provided for the previous concern) to reduce measurement uncertainty.

Long-Term (future recommendations): The EAG highlights the need for future work to:

- Validate HRQoL instruments in the PH-ILD population,

- Collect and incorporate long-term utility data, particularly beyond Week 48, to better capture the chronic and progressive nature of PH-ILD and the sustained treatment effects of inhaled treprostinil.

4.2.6.2 Mapping to EQ-5D

To convert SGRQ scores into utility values compatible with health economic modelling, two mapping algorithms were evaluated: Freemantle et al. (2015),[55] based on patients with idiopathic pulmonary fibrosis (IPF), and Starkie et al. (2011),[58] based on patients with chronic obstructive pulmonary disease (COPD). The company stated that, the Freemantle algorithm was selected for the base-case analysis due to greater physiological and clinical similarity between IPF and PH-ILD, as compared to COPD. The formula used was:

$$EQ - 5D - 3L = 1.3246 - 0.01276 \times SGRQ$$

The second algorithm (Starkie, 2011)[58] was developed using data from 3,640 COPD patients (14,612 observations) and estimates EQ-5D-3L scores using the formula:

$$EQ - 5D - 3L = 0.9617 - (0.0013 \times SGRQ) - 0.001 \times SGRQ^2 + 0.0231 \times \%male$$

To ensure consistency with population-level HRQoL trajectories, EQ-5D values were adjusted for age and gender using estimates from the Health Survey for England and methods described by Hernández-Alava (2022).[59] A relative adjustment factor (AF) was calculated by comparing trial-based utilities to the general population norm (0.81 for the modelled cohort) and applied dynamically as the cohort aged.

EAG comments:

The EAG considers the company's selection of the Freemantle algorithm appropriate, given its derivation from an idiopathic pulmonary fibrosis population, which is more clinically aligned with PH-ILD than the COPD cohort underpinning the Starkie model. Overall, the choice of Freemantle for the base-case analysis is methodologically justified and consistent with best practice in the absence of PH-ILD-specific mapping algorithms.

4.2.6.3 Consideration of adverse events

Although adverse events were common in the INCREASE trial, over 90% were minor (Grade 1 or 2). The impact of adverse events on HRQoL was not modelled separately. The rationale was that any decrements due to clinical worsening events, including associated adverse events, were likely already reflected in the derived HRQoL values for the respective health states.

EAG comments:

The decision not to include adverse events as separate model inputs to avoid double-counting is reasonable.

4.2.7 Resources and costs

The company stated that, for estimating the costs in this evaluation, it followed the NICE guidelines, using standardized cost sources, clinical trial data, and assumptions to address data gaps. The company also stated that all costs were inflated to the 2023/24 cost year.

Six types of costs were captured in the company's model:

- Inhaled treprostinil treatment costs
- BSC treatment costs
- Background medication costs
- One-off event-specific costs
- Ongoing health-state-specific resource use
- One-off end-of-life costs

4.2.7.1 Intervention and Comparator Costs and Resource Use

The company stated that each ampule should be used within one day and contains more treprostinil than the maximum daily dose. This leads to a fixed daily cost (one ampule) for the entire treatment duration. Each patient requires 7 ampules per cycle (one week), resulting in an annual per-person cost of inhaled treprostinil of £[redacted] (£[redacted] after PAS).

The company stated that patients in the BSC arm (placebo) received no treatment other than background medications for ILD management, with a higher baseline use of pirfenidone and nintedanib compared to the inhaled treprostinil arm (see Table 31), reflecting INCREASE trial data. The company stated that only background medications received by more than 1% of patients in the INCREASE and INCREASE OLE trials were included in the evaluation. The company also stated that the model uses treatment-dependent background medication proportions to align with clinical evidence, ensuring accurate cost comparisons between the intervention and comparator arms.

Table 31: Background medications received by more than 1% patients in INCREASE and INCREASE OLE (obtained from the company's response to the EAG's clarification question B1, and CS, section 3.5.1)

Background medication	Inhaled Treprostinil % (n)	BSC % (n)	Required Number of Doses	Pack cost (Pack size)	Per-dose cost
Pirfenidone	[redacted]	15.3% (25)	801mg 3 times daily Weekly dose = 801mg x 3 x 7 days = 16,821mg per week	£106 (84)	£1.25
Nintedanib	[redacted]	11.7% (19)	150mg 2 times daily Weekly dose= 150mg x 2 x 7 days=4,200mg per week	£2,151 (60)	£35.85

Abbreviations: BSC: best support care; mg: milligram

The company excluded PDE5 inhibitors from the base case, noting that these drugs were not used in the INCREASE trial and show limited and inconsistent effectiveness. Their off-label use in PH-ILD is rare and reflects the lack of approved treatments.

EAG comment

EAG concern: Inaccuracies in dosing and costing assumptions for background medications

Company's approach: The company estimated the cost of inhaled treprostinil based on a fixed daily ampule use, leading to a weekly cost based on 7 ampules per patient. Background medications (pirfenidone and nintedanib) were included in the model only if used by more than 1% of patients in the INCREASE and INCREASE OLE trials. Costs were calculated using per-dose data based on standard dosing assumptions.

EAG's critiques and rationale: There is an error in the dosing calculation for nintedanib. The company states a weekly dose of 4,200 mg (150 mg twice daily for seven days), but this should equate to 2,100 mg per week (150 mg × 2 × 7), not 4,200 mg. This overstates the drug's weekly usage and therefore its cost. According to the BNF, the recommended dose is 150 mg twice daily, with possible dose reductions based on tolerability.[60]

In addition, the reported pack price for pirfenidone appears inconsistent with publicly available data. The company cites a price of £106 for a pack of 84 tablets of pirfenidone 801 mg, whereas the eMIT database lists a weighted average price of £61.45 for the same pack size.[61] This discrepancy could lead to an overestimation of background medication costs in the comparator arm (BSC), potentially biasing the cost-effectiveness results in favour of inhaled treprostinil.

EAG Solution: The EAG recommends correcting the weekly dose of nintedanib to 2,100 mg and updating the pirfenidone unit cost using the current eMIT average price. These adjustments should be reflected in the model to ensure accurate estimation of background medication costs and improve the credibility of comparative cost-effectiveness results.

4.2.7.2 Event-specific one-off costs

The company incorporated one-off costs for patients in the first cycle of the model for the following clinical worsening events in the base-case:

- A lung disease exacerbation (unit cost of £2,662)
- A cardiopulmonary hospitalisation (unit cost of £2,382)

Furthermore, the company conducted a scenario analysis that incorporated the one-off costs of a lung transplant (unit cost of £71,848). According to the company, each unit cost was sourced from the National Cost Collection 2023/24 database.

Regarding other clinical worsening events, including patients experiencing a fall in 6MWD and FVC%, the company stated that these costs were set to

zero in the base case. These events were not expected to be associated with an immediate increase in resource use, as the impact may not be immediate and the patient might not be aware that the event had occurred.

EAG Comment

EAG concern: Exclusion of lung transplant costs from base case despite inclusion in clinical worsening events

Company's Approach: The company excluded lung transplant costs from the base-case analysis, citing its low relevance in the UK population (<1% in the INCREASE trial; rare in PH-ILD patients aged >65). Lung transplant was only costed in a scenario analysis. However, it was included in the clinical worsening events and time-to-event modelling. The cost used in the scenario analysis was £71,848 based on National Cost Collection data.

EAG's Critiques and Rationale: The company's approach leads to a structural inconsistency between clinical and economic components of the model. By including lung transplant as a CW event and in time-to-event analyses, its occurrence contributes to health outcomes. Therefore, excluding the cost from the base case underestimates the true economic burden of CW. Even if rare, such high-cost events can materially impact cost-effectiveness outcomes due to their magnitude.

EAG Solution:

Base Case: Lung transplant costs should be included in the base-case analysis to ensure consistency with the time-to-event framework and the definition of clinical worsening.

Scenario Analysis: A scenario analysis could explore the impact of excluding this cost, reflecting uncertainty around its frequency.

4.2.7.3 Health-state unit costs and resource use

The company stated that ongoing background resource use was included in the model to account for additional healthcare costs incurred by patients with PH-ILD, particularly following clinical worsening events. However, the company stated that, no PH-ILD-specific resource-use data were found in the literature, and UK-specific data could not be obtained from the INCREASE trials, as key resource-use categories were not collected. The company also noted that key opinion leaders were unable to provide reliable estimates. As a result, healthcare visit data by health state were sourced from an ongoing real-world evidence (RWE) study in France, which used claims data from France, Germany, and the UK. Despite this, it was not possible to differentiate resource use by health state, so the company assumed equal resource use across all health states and treatment arms. Frequency and proportion of cost items were detailed in Table 32.

Table 32: Health-state specific resource use (obtained from CS, section 3.5.3)

Clinical worsening free	**Clinical worsening Free**	
	Frequency per weekly cycle	**Proportion**
General practitioner appointment	0.0192	100.0%
Respiratory medicines outpatient appointment	0.0364	100.0%
Cardiology service outpatient appointment	0.0115	100.0%
Rheumatology service outpatient appointment	0.0057	100.0%
Emergency room visit	0.0057	100.0%

One clinical worsening event	**Fall in 6MWD ≥15%**		**Fall in FVC% ≥10%**		**Cardiopulmonary hospitalisation**		**Exacerbation**	
	Frequency	**Proportion**	**Frequency**	**Proportion**	**Frequency**	**Proportion**	**Frequency**	**Proportion**
General practitioner appointment	0.0192	100.0%	0.0192	100.0%	0.0192	100.0%	0.0192	100.0%
Respiratory medicines outpatient appointment	0.0364	100.0%	0.0364	100.0%	0.0364	100.0%	0.0364	100.0%
Cardiology service outpatient appointment	0.0115	100.0%	0.0115	100.0%	0.0115	100.0%	0.0115	100.0%
Rheumatology service outpatient appointment	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%
Emergency room visit	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%
Supplemental oxygen		50.0%*		50.0%*		50.0%*		50.0%*

Two or more clinical worsening events	**Fall in 6MWD ≥15%**		**Fall in FVC% ≥10%**		**Cardiopulmonary hospitalisation**		**Exacerbation**	
	Frequency	**Proportion**	**Frequency**	**Proportion**	**Frequency**	**Proportion**	**Frequency**	**Proportion**
General practitioner appointment	0.0192	100.0%	0.0192	100.0%	0.0192	100.0%	0.0192	100.0%
Respiratory medicines outpatient appointment	0.0364	100.0%	0.0364	100.0%	0.0364	100.0%	0.0364	100.0%
Cardiology service outpatient appointment	0.0115	100.0%	0.0115	100.0%	0.0115	100.0%	0.0115	100.0%
Emergency room visit	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%
Rheumatology service outpatient appointment	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%	0.0057	100.0%
Supplemental oxygen		50.0%*		50.0%*		50.0%*		50.0%*

Key: 6MWD: 6-Minute Walk Distance, FVC%: Forced Vital Capacity (percent predicted), GP: General Practitioner. *Assumption

Regarding cardiopulmonary hospitalisations after the 2nd clinical worsening event, the company used findings from a post hoc analysis (Nathan 2022), which showed that inhaled treprostinil reduced the risk of further cardiopulmonary hospitalisations compared to best supportive care (BSC).[44] To reflect this in the model, treatment-specific weekly hospitalisation rates were applied to patients in the CW≥2 health state only. These rates were based on individual patient data from the INCREASE and OLE trials. The weekly hospitalisation rate was 0.0129 for inhaled treprostinil and 0.0132 for placebo, yielding a risk ratio of 1.02, which was used in the model to adjust hospitalisation costs.

EAG comment

EAG concern: Underestimation and simplification of ongoing resource use and costs

Company's approach: The company included ongoing resource use to capture the burden of PH-ILD, especially post-CW events. The company stated that due to the lack of PH-ILD-specific or UK-specific resource-use data in the literature or from the INCREASE trials, and limited input from key opinion leaders, the company used data from a real-world evidence (RWE) study across France, Germany, and the UK. However, it was not possible to differentiate resource use by health state or treatment arm, so the company applied uniform frequencies across all states. The ongoing cost categories were limited mainly to specialist outpatient visits. (Table 32) The company assumed a flat 50% supplemental oxygen use for all post-CW states and incorporated treatment-specific hospitalisation costs only for patients in the CW≥2 state, based on trial-derived risk ratios.

EAG's critiques, assumptions, and justification:

1. **Selective use of available UK data:** The company has not fully utilised UK-specific data available from its own Ferrer International PH-ILD CPRD-HES Report (2024),[41] submitted as data on file. Comparison with the company's model inputs shows that only a subset of the "Specialist visits (hospital attendance)" data (Table 38) was approximately incorporated, while broader cost categories detailed in other tables were omitted.

2. **Underestimation of supplemental oxygen use:** The EAG believes that the assumption of 50% oxygen use post-CW does not align with clinical reality. At baseline in the INCREASE trial, 73% (inhaled treprostinil) and 69.9% (placebo) patients were already (at the baseline point) receiving oxygen at rest (CSR- INCREASE Table 14.3.4.4).[62] Clinical input (received from the EAG's clinical advisers) suggests that nearly all patients post-exacerbation or cardiopulmonary hospitalisation would require oxygen (ambulatory, nocturnal, or long-term), especially in CW≥2 states.
3. **Partial application of treatment effects:**
   The company adjusted hospitalisation frequency based on treatment arm (using a risk ratio of 1.02), but all other resources were applied identically across arms, despite the premise that inhaled treprostinil could reduce overall disease burden. EAG followed the company's hospitalisation approach but considers it inconsistent not to explore differential resource use elsewhere.

EAG Solution:

Base Case:

- Replace the model's background resource use with UK-specific values from the Ferrer CPRD-HES report (2024), long with updated assumptions for higher supplemental oxygen use (Table 33 and Table 34)

Table 33: Health-state specific resource use, the company's values and the EAG's values

Resource use	Company values		EAG suggestions	
	Frequency per year	Proportion	Frequency per year	Proportion
General practitioner appointment	1.00	100.0%	37.545 (37.31- 37.78)	100.0%
Respiratory medicines outpatient appointment	1.90	100.0%	2.31 (2.25- 2.37)	100.0%
Cardiology service outpatient appointment	0.60	100.0%	0.87 (0.83- 0.9)	100.0%
Rheumatology service outpatient appointment	0.30	100.0%	1.25 (1.21- 1.29)	100.0%
Emergency room visit	0.30	100.0%	0.121 (0.11-0.14)	100.0%
Accident and emergency visits	-	-	1.39 (1.35- 1.44)	100.0%
Other specialist visits (hospital attendance)	-	-	6.32 (6.23- 6.42)	100.0%
Inpatient hospitalizations (with using a risk ratio of 1.02 for BSC vs inhaled treprostinil)	0.67	100.0%	The company's approach	
Length of hospitalization Mean-days (SD)	In line with the related tariff			
CT	-	-	0.48 (0.46- 0.51)	100.0%
Angiography	-	-	0.03 (0.02- 0.04)	100.0%
MRI	-	-	0.044 (0.04- 0.05)	100.0%
TTE	-	-	0.29 (0.27- 0.31)	100.0%
Supplemental oxygen (Clinical worsening free)	-	-	-	50.0%
Supplemental oxygen (One clinical worsening event)	-	50.0%	-	75.0%
Supplemental oxygen (Two or more clinical worsening events)	-	50.0%	-	90.0%

ER: Emergency Room; A&E: Accident and Emergency; BSC: Best Supportive Care; SD: Standard Deviation; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; TTE: Transthoracic Echocardiogram.

Note: EAG values, except for supplemental oxygen, are derived from the *Ferrer International_PH_CPRD_Report_2024* using real-world evidence from the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES). All values reflect average rates per patient-year for the incident PH-ILD population during the follow-up period.

Table 34: Unit cost of procedures

Resource use	Unit cost	Source
CT	£144	Weighted average of Currency of Codes RD20A, RD21A, RD60Z RD20A, RD21A, RD60Z (NHS reference costs_2022-2023)
Angiography	£8,267	Currency Code of EY43A (NHS reference costs_2022-2023)
MRI	£243	Weighted average of Currency of Codes RD01A, RD08Z, RD01A, RD08Z, and RD10Z (NHS reference costs_2022-2023)
TTE	£118	Weighted average of Currency Codes RD51A and RD51A (NHS reference costs_2022-2023)

CT: Computerised Tomography; MRI: Magnetic Resonance Imaging; TTE: Transthoracic Echocardiogram;

Scenario Analyses:

- Scenario A: Use the company's base case values.
- Scenario B: Use the company's base case values with the supplemental oxygen use at 50%, 75%, and 90% across CW states.

4.2.7.4 Adverse reaction unit costs and resource use

The company stated that costs related to adverse event management were not included in the model, as the incidence of adverse events was low in both the INCREASE 16-week and OLE trials.

EAG comment

EAG Concern: Exclusion of the adverse event management costs from the model

Company's Approach: The company stated that adverse event (AE) management costs were not included in the economic model, as the incidence of serious adverse events was low in both the INCREASE 16-week and OLE trials.

EAG's Critiques, Assumptions, and Justification: EAG acknowledges that the majority of AEs were minor (based on CS) and unlikely to significantly impact costs. However, EAG is concerned that the complete exclusion of AE-related management costs may underestimate the total cost burden associated with inhaled treprostinil. Even with low incidence rates, serious AEs such as acute respiratory failure and pneumonia may incur non-trivial costs, particularly when critical care or follow-up interventions are required. EAG considers that the justification to exclude AE costs due to possible overlap with the CW endpoint is not sufficient without further disaggregation or quantification of AE-related resource use.

EAG Solution: In section 4.2.7.3 of the ERG report, EAG recommended the use of a revised list of resource use to better reflect the management of AEs and health state resource use and cost. This updated list includes categories likely to capture some of the AE-related resource use, such as technical procedures conducted at the hospital during follow-up and critical care attendance costs.

4.2.7.5 Miscellaneous unit costs and resource use: Wheelchair use

The company included the wheelchair costs due to NHS funding, cover non-powered (£712.34 upfront, £3.76/week maintenance) and powered wheelchairs (£1,219.12 upfront, £16.08/week maintenance), applied after the first clinical worsening event (e.g., 30% non-powered, 20% powered for 6MWD ≥15% or exacerbation) (see Table 35). Costs are incurred once upfront, with ongoing maintenance until death, assuming no wheelchair use until a clinical worsening event and preventing duplicate costs, aligning with practical NHS resource use patterns.

Table 35: Wheelchair resource use (all assumed inputs) (Obtained from CS, section 3.5.3)

One clinical worsening event	Fall in 6MWD ≥15%		Fall in FVC% ≥10%		Cardiopulmonary hospitalisation		Exacerbation	
	Proportion	SE	Proportion	SE	Proportion	SE	Proportion	SE
Non-powered wheelchair	30.0%	0.03	10.0%	0.01	10.0%	0.01	30.0%	0.03
Powered wheelchair	20.0%	0.02	10.0%	0.01	10.0%	0.01	20.0%	0.02
Two clinical worsening events	**Fall in 6MWD ≥15%**		**Fall in FVC% ≥10%**		**Cardiopulmonary hospitalisation**		**Exacerbation**	
	Proportion	**SE**	**Proportion**	**SE**	**Proportion**	**SE**	**Proportion**	**SE**
Non-powered wheelchair	30.0%	0.03	10.0%	0.01	10.0%	0.01	30.0%	0.03
Powered wheelchair	20.0%	0.02	10.0%	0.01	10.0%	0.01	20.0%	0.02

Key: 6MWD, 6-minute walking distance; FVC%, forced vital capacity; SE, standard error.

EAG comment:

The EAG is moderately satisfied with the company's approach to include miscellaneous unit costs and resource use: Wheelchair use in the model, as it demonstrates some recognition of broader patient needs and associated resource use. Given the lack of other robust sources for this type of cost, the inclusion is considered a reasonable and pragmatic approach.

4.2.7.6 End-of-life costs

The company stated that, end-of-life costs of £15,427 were applied once when patients entered the ‘dead’ health state, based on PSSRU data for respiratory infection. Incremental cost differences arose solely from discounted costs over the model’s 30-year time horizon, due to varying time-to-death between treatments.

5 Cost-effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 explores decision modifiers, including the company's and EAG's preferred QALY weighting for severity. Section 5.4 includes information regarding the confidential appendix related to this evaluation, while Section 5.5 outlines the conclusions drawn from the cost-effectiveness analysis.

5.1 Company's cost-effectiveness results

5.1.1 Company's deterministic and probabilistic base case and sensitivity analyses results

The results of the company's deterministic and probabilistic base case analyses are presented in Table 36 and Table 37, respectively. Both analyses include total and incremental costs, life years, QALYs (with a 1.2 severity weighting), ICERs, and net health benefits at £20,000 and £30,000 per QALY thresholds. In both analyses, inhaled treprostinil is associated with higher total costs and greater health benefits (LYGs and QALYs) than BSC. The resulting ICERs are £28,000 per QALY in the deterministic analysis and £31,808 per QALY in the PSA, both exceeding the £20,000 threshold and approaching the upper limit of £30,000, indicating moderate cost-effectiveness under current assumptions.

Figure 15 and Figure 16 display the cost-effectiveness scatterplot and cost-effectiveness acceptability curve, respectively. Figure 15 illustrates that all iterations (samples) fall within the northeast quadrant, indicating that inhaled treprostinil is both [redacted] and [redacted] compared to best supportive care (BSC).

Table 36: Company's deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 (QALYs)	NHB at £30,000 (QALYs)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,000	-0.81	0.14

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
QALY outcomes include the 1.2 severity multiplier.

Table 37: Company's probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000 (QALYs)	NHB at £30,000 (QALYs)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,808	-1.17	-0.12

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years
QALY outcomes include the 1.2 severity multiplier.

Figure 15: Company's cost-effectiveness scatterplot showing 1,000 model iterations from the probabilistic sensitivity analysis

Figure 16: Company's cost-effectiveness acceptability curve based on 1,000 model iterations in the probabilistic sensitivity analysis

The company stated that deterministic sensitivity analysis (DSA) was conducted to assess first-order uncertainty around key input parameters, including cost inputs, utilities, and hazard ratios. Certain parameters, such as those informing survival analysis efficacy and the generalised linear model, were excluded from DSA as their effects were evaluated through separate scenario analyses. The DSA method involved varying individual parameter values within plausible ranges to observe their impact on model outcomes. Results were summarised using a tornado diagram, which highlights the parameters exerting the greatest influence on the results, allowing for easy identification of key drivers. In cases where statistical uncertainty was not available from the literature, a ±15% range around the base-case point estimate was applied. The findings of this analysis are presented to demonstrate the robustness of the model and identify parameters that most affect cost-effectiveness estimates. (Figure 17)

Key: 6MWD, 6-Minute Walk Distance; BSC, Best Supportive Care; CW1, Clinical Worsening One; CW2, Clinical Worsening Two; CWF, Clinical Worsening Free; ICER, Incremental Cost-Effectiveness Ratio; PVR, Pulmonary Vascular Resistance; QALY, Quality-Adjusted Life Year; SGRQ, St. George's Respiratory Questionnaire.

Figure 17: Company's tornado diagram showing the results of the 15 deterministic sensitivity analyses having the greatest effect on the ICER

5.1.2 Company's scenario analyses

A series of scenario analyses were performed by the company to assess the impact of various modelling assumptions on survival and clinical worsening outcomes. These included modifications to the underlying time-to-event distributions in the survival and clinical worsening models, changes to discount rates (0% and 6%), inclusion of lung transplant costs, and alternative methods for estimating health state utility values. Specifically, different utility estimation approaches were tested, such as switching the mapping algorithm from Starkie et al. instead of Freemantle et al. used in the base case, and adopting the SGRQ utility regression method. Additionally, alternative modelling approaches for overall survival (OS) in best supportive care (BSC) were explored. These included using Weibull distributions for inhaled treprostinil and BSC (Dawes 2022), a matching-adjusted indirect comparison (MAIC) with a hazard ratio (HR) of 6.29, and a rank-preserving structural failure time model (RPSFT) from Nathan 2023 with an HR of 3.85. The company stated that these scenario analyses aimed to test the robustness of the base-case results to key assumptions around survival, utility estimation, and costs. The outcomes of all scenario analyses are summarised in Table 38, providing insight into how these variations influence cost-effectiveness results.

Table 38: Tabulated results of the company's scenario analysis

Analysis	BSC QALYs	Inhaled treprostinil QALYs	Incremental QALYs	BSC costs (£)	Inhaled treprostinil costs (£)	Incremental costs (£)	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,000
0% discounting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,897
6% discounting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,461
Lung transplant cost included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,572
Starkie *et al.* SGRQ mapping	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,294
Utility regression approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,455
OS model							
OS: inhaled treprostinil Weibull, BSC Dawes 2022 exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,747
OS: inhaled treprostinil Weibull, BSC MAIC (HR=6.29)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,487
OS: inhaled treprostinil Weibull, BSC RPSFT from Nathan 2023 [22] (HR=3.85)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,913
OS: exponential both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,883
OS: log-logistic both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,215
OS: log-normal both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,518
OS: Generalised gamma both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,565
CW1 model							
CW1: exponential both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,451
CW1: Weibull both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,292
CW1: Gompertz both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,219
CW1: log-normal both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,345
CW1: Generalised gamma both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,943

Analysis	BSC QALYs	Inhaled treprostinil QALYs	Incremental QALYs	BSC costs (£)	Inhaled treprostinil costs (£)	Incremental costs (£)	ICER (£/QALY)
CW2 model							
CW2: exponential both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,421
CW2: Weibull both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,408
CW2: Gompertz both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,569
CW2: log-logistic both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,715
CW2: Generalised gamma both arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,869

Key: BSC, best supportive care; CW, clinical worsening; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MAIC, matching-adjusted indirect comparison; OS, overall survival; QALYs, quality-adjusted life years; SGRQ, St. George's Respiratory Questionnaire

5.1.2.1 Company's subgroup analysis

A subgroup analysis (conducted by the company) excluding patients with CPFE was performed, with results shown in Table 39. This exclusion led to an ICER of £28,698 per QALY gained, which is £698 higher than the base-case ICER. The change was driven by an increase in incremental QALYs to [redacted] (from [redacted]) and higher incremental costs, rising from £[redacted] to £[redacted] over the full-time horizon.

Table 39: Company's subgroup analysis excluding patients with CPFE

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,698

Key: CPFE, combined pulmonary fibrosis and emphysema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.2 EAG's additional analyses

5.2.1 Company's model validation and face validity check

The company stated that the cost-effectiveness model was clinically validated throughout its development. Initially, interviews with UK respiratory consultants informed the PH-ILD treatment pathway. The company also stated that two advisory boards, held in March and July 2023 with respiratory physicians and health economics experts, provided further validation of model structure and parameters. Additional individual interviews with consultants and health economists reviewed the modelling approach and results. Finally, a workshop in April 2025 with UK clinicians validated clinical data, including long-term extrapolations for time-to-event parameters and utility values.

EAG comment

The EAG recognises that the company undertook a multi-step validation process for its cost-effectiveness model assessing inhaled treprostinil in PH-ILD. The company stated that this process included consultations with UK clinicians and health economists through interviews, advisory board meetings, and a dedicated workshop. Such stakeholder engagement is considered a notable strength and supports the model's alignment with UK clinical practice.

Despite these strengths, the EAG identified limitations in the depth, clarity, and completeness of the validation activities. Key concerns include the crossover adjustment for the INCREASE comparator arm, the approach to extrapolating time to treatment discontinuation for inhaled treprostinil, the limited use of UK-specific real-world data (particularly from the 2024 CPRD-HES report), the assumption of uniform healthcare utilisation across health states and treatment arms, and the model's utility inputs. Furthermore, a technical issue affecting the survival extrapolation in the inhaled treprostinil arm was not identified during model validation, raising concerns about the reliability of long-term survival projections. The EAG outlines several recommendations to address these issues in section 4.2.

Company's modelling errors identified by the EAG

While the overall structure and conceptual framework of the model were deemed appropriate, some minor technical issues were raised by the EAG:

Computational Error in Survival Analysis: A technical problem arises when certain survival functions are chosen for inhaled treprostinil and the hazard ratio is applied to best supportive care (BSC). Specifically, the formula –LN(0) results in a #NUM! error within the OS calculation sheet (column R, H(t)).

Incorrect Costing of Lung Transplants: The model inaccurately calculates total costs for lung transplants by not correctly applying the proportion of

patients receiving a transplant (2 out of 163). The correct, undiscounted figure should be approximately £960, calculated as: (2/163)×£78,316= £960 Despite this discrepancy, the EAG confirms it has negligible impact on the ICER outcome.

Misapplication of severity modifier: In its base case, the company applied the severity modifier by multiplying the total QALYs by the modifier in both treatment arms. This is inconsistent with guidance in the NICE Reference Case (2023), which states that such modifiers should be considered separately from QALY estimates, as they are based on value judgments. Incorporating the modifier directly into QALY values risks misrepresenting the true magnitude of benefit and may distort decision-making.

Inconsistency in PSA results: The probabilistic sensitivity analysis (PSA) results presented in the main company submission are not consistent with the outputs generated by the company's economic model. Specifically, the ICER reported in the submission is £31,808, whereas the ICER calculated from both the original model and the updated version (post-clarification) is £30,570. This discrepancy raises concerns regarding the accuracy and transparency of the submitted results.

Table 40 and Table 41 present the revised version of the company’s base case, with the misapplication of the severity modifier and the inconsistency in PSA results resolved.

Table 40: Revised company's deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (Without severity weighting)	ICER (£/QALY) (Without severity weighting)	Results with severity weighting (x1.2)		
								ICER (£/QALY)	NHB at £20,000 (QALYs)	NHB at £30,000 (QALYs)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,600	£28,000	-0.81	0.14

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 41: Revised company's probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (Without severity weighting)	ICER (£/QALY) (Without severity weighting)	With severity weighting (x1.2)		
								ICER (£/QALY)	NHB at £20,000 (QALYs)	NHB at £30,000 (QALYs)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£36,684	£30,570	-1.06	-0.04

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.2.2 EAG's exploratory analyses (preferred assumptions) using company's base case

Table 42 provides a summary of the of the EAG's exploratory analyses items compared to the company's base case assumptions. For each item, Table 42 contrasts the company's preferred methodological approach with that recommended or preferred by the EAG, highlighting differences in data sources, statistical distributions, assumptions, and parameter values. The final column references the relevant sections in the EAG report where these analyses are discussed in detail. This comparison illustrates how the EAG's exploratory analyses differ from the company's approach and informs the interpretation of results presented in subsequent sections.

Table 42: Summary of EAG's exploratory analyses using company's base case

Row	Variable	Company's preferred approach	EAG's preferred approach	Section in EAG report
1	OS for inhaled treprostinil	Source: INCREASE-OLE Distribution: Weibull	Source: INCREASE-OLE Distribution: Generalised gamma	Section 4.2.5
2	OS for BSC	Source: Crossover analysis Distribution: Weibull	Source: Using the HR (BSC vs inhaled treprostinil) ITT-HR = 1.40845 (1/0.71)	Section 4.2.5
3	Time to first CW1 for inhaled treprostinil	Source: INCREASE-OLE Distribution: Log-normal	Source: INCREASE-OLE Distribution: log-logistic	Section 4.2.5
4	Time to first CW1 for BSC	Source: INCREASE 16 weeks Distribution: Exponential	Source: INCREASE 16 weeks Distribution: log-logistic	Section 4.2.5
5	TTD for inhaled treprostinil	Source: INCREASE-OLE Distribution: Generalised gamma	Source: INCREASE-OLE Distribution: General gamma, with a constraint that the TTD does not fall below CW2	Section4.2.5 and 4.2.2.3
6	Discount factor	Per-cycle (weekly) discount factor-applying for first year	Per-year discount factor-no discount for first year	Section 4.2.2.4
7	HRQoL- type of utility	Univariate analysis of INCREASE OLE treatment-independent SGRQ data	Multivariate GLM approach from the source of INCREASE OLE treatment-independent SGRQ data	Section 4.2.6

8	Dosing and pricing for background medications	Assumed a weekly dose of 4,200 mg for nintedanib and applied an eMIT price of £106 per 84-tablet pack of pirfenidone (801 mg)	Used a lower weekly dose of 2,100 mg for nintedanib and applied the most recent eMIT price of £61.45 per 84-tablet pack of pirfenidone (801 mg).	Section 4.2.7.1
9	Ongoing resource use and cost	Ongoing costs were mainly specialist outpatient visits, with assumptions such as 50% oxygen use post-CW	Replaced the model's ongoing resource use with UK-specific values from the Ferrer CPRD-HES report (2024), long with updated assumptions for higher supplemental oxygen use	Section 4.2.7.3
10	Cost of lung transplants	Excluded	Included	Section 4.2.7.2

Abbreviations: EAG: External Assessment Group; OS: Overall Survival; BSC: Best Supportive Care; HR: Hazard Ratio; ITT: Intention-To-Treat; CW: Clinical Worsening; TTD: Time to Treatment Discontinuation; HRQoL: Health-Related Quality of Life; SGRQ: St. George's Respiratory Questionnaire; GLM: Generalized Linear Model; eMIT: Electronic Market Information Tool; CPRD-HES: Clinical Practice Research Datalink - Hospital Episode Statistics; OLE: Open-Label Extension.

Table 43 summarises the results of the EAG's exploratory analyses, where individual preferred assumptions were applied to the company's base case to test their impact on costs, QALYs, and the ICER. The most notable [redacted] in the ICER was seen in scenario 2, where the ITT hazard ratio for overall survival (OS) in the BSC arm was used, resulting in an ICER of £65,919 (+135.43%) due to a sharp reduction in QALYs gained ([redacted]). The lowest ICER (£27,854) occurred in scenario 3 when the log-logistic distribution was applied to time to first clinical worsening (CW1) for inhaled treprostinil (–0.52% change). Scenario 5, applying a more conservative TTD curve, led to the [redacted] incremental cost (£[redacted]).

Table 43: Results of EAG's exploratory (preferred assumptions) analyses using company's base case

Changes applied to company's base case**		Incremental costs (£)	Incremental QALYs *	ICER £/QALY	Impact
The company's base case		[redacted]	[redacted]	£28,000	-
1	OS for inhaled treprostinil: using generalised gamma	[redacted]	[redacted]	£36,308	29.67%
2	OS for BSC: using the ITT-HR (BSC vs inhaled treprostinil) of 1.40845 (1/0.71)	[redacted]	[redacted]	£65,919	135.43%
3	Time to first CW1 for inhaled treprostinil: using log-logistic	[redacted]	[redacted]	£27,854	-0.52%
4	Time to first CW1 for BSC: using log-logistic	[redacted]	[redacted]	£28,251	0.90%
5	TTD for inhaled treprostinil: using general gamma, with a constraint that the TTD does not fall below CW2	[redacted]	[redacted]	£33,952	21.26%
6	Discount factor: using per-year discount factor- no discount for first year	[redacted]	[redacted]	£27,960	-0.14%
7	HRQoL- type of utility: using multivariate GLM approach	[redacted]	[redacted]	£30,455	8.77%
8	Dosing and pricing for background medications: 2,100 mg for nintedanib and eMIT price of £61.45 for pirfenidone	[redacted]	[redacted]	£27,682	-1.14%
9	Ongoing resource use and cost: using the UK-specific values from the Ferrer CPRD-HES report (2024), and higher supplemental oxygen use	[redacted]	[redacted]	£29,565	5.59%
10	Cost of lung transplants: included	[redacted]	[redacted]	£28,572	2.04%
Combined 1-10 (EAG's base case)		[redacted]	[redacted]	£122,475	337.41%

OS: Overall Survival; BSC: Best Supportive Care; ITT-HR: Intention-To-Treat Hazard Ratio; CW: Clinical Worsening; TTD: Time To Discontinuation; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; HRQoL: Health-Related Quality of Life; GLM: Generalised Linear Model; eMIT: Electronic Market Information Tool; CPRD-HES: Clinical Practice Research Datalink – Hospital Episode Statistics; EAG: External Assessment Group.

*The severity modifier of 1.2 is applied for all exploratory analyses.

** The technical guidance related to the model changes can be found in the 'EAG-Changes' worksheet

5.2.3 EAG's deterministic and probabilistic base case and sensitivity analyses results

Table 44 and Table 45 present the results of the deterministic and probabilistic base-case cost-effectiveness analyses conducted by the EAG. These analyses compare inhaled treprostinil to best supportive care (BSC) in terms of total costs, life years gained (LYG), and quality-adjusted life years (QALYs).

Table 44 (Deterministic analysis) shows that inhaled treprostinil leads to an additional [redacted] QALYs (with applying QALY's weight of 1.2) at an incremental cost of £[redacted], resulting in an ICER of £122,475 per QALY. The negative net health benefits (NHB) at both £20,000 and £30,000 willingness-to-pay thresholds indicate that the treatment is not cost-effective under standard NICE benchmarks.

Table 45 (Probabilistic sensitivity analysis) incorporates uncertainty in model inputs. Results showing an incremental cost of £[redacted] and an ICER of £109,402 per QALY. Again, the NHB values are negative, reinforcing that inhaled treprostinil is unlikely to be considered cost-effective at commonly accepted thresholds.

Figure 18 presents the cost-effectiveness scatterplot. Most of the iterations fall within the [redacted] quadrant, indicating that inhaled treprostinil is generally [redacted] effective but also [redacted] costly compared to BSC. A smaller number of samples appear in the [redacted] quadrant, suggesting scenarios where inhaled treprostinil is both [redacted] effective and [redacted] expensive. The cost-effectiveness acceptability curve (Figure 19) shows that, at a willingness-to-pay threshold of £30,000 per QALY, the probability of inhaled treprostinil being cost-effective compared to BSC is [redacted].

Table 44: EAG's deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (Without severity weighting)	ICER (£/QALY) (Without severity weighting)	Results with severity weighting (x1.2)	
							ICER (£/QALY)	NHB at £20,000 (QALYs)	NHB at £30,000 (QALYs)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£146,970	£122,475	-2.44	-1.47

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 45: EAG's probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (Without severity weighting)	ICER (£/QALY) (Without severity weighting)	With severity weighting (x1.2)	
								ICER (£/QALY)	NHB at £20,000 (QALYs)	NHB at £30,000 (QALYs)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£131,283	£109,402	-2.61	-1.54

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 18: Cost-effectiveness scatterplot showing 1,000 model iterations from the probabilistic sensitivity analysis

Figure 19: Cost-effectiveness acceptability curve based on 1,000 model iterations in the probabilistic sensitivity analysis

The one-way sensitivity analysis (Figure 20) indicates that the key drivers of the ICER for inhaled treprostinil versus BSC are the

Key: 6MWD, 6-Minute Walk Distance; BSC, Best Supportive Care; CW1, Clinical Worsening One; CW2, Clinical Worsening Two; CWF, Clinical Worsening Free; ICER, Incremental Cost-Effectiveness Ratio; PVR, Pulmonary Vascular Resistance; QALY, Quality-Adjusted Life Year; SGRQ, St. George's Respiratory Questionnaire.

Figure 20: Deterministic sensitivity analysis: tornado diagram

5.2.4 Scenario analyses using EAG's preferred assumptions

Table 46 provides a summary of the EAG's scenario analyses, outlining the base-case assumptions and the alternative scenarios tested to explore uncertainty in key model parameters. These scenarios include variations in survival modelling, time to clinical worsening, time to treatment discontinuation (TTD), health-related quality of life (HRQoL) utilities, drug dosing and pricing, resource use, and the cost of lung transplants.

Table 47 presents the results of EAG's scenario analyses, using its preferred base-case assumptions to test the sensitivity of the ICER to various alternative inputs. The greatest reduction in ICER was observed in Scenario 5 (MAIC OS HR = 6.29), where the ICER dropped by 76.6%, driven by increased QALYs and costs.

The highest ICER increase occurred in Scenario 2 (OS Gompertz for inhaled treprostinil), with a 18.8% rise to £145,478, reflecting lower estimated QALYs. In terms of QALY gain, Scenario 5 again showed the largest increase, while the lowest QALY was also seen in Scenario 2.

The lowest incremental cost occurred in Scenario 12 (£[redacted]), while the highest incremental cost was observed in Scenario 5 (£[redacted]).

These findings highlight that survival assumptions, particularly for BSC and inhaled treprostinil, are the most influential drivers of cost-effectiveness results.

Table 46: Summary of EAG's scenario analyses using EAG's preferred assumptions

Variable	EAG's base-case assumption	S.N	EAG's scenario
OS for inhaled treprostinil	Distribution: Generalised gamma	1	Distribution: Weibull (company's approach)
		2	Distribution: Gompertz
OS for BSC	Source: Using the HR (BSC vs inhaled treprostinil) - ITT-HR = 1.40845 (1/0.71)	3	Distribution: Weibull ((company's approach))
		4	Using the source of Dawes 2022 and distribution of Weibull
		5	MAIC-(BSC vs inhaled treprostinil)- HR=6.29
		6	RPSFT from Nathan 2023 (HR=3.85)
		7	IPCW HR. (1/0.62)
Time to first CW1 (both arms)	Distribution: log-logistic	8	Distribution: Log-normal for inhaled treprostinil and Exponential for BSC (company's approach)
		9	Distribution: Gompertz
Time to first CW2 (both arms)	Distribution: Log-normal	10	Distribution: Exponential
		11	Distribution: Generalised gamma
TTD for inhaled treprostinil	Distribution: General gamma, with a constraint that the TTD does not fall below CW2	12	Distribution: Generalised gamma (company's approach)
Discount factor	Per-year discount factor- no discount for first year	13	Per-cycle (weekly) discount factor- applying for first year (company's approach)
HRQoL- type of utility	Multivariate GLM approach	14	Univariate analysis (company's approach)
	Freemantle 2015 SGRQ mapping	15	Starkie *et al.* SGRQ mapping
Dosing and pricing for background medications	2,100 mg for nintedanib and eMIT price of £61.45 for pirfenidone	16	4,200 mg for nintedanib and eMIT price of £106 for pirfenidone (company's approach)
Ongoing resource use and cost	using the UK-specific values from the Ferrer CPRD-HES report (2024), and higher	17	Ongoing costs were mainly specialist outpatient visits, with assumptions such as 50% oxygen use post-CW (company's approach)

	supplemental oxygen use	18	Applying 50% in CWF, 75% in CW1, and 90% in CW2+
Cost of lung transplants	Included	19	Excluded (company's approach)

Abbreviations: OS: Overall Survival; BSC: Best Supportive Care; HR: Hazard Ratio; ITT: Intention-To-Treat; MAIC: Matching-Adjusted Indirect Comparison; RPSFT: Rank Preserving Structural Failure Time; CW: Clinical Worsening; TTD: Time To Discontinuation; GLM: Generalised Linear Model; HRQoL: Health-Related Quality of Life; SGRQ: St. George's Respiratory Questionnaire; eMIT: Electronic Market Information Tool; CPRD-HES: Clinical Practice Research Datalink – Hospital Episode Statistics; EAG: External Assessment Group; S.N: Scenario Number (row); IPCW: Inverse Probability Censored Weighting

Table 47: Results of EAG's scenario analyses using EAG's preferred assumptions

Variable	S.N	EAG's scenario	Incremental costs (£)	Incremental QALYs *	ICER (£/QALY)	Impact
		The EAG's base case	[redacted]	[redacted]	£122,475	-
OS for inhaled treprostinil	1	Distribution: Weibull (company's approach)	[redacted]	[redacted]	£107,051	-12.59%
	2	Distribution: Gompertz	[redacted]	[redacted]	£145,478	18.78%
OS for BSC	3	Distribution: Weibull ((company's approach))	[redacted]	[redacted]	£48,424	-60.46%
	4	Using the source of Dawes 2022 and distribution of Weibull	[redacted]	[redacted]	£50,904	-58.44%
	5	MAIC-(BSC vs inhaled treprostinil)- HR=6.29	[redacted]	[redacted]	£28,685	-76.58%
	6	RPSFT from Nathan 2023 (HR=3.85)	[redacted]	[redacted]	£47,096	-61.55%
	7	IPCW HR. (1/0.62)	[redacted]	[redacted]	£94,555	-22.80%
Time to first CW1 (both arms)	8	Distribution: Log-normal for inhaled treprostinil and Exponential for BSC(company's approach)	[redacted]	[redacted]	£121,926	-0.45%
	9	Distribution: Gompertz	[redacted]	[redacted]	£120,659	-1.48%
Time to first CW2 (both arms)	10	Distribution: Exponential	[redacted]	[redacted]	£111,558	-8.91%
	11	Distribution: Generalised gamma	[redacted]	[redacted]	£124,250	1.45%
TTD for inhaled treprostinil	12	Distribution: Generalised gamma (company's approach)	[redacted]	[redacted]	£106,182	-13.30%
	13	Generalized gamma model, ensuring that the proportion of patients remaining on treatment stays at or above 37%	[redacted]	[redacted]	£122,622	0.12%
Discount factor	14	Per-cycle (weekly) discount factor- applying for first year (company's approach)	[redacted]	[redacted]	£122,672	0.16%
HRQoL- type of utility	15	Univariate analysis (company's approach)	[redacted]	[redacted]	£115,256	-5.89%
	16	Using the Starkie *et al.* SGRQ mapping	[redacted]	[redacted]	£126,989	3.69%
Dosing and pricing for background medications	17	4,200 mg for nintedanib and eMIT price of £106 for pirfenidone (company's approach)	[redacted]	[redacted]	£119,613	-2.34%

Variable	S.N	EAG's scenario	Incremental costs (£)	Incremental QALYs *	ICER (£/QALY)	Impact
		The EAG's base case	[redacted]	[redacted]	£122,475	-
Ongoing resource use and cost	18	Ongoing costs were mainly specialist outpatient visits, with assumptions such as 50% oxygen use post-CW (company's approach)	[redacted]	[redacted]	£121,175	-1.06%
	19	Applying 50% in CWF, 75% in CW1, and 90% in CW2+	[redacted]	[redacted]	£122,022	-0.37%
Cost of lung transplants	20	Excluded (company's approach)	[redacted]	[redacted]	£119,968	-2.05%

S.N: Scenario Number; EAG: External Assessment Group; QALYs: Quality-Adjusted Life Years; ICER: Incremental Cost-Effectiveness Ratio; OS: Overall Survival; BSC: Best Supportive Care; MAIC: Matching-Adjusted Indirect Comparison; HR: Hazard Ratio; RPSFT: Rank Preserving Structural Failure Time; IPCW: Inverse Probability of Censoring Weighting; CW1: Clinical Worsening; TTD: Time to Treatment Discontinuation; HRQoL: Health-Related Quality of Life; SGRQ: St. George's Respiratory Questionnaire; eMIT: Electronic Market Information Tool.

5.2.4.1 EAG's subgroup analysis

A subgroup analysis excluding patients with CPFE was performed, with results shown in Table 48. This exclusion led to an ICER of £152,443 per QALY gained.

Table 48: EAG's subgroup analysis excluding patients with CPFE

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) with severity weighting (x1.2)
Inhaled treprostinil	[redacted]	[redacted]	[redacted]	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£152,443

Key: CPFE, combined pulmonary fibrosis and emphysema; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company stated that the severity modifier tool developed by ScHARR was employed to determine the appropriate severity weighting for inhaled treprostinil in patients with PH-ILD. This assessment was based on both absolute and proportional QALY shortfalls. According to the RPSFT-adjusted BSC arm of the INCREASE trial, patients receiving BSC were projected to experience 0.86 discounted QALYs (0.89 undiscounted) over 1.35 discounted life years (1.40 undiscounted), using a Weibull model for overall survival (OS).

This equates to a 91.9% proportional QALY shortfall compared to an age- and sex-matched general UK population, estimated to achieve an additional 10.59 QALYs, based on an adjusted limited dependent variable mixture model (ALDVMM) applied to 2014 Health Survey for England (HSE) data (Hernandez Alava et al.; York QALY Shortfall Calculator reference case).

The company stated that sensitivity analyses (see Table 50) confirmed the robustness of this finding. Consequently, inhaled treprostinil qualifies for a 1.2x QALY weighting under the proportional shortfall criterion.

Table 49. Summary features of QALY shortfall analysis (obtain from the CS, section 3.6)

Factor	Value (reference to appropriate table or figure in submission)
Sex distribution	53.07% male
Starting age (years)	66.45

Table 50. Summary of QALY shortfall analysis (obtain from the CS, section 3.6)

Severity analysis	Expected total QALYs for the general population (QALYs)	Total QALYs that patients living with the condition would be expected to have with current treatment	QALY shortfall
Reference case	10.59	0.86	9.73 QALYs or 91.9%
EQ-5D-5L to EQ-5D-3L mapping from Hernandez Alava *et al.* with HSE 2017-18 data	10.43	0.86	9.57 QALYs or 91.8%
EQ-5D-5L to EQ-5D-3L mapping from van Hout *et al.* with HSE 2017-18 data	10.48	0.86	9.62 QALYs or 91.8%
Measurement and valuation of health value set and health state profile	10.33	0.86	9.47 QALYs or 91.7%
Crossover-adjusted exponential OS model	10.59	[redacted]	[redacted]
Crossover-adjusted Gompertz OS model	10.59	[redacted]	[redacted]

Severity analysis	Expected total QALYs for the general population (QALYs)	Total QALYs that patients living with the condition would be expected to have with current treatment	QALY shortfall
Crossover-adjusted log-normal OS model	10.59	[redacted]	[redacted]
Crossover-adjusted log-logistic OS model	10.59	[redacted]	[redacted]
Crossover-adjusted generalised gamma OS model	10.59	[redacted]	[redacted]

EAG comment:

Following an independent assessment by the EAG, the application of the severity modifier was re-examined using the company's utility estimate for the BSC arm as the baseline for QALY calculations. Incorporating a revised estimate of [redacted] discounted QALYs (based on the EAG base case) for BSC, the resulting proportional shortfall for patients receiving BSC remained above the 85% (less than 95%) threshold (see Table 52) required to justify the application of a 1.2 severity weight. This indicates that the burden of disease associated with PH-ILD is substantial, even under updated general population assumptions. On this basis, the EAG considers the use of a 1.2 QALY weight to be appropriate and consistent with the criteria outlined in the severity modifier framework.

Table 51: Severity Modifier Weight Definitions

QALY weight	Proportional shortfall	Absolute shortfall
x1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Table 52: Summary of EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Value or source (reference to appropriate table or figure in submission)
Sex distribution (proportion of female)	46.93%
Starting age	66 years
Expected years of life	[redacted]
Quality of life by age	[redacted]
Discount rate	3.5%
Expected total QALYs for the general population (QALYs)	10.59
absolute shortfall	[redacted]
proportional shortfall	[redacted]
QALY weight	x 1.2

5.3.2 Uncaptured benefits

The company stated that the model did not incorporate the impact of PH-ILD on caregivers, primarily due to insufficient data. The company also stated that the progressive and severe nature of PH-ILD contributes to emotional and psychological distress for both patients and caregivers, including feelings of frustration, insecurity, and confusion. Furthermore, the company stated that the model did not account for the potential effects of patient mortality and caregiver bereavement. Although such effects are often described as modest and transient in other populations, delaying these impacts through life extension with inhaled treprostinil would result in their greater discounting in the model. Consequently, this would enhance the economic justification for the use of inhaled treprostinil by shifting these negative outcomes to later periods with reduced present value. Thus, the exclusion of caregiver-related outcomes may underestimate the full benefits of the treatment.

EAG comment

The EAG notes that NICE requires inclusion of all relevant health effects, including those on caregivers. However, the company's model excludes caregiver burden due to insufficient data, which may underestimate the full benefits of treatment. Although the company acknowledges the emotional and psychological distress experienced by caregivers, these effects are neither quantified nor incorporated. Given the current evidence, the EAG considers it difficult to determine the magnitude of these effects on the ICER or to justify their inclusion in the model with any certainty.

5.3.3 Health inequalities

The company stated that this evaluation is not expected to: disqualify any individuals covered under equality legislation from receiving treatment; result in recommendations that affect those protected by equality laws differently than the general population; or produce guidance that negatively impacts individuals with a specific disability or disabilities.

EAG comment

The EAG believes that equality considerations could be relevant due to the need for Right Heart Catheterisation. Although other diagnostic methods exist, confirmation is achieved through Right Heart Catheterisation, which remains the gold standard technique. This may limit access for patients in remote areas or those with mobility issues. The inhaled treatment's complexity (e.g. nebuliser use) may disadvantage frail, disabled, or isolated individuals. Given the limited evidence in the field, EAG remains uncertain about which solutions might effectively address the inequalities.

5.4 Confidential comparator and subsequent treatment prices

The confidential appendix presents the analyses conducted as part of this appraisal, incorporating the confidential price discounts applied to the intervention, comparators, and subsequent treatments used in the company's economic model. These discounts include simple and complex Patient Access Schemes (PAS), Commercial Access Agreements (CAA), and Medicines Procurement and Supply Chain (MPSC) prices. Where MPSC prices are used, the analysis reflects the highest, lowest, and midpoint values as provided by NICE. The aim of this appendix is to provide the NICE evaluation committee with all relevant results based on the true cost to the NHS, ensuring robust decision-making.

The confidential appendix replicates all relevant analyses from the main EAG's report and the company submission, including deterministic and probabilistic base-case results, sensitivity analyses, and scenario analyses. It also includes EAG-led exploratory and preferred analyses using confidential pricing.

The prices used in the EAG confidential appendix were provided by NICE in July 2025. An overview of the relevant technologies and the source of their prices is provided in Table 53.

Table 53: Overview of prices used in EAG cPAS appendix

Name	Form	Dose per unit	Vial/Pack size (mg)	Source
Inhaled treprostinil	Solution for oral inhalation	One ampule per day	28 ampoules	Manufacturer
Pirfenidone	Tablets	801 mg	84	eMIT
Nintedanib	Capsules	150 mg	60	cPAS
Sildenafil	Tablets	50 mg	4	eMIT
Tadalafil	Tablets	20 mg	4	eMIT

5.5 Conclusions of the cost-effectiveness section

The company's submission addresses the defined NICE decision problem and includes cost-effectiveness data relevant to the PH-ILD population. The economic model incorporated adapted definitions of clinical worsening, adding events not prespecified in the INCREASE trial, which introduces structural uncertainty.

The company’s cost-effectiveness evidence does not fully account for key uncertainties. These include the choice of survival extrapolation, crossover adjustment, utility estimation, and treatment discontinuation modelling. Furthermore, the submission overlooks critical UK-specific data sources (particularly the CPRD-HES report) resulting in limited generalisability to NHS practice.

While clinical expert input and stakeholder validation add strength to the model (based on the company statement), several methodological limitations persist. The EAG identified biased or overly optimistic assumptions in survival modelling and resource use (overlooks critical UK-specific data sources like the CPRD-HES report). Scenario analyses using EAG-preferred assumptions often produced substantially different ICERs, revealing the model’s sensitivity to structural assumptions and data choices. Consequently, the company’s

base-case ICER of £28,000 is likely to undervalue the actual cost-effectiveness ratio, particularly when compared to the EAG's base-case estimate of £122,475.

Despite the efforts, substantial residual uncertainty remains in the model, particularly in survival projections, comparator efficacy, and the validity of utility values. The EAG is able to suggest the likely direction of some biases (e.g., ICERs likely being underestimated) but cannot quantify them definitively due to data limitations. Future analyses should incorporate UK-specific real-world evidence and test key assumptions more robustly through sensitivity and scenario analysis.

6 References

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7 Appendices

7.1 EAG assessment of risks of bias of the CS systematic review about the scope of the appraisal (modified ROBIS)

Table 54: EAG ROBIS evaluation of the company's SLR

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Probably yes	Eligibility criteria are detailed in Table 4 of the Appendices.

1.2 Were the eligibility criteria appropriate for the review question?	No	Text in CS 2.1 and Appendix B.1 suggests that evidence from only RCTs and observational studies was sought, and the use of study type search filters is in line with this restriction (see 2.3 below). However, the eligibility criteria (Appendix B.1.2, Table 4) include single-arm and non-randomised trials as well, which would be a more logical selection of study types. The comparator arm is broad and lacks clarity in relation to the decision problem. Essential details such as medication dose, frequency of administration, and concurrent treatments were not specified for either the intervention or the comparators. The population considered is narrowly defined as PH-ILD, which aligns with the NICE scope. However, studies involving broader populations such as those with pulmonary hypertension (PH) Group 3, which includes PH-ILD as well as PH associated with other lung diseases, hypoxia, or cases of PH or ILD alone may still offer relevant insights and should not be dismissed outright. In response to clarification question C9, the company described their approach regarding eligibility of studies in broader or mixed populations. However, these “pragmatic” inclusion/exclusion criteria were not specified *a priori* and it is difficult to ascertain whether they were systematically and consistently applied. Furthermore, not all exclusion reasons were explicitly stated. For instance, Balakrishnan et al. (2024)[63] and Kyle et al. (2024)[64] were excluded due to missing data, heterogeneity, and the inclusion of elderly and frail patients, none of which were predefined exclusion criteria. As a result, studies involving relevant subgroups may have been excluded inappropriately. Additionally, conference abstracts were not mentioned in the eligibility criteria, making it unclear how many may have been overlooked. Given
1.3 Were eligibility criteria unambiguous?	No	

		the scarcity of evidence from observational studies, such abstracts could potentially offer valuable insights such as Kiely et al. (2024)[6]
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	Probably yes	
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	Probably yes	
Concerns regarding specification of study eligibility criteria	High concern	Studies that would have been important and relevant to answering the review question are likely to have been excluded from the review.
2: Identification and selection of studies		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	No	An appropriate selection of bibliographic databases (PubMed, Embase and Cochrane CENTRAL) were searched. Trial registries and other sources of unpublished studies (such as health technology assessment (HTA) agencies and internet searching) were not considered.
2.2 Were methods additional to database searching used to identify relevant reports?	Probably yes	”Reference lists of included studies (and pertinent systematic reviews) were also screened” (Appendix B.1.1.1); however, full details, such as which systematic reviews were examined, are not provided, and the PRISMA diagram (Appendices Figure 1) suggests no additional records were identified in this way. Recent (last three years) proceedings of three relevant conference abstracts were hand-searched.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No	The search terms relating to the population aim to identify studies in PH-ILD only, not broader groups such as PH Group 3 (see 1.3 above). A reasonable selection of search terms for PH-ILD are used, though some are missing, including the acronym “PH-ILD” and “fibrosing alveolitis” as a free text term. In the PubMed and Embase search strategies

		(Appendix B.1.1, Tables 1 and 2), only the title and abstract fields are searched, not keyword field which would have increased the sensitivity of the search. Scottish Intercollegiate Guidelines Network (SIGN) study filters[65] for RCTs and observational studies are used in the PubMed and Embase search strategies (Appendix B.1.1, Tables 1 and 2). These filters are not the most sensitive filters available; they have not been validated in an experimental study and are also not designed to capture non-randomised nor single-arm trials, despite these study types being eligible for inclusion in the SLR (Appendix B.1.2, Table 4). Given the inclusion of most study types in the SLR, the sensitivity of the PubMed and Embase searches could have been improved by not using study type filters at all, but rather excluding unwanted publication types such as case reports, bibliographies and editorials.
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably yes	Peer-reviewed conference proceedings were hand-searched only for the years 2022–2024, potentially overlooking relevant publications from earlier years or those missed in the primary search.
2.5 Were efforts made to minimise errors in selection of studies?	No	In response to clarification question C7, the company confirmed that the wrong set of results was downloaded and screened from the Cochrane CENTRAL search. The company attempted to remedy this by re-running the search on 10th June 2025 and screening the new results, stating: “Among the 243 additional records identified, no new studies met the inclusion criteria for the clinical SLR that had not already been included from other sources”. However, details of this screening process and exclusion reasons were not provided.
Concerns regarding methods used to identify and/or select studies	High concern	The search strategy and study identification process may not have been fully comprehensive. Several uncertainties and ambiguities remain, and potentially some valuable studies were inadvertently missed.

3: Data collection and study appraisal sections		
3.1 Were efforts made to minimise error in data collection?	Unclear	
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	No information	No information on data collection, extraction, baseline and results of included studies was reported.
3.3 Were all relevant study results collected for use in the synthesis?	Probably no	Out of 35 included studies, merely 20 were deemed relevant to the decision problem appendix doc, Table 5. No justification for this omission was provided. Then, only 3 of these studies were included and similarly, no justifications were reported.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably no	The JBI checklist was used by the company in appendix doc, Table 8. JBI, while accessible and easy to apply, lacks the depth and domain-specific rigor of Cochrane's recommendations. For example, in case of RCTs, JBI may simply ask whether randomization was used, but it does not probe how it was implemented or whether allocation was concealed, key factors that RoB 2 explicitly addresses through signalling questions. Similarly, JBI asks whether blinding was applied, but it doesn't distinguish between blinding of participants, personnel, or outcome assessors, nor does it assess the potential impact of lack of blinding on outcomes. These oversights can lead to underestimating the risk of bias, especially in trials with complex designs or subjective outcomes. Also, a ROBIS tool, recommended by Cochrane's, would have comprehensively evaluated the SLR.
3.5 Were efforts made to minimise error in risk of bias assessment?	Unclear	
Concerns regarding methods used to collect	Some concerns	Some bias may have been introduced through the data collection or risk of bias assessment processes.

data and appraise studies		
4: Synthesis and findings		
4.1 Did the synthesis include all studies that it should?	Probably no	Although the CPRD-HES dataset collected by the company is referenced in Document B, it was not used in the analysis. Additionally, while evidence was identified across 35 included studies, only 3 were ultimately used in the analysis, raising concerns about the selective use of available data.
4.2 Were all predefined analyses followed or departures explained?	Probably no	None of the analyses conducted as MAIC were pre-defined. No published protocol was noted.
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Probably no	The MAIC analysis performed was the most appropriate technique however, there are clear limitations to its implementation. Use of alternative sources of data were not explored.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	Probably no	The MAIC analysis was unlikely to fully account for the differences between the INCREASE trial and real-world population of Dawes et al.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably no	Sensitivity analyses have been mentioned, but the details were not provided.
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No	Cochrane's recommended risk of bias tool for the systematic literature reviews was not found.
Concerns regarding the synthesis and findings	Some concerns	There are some ambiguities not addressed. The included studies have been excluded due to not unspecified reason. The details on sensitivity analyses were not provided.
Risk of bias	High risk of bias	One or more issues identified through the ROBIS assessment may have contributed to a potential risk of bias, potentially resulting in the omission of

		relevant data or the reporting of less reliable findings due to unclear methodological approaches.

7.2 Risk of bias for INCREASE and INCREASE OLE trial

The company assessed 6MWD mean change from baseline at week 16 for INCREASE and week 52 for OLE, but a full outcome list by week 108 (final data cut) would have been preferable.

Domain	Signalling question	Company judgement		EAG judgement		EAG Comments
		INCREASE	**INCREASE OLE**	**INCREASE**	**INCREASE OLE**	
Bias arising from the randomisation process	1.1 Was the allocation sequence random?	Y	NA	Y	N	Randomization used permuted blocks and was stratified by baseline 6MWD (≤350 m vs. >350 m), implemented via a centralized IXRS system, ensuring allocation concealment. In contrast, the OLE was a single-arm, open-label extension with no randomization or allocation concealment.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY	NA	PY	N	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	NA	PY	NA	Randomization was stratified solely by baseline 6MWD (≤350 m vs. >350 m), with no other prognostic factors considered. Observable imbalances in sex, age ≥65, White ethnicity, disease aetiology, and background treatments exist between inhaled treprostinil and placebo groups, but no statistical tests were conducted to assess these differences.
	Risk of bias judgement	**Low**	**NA**	**Some concerns**	**High**	Some imbalances are observable in the INCREASE. The OLE has been single arm with open-label structure which raises potential risk of bias.
Bias due to deviations	2.1. Were participants aware of their	N	Y	N	Y	The OLE followed a single-arm, open-label design with both participants and investigators unblinded.

Domain	Signalling question	Company judgement		EAG judgement		EAG Comments
		INCREASE	INCREASE OLE	INCREASE	INCREASE OLE	
from intended interventions	assigned intervention during the trial? 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	Y	N	Y	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	NA	NA	PY	"*Some patients discontinued early or missed doses due to adverse events or disease progression. Non-adherence due to dropouts or dose interruptions likely occurred and may have affected functional outcomes (e.g., 6MWD).*" (clarification question C1)
	2.4 If Y/PY to 2.3: Were these deviations likely	NA	NA	NA	PY	

Domain	Signalling question	Company judgement		EAG judgement		EAG Comments
		INCREASE	INCREASE OLE	INCREASE	INCREASE OLE	
	to have affected the outcome?					
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA	NA	PN	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	NA	Y	N	"*The analysis was descriptive, with no statistical adjustment (e.g., per-protocol or inverse-probability weighting) to account for varying adherence levels*." (clarification question C1)
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in	NA	NA	NA	NA	

Domain	Signalling question	Company judgement		EAG judgement		EAG Comments
		INCREASE	**INCREASE OLE**	**INCREASE**	**INCREASE OLE**	
	the group to which they were randomized?					
	Risk of bias judgement	**Low**	**Some concerns**	**Low**	**High**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N	N	N	N	In the RCT, 20% of patients in the inhaled treprostinil arm and 21% in the placebo arm discontinued participation. In the OLE, substantial attrition occurred, with only 29% completing the full 108-week follow-up (52-week attrition not reported), and no imputation or sensitivity analyses were conducted. Sensitivity analyses exploring the impact of missing data were unavailable for many outcomes. Discontinuations were often due to [redacted], potentially affecting functional outcomes.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	PY	PN	PN	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	PY	PY	PY	

Domain	Signalling question	Company judgement		EAG judgement		EAG Comments
		INCREASE	**INCREASE OLE**	**INCREASE**	**INCREASE OLE**	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	PY	PY	PY	
	Risk of bias judgement	**Low**	**Some concerns**	**Some concerns**	**Some concerns**	There is a possibility that a high rate of discontinuations and lack of bias corrections may have led to risk of bias.
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	N	PY	PY	Acute exacerbations were determined solely by site investigators without centralized adjudication, coinciding with unexpectedly high rates across both study arms -particularly in the placebo group. This suggests that patients with more advanced disease may have been more readily labelled as experiencing an exacerbation based on clinical decline, even if formal diagnostic criteria were not fully met.[44, 53]
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	PY	PY	
	4.3 Were outcome assessors	N	Y	N	Y	

Domain	Signalling question	Company judgement		EAG judgement		EAG Comments
		INCREASE	**INCREASE OLE**	**INCREASE**	**INCREASE OLE**	
	aware of the intervention received by study participants?					
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	PN	NA	Y	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	N	NA	PY	
	Risk of bias judgement	**Low**	**Low**	**High**	**High**	

Domain	Signalling question	Company judgement		EAG judgement		EAG Comments
		INCREASE	INCREASE OLE	INCREASE	INCREASE OLE	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	PN	PN	N	No statistical analysis plan or protocol was published for the OLE. In the RCT, disease progression, used as a complementary outcome in this appraisal, was not prespecified and was analysed post hoc. Similarly, overall survival, event-free survival, and time to discontinuation were deemed post-hoc outcomes.
	5.2 … multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	PY	PN	PY	
	5.3 … multiple eligible analyses of the data?	N	PY	N	PY	

Domain	Signalling question	Company judgement		EAG judgement		EAG Comments
		INCREASE	INCREASE OLE	INCREASE	INCREASE OLE	
	Risk of bias judgement	Low	Some concerns	Some concerns	High	
Overall bias	Risk of bias judgement	Low	Some concerns	Some concerns	High	

7.3 Dawes et al. (2022) JBI critical appraisal tool

Domains	Comments
1. Were there clear criteria for inclusion in the case series?	Some inclusion/exclusion criteria have been noted and applied.
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes, it was. A wider data cut would have reduced the small sample size, which underlines the uncertainties of results interpretations.
3. Were valid methods used for identification of the condition for all participants included in the case series?	Probably yes
4. Did the case series have consecutive inclusion of participants?	Yes
5. Did the case series have complete inclusion of participants?	Yes
6. Was there clear reporting of the demographics of the participants in the study?	Probably yes
7. Was there clear reporting of clinical information of the participants?	Probably yes
8. Were the outcomes or follow-up results of cases clearly reported?	Adverse events and clinical worsening, and disease progression, while important, were not reported.
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	The majority of prognostic factors were captured and reported. However, some aetiologies (e.g. CTD) were not included, which challenges comparisons with real-world evidence.
10. Was statistical analysis appropriate?	Yes

7.4 Additional searches undertaken by the EAG

Targeted search for additional studies containing useful comparator data

Connected Papers https://www.connectedpapers.com/
Date searched: 09/07/25

Connected papers was used to find related studies to the following papers:

- Dawes, T., et al. (2022). "Phosphodiesterase 5 inhibitor treatment and survival in interstitial lung disease pulmonary hypertension: A Bayesian retrospective observational cohort study." Respirology 28: 262 - 272.
- Alhamad, E., et al. (2020). "Clinical characteristics, comorbidities, and outcomes in patients with idiopathic pulmonary fibrosis." Annals of Thoracic Medicine 15: 208 - 214.

20 papers were highlighted for further consideration or reference list checking.

Reviews checked for useful references (10/07/25)**:**

- Swisher JW, Weaver E. Therapeutic options for patients with pulmonary hypertension and interstitial lung disease. Ther Adv Respir Dis. 2025 Jan-Dec;19:17534666251335815. doi: 10.1177/17534666251335815. *[Identified via email alerts]*
- Arslan A, Smith J, Qureshi MR, Uysal A, Patel KK, Herazo-Maya JD, Bandyopadhyay D. Evolution of pulmonary hypertension in interstitial lung disease: A journey through past, present, and future. Frontiers in Medicine. 2024 Jan 17;10:1306032. *[Identified via Connected Papers search]*
    - *One potentially useful study cited:* Grünig E, Huscher D, Pitrow D, Vizza D, Hoeper MM. Pulmonary hypertension due to lung disease – Results from COMPERA. European Respiratory Journal 2015 46(suppl 59): OA5000; https://doi.org/10.1183/13993003.congress-2015.OA5000
- Kattih Z, Kim HC, Aryal S, Nathan SD. Review of the Diagnosis and Management of Pulmonary Hypertension Associated with Interstitial Lung

Disease (ILD-PH). Journal of Clinical Medicine. 2025 Mar 17;14(6):2029. *[Identified via Connected Papers search]*

- Genecand L, Wacker J, Guerreiro I, Lechartier B, Beghetti M, Pohle S, et al. Pulmonary Hypertension Associated with Interstitial Lung Disease: A Review on Diagnosis and Treatment with a Focus on Emerging Therapies. Respiration 2025:1-11. http://dx.doi.org/10.1159/000544800 *[identified via previous scoping searches]*

Additional study of interest from previous scoping searches:

- Fahim A, et al. Idiopathic pulmonary fibrosis in the UK: findings from the British Thoracic Society UK Idiopathic Pulmonary Fibrosis Registry: BMJ Open Respiratory Research 2025;12:e002773. https://doi.org/10.1136/bmjresp-2024-002773

Google search 11/07/25

Search: COMPERA registry
Browsed first 30 results; mostly about pulmonary arterial hypertension.
Checked:

- https://www.compera.org/
- https://clinicaltrials.gov/study/NCT01347216#publications
- https://publications.ersnet.org/content/erj/58/2/2101483

Search: COMPERA registry interstitial lung disease
Browsed first 30 results. Checked:

- https://catalogues.ema.europa.eu/node/4004/administrative-details
- https://catalogues.ema.europa.eu/node/4010/administrative-details & https://catalogues.ema.europa.eu/node/4139/administrative-details
- https://www.sciencedirect.com/science/article/pii/S2772374724000395 - Japanese registry study

- Hoeper MM, Behr J, Held M, Grunig E, Vizza CD, Vonk-Noordegraaf A, et al. (2015) Pulmonary Hypertension in Patients with Chronic Fibrosing Idiopathic Interstitial Pneumonias. PLoS ONE 10(12): e0141911. https://doi.org/10.1371/journal.pone.0141911

Update of company's searches for Cost effectiveness and costs/resource use (CS Appendices E.1.1 and G.1.1)

PubMed Date searched: 30/06/25

(((("idiopathic pulmonary fibrosis"[MeSH Terms] OR "idiopathic pulmonary fibrosis"[Title/Abstract] OR "interstitial pneumoniti*"[Title/Abstract] OR "interstitial lung disease*"[Title/Abstract] OR "diffuse parenchymal lung diseas*"[Title/Abstract] OR ("connective tissue disease"[Title/Abstract] AND "interstitial lung disease"[Title/Abstract]) OR "combined pulmonary fibrosis and emphysema"[Title/Abstract]) AND ("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension"[Title/Abstract] OR "pulmonary arterial hypertension"[Title/Abstract]) AND ("economics"[MeSH Terms:noexp] OR "Costs and Cost Analysis"[MeSH Terms] OR "economics, nursing"[MeSH Terms] OR "economics, medical"[MeSH Terms] OR "economics, pharmaceutical"[MeSH Terms] OR "economics, hospital"[MeSH Terms] OR "economics, dental"[MeSH Terms] OR "Fees and Charges"[MeSH Terms] OR "budgets"[MeSH Terms] OR "budget*"[Title/Abstract] OR "economic*"[Title/Abstract] OR "cost"[Title/Abstract] OR "costs"[Title/Abstract] OR "costly"[Title/Abstract] OR "costing"[Title/Abstract] OR "price"[Title/Abstract] OR "prices"[Title/Abstract] OR "pricing"[Title/Abstract] OR "pharmacoeconomic*"[Title/Abstract] OR "pharmaco economic*"[Title/Abstract] OR "expenditure"[Title/Abstract] OR "expenditures"[Title/Abstract] OR "expense"[Title/Abstract] OR "expenses"[Title/Abstract] OR "financial"[Title/Abstract] OR "finance"[Title/Abstract] OR "finances"[Title/Abstract] OR "financed"[Title/Abstract] OR "value for money"[Title/Abstract] OR "monetary value*"[Title/Abstract] OR "models, economic"[MeSH Terms] OR "economic model*"[Title/Abstract] OR "markov chains"[MeSH Terms] OR "markov"[Title/Abstract] OR "monte carlo method"[MeSH Terms] OR "monte carlo"[Title/Abstract] OR "Decision Theory"[MeSH Terms] OR "decision tree*"[Title/Abstract] OR "decision analy*"[Title/Abstract] OR "decision model*"[Title/Abstract])) NOT ("Animals"[MeSH Terms] NOT "Humans"[MeSH Terms])) AND (2025/01/22:3000/12/31[Date - Entry] OR 2025/01/22:3000/12/31[Date - MeSH] OR 2025/01/22:3000/12/31[Date - Create])

2 results

Ovid Embase <1974 to 2025 June 27> Date searched: 30/06/25

Note; the search was adapted for use in Ovid Embase (the company used Embase.com), and an additional, broader filter for economic evaluations and models (from CDA) was applied

1 exp fibrosing alveolitis/ 39132
2 (idiopathic pulmonary fibrosis or interstitial pneumoniti* or interstitial lung disease* or diffuse parenchymal lung diseas* or (connective tissue disease* and interstitial lung disease) or "combined pulmonary fibrosis and emphysema").ab,ti. 58550
3 1 or 2 76386
4 exp pulmonary hypertension/ 130566
5 (pulmonary adj2 hypertension).ab,ti. 102995
6 4 or 5 142737
7 3 and 6 6976
8 Economics/ 246613
9 Cost/ 66120
10 exp Health Economics/ 1154478
11 Budget/ 36855
12 budget*.ti,ab,kw. 53408
13 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. 348848
14 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 632497
15 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. 342174
16 (value adj2 (money or monetary)).ti,ab,kw. 4614
17 Statistical Model/ 181414
18 economic model*.ab,kw. 7118
19 Probability/ 171158
20 markov.ti,ab,kw. 41403
21 monte carlo method/ 58042
22 monte carlo.ti,ab,kw. 69094
23 Decision Theory/ 1924
24 Decision Tree/ 29147
25 (decision* adj3 (tree* or analy* or model*)).ti,ab,kw. 73704
26 or/8-25 [Economic Evaluations & Models - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/15.] 2269974

27 7 and 26 258
28 "cost benefit analysis"/ or "cost control"/ or cost effectiveness analysis/ or "cost minimization analysis"/ or "cost of illness"/ or economic aspect/ or financial management/ or "health care cost"/ or health care financing/ or health economics/ or "hospital cost"/ or socioeconomics/ 990024
29 (fiscal or financial or finance or funding).ab,ti. 376549
30 ((cost adj2 estimate*) or (cost adj2 variable*)).mp. or (unit adj2 cost*).ab,kf,ti. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 29773
31 28 or 29 or 30 [filter used by company in appendix F.1.1, but appears to be costs/HRU focused not cost effectiveness/models] 1294948
32 7 and 31 129
33 limit 27 to human 252
34 limit 32 to human 125
35 33 not 34 [studies potentially missed by company not using broader economic studies filter] 176
36 limit 33 to dc=20250122-20250630 23
37 limit 33 to dd=20250122-20250630 22
38 limit 33 to rd=20250122-20250630 21
39 36 or 37 or 38 [new studies since company's search but using a better economic studies filter] 26
40 limit 34 to dc=20250122-20250630 11
41 limit 34 to dd=20250122-20250630 11
42 limit 34 to rd=20250122-20250630 7
43 40 or 41 or 42 [new studies since company's search if using translation of filter they used in Embase.com] 11
44 39 or 43 33
45 clinicaltrialsgov.jn. 533511
46 35 not 45 168
47 39 not 45 15
48 43 not 45 6
49 44 not 45 20

Update of company's searches for HRQoL (CS Appendix F.1.1)

PubMed Date searched: 30/06/25

(((("idiopathic pulmonary fibrosis"[MeSH Terms] OR "idiopathic pulmonary fibrosis"[Title/Abstract] OR "interstitial pneumoniti*"[Title/Abstract] OR "interstitial lung disease*"[Title/Abstract] OR "diffuse parenchymal lung diseas*"[Title/Abstract] OR ("connective tissue disease"[Title/Abstract] AND "interstitial lung disease"[Title/Abstract]) OR "combined pulmonary fibrosis and emphysema"[Title/Abstract]) AND ("hypertension, pulmonary"[MeSH

Terms] OR "pulmonary hypertension"[Title/Abstract] OR "pulmonary arterial hypertension"[Title/Abstract]) AND ("Value of Life"[MeSH Terms] OR "Quality of Life"[MeSH Terms] OR "Quality of Life"[Title/Abstract] OR "Quality-Adjusted Life Years"[MeSH Terms] OR "quality adjusted life"[Title/Abstract] OR "qaly*"[Title/Abstract] OR "qald*"[Title/Abstract] OR "qale*"[Title/Abstract] OR "qtime*"[Title/Abstract] OR "life year"[Title/Abstract] OR "life years"[Title/Abstract] OR "disability adjusted life"[Title/Abstract] OR "daly*"[Title/Abstract] OR "sf36"[Title/Abstract] OR "sf 36"[Title/Abstract] OR "short form 36"[Title/Abstract] OR "shortform 36"[Title/Abstract] OR "short form36"[Title/Abstract] OR "shortform36"[Title/Abstract] OR "sf6"[Title/Abstract] OR "sf 6"[Title/Abstract] OR "short form 6"[Title/Abstract] OR "shortform6"[Title/Abstract] OR "sf6d"[Title/Abstract] OR "sf 6d"[Title/Abstract] OR "short form 6d"[Title/Abstract] OR "shortform 6d"[Title/Abstract] OR "sf six"[Title/Abstract] OR "sfsix"[Title/Abstract] OR "short form six"[Title/Abstract] OR "sf8"[Title/Abstract] OR "sf 8"[Title/Abstract] OR "short form 8"[Title/Abstract] OR "shortform8"[Title/Abstract] OR "sf12"[Title/Abstract] OR "sf 12"[Title/Abstract] OR "short form 12"[Title/Abstract] OR "shortform 12"[Title/Abstract] OR "short form12"[Title/Abstract] OR "shortform12"[Title/Abstract] OR "sf16"[Title/Abstract] OR "sf 16"[Title/Abstract] OR "sf20"[Title/Abstract] OR "sf 20"[Title/Abstract] OR "short form 20"[Title/Abstract] OR "hql"[Title/Abstract] OR "hqol"[Title/Abstract] OR "h qol"[Title/Abstract] OR "hrqol"[Title/Abstract] OR "hr qol"[Title/Abstract] OR "hye"[Title/Abstract] OR "hyes"[Title/Abstract] OR "healthy year equivalent*"[Title/Abstract] OR "healthy years equivalent*"[Title/Abstract] OR "pqol"[Title/Abstract] OR "qls"[Title/Abstract] OR "quality of wellbeing"[Title/Abstract] OR "quality of well being"[Title/Abstract] OR "index of wellbeing"[Title/Abstract] OR "index of well being"[Title/Abstract] OR "qwb"[Title/Abstract] OR "nottingham health profile*"[Title/Abstract] OR "sickness impact profile"[Title/Abstract] OR "health status indicators"[MeSH Terms] OR "health utilit*"[Title/Abstract] OR "health status"[Title/Abstract] OR "disutilit*"[Title/Abstract] OR "rosser"[Title/Abstract] OR "willingness to pay"[Title/Abstract] OR "standard gamble*"[Title/Abstract] OR "time trade off"[Title/Abstract] OR "time tradeoff"[Title/Abstract] OR "tto"[Title/Abstract] OR "hui"[Title/Abstract] OR "hui1"[Title/Abstract] OR "hui2"[Title/Abstract] OR "hui3"[Title/Abstract] OR "eq"[Title/Abstract] OR "euroqol"[Title/Abstract] OR "euro qol"[Title/Abstract] OR "eq5d"[Title/Abstract] OR "eq 5d"[Title/Abstract] OR "euroqual"[Title/Abstract] OR "euro qual"[Title/Abstract] OR "duke health profile"[Title/Abstract] OR "functional status questionnaire"[Title/Abstract] OR "dartmouth coop functional health assessment*"[Title/Abstract] OR ("utilit*"[Title/Abstract] AND ("valu*"[Title/Abstract] OR "measur*"[Title/Abstract] OR "health"[Title/Abstract] OR "life"[Title/Abstract] OR "estimat*"[Title/Abstract] OR "elicit*"[Title/Abstract] OR "disease"[Title/Abstract] OR "score*"[Title/Abstract] OR "weight"[Title/Abstract])) OR ("preference*"[Title/Abstract] AND ("valu*"[Title/Abstract] OR "measur*"[Title/Abstract] OR "health"[Title/Abstract] OR "life"[Title/Abstract] OR "estimat*"[Title/Abstract] OR "elicit*"[Title/Abstract]

OR "disease"[Title/Abstract] OR "score*"[Title/Abstract] OR "instrument"[Title/Abstract] OR "instruments"[Title/Abstract]))))) NOT ("Animals"[MeSH Terms] NOT "Humans"[MeSH Terms])) AND (2025/02/14:3000/12/31[Date - Entry] OR 2025/02/14:3000/12/31[Date - MeSH] OR 2025/02/14:3000/12/31[Date - Create])
18 results

Ovid Embase <1974 to 2025 June 27> Date searched: 30/06/25
Note; the search was adapted for use in Ovid Embase (the company used Embase.com

1 exp fibrosing alveolitis/ 39132
2 (idiopathic pulmonary fibrosis or interstitial pneumoniti* or interstitial lung disease* or diffuse parenchymal lung diseas* or (connective tissue disease* and interstitial lung disease) or "combined pulmonary fibrosis and emphysema").ab,ti. 58550
3 1 or 2 76386
4 exp pulmonary hypertension/ 130566
5 (pulmonary adj2 hypertension).ab,ti. 102995
6 4 or 5 142737
7 3 and 6 6976
8 socioeconomics/ 178187
9 exp Quality of Life/ 819755
10 quality of life.ti,kw. 207261
11 ((instrument or instruments) adj3 quality of life).ab. 6102
12 Quality-Adjusted Life Year/ 40991
13 quality adjusted life.ti,ab,kw. 30500
14 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. 53190
15 disability adjusted life.ti,ab,kw. 9638
16 daly*.ti,ab,kw. 9328
17 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw. 57036
18 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw. 3365
19 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw. 1141
20 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw. 14411

21 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw. 82
22 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw. 594
23 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. 46532
24 (hye or hyes).ti,ab,kw. 220
25 (health* adj2 year* adj2 equivalent*).ti,ab,kw. 53
26 (pqol or qls).ti,ab,kw. 845
27 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw. 1040
28 nottingham health profile*.ti,ab,kw. 1807
29 nottingham health profile/ 797
30 sickness impact profile.ti,ab,kw. 1324
31 sickness impact profile/ 2380
32 health status indicator/ 3659
33 (health adj3 (utilit* or status)).ti,ab,kw. 138243
34 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw. 29536
35 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw. 22371
36 disutilit*.ti,ab,kw. 1469
37 rosser.ti,ab,kw. 153
38 willingness to pay.ti,ab,kw. 15603
39 standard gamble*.ti,ab,kw. 1271
40 (time trade off or time tradeoff).ti,ab,kw. 2598
41 tto.ti,ab,kw. 2583
42 (hui or hui1 or hui2 or hui3).ti,ab,kw. 3713
43 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. 47345
44 duke health profile.ti,ab,kw. 127
45 functional status questionnaire.ti,ab,kw. 194
46 dartmouth coop functional health assessment*.ti,ab,kw. 14
47 or/8-46 [Economic - Health Utilities / Quality of Life - Standard - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2022: https://searchfilters.cadth.ca/link/18.] 1205474
48 7 and 47 503
49 limit 48 to human 491
50 clinicaltrialsgov.jn. 533511
51 49 not 50 460
52 limit 51 to dc=20250214-20250630 22
53 limit 51 to dd=20250214-20250630 19
54 limit 51 to rd=20250214-20250630 16
55 52 or 53 or 54 23

UNIVERSITY OF BIRMINGHAM

External Assessment Group (EAG) Report

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease [ID6459]

Produced by	Centre for Evidence and Implementation Science, University of Birmingham
Authors	Amin Mehrabian, Research Fellow, University of Birmingham Mehdi Yousefi, Research Fellow, University of Birmingham Anna Brown, Information Specialist, University of Birmingham April Coombe, Information Specialist, University of Birmingham Daniel Gallacher, Assistant Professor, University of Birmingham
Correspondence to	Dr Daniel Gallacher; d.c.gallacher@bham.ac.uk
Date completed	Date completed (30/10/2025)

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Copyright statement

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Table of Abbreviations

Abbreviation	Definition
6MWD	6-minute walk distance
BMI	Body mass index
BSC	Best supportive care
CI	Confidence interval
CPFE	Combined pulmonary fibrosis and emphysema
DLCO	Diffusing capacity of the lungs for carbon monoxide
DSU	Decision Support Unit
EAG	External Assessment Group
FEV	Forced expiratory volume
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro B-type natriuretic peptide
OLE	Open-label extension
OS	Overall survival
PDE5i	Phosphodiesterase Type 5 Inhibitors
PH	Pulmonary Hypertension
PH-ILD	Pulmonary Hypertension associated with Interstitial Lung Disease
PVR	Pulmonary vascular resistance
QALY	Quality-adjusted life year
RPSFT	Rank-preserving structural failure time
TEM	Treatment effect modifiers
WHO	World Health Organization
WHO FC	World Health Organization functional class

1 Introduction

This addendum summarises and critiques information submitted by the company relating to a comparison of the clinical and cost effectiveness of treprostinil and phosphodiesterase type 5 inhibitors (PDE5is).

The company submitted this information following receipt of the original EAG report, which highlighted the relevance of PDE5is as a comparator for this appraisal. However, the company maintains its position that PDE5is are not a relevant comparator for treprostinil.

No evidence was available for a direct comparison, nor for a connected network; hence, the company relied on an unanchored matching-adjusted indirect comparison (MAIC) to estimate relative efficacy between treprostinil and PDE5is. The company's sources of data were the INCREASE trial[1] and a publication by Dawes et al.[2]

1.1 Methodology for indirect comparison to PDE5s

The company listed prognostic factors and treatment effect modifiers (TEMs) they had identified in the addendum section 1.1.1. A MAIC assumes that there all confounders are measured and included in the analysis. It was noted by the EAG's clinical expert that potential covariates such as pulmonary vascular resistance (PVR), N-terminal pro B-type natriuretic peptide (NT-proBNP), number of exacerbations, World Health Organization functional class (WHO FC), and cardiovascular comorbidities were not considered. In addition, not all disease aetiologies (e.g., combined pulmonary fibrosis and emphysema (CPFE), idiopathic interstitial pneumonia (IIP)) appear to have been accounted for.

In addition to these, limited collection/reporting of data in the Dawes et al. paper prevented use of body mass index (BMI) and smoking history in the MAIC. The EAG considers the main assumption of no unmeasured confounders to be strongly violated and advises caution when interpreting the

MAIC results. Depending on the magnitude of difference and effect of the unmeasured confounders, it is possible that a naïve comparison is more reliable than the MAIC.

Table 1 shows the covariates included in the MAIC analysis alongside the distribution of them in INCREASE data before and after matching to the Dawes et al population.[2] The EAG has included the characteristics from another real-world evidence source for PDE5i, published by Yogeswaran et al.[3], which will be discussed later in the document. The EAG summarises and appraises the Dawes et al. and Yogeswaran et al. publications.

Table 1: Adjusted TEM and comparison with Yogeswaran et al.

Effect modifier	**Original distribution in INCREASE (N=163) [CSR, table 11-1, Table 14.1.3, Table 14.3.4.6]**	**MAIC population in INCREASE (un-weighted)**	**MAIC population in INCREASE (weighted)**	**Reported distribution in Dawes *et al.* (2022) (N=50)**	**Yogeswaran N=511**
Mean age (years) [median]	[redacted]	68.36	65.0	65.0	[67.0]
Mean BMI (kg/m^2) [median]	[redacted]	NA	NA	NR	27 (3.5% missing)
Sex (prop male)	0.48	0.59	0.42	0.42	0.52
Hypertension (prop with)	0.63	0.50	0.26	0.26	Unclear
Oxygenation (prop receiving)	0.73	0.46	0.76	0.76	0.59
6MWD (metres) (median)	256.0	261.0	258.0	258.0	NR
DLCO %predicted [median]	29.0	28.4	25.0	25.0	26 (29% missing)
FEV1 %	63.0	67.0	59.0	59.0	NR

predicted (median)					
NTproBNP (pg/mL) (median)	[redacted]	NA	NA	135.0	150 (29% missing)
FVC %predicted (median)	60.0	NA	NA	57.0	58 (24% missing)
mPAP (mmHg) (median)	35.0	NA	NA	38.0	38.0
PVR (WU) (median)	5.57	NA	NA	6.7	6.6
PCWP (mmHg) (median)	10.0	NA	NA	11.0 (mean)	8.0
TLC %predicted (median)	[redacted]	NA	NA	NR	62 (36% missing)
Aetiology: IPF NSIP Other	 0.22 0.03 Unclear*	 0.33 0.33 0.55	 0.40 0.10 0.50	 0.40 0.10 0.50	 0.19 NR Unclear

*It is unclear if the other aetiology is referring to all remaining unreported aetiologies or CS, Table 4 with 0.6% frequency.

Abbreviations: 6MWD, 6-minute walk distance; DLCO, Diffusing capacity of the lungs for carbon monoxide; FEV1, Forced expiratory volume in 1 second; IPF, Idiopathic pulmonary fibrosis; NSIP, Non-specific interstitial pneumonia; NA, not adjusted; NR, not reported.

1.1.1 Sources of real-world evidence for comparison

1.1.1.1 Dawes et al. (2022)

This retrospective cohort single centre study from the Royal Brompton Hospital (2000–2021) assessed survival in patients with interstitial lung disease-associated pulmonary hypertension (ILD-PH) using a Bayesian approach.[2] Of 932 ILD patients screened, 128 with confirmed ILD-PH were included. Exclusions were primarily due to the absence of right heart catheterisation (RHC; n=473), echocardiography (n=397), spirometry (n=214), or the presence of connective tissue disease (CTD).

Critique of Dawes et al. (2022)

The EAG has provided a detailed critique of this study in the EAG final report, section 3.2.3.2, as this study informed a previous MAIC analysis by the company, which compared treprostinil with best supportive care.

Briefly, the retrospective design introduces potential for selection bias. Several measures used in the study, such as the Composite Physiologic Index (CPI) and emPHasis-10, lack validation in the ILD-PH population. Notably, only 20% of IPF patients were male (15 of 74), which contrasts with the expected male predominance, as highlighted by EAG clinical experts.

The exclusion of CTD patients and the absence or unclear reporting of covariates (such as smoking status, BMI, and treatment delays) raise concerns about the study's generalisability. Additionally, inconsistencies in reporting the sex distribution (Table S3 vs Table S1) suggest possible misclassification.

In support of using Dawes et al. for MAIC, the company excluded patients from the INCREASE trial with CTD aetiology (24.5%) and those with a time since diagnosis >2 years prior to conducting the analysis. However, the median time to diagnosis in the INCREASE trial was [redacted] years (range: [redacted]) for all patients (N=326), and [redacted] years (range: [redacted]) for those treated with inhaled treprostinil (N=163). This suggests that a non-negligible proportion of patients may have been excluded, with unclear implications for treatment effect estimation.

Further covariates (such as BMI and smoking (noted by the company), and PVR thresholds, ILD subtypes (e.g., IIP, CPFE), NT-proBNP levels, and cardiovascular comorbidities (highlighted by EAG experts)) were not adequately adjusted for. Due to insufficient evidence, the robustness and relevance of these potential effect modifiers remain uncertain, undermining the overlap assumption required for MAIC.

Moreover, the study does not address changes in PH definitions pre-2019 (mean pulmonary arterial pressure (mPAP) ≥25 mmHg, pulmonary vascular

resistance (PVR) >3 WU, pulmonary arterial wedge pressure (PAWP) ≤15 mmHg) and post-2019 (mPAP >20 mmHg, PVR ≥3 WU, PAWP ≤15 mmHg). The use of mixed thresholds may introduce clinical heterogeneity, potentially encompassing patients with differing disease severity, pathophysiology, and prognosis. This could compromise the study's internal validity and limit the reliability of subsequent interpretations. The INCREASE trial adhered to the pre-2019 criteria, and the lack of alignment in disease classification between Dawes et al. and INCREASE further contributes to the observed heterogeneity.

1.1.1.2 Yogeswaran et al. (2025)

An alternative source of evidence identified by the EAG was a study which evaluated 34,482 patients with PH-ILD as of April 2025, across 25 centres participating in the global PVRI GoDeep Registry (NCT05329714).[3] All RHC confirmed patients' data were harmonised and validated to ensure alignment with international diagnostic standards. The exact range of time covered by the presented data is not reported, but is described as spanning "more than three decades".

A total of 940 adults met the inclusion criteria for Group 3.2 PH (PH-ILD), defined by RHC-confirmed mPAP >20 mmHg, PVR >2 WU, and PAWP ≤15 mmHg. Patients with combined pulmonary fibrosis and emphysema (CPFE) were excluded.

To validate the results, survival data from the European pulmonary hypertension registry COMPERA (NCT01347216) were utilised. COMPERA is an ongoing, prospective registry established in 2007 that collects baseline, follow-up, and outcome data on newly diagnosed patients receiving targeted therapies for various forms of pulmonary hypertension. Participating centres span multiple European countries, including the UK. To avoid duplication of patient records, centres contributing data to the GoDeep registry were excluded from the COMPERA validation cohort.

In total, 940 patients were included in the study, of whom 511 received PDE5i treatment. The remaining patients were not entirely treatment-naïve and, therefore, were not considered further in this appraisal.

In Yogeswaran et al. PDE5i treated patients (N=511), the median age was 67 years, with 52% male. Of these, 67% received PDE5i monotherapy and 33% received combination therapies (including sGC stimulators, prostacyclin analogues (i.e. PGI_2), or endothelin receptor antagonists). According to EAG clinical experts, the male/female distribution in IPF and IIP subgroups aligns more closely with NHS practice than Dawes et al. The treatment patterns also reflect current prescribing trends, including the use of combination therapies in CTD-PH (likely classified under autoimmune-PH in GoDeep). However, the proportion of combination therapy use appears slightly higher than typically observed in NHS settings. Additionally, nebulised iloprost (prostacyclin) was noted as an off-label, non-commissioned treatment used in smaller proportions.

Yogeswaran et al states that "*The diagnosis date was defined as the first RHC, with baseline data from −1 to 6 months around diagnosis*". This phrasing appears to imply that the baseline characteristics were collected within a window extending from one month prior to six months following the first RHC. However, the precise definition of time zero for the survival analysis is unclear and remains a potential source of bias.

Critique of Yogeswaran et al. (2025)

The study is limited by missing data and the retrospective/prospective nature of data collection. However, by using the Target Trial Validation Framework and additional diagnostic analyses, the authors suggest that the missingness is likely random and unlikely to introduce systematic bias. Therefore, they argue that the study's conclusions remain reliable despite these limitations.

A further limitation stems from the extended data collection period (spanning over three decades), during which definitions of PH and clinical management

strategies have evolved. The EAG notes that similar concerns were raised in the comparison between Dawes et al. and the INCREASE trial. In the case of Yogeswaran et al., when earlier definitions of pre-capillary PH were applied and analyses focused on patients receiving antifibrotic background therapy, the survival benefit associated with PDE5i treatment appeared to persist.

As a multi-centre study, Yogeswaran et al. benefits from a substantially larger sample. Notably, the UK cohort sourced from centres in London and Sheffield in Yogeswaran et al. (138 patients) exceeds that of Dawes et al. (128 patients), which was conducted at a single centre (Royal Brompton Hospital National Pulmonary Hypertension Service (London)). The EAG's clinical experts noted that PDE5i's administration varies across UK PH centres (8-60%). The EAG concluded that a multi-centre dataset would be preferable to better capture the diversity of clinical practice and treatment patterns across the NHS. Given the lack of approved treatments for PH-ILD, outcomes are not expected to vary considerably across countries.

The EAG's clinical experts supported the generalisability of Yogeswaran et al. to NHS practice and further noted that, in the absence of prospective RCTs for generally safe and affordable PDE5is, prescribing decisions are largely based on clinical experience within PH centres. Nevertheless, the emerging data and analyses presented in Yogeswaran et al. likely influence onwards prescribing practices.

Critique of the company's notes on Yogeswaran et al.

In response to the EAG's request to consider Yogeswaran et al. as a comparator to the INCREASE trial, via email correspondence, the company stated that MAIC was not feasible due to missing data and greater heterogeneity in baseline characteristics between the two populations. The company also noted that the study was "*less representative of UK clinical*

practice than Dawes et al", as the majority of patients (86%) were from outside the UK.

A comparison of covariates is presented in Table 1. While missing and unreported covariates in Yogeswaran et al. would indeed pose challenges for conducting a robust MAIC, the EAG's clinical experts highlighted that the multi-centre study is more likely to accurately reflect wider NHS practice than the single-centre Dawes dataset. Regional patient distribution in Yogeswaran et al. includes 138 from the UK, 517 from Europe, 275 from the US, and 10 from other regions, suggesting a larger UK cohort than Dawes et al. (128 patients). Therefore, the EAG considers Yogeswaran et al. to be a relevant source of real-world evidence.

EAG's summary

The EAG are concerned that the company's MAIC analysis to Dawes et al. may provide a biased comparison of relative efficacy due to the covariates that could not be included in the MAIC, and may offer no improvement over a naïve comparison. The EAG considers that a naïve comparison to the relevant data from Yogeswaran et al. is helpful to provide an alternative point of reference. Whilst a detailed comparison is not possible, based on the reported characteristics (age, sex, oxygenation), the population of INCREASE appears more similar to that of Yogeswaran et al. than the Dawes et al. population, potentially reducing the need for a MAIC.

1.2 Results for indirect comparison to PDE5s

The company's MAIC was successful at matching the following baseline covariates between the populations: age (mean), sex (% male), hypertension (% yes), oxygenation (% yes), 6MWD, DLCO, FEV1, and disease aetiology

(IPF, NSIP or other). The effective sample size was 135, reduced from the starting sample size of 227.

The estimated hazard ratio for OS of treprostinil vs PDE5is is 0.44 (95% CI: 0.24, 0.80), which suggests a larger effect size than a naïve comparison (0.58 [95% CI: 0.36, 0.95]). This pattern between the naïve and MAIC hazard ratios was also observed in the MAIC against BSC. The EAG noted this is a cause for concern, because the MAIC is comparing trial data to real-world data. Typically, real-world data has worse outcomes than trial populations, and so the fact that the outcomes for the treprostinil population improve when the MAIC weights are applied bring into question whether the MAIC holds face validity.

An examination of the Schoenfeld residual plot suggests the proportional hazards assumption was not violated for output from the company's MAIC.

1.2.1 EAG Analysis vs PDE5is

The company declined the EAG's request to undertake a MAIC vs the Yogeswaran et al. population, and so the EAG undertook a naïve comparison of overall survival for people in INCREASE who were randomised to treprostinil versus people in Yogeswaran et al. who had PH-ILD and received PDE5i treatment. The INCREASE population included in this naïve comparison was broader than that used in the company's MAIC analysis. From Yogeswaran et al. the EAG digitally recreated the data from figures S4C and S4D, which combined people with PVR ≤ 5 WU and PVR > 5 WU (Figure 1).

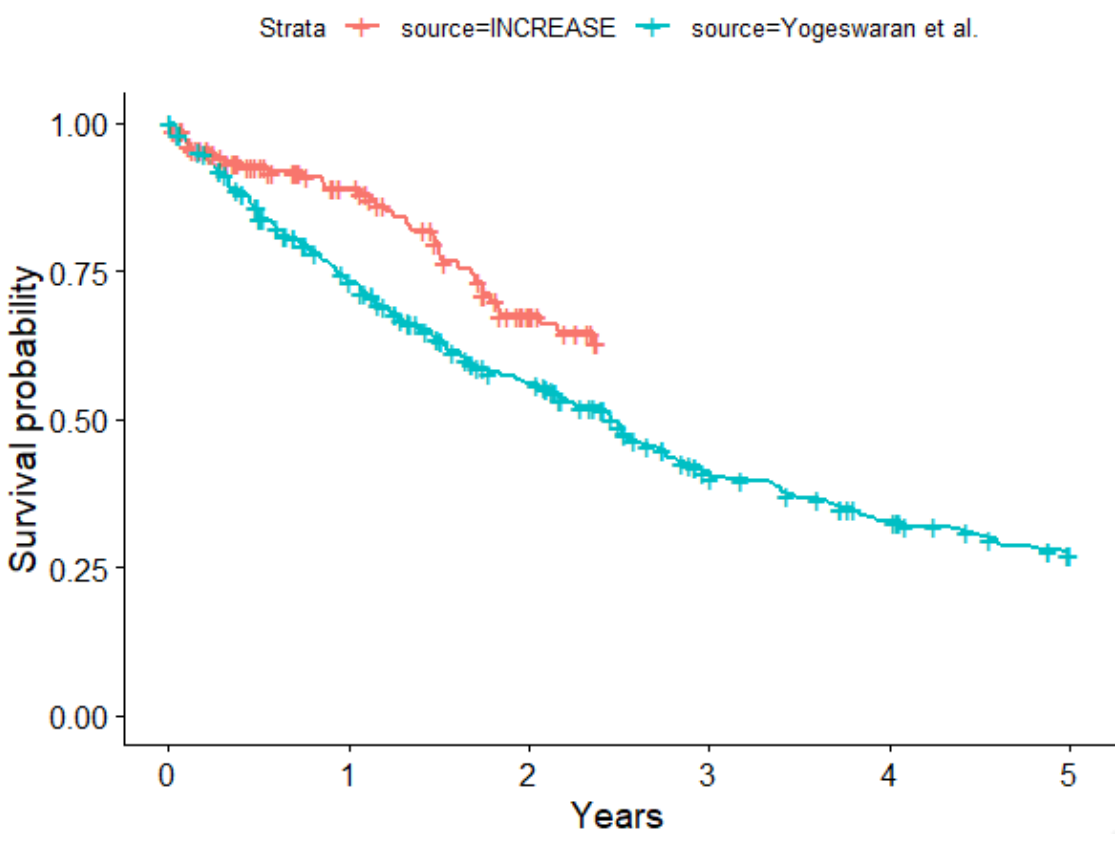

Figure 1: Comparison of overall survival from Yogeswaran PDE5i population and INCREASE treprostinil population

A Cox proportional hazards model estimated a hazard ratio of 1.58 (95% CI: 1.12, 2.24), agreeing with the company's MAIC vs Dawes et al. that treprostinil is likely to offer benefit over PDE5is, however, the magnitude of benefit is lower when using the Yogeswaran et al. data.

The EAG noted that for the comparison to Yogeswaran et al., the assumption of proportional hazards is potentially violated, as demonstrated in Figure 2 showing the Schoenfeld residual plot, where proportional hazards would be represented by a horizontal line. The test for proportionality is just above the typical 0.05 threshold. Additionally, Figure 3 shows the extrapolation of the EAG hazard ratio applied to Weibull treprostinil extrapolation, which shows how the mortality is overestimated relative to the Kaplan-Meier estimator for

Yogeswaran et al. from 3 years. Switching to the generalised gamma extrapolation for treprostinil, as preferred by the EAG, exacerbates this issue.

Hence, the EAG explores the impact of relaxing this assumption, and fitting separate parametric models to the Yogeswaran et al. data in a scenario analysis. A comparison of the AIC and BIC suggested that exponential, log-logistic, and generalised gamma were the best three fitting models. Based on the plausibility of the predictions, the EAG selects the exponential model, which was the most pessimistic of the candidate models.

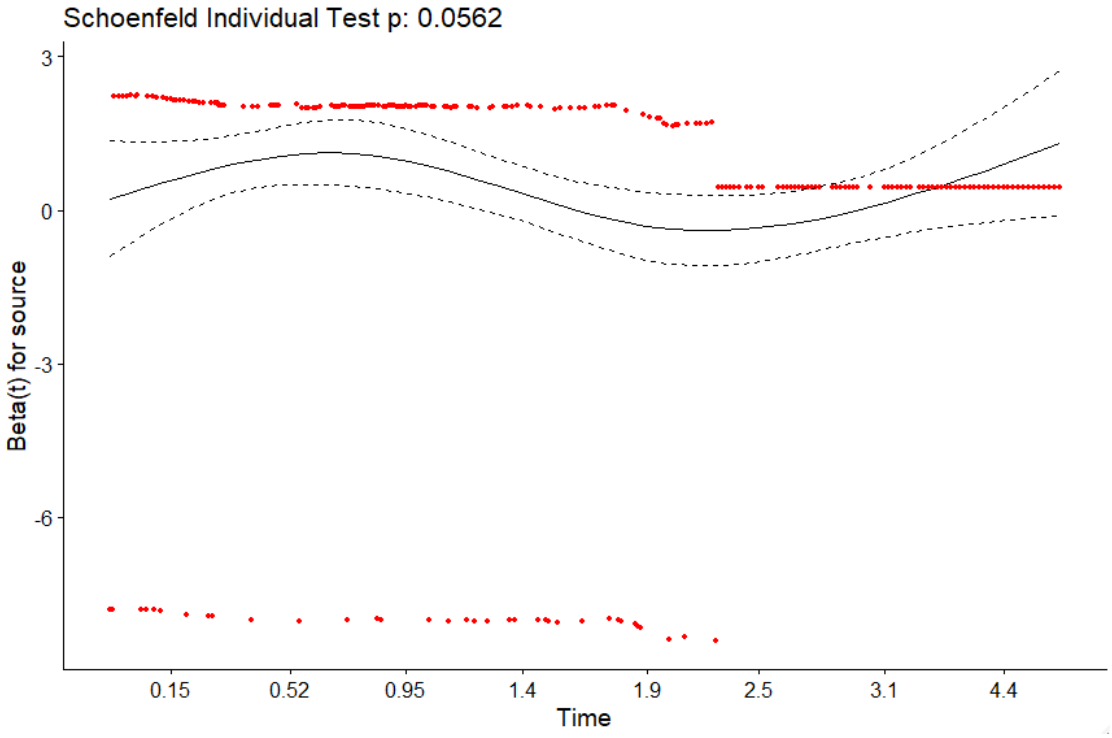

Figure 2: Schoenfeld residual plot and test for naïve comparison between INCREASE and Yogeswaran PDE5i population

Figure 3: Extrapolation of EAG hazard ratio for PDE5i applied to Weibull extrapolation of INCREASE data.

A MAIC analysis is possible, though matching would be limited to BMI, sex, oxygenation status, DLCO % predicted, NT-proBNP, FVC % predicted, mPAP, PVR, TLC % predicted, and IPF aetiology. One caveat is that some of these covariates have missing data, which may affect the robustness of the matching.

The EAG has compiled the range of OS hazard ratios relevant for the comparisons in Table 2.

The EAG is aware that a comparison of the EAG-preferred HR for PDE5is and BSC suggests that PDE5is are inferior to BSC, which is not supported by the evidence. The EAG considers that the INCREASE ITT HR comparing treprostinil to BSC is the most robust estimate, out of the two preferred by the EAG, as it relies on randomised participants. Meanwhile, the naïve comparison to PDE5i is limited due to being a naïve comparison of a real-world and trial dataset, which may explain the unexpected implied difference

between PDE5i and BSC. A high degree of uncertainty clearly remains, as the estimates vary considerably based on source and statistical adjustment. The source not represented here is the CPRD report which suggested more optimistic outcomes for people not treated with treprostinil than were observed in INCREASE for people who did receive treprostinil.

Table 2: OS hazard ratios for treprostinil relative efficacy

Source	HR	Preference
ITT HR from INCREASE (BSC)	0.71 (0.46, 1.10)	EAG preference vs BSC
RPSFT HR from INCREASE (BSC)	0.26 (0.07, 0.98)	Company preference vs BSC
IPCW HR from INCREASE (BSC)	0.62 (0.39, 0.99)	
MAIC HR vs Dawes (BSC)	0.16 (0.09, 0.28)	
Naive HR vs Dawes (BSC)	0.28 (0.19, 0.40)	
MAIC HR vs Dawes (PDE5i)	0.44 (0.24, 0.80)	Company preference vs PDE5i
Naive HR vs Dawes (PDE5i)	0.58 (0.36, 0.95)	
Naïve HR vs Yogeswaran (PDE5i)	0.63 (0.45, 0.89)	EAG preference vs PDE5i

1.3 Review of evidence for PDE5i usage

In the economic model, the company applied a weighted PDE5i usage rate of 8%, based on CPRD data (a UK real-world study by the company). However, clinical input provided to the EAG indicated that current NHS practice varies widely across centres, with usage rates reaching over 60%. The EAG's experts noted that existing guidelines do not clearly support PDE5i use,

primarily due to the absence of direct evidence from randomised controlled trials evaluating their safety and efficacy. The indirect data referenced in the guidelines are insufficient to support firm conclusions. Consequently, no recommendation has been made for or against PDE5i use in patients with ILD and severe PH; instead, referral to specialist PH centres for individualised decision-making is advised. Although PDE5is are generally considered safe and affordable, the need for frail, functionally limited patients to travel long distances for annual specialist reviews may pose additional burdens. Nonetheless, emerging evidence, such as the Yogeswaran et al. study, may prompt clinicians to use them more widely.

The EAG clinical experts noted that PDE5i contraindications are rare, typically limited to patients on nitrates for ischaemic heart disease or those with unilateral blindness, due to the small but serious risk of vision loss in the remaining eye. Patients with connective tissue disease-associated ILD often present with venous congestion, and due to their older age and higher comorbidity burden, left heart disease is more common in this group. While these factors do not preclude PDE5i use, clinicians may proceed more cautiously, often initiating therapy in an inpatient setting to monitor for pulmonary oedema. In practice, prescribing patterns are largely shaped by anecdotal experience within individual PH centres.

The EAG notes that the company previously rejected using the efficacy outcomes from the CPRD data source as it was not deemed representative of UK practice. The EAG clinical experts commented this could be down to potential mis-classification of patients. Regardless of the cause, the EAG is unclear why this source is now deemed appropriate by the company to inform PDE5i usage rates. As stated in the original EAG report, if the CPRD report was used as the source of efficacy for BSC OS, using follow-up for people with PH-ILD confirmed by RHC, and was compared naively to INCREASE trial and OLE follow-up then BSC would dominate treprostinil.

2 Cost-effectiveness analysis

2.1 Methods

The company conducted cost-effectiveness analyses comparing inhaled treprostinil with best supportive care (BSC) and phosphodiesterase type 5 inhibitors (PDE5is). Separate analyses for each comparator were combined using weighted averages of incremental costs and QALYs to estimate outcomes for mixed patient populations. The weighting reflected the proportions of patients receiving each treatment (8% or 10% on PDE5is), consistent with UK epidemiological data and NHS England budget impact estimates. Survival outcomes were modelled using either Weibull or generalised gamma distributions, with the BSC arm based on RPSFT-adjusted crossover data from INCREASE OLE. For the PDE5i comparison, a hazard ratio of 2.27 (the reciprocal of 0.44 from the MAIC) was applied to derive the PDE5i survival curve.

EAG Comment:

The company's approach to modelling mixed comparator populations (BSC + PDE5i) involves conducting separate analyses for inhaled treprostinil versus BSC and versus PDE5i, followed by post hoc weighting of total incremental costs and QALYs. Although this represents a pragmatic solution, several methodological concerns remain.

First, the assumptions regarding the proportions of patients receiving PDE5i treatment (8% or 10%) warrant further scrutiny. While these estimates are informed by CPRD and NHSE data, the company benefits from using a lower proportion. The EAG considers that a standalone analysis using PDE5is as the comparator may be more appropriate (i.e. 100% weighting), as no evidence was identified to suggest meaningful clinical or eligibility differences between patients suitable for treprostinil and those eligible for PDE5i treatment (see Sections 1.1 and 1.3 for details). Scenario analyses

incorporating 54% (based on proportion reported in Yogeswaran et al.) and 8% (company assumption based on CPRD data, the UK real-world study by the company-see section 1.3 for more details) would therefore be informative.

Secondly, in the economic model, PDE5i treatment is represented solely by sildenafil. However, only its effect on overall survival has been modelled, with the associated drug costs excluded. This omission is likely to bias the results. No other parameters were changed in the company's modelling from BSC to PDE5is, aside from the OS hazard ratio.

The company used a MAIC approach to estimate the relative efficacy of treprostinil versus PDE5is, resulting in a hazard ratio of 0.44 (treprostinil vs PDE5i). In contrast, the EAG prefers a naïve comparison between the INCREASE (treprostinil) and Yogeswaran et al. (PDE5i) populations, which yields a hazard ratio of 0.63 (95% CI: 0.45–0.89), as described in section 1.2. Ideally, treatment specific hazard ratios would also be applied to CW1 and CW2; however, due to a lack of evidence and small impact on the ICER, the EAG follows the company's use of the BSC-related trial data as a proxy for these transitions.

Finally, the company's weighting method - applying weights only to total incremental costs, QALYs, and ICER at the end of the model - oversimplifies temporal dynamics and assumes linearity of outcomes. Two key concerns arise from this approach.

First, the company effectively takes a weighted average of ICERs across subgroups (for example, patients receiving PDE5i and those not receiving it). This approach is mathematically invalid because ICERs are ratios and cannot be combined arithmetically. For instance, when using the Generalised Gamma distribution for treprostinil OS, the company's weighted ICER for the 8% PDE5i use scenario was £[redacted], derived by averaging subgroup ICERs (£[redacted] and £[redacted]). However, when recalculated correctly from the weighted incremental costs and QALYs (£[redacted] / [redacted]), the ICER falls to £[redacted]. This discrepancy illustrates that simple averaging introduces bias,

even if the difference appears numerically small at this level of PDE5i use. Importantly, the magnitude of the bias would increase with a higher proportion of PDE5i-treated patients, as the non-linearity between costs and QALYs becomes more pronounced.

Second, applying subgroup weights only at the end of the model ignores time-dependent effects. A more appropriate approach would apply the relevant subgroup weights across all model cycles- covering overall survival (OS), progression-free survival (PFS), costs, and QALYs- to ensure temporal consistency and avoid structural bias in results. Nonetheless, the EAG recognises that in this specific model, the numerical differences between the two methods (related to second concern) are minor, and therefore this issue is noted primarily as a methodological observation rather than a material driver of cost-effectiveness outcomes.

2.2 Company's cost-effectiveness results

Table 3 summarises the company's scenario analyses assessing the cost-effectiveness of treprostinil under varying assumptions regarding PDE5 inhibitor (PDE5i) use and alternative overall survival (OS) model specifications. The base-case analysis assumes that no patients receive PDE5i and all receive best supportive care (BSC) only. Scenario analyses explore the impact of different OS hazard ratios, levels of PDE5i use, and survival model choices (Weibull and generalised gamma) on incremental costs, life-years gained (LYG), quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio (ICER). In all exploratory analyses, a severity modifier of 1.2 has been applied. The company provided results only for scenarios with 8% or 10% PDE5i use, while the EAG conducted additional scenarios using the company's economic model to test the robustness of results.

Table 3. Company's scenario analyses results**

Scenarios		Incremental costs (£)	Incremental LYG	Incremental QALYs *	ICER (£/QALY at [redacted]% PAS)**	Impact
The company's base case (no patients received PDE5i, all received only BSC)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	OS-HR (Treprostinil vs PDE5i) = 0.44; all patients received PDE5i; PDE5i cost excluded, using Weibull for Treprostinil OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	OS-HR (Treprostinil vs PDE5i) = 0.44; 8% PDE5i use; PDE5i cost excluded, using Weibull for Treprostinil OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	OS-HR (Treprostinil vs PDE5i) = 0.44; all patients received PDE5i; PDE5i cost excluded, using Generalised gamma for Treprostinil OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	OS-HR (Treprostinil vs PDE5i) = 0.44; No patients received PDE5i; PDE5i cost excluded, using Generalised gamma for Treprostinil OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	OS-HR (Treprostinil vs PDE5i) = 0.44; 8% PDE5i use; PDE5i cost excluded, using Generalised gamma for Treprostinil OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	OS-HR (Treprostinil vs PDE5i) = 0.44; 10% PDE5i use; PDE5i cost excluded, using Weibull for Treprostinil OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	OS-HR (Treprostinil vs PDE5i) = 0.44; 10% PDE5i use; PDE5i cost excluded, using Generalised gamma for Treprostinil OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: OS: Overall Survival; BSC: Best Supportive Care; HR: Hazard Ratio; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; EAG: External Assessment Group.

*The severity modifier of 1.2 is applied for all exploratory analyses.

** The company provided results only for scenarios with 8% or 10% PDE5i use (remaining patients on best supportive care), whereas the EAG generated additional scenarios using the company's model.

*** Incremental costs, QALYs, and ICERs are calculated through simple weighting.

2.3 EAG's additional analyses

2.3.1 EAG's preferred scenarios

To explore the impact of key assumptions and methodological choices in the company's modelling, the EAG conducted a series of additional analyses. These analyses were designed to test the sensitivity of cost-effectiveness results to the assumed proportion of patients receiving PDE5 inhibitors (PDE5is), the inclusion of PDE5i drug costs, and the choice of overall survival (OS) hazard ratios (HRs) and survival distributions. The EAG's base case remains consistent with that presented in the final report. Details of the base case and the scenario analyses are provided below:

Base case (similar to that in the EAG final report), (OS-HR of Treprostinil vs BSC = 0.71; no patients received PDE5i.) (see table 42 in the EAG final report, section 5.2.2)

Scenarios:

1. OS-HR (Treprostinil vs PDE5i) = 0.63; all patients received PDE5i; PDE5i cost included.
2. OS-HR (Treprostinil vs PDE5i) = 0.63; 54% of patients received PDE5i; PDE5i cost included; OS-HR of Treprostinil vs BSC = 0.71.
3. OS-HR (Treprostinil vs PDE5i) = 0.63; all patients received PDE5i; PDE5i cost included, using Weibull for Treprostinil OS
4. All patients received PDE5i; PDE5i cost included, using direct extrapolation for PDE5i (exponential. rate = 0.005352) (not a HR)
5. OS-HR (Treprostinil vs PDE5i) = 0.44; all patients received PDE5i; PDE5i cost included; OS-HR of Treprostinil vs BSC = 0.71.
6. OS-HR (Treprostinil vs PDE5i) = 0.44; 54% of patients received PDE5i; PDE5i cost included; OS-HR of Treprostinil vs BSC = 0.71.
7. OS-HR (Treprostinil vs PDE5i) = 0.44; 8% of patients received PDE5i; PDE5i cost excluded (company's approach); OS-HR of Treprostinil vs BSC = 0.71.

2.3.2 Results of the EAG preferred scenarios

Table 4 presents the EAG's scenario analyses using the EAG's preferred assumptions for overall survival (OS) and treatment costs. The EAG's base-case assumes a hazard ratio (HR) of 0.71 for treprostinil versus best supportive care (BSC), with no use of PDE5 inhibitors (PDE5i). Scenario analyses explore the impact of alternative OS hazard ratios, varying proportions of PDE5i use, and inclusion of PDE5i costs, as well as different parametric survival model choices. One scenario also incorporates direct exponential extrapolation for PDE5i (rate = 0.005352) rather than using a hazard ratio. The analyses demonstrate the sensitivity of the incremental cost-effectiveness ratio (ICER) to both survival assumptions and PDE5i utilisation patterns. A severity modifier of 1.2 has been applied across all exploratory scenarios.

Table 4: Results of EAG's scenario analyses using EAG's preferred assumptions

EAG's scenario		Incremental costs (£)	Incremental LYG	Incremental QALYs *	ICER (£/QALY)**	Impact
The EAG's base case (OS-HR of Treprostinil vs BSC = 0.71; no patients received PDE5i, all received BSC)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	OS-HR (Treprostinil vs PDE5i) = 0.63; all patients received PDE5i; PDE5i cost included.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	OS-HR (Treprostinil vs PDE5i) = 0.63; 54% of patients received PDE5i; PDE5i cost included; OS-HR of Treprostinil vs BSC = 0.71.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	OS-HR (Treprostinil vs PDE5i) = 0.63; all patients received PDE5i; PDE5i cost included, using Weibull for Treprostinil OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	All patients received PDE5i; PDE5i cost included, using direct extrapolation for PDE5i (exponential. rate = 0.005352) (not a HR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	OS-HR (Treprostinil vs PDE5i) = 0.44; all patients received PDE5i; PDE5i cost included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	OS-HR (Treprostinil vs PDE5i) = 0.44; 54% of patients received PDE5i; PDE5i cost included; OS-HR of Treprostinil vs BSC = 0.71.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	OS-HR (Treprostinil vs PDE5i) = 0.44; 8% of patients received PDE5i; PDE5i cost excluded (company's approach); OS-HR of Treprostinil vs BSC = 0.71.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: OS: Overall Survival; BSC: Best Supportive Care; HR: Hazard Ratio; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; EAG: External Assessment Group.

*The severity modifier of 1.2 is applied for all exploratory analyses.

** ICERs are calculated as incremental costs divided by incremental QALYs in each scenario.

3 References

1. Nathan S, Argula R, Rajagopal S, Johri S, De La Zerda D, McGlothlin D*, et al.* Inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease: event-free survival in INCREASE study open-label extension. *Eur Respir J* 2022;**60**(suppl 66):2133. http://dx.doi.org/10.1183/13993003.congress-2022.2133

2. Dawes TJ, McCabe C, Dimopoulos K, Stewart I, Bax S, Harries C*, et al.* Phosphodiesterase 5 inhibitor treatment and survival in interstitial lung disease pulmonary hypertension: a Bayesian retrospective observational cohort study. *Respirology* 2023;**28**(3):262-72. http://dx.doi.org/10.1111/resp.14378

3. Yogeswaran A, Hassoun PM, Saleh K, Fünderich M, Balasubramanian A, Konswa Z*, et al.* Hemodynamics and phosphodiesterase-5 inhibitor treatment associated with survival in pulmonary hypertension in interstitial lung disease: a PVRI GoDeep meta-registry analysis. *Am J Respir Crit Care Med* 2025;**211**(10):1855-66. http://dx.doi.org/10.1164/rccm.202412-2371OC

Single Technology Appraisal

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease [ID6459]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 20 August 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Language describing PH-ILD

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26: Pulmonary hypertension (PH) classified as World Health Organization (WHO) Group 3 is characterised by elevated pulmonary arterial pressure and vascular resistance, typically resulting from chronic lung diseases such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD).	Pulmonary hypertension (PH) **associated with lung disease and/or hypoxia,** classified as World Health Organization (WHO) Group 3**,** is characterised by elevated pulmonary arterial pressure and vascular resistance, typically resulting from chronic lung diseases such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD).	Current wording is open to interpretation that all PH is defined as WHO Group 3. Proposed revised wording clarifies that WHO Group 3 only refers to patients with PH associated with lung disease and/or hypoxia.	The EAG accepts the suggested change.
Page 26: “Group 3 PH arises due to impaired oxygen exchange caused by these conditions, including sleep-disordered breathing.”	Remove “including sleep-disordered breathing”.	Sleep-disordered breathing has recently been reclassified and is no longer considered part of Group 3 pulmonary hypertension (European Respiratory Journal, Task Force Report, G. Kovacs et al).	The EAG accepts the suggested change.

Page 26: "**As ILD progresses, chronic hypoxia can lead to pulmonary hypertension**, placing patients in WHO Group 3, which significantly worsens prognosis and quality of life."	As ILD progresses, chronic hypoxia, **fibrosis and inflammation can lead to vascular remodelling resulting in** pulmonary hypertension, placing patients in WHO Group 3, which significantly worsens prognosis and quality of life.	Chronic hypoxia alone is not sufficient to explain pulmonary hypertension in ILD. Inflammation and vascular remodelling also play an important role in the pathophysiology of PH-ILD. The revised wording is reflective of the clinical picture, to capture the vascular remodelling of the disease.	The EAG accepts the suggested change.
Page 27: PH is reported in up to 86% of ILD patients, contributing to reduced exercise capacity, increased oxygen needs, lower quality of life, and earlier death	**Estimates of the prevalence of PH-ILD vary and may be as high as 86%, depending on the type of ILD and disease severity. Patients with PH-ILD experience reduced** exercise capacity, increased oxygen needs, lower quality of life, and earlier death **compared to those with ILD or PH alone.**	Update text on prevalence for accuracy to reflect source material and highlight that this is a maximum value reported that varies depending on the population. Specify the comparative population for the statements on burden.	The EAG accepts the suggested change.
Page 27: In PH-ILD, prognosis worsens with severe PH (mPAP ≥35 mmHg or PVR >5 Wood units), particularly in IPF	In PH-ILD, prognosis worsens **in patients with severe PH (PVR >5 Wood units)**, particularly in those with IPF.	Current European guidelines (2022 ESC/ERS) use PVR to distinguish between non-severe PH (PVR ≤5 WU) and severe PH (PVR >5 WU). mPAP is	The EAG accepts the suggested change.

		no longer recommended to assess severity.	
Page 27: This submission focuses on patients with confirmed diffuse parenchymal lung disease (DPLD), including ILD and combined pulmonary fibrosis and emphysema (CPFE), diagnosed via right heart catheterization (RHC) as part of the PH-ILD pathway	This submission focuses on patients with PH-ILD (WHO Group 3 PH), diagnosed via right heart catheterisation as part of the PH-ILD pathway.	Current wording is not accurate as the submission focusses on PH-ILD, not ILD alone, and right heart catheterisation (RHC) is used to diagnose PH in patients with ILD. The current wording states ILD is diagnosed via RHC, which is incorrect.	The EAG accepts the suggested change.
Page 27: Group 3 PH is suspected in patients with exertional shortness of breath, though symptoms often overlap with underlying lung disease. Diagnosis involves echocardiography, pulmonary function tests (PFTs) including diffusion capacity for carbon monoxide (DLCO), arterial blood gas analysis, NT-proBNP levels, electrocardiogram (ECG),	Group 3 PH is suspected in patients with ILD based on their NT-proBNP levels and/or echocardiogram results, or if they are experiencing worsening breathlessness or have high oxygen requirements. Other key diagnostic indicators are diffusing capacity of the lungs for carbon monoxide (DLCO) tests, indicating poor gas transfer; computed tomography (CT) scans showing pulmonary artery dilation or echocardiograms showing a high probability of PH.	Current wording misses that this applies in patients already with ILD, and is limiting (e.g. clinicians consider worsening breathlessness, not limited to exercise). The other tools have been defined by clinicians as diagnostic indicators rather than diagnosis, as currently only RHC allows diagnosis.	The EAG accepts the suggested change.

and contrast-enhanced computed tomography. Cardiopulmonary exercise testing (CPET), ventilation/perfusion scans, or single-photon emission computed tomography may assist in complex cases			
Page 28: PH is classified as severe if pulmonary vascular resistance (PVR) exceeds 5 Wood units (WU), mean pulmonary artery pressure (mPAP) is over 35 mmHg, or is at least 25 mmHg with a cardiac index below 2.5 liters per minute per square meter; otherwise, it is considered non-severe	PH is classified as severe if pulmonary vascular resistance (PVR) exceeds 5 Wood units (WU); otherwise, it is considered non-severe.	Current European guidelines (2022 ESC/ERS) use PVR to distinguish between non-severe PH (PVR ≤5 WU) and severe PH (PVR >5 WU). mPAP and cardiac index are no longer recommended to assess severity.	The EAG accepts the suggested change.
Page 29: “Group 1 may include patients with pulmonary arterial hypertension associated with connective tissue	Remove this sentence.	This would only be the case if the ILD is not the main cause of PH, and therefore, this sentence is not relevant here.	Not a factual error, but the EAG has revised this section of text.

disease and some interstitial lung disease”			

Issue 2 Language regarding the treatment pathway for PH-ILD

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17: “Some people with suspected or confirmed PH-ILD are **turned away from specialist centres as their disease is not severe enough**, and there is a lack of treatment options”	“Some people with suspected PH-ILD are not referred to PH specialist centres, especially if their disease is not severe, as there are no approved treatment options.”	As per clinician feedback in 2025 advisory board and input during NICE system engagement, the current wording is not accurate as patients are not “turned away” from specialist centres. The key reason for patients not being referred from ILD to PH specialist centres is that there are no approved treatment options.	The EAG has amended the text to better reflect how patients may not be referred to, or may be referred and discharged from, specialist centres.
Page 28: “The management of Group 3 PH, which includes PH associated with chronic lung diseases and/or hypoxia, **primarily** focuses on optimizing the underlying pulmonary condition”	“The management of Group 3 PH, which includes PH associated with chronic lung diseases and/or hypoxia, **currently** focuses on optimi**s**ing the underlying pulmonary condition”	Update to ‘currently’ for clarity that this is the current approach due to the lack of treatment options for the vascular component of PH-ILD, and current therapies do not target PH-specific mechanisms.	Not a factual error, but the EAG has revised this section of text.

Page 28: “This includes the use of antifibrotic or immunosuppressive agents where appropriate”	“This includes the use of antifibrotic, **parenteral cytotoxic, biological and chemotherapeutic** agents, as well as plasmapheresis and IV immunoglobulins”	Current wording is incomplete, with more treatments used in practice.	The EAG has amended the sentence.
Page 28: “Referral to specialised PH centres is strongly recommended for patients with severe PH, diagnostic uncertainty, or when considering advanced therapies.”	“Referral is typically reserved for patients strongly suspected of having severe PH who are deemed potential candidates for off-label treatment.”	The initial wording implies the existence of recommendations/guidelines on referrals, which do not exist. The clinician advisory board conducted by Ferrer in 2025 provides wording more reflective of the treatment pathway.	The EAG has removed the sentence.
Page 30: “Background treatments such as pirfenidone or nintedanib have been reported; however, data regarding the efficacy of inhaled treprostinil in combination with these or other concomitant therapies remain unavailable.”	Background treatments such as pirfenidone or nintedanib have been reported (9.2% and 13.5% respectively in INCREASE, 9.1% and 12.4% respectively in ICREASE OLE); and although no specific efficacy analyses were performed due to small patient numbers, there were no raised safety or pharmacokinetic concerns regarding co-treatment with these background therapies.	The current wording is incomplete and potentially misleading, as it implies that no data exist and may suggest that concomitant use is problematic. While no formal efficacy analyses were conducted, patients did receive background treatments and no safety or pharmacogenetic concerns were reported.	Not a factual error, but the EAG has revised this section of text.

Issue 3 Language regarding the crossover adjustment

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18: "The EAG does not consider that the assumption of a common treatment effect is supported by the data, **nor that the magnitude of the RPSFT adjustment holds any face validity"**	"The EAG does not consider that the assumption of a common treatment effect is supported by the data and considers that the magnitude of the RPSFT adjustment may lack face validity"	It is unclear whether the statement takes into account all of the available evidence. For example, the HR from the MAIC was more favourable towards iTrep and even with no adjustment for the MAIC, the HR was comparable to the RPSFT adjustment (0.28 unweighted MAIC vs 0.26 from RPSFT). The suggested revised wording corresponds to that used on page 64 of the EAG report.	The EAG has revised the text on page 64 to ensure consistency with the text of page 18. The EAG does not consider the MAIC analysis as a reliable source for comparing estimates of relative effect.
Page 63-64 "The EAG considers that the subsequent results do not show a clear benefit of treprostinil to people who switched across outcomes, and it is unclear whether a survival benefit requires adjusting."	Amend the wording to "The EAG considers that the subsequent results do not show a clear benefit of treprostinil in people who switched from placebo, and it is unclear whether a survival benefit requires adjusting."	The current wording is incorrect, as people did not switch between outcomes they switched from placebo to treprostinil.	The EAG revised the sentence to enhance clarity.

Page 64: “In response to clarification question A18, the company confirmed that no covariate adjustments or re-censoring were applied, citing that all patients became eligible for switching. They declined to provide a hazard ratio or acceleration factor to report the magnitude of the RPSFT adjustment, arguing that all placebo patients switched to treprostinil.”	Amend the wording to “In response to clarification question A18, the company confirmed that no covariate adjustments or re-censoring were applied, citing that all patients became eligible for switching. They stated that a hazard ratio for the RPSFTM-adjusted treated versus untreated populations cannot be provided as there are no RPSFTM-adjusted untreated patients, as all placebo patients switched to inhaled treprostinil.”	The suggested wording aligns with the Company response to clarification question A18.	Not a factual error. The company has misunderstood the EAG’s point. The EAG were referring to the fact that the RPSFTM generates a counterfactual event time. The company could report either the hazard ratio between the observed and counterfactual even times, or could report the acceleration factor estimated in the RPSFTM adjustment process.
Page 64: “The EAG does not agree, as not all patients enrolled into the OLE, and there is the potential for some selection bias, and considers that recensoring would be important in this	Amend the wording to “The EAG does not agree, as not all patients enrolled into the OLE, and there is the potential for some selection bias, and considers that a scenario with re-censoring would be important in this case, in line with TSD24 which states that analyses	TSD 18 does not include information on re-censoring related to RPSFT; the suggested wording aligns with TSD 24.	The EAG has amended this sentence to refer to the appropriate TSD.

case as recommended by NICE TSD 18."	should be performed with and without re-censoring."		
Page 64: "The EAG requested a comparison of the adjusted and unadjusted survival times to explore the magnitude of the adjustment."	Amend the wording to "The EAG requested a comparison of the adjusted and unadjusted survival times to explore the magnitude of the adjustment. In response to clarification question A18, the company provided a Kaplan-Meier plot comparing mortality in the RPSFT-adjusted patients versus the original placebo arm."	The current sentence is missing details of what the company provided.	The EAG has amended the text to add clarity.
Page 64: "provides a more plausible estimate of potential switching benefit"	Further detail needed on why the IPCW is considered more plausible versus the RPSFT.	Current statement is incomplete as it does not explain why this approach is considered more plausible.	Not a factual error. The rationale is discussed on pages 64–65.
Page 65: "however, the company declined to provide these analyses (clarification A17)"	"however, the company declined to provide these analyses due to the 2-stage adjustment method not being appropriate for inhaled treprostinil"	Statement is missing detail on why this was not provided. The 2-stage adjustment method is only applicable when switching occurs immediately after an appropriate secondary disease-related baseline, such as disease progression. However, all patients who received placebo during the 16-week INCREASE RCT	Not a factual error. The two stage adjustment does not require treatment switching to be anchored to disease progression, necessarily. Considering that patients in INCREASE did not have an equal number of previous clinical

		switched to inhaled treprostinil at the start of the OLE rather than this being determined by a disease-related event (e.g., disease progression).	worsenings at baseline, and the EAG considers the patients receiving placebo are unlikely to be significantly less similar at 16 weeks than at baseline. The EAG considers the point of entry into OLE could be a suitable anchoring point for a two-stage adjustment to be applied, and could utilise information on people who did not switch to treprostinil. The EAG maintains the two-stage adjustment has the potential to be useful, particularly over the RPSFTM adjustment which also struggles to adhere to its assumptions and lacks face validity. The EAG has added text to reflect the company's position.

Page 65: “The EAG rejects the RPSFT adjustment on plausibility grounds. The IPCW adjustment is more plausible”	Further detail needed on why the IPCW is considered more plausible versus the RPSFT.	Current statement is incomplete as it does not explain why the EAG consider the RPSFT not plausible and why the IPCW approach is considered more plausible.	Not a factual error. This is addressed in the preceding text of the EAG report.

Issue 4 Language regarding INCREASE RCT and INCREASE OLE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 42: “Only a small proportion of participants completed long-term follow-up (OLE phase), with varied follow-up durations. No imputation was used to account for early discontinuations, which may have included patients with clinical deterioration”.	Amend the wording to “Only a small proportion of participants completed long-term follow-up (OLE study), with varied follow-up durations. In the OLE study, no imputation was used to account for early discontinuations, which may have included patients with clinical deterioration.”	The current wording implies that no imputation was used to account for early discontinuations in the INCREASE RCT and the OLE study. However, this is only true for the OLE study. The suggested wording makes it clear that no imputation was used in the OLE study.	Not a factual error, however the EAG revised the text to improve clarity.
Page 44, Table 5: “The OLE phase has aimed to provide observational data on long-	Amend the wording to “The OLE study has aimed to provide observational data on long-term safety and efficacy in an open-label setting.”	The suggested wording aligns with trial design of the INCREASE OLE study.	Not a factual error, however the EAG revised the text to improve clarity.

term safety and efficacy in an open setting".			
Page 44, Table 5: "To detect a 30-meter difference in peak 6-minute walk distance between treprostinil and placebo groups at week 16, 314 patients were enrolled, accounting for a likely 15% dropout rate."	Amend the wording to "To detect a 30-metre difference in peak 6-minute walk distance between treprostinil and placebo groups at week 16, approximately 314 patients were randomised, accounting for a likely 15% dropout rate."	The current wording is incorrect; the suggested wording aligns with page 9 of the INCREASE RCT CSR.	Not a factual error, as language is consistent with INCREASE CSR, however the EAG revised the text to improve clarity.
Page 45: "The 350-metre baseline 6MWD threshold used for randomisation was sourced from COPD literature (clarification question A4) and may not be appropriate for PH-ILD, where prognostic indicators differ".	Amend the wording to "The 350-metre baseline 6MWD threshold used for randomisation was sourced from COPD literature and has been shown to inversely correlate with risk of hospitalisation and mortality in PH-ILD (clarification question A4)".	The current wording is misleading; the suggested wording aligns with the CS and the company response to question A4.	Not a factual error, however the EAG revised the text to improve clarity.
Page 45: "Stratifying solely by this cut-off may overlook other relevant factors such as pulmonary function (FVC, DLCO), age, sex, extent of fibrosis, and biomarkers like NT-proBNP. While the company justified this	Amend the wording to "Stratifying solely by this cut-off may overlook other relevant factors such as pulmonary function (FVC, DLCO), age, sex, extent of fibrosis, and biomarkers like NT-proBNP. While the company justified this approach based on the fact that baseline 6MWD was the key	The current wording is misleading; the suggested wording aligns with the CS and company response to question A4.	Not a factual error. In response to why other relevant prognostic factors were not included in the stratification, the small number of patients in these subgroups was

approach based on the small sample size (clarification question A4), some of these prognostic variables could have been incorporated, raising concerns about the adequacy of risk stratification".	prognostic factor expected to impact the primary outcome and the small number of patients in these prognostic groups (clarification question A4), which prevented stratification, the EAG believes some of these prognostic variables could have been incorporated, raising concerns about the adequacy of risk stratification".		noted as the reason. Minor revision made to text.
Page 57: "The EAG's clinical expert noted that in patients receiving PDE5 inhibitors—as the only comparator in the NHS—median PVR values tend to exceed 6 WU, which would be classified as severe PH according to ERS/ESC guidelines (PVR >5 WU), in contrast to the INCREASE trial population. Additionally, in the UK, right ventricular function will be assessed, although this was not part of the original trial protocol."	Amend the wording to "The EAG's clinical expert noted that in patients receiving PDE5 inhibitors, median PVR values tend to exceed 6 WU, which would be classified as severe PH according to ERS/ESC guidelines (PVR >5 WU), in contrast to the INCREASE trial population. Additionally, in the UK, right ventricular function will be assessed. This was assessed in the INCREASE trial using RHC, which was included as part of the original trial protocol."	The current wording is incorrect, as PDE5 inhibitors are not the only comparator in the NHS. Also, RHC provides haemodynamic measures which collectively inform right ventricular function, and this measurement was included in the trial protocol.	The EAG has amended the text to better reflect the EAG's understanding. It is unclear whether the company's haemodynamic measures are equivalent to measures of functionality used in UK practice.
Page 57: "The efficacy of treprostinil in the real world is potentially thus uncertain	Amend the wording to "The efficacy of treprostinil in the real world is potentially thus uncertain due to	The current wording is misleading; the suggested wording aligns with the	Not a factual error, however the EAG

due to potential interaction with other treatments. Additionally, in response to clarification question A1, the company did not provide post-hoc analyses on background treatments, citing differing mechanisms of action.”	potential interaction with other treatments. Additionally, in response to clarification question A1, the company did not provide post-hoc analyses on background treatments, stating that the low proportion of patients receiving background therapies in the INCREASE trial (overall: 22.7%, pirfenidone: 13.5%, nintedanib: 9.2%) would prevent these analyses being statistically powered, but that the treatments have differing mechanisms of action to inhaled treprostinil so are not expected to impact treatment efficacy.”	company response to question A1.	revised the text to improve clarity.
Page 59: “The primary endpoint of the INCREASE RCT, change in 6-minute walk distance (6MWD) from baseline to week 16, was later evaluated as a secondary objective in the OLE phase.”	Amend the wording to “The primary endpoint of the INCREASE RCT was the change in 6-minute walk distance (6MWD) from baseline to week 16. Change in 6MWD was later evaluated as a secondary objective in the OLE phase.”	The current wording suggests that the 6MWD was assessed after 16-weeks of treatment in the OLE. The suggested wording aligns with the trial design of the INCREASE RCT and OLE study.	Not a factual error, however the EAG revised the text to improve clarity.
Page 59: “The INCREASE trial prespecified a standard deviation of 75 meters in 6MWD to detect a 30-meter difference with 90% power	Amend the wording to “The INCREASE trial prespecified a standard deviation of 75 met**re**s in 6MWD to detect a 30-met**re** between-treatment difference with at least 90% power based on a	The current wording is incorrect; the suggested wording aligns with the trial design and what is reported	The EAG has amended this text for clarity.

(n=266), but premature discontinuations (40 treprostinil, 38 placebo) were expected to reduce the evaluable population to 248 (CSR INCREASE, p. 1473). Sponsor retention efforts lowered discontinuations to 68 (33 treprostinil, 35 placebo), resulting in 258 completions; however, the final sample remained below target, and the higher-than-expected dropout rate (21% vs. 15% projected) may have reduced statistical power and affected interpretability."	sample size of 266 patients. To account for approximately 15% of participants discontinuing the trial, 314 patients would need to be enrolled (CSR INCREASE, p. 1473). Sponsor retention efforts led to 68 discontinuations (33 treprostinil, 35 placebo), resulting in 258 completions. The final sample was below target, and the higher-than-expected dropout rate (21% vs. 15% projected) may have reduced statistical power and affected interpretability."	in the CSR for the INCREASE RCT.	
Page 68: "which may have obscured the broader extent of disease instability"	Delete this part of the sentence.	The current wording is subjective.	Not a factual error.
Page 71: "This pattern suggests that patients with more advanced disease may have been more readily labelled as experiencing an exacerbation in response to any clinical decline,	Delete sentence.	Although the statement "Acute exacerbations were determined solely by local site investigators without centralized adjudication" is supported by publications, the sentence proposing a pattern	Not a factual error. As acknowledged by the company, the sentence is supported by evidence from its

regardless of whether formal diagnostic criteria were fully met”		is subjective and not evidence-based.	publications and referenced materials.
Page 76: “Table 12 presents a summary of longitudinal changes in key pulmonary function parameters (FVC, DLCO, FEV1) over 108 weeks.”	Amend the wording to “Table 12 presents a summary of longitudinal changes from baseline in key pulmonary function parameters (FVC, DLCO, FEV1) over 108 weeks in the OLE.”	The current wording is misleading; the suggested wording makes it clear that the change from baseline data is from the start of the OLE and not from the start of the INCREASE RCT.	Not a factual error, however the EAG revised the sentence to improve clarity.
Page 76: “The observed minimum-to-maximum ranges are particularly striking and may suggest that a subset of individuals experienced marked declines in pulmonary function.”	Delete sentence.	The sentence is subjective, and not substantiated by evidence.	Not a factual error.
Page 78: “No statistically significant differences are observable between treprostinil and placebo in respiratory quality of life measures.”	Amend the wording to “No statistically significant differences are observable between treprostinil and placebo using the SGRQ.”	Current wording suggest multiple quality of life measures were used. The updated wording makes it clear that only the SGRQ was used to measure quality of life.	Not a factual error, however the EAG revised the text to improve clarity.

Page 82: “Notably, some patients—previously assigned to placebo—were hospitalised as early as [redacted] weeks following initiation of treprostinil, while others remained at risk of hospitalisation even toward the study’s conclusion.”	Amend the wording to “Notably, some patients—previously assigned to placebo—were hospitalised as early as [redacted] weeks following initiation of treprostinil.”	The company cannot clarify what data the latter part of the sentence is based on so suggest removing this.	Not a factual error, however the EAG revised the text to improve clarity.

Issue 5 Language regarding the MAIC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 88: “The EAG requested that the company repeat the MAIC analysis using information from the placebo arm of INCREASE to investigate whether the effect size might be attributable to remaining underlying differences in the populations rather than treatment with treprostinil. However, the company	Amend the wording to “The EAG requested that the company repeat the MAIC analysis using information from the placebo arm of INCREASE to investigate whether the effect size might be attributable to remaining underlying differences in the populations rather than treatment with treprostinil. However, the company declined to perform this analysis due to the immaturity of the survival data from the 16-week period of the INCREASE study, which would result in high	The current wording refers to the wrong clarification question and does not provide sufficient justification as to why the company declined to perform this analysis.	The EAG has amended the text to add greater clarity.

declined to perform this analysis (clarification A25).”	uncertainty associated with survival estimates from this time period alone (clarification A19).”		

Issue 6 Subjective language

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19, Issue 5: “explored the impact of using a Gompertz model, which is the only other plausible extrapolation”	“which is the only other plausible extrapolation, in the opinion of the EAG”	Stating that Gompertz is the only other plausible extrapolation is subjective	The EAG has clarified this was in reference to an increasing hazard rate.
Page 32: “The potential for dosing errors, particularly in the context of patient-dependent administration, raises concern, as even minor deviations may precipitate life-threatening hypotension or rebound pulmonary hypertension.”	Delete sentence.	The current statement regarding dosing errors leading to rebound pulmonary hypertension should be removed, as there is no evidence to support this for inhaled administration. Sources such as SmPC and FDA prescribing information do not describe rebound effects with the inhaled formulation, whereas such effect can be associated with subcutaneous/intravenous treprostinil formulations.	Not a factual error. Although rebound pulmonary hypertension has not been formally reported for inhaled treprostinil as a recently introduced therapy, the risk cannot be excluded. Farber et al. noted that inhaled agents such as iloprost and treprostinil, due to

			intermittent dosing and lack of overnight administration, may lead to suboptimal plasma levels and potential rebound effects if interrupted. Missing doses by patients may further increase the risk of rebound pulmonary hypertension and, in severe cases, cardiogenic shock.[1, 2]
Page 32: “challenges include the probability”	“challenges **may** include”	This wording is subjective, and no evidence is presented to support the points as challenges.	Not a factual error.
Page 33: “A recent study by Ranka et al. (2021)38 found that among 236,156 patients with cardiogenic shock, those who underwent RHC tended to be younger, with a mean age (SD) of 61.6 (14.4) years compared to 67.3 (14.3) years in the non-RHC group. The study also reported that RHC use in the	Delete sentences.	Evidence in patients with cardiogenic shock is not considered generalisable to patients with PH-ILD. This information is therefore not considered appropriate for inclusion in the report as there is no evidence to support extrapolation of data in cardiogenic shock to PH-ILD.	The EAG has removed this section of text.

context of cardiogenic shock was associated with improved survival.”			
Page 40 “The comparator arm was broadly defined, with limited detail provided, which may affect the clarity of comparisons”	Amend the wording to: “The comparator arm was broadly defined, which may affect the clarity of comparisons.”	Given the relative paucity of data from any interventions in the target population, the comparator arm was deliberately broadly defined to pick up any clinical study in the target PH-ILD population. This was intentional, as our review aimed to be comprehensive and inclusive by allowing “any” interventions and comparators. This approach ensured we captured all relevant evidence, regardless of comparator type. While this breadth may reduce the specificity of direct comparisons, it aligns with our objective to synthesise findings across a wide range of study designs and settings. We would contest the assertion that limited detail was provided as the comparator was defined as "any pharmacological	Not a factual error. The eligibility criteria should stem from the review question, decision problem and should provide sufficient detail to enable judgement about whether the studies that are included/excluded were considered justly.

		intervention" in the PICOS table and the search terms were deliberately (and transparently) not restrictive with regard to the comparator.	
Page 41 “and may not have fully captured relevant evidence, particularly from earlier conference abstracts, non-randomised or single-arm trials, or broader PH populations”	Amend the wording to: “…and may not have fully captured relevant evidence, particularly from broader PH populations”	Conference abstracts were not excluded from Embase. In total, 899 conference abstracts were retrieved from Embase and screened as part of the review, ensuring that relevant evidence from earlier conference proceedings was considered. Furthermore, the search strategy employed the SIGN filters (both for RCT or observational studies), which is not restricted to randomised controlled trials and includes terms for a wide range of study designs. Specifically, it incorporates indexing and text word terms for non-randomised designs such as cohort, case-control, cross-sectional, observational, longitudinal, and retrospective studies, as well as broad clinical	No amendments needed. Whilst the EAG agrees that Embase is a valuable source of conference abstracts, it does not include all conferences from all years, so additional targeted hand-searching may have been useful. Neither of the search filters used are designed to capture prospective, interventional but non-randomised studies, such as phase I/II trials, which would have been valid for inclusion in the SLR.

		trial terms that capture uncontrolled and single-arm trials. This approach ensured that relevant non-randomised and single-arm trials were identified and screened.	They do not include terms such as “comparative studies” or “evaluation studies”, which are used in Waffenschmidt et al’s validated study filter for controlled non-randomized studies.[3] Additionally, the SIGN filters have not been validated in an experimental study and: “SIGN's filters may provide less sensitive searches than used by other systematic reviewers such as The Cochrane Collaboration”[4] As written in the EAG report Appendix 7.1, “Given the inclusion of most study types in the SLR, the

			sensitivity of the PubMed and Embase searches could have been improved by not using study type filters at all, but rather excluding unwanted publication types such as case reports, bibliographies and editorials."
Page 41: "The use of the JBI checklist may have underestimated bias due to its lack of depth compared to Cochrane's recommendations."	The use of the JBI checklist may result in a different assessment of bias from Cochrane's recommendations.	We acknowledge that the JBI critical appraisal tools are less fine-grained in certain domains compared to the Cochrane Risk of Bias tool. The JBI checklist was selected because our review included a mix of study designs (randomised, non-randomised, and observational), and JBI provides validated, design-specific tools applicable across this range. This allowed for consistent and comparable assessment of methodological quality within the scope and resources of our review. While the JBI approach may be less detailed in some domains, it	Not a factual error. It would have been preferred to use Cochrane's recommended risk of bias tools for each type of study design (such as RoB2, ROBINS-I, ROBINS-E, etc.). On the differences between JBI and Cochrane risk of bias tools, please refer to Domain 3 in Appendix

		remains a widely recognised and rigorous method for assessing risk of bias, and its use was appropriate for the diverse evidence base in our review. The exact effect of the differences between the JBI and Cochrane bias assessment instruments has not, to the best of our knowledge, been quantified and the proposal that the JBI critical appraisal tools "may have underestimated bias" is therefore subjective.	7.1 of the EAG's report.
Page 41: "Key sources such as trial registries and HTA databases were not considered"	"Key sources such as HTA databases were not considered"	Trial registries were covered in our searches. Cochrane Central (CENTRAL) includes records from major trial registries such as ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), which together capture a wide range of national and international trial registries. While HTA reports may cite clinical trials, these databases	Cochrane CENTRAL is a bibliographic database containing records from various sources, including Clinicaltrials.gov and WHO ICTRP, but is not in itself a trial registry.[5] Authorities such as the Cochrane Handbook recommend searching source trial registries

		are not designed to systematically index or capture individual trial records in the way that trial registries or bibliographic databases do. As such, they would not be a primary source for trial identification, and searching them would be unlikely to identify additional trials beyond those retrieved through our existing strategy, which included Cochrane Central (covering major trial registries).	(clinicaltrials.gov and WHO ICTRP at a minimum).[6] Limitations of Cochrane CENTRAL compared to source registries include the time taken for records to appear and fewer content fields.[7] The EAG acknowledges that HTA reports may have had limited usefulness for the clinical effectiveness SLR.
Page 60: "The EAG presents the most relevant representation of this outcome, using mean change from baseline instead of absolute score, the latter of which is more prone to bias from non-random missing data."	Amend the wording to "The EAG presents what it considers to be the most relevant representation of this outcome, using mean change from baseline instead of absolute score, the latter of which is more prone to bias from non-random missing data."	Make it clear that this is the opinion of the EAG, as the other representations of the outcome are also relevant.	Not a factual error.

Page 68: “At the time of protocol development, harmful effects of treprostinil in patients had not been anticipated—an oversight that, in retrospect, may have contributed to treatment-related risks.”	Amend the wording to “At the time of protocol development, harmful effects of treprostinil in patients had not been anticipated.”	The latter part of the sentence is conjecture and not supported by evidence.	Not a factual error.
Page 79: “Furthermore, the imputation strategy employed for handling missing 6MWD data warrants careful scrutiny.”	Amend the wording to “Furthermore, the imputation strategy employed for handling missing 6MWD data is associated with uncertainty.”	The current wording is subjective and misleading.	Not a factual error.
Page 81: “The interpretability of the 16-week INCREASE trial findings is inherently constrained by the limited duration of follow-up.”	Amend the wording to “The interpretability of the 16-week INCREASE trial findings are limited due to the duration of follow-up.”	The current wording is conjecture and not supported by evidence.	Not a factual error.
Page 81: “During the OLE phase, where both arms received the same intervention, discontinuation rates rose markedly, reaching as high as [redacted]%, a figure that warrants careful consideration.”	Amend the wording to “During the OLE phase, where both arms received the same intervention, discontinuation rates reached as high as [redacted]%.”	The current wording to describe the increase in discontinuation rates is conjecture and not supported by evidence.	The EAG has amended the text for clarity.

Page 91: "…only title and abstract fields are searched for the disease terms…"	"…only title, abstract, and index term fields are searched for the disease terms…"	As stated, this is not correct. Appendix tables 9, 13, and 18 in the original submission include both the Idiopathic Pulmonary Fibrosis and Hypertension, pulmonary MeSH terms. Appendix tables 10, 14, and 19 include the corresponding Emtree index terms "fibrosing alveolitis" and "pulmonary hypertension".	Text amended to clarify that the statement was related to the CS statement about the fields searched for free text terms. "only title and abstract fields are searched for the **free text** disease terms,"
Page 99 "This convergence indicates that TTD assumptions falling below CW2 (or lower than CW1) may be inconsistent with trial evidence"	Remove this sentence.	Clinical worsening events are only one possible reason for treatment discontinuation (i.e. they are not the only reason to justify discontinuation, nor are they always sufficient) and the suggestion that the TTD curve should never fall below the *second* clinical worsening event model curve appears to be neither evidence-based nor informed by the INCREASE trial design. The note that this "may be inconsistent with trial evidence" is therefore unfounded. As the concern	The EAG has amended this text to better communicate the issue.

		raised is based on extrapolated data, the “TTD assumptions falling below CW2” may or may not be inconsistent with trial evidence, but any convergence of the TTD and CW2 curves does not support either position.	
Page 101 “Using a per-cycle discount rate deviates from the guideline as it splits the annual discount rate into smaller time intervals (7 days), potentially leading to inconsistencies in discounting across the model's time horizon.”	Amend the wording to “Using a per-cycle discount splits the annual discount rate into smaller time intervals (7 days), leading to earlier discounting of outcomes than an annually applied discount rate”	Discounting on a weekly basis would not lead to any “inconsistences across the model time horizon”, but would rather only start discounting outcomes within each year rather than starting to discount outcomes only after a full year (and then each subsequent year) has elapsed. Whether this deviates from the NICE guidelines is subjective as the annual rate in use is still 3.5% (i.e. costs and effects after 1 year are still valued at 96.5% of the present-day costs and effects with a weekly cycle length). The converse (changing the rate only in annual intervals) could quite easily be argued to	The EAG has revised the text to clarify this point.

		be unrealistic, as it leads to values at week 51 still being valued at 100% of the present-day value, while costs at week 53 would be valued at 96.5% of the present-day value.	

Issue 7 Data and omission errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Issue 1: "It is unknown whether treprostinil would be more or less cost-effective against PDE5is"	Add "compared with best supportive care" to the end of this sentence.	Context of the relative comparison being referred to here is missing.	The EAG has amended the text.
Page 18, Issue 4: "A naïve comparison of INCREASE to the CPRD study is the only way to explore using this alternative source, **as the company did not complete a MAIC"**	Add "using the CPRD study" to the end of this sentence.	Additional wording needed for clarity that the company did complete a MAIC, but not using the CPRD study.	The EAG has amended the text.
Page 18, Issue 4: "The company could implement a MAIC adjusting for age and	Add "however, no further data are available to match between the populations so this MAIC would be	Additional context needed to adequately encompass that such an approach would be	The EAG has amended the text.

sex differences between the two sources."	subject to substantial limitations/uncertainty" at the end of the sentence.	associated with considerable uncertainty.	
Page 32: "This is driven by the historical lack of licensed treatments and logistical barriers"	Remove "historical".	These are current challenges in the landscape, not historical.	The EAG has made the requested adjustment.
Page 47 of the EAG report states "Reasons included adverse events (13.5% vs. 10.4%), death (3.1% vs. 4.3%), protocol violations (2.5% vs. 3.1%), and other causes (5.5% in both arms)."	Update the percentages to the correct values presented in Table 10-1 of the INCREASE CSR to state "Reasons included adverse events (9.8% vs. 8.0%), progressive disease (3.7% vs. 6.1%), death (3.7% vs. 3.1%), withdrawal by subject (4.3% vs. 5.5%), protocol violations (1.8% vs. 0.0%), and other causes (1.2% vs. 0.6%)."	Reasons for discontinuation currently presented for the INCREASE trial are incorrect and need to be updated to align with the INCREASE CSR and CS document.	The EAG has amended the proportions to be in line with the CSR, Table 10-1.
Page 47 of the EAG report states "By study end, 80.6% reached at least 9 breaths (suggested optimal dose) four times daily, though 20% did not exceed this dose and only [redacted] surpassed 15, suggesting tolerability limitations. The maximum recommended dose is 12 breaths per session, four	Update the percentage of patients in the OLE who achieved a maximum dose of 15 or more breaths per session to the correct values presented in Table 12-2 of the OLE CSR to state "By study end, 80.6% reached at least 9 breaths (suggested optimal dose) four times daily, though 20% did not exceed this dose and only [redacted] surpassed 15, suggesting tolerability limitations. The maximum recommended dose is 12	The values currently presented for the percentage of patients in the OLE who achieved a maximum dose of 15 or more breaths per session at the end of the study are incorrect and need to be updated to align with the OLE CSR.	The EAG has amended this text for clarity.

sessions daily (CS, doc B, Table 2)."	breaths per session, four sessions daily (CS, doc B, Table 2)."		
Page 75, Table 13 of the EAG report states that the DLCO change from baseline for the placebo group at week twelve was [redacted].	Update the change from baseline to the correct values presented in Table 14.3.3.6 in the OLE CSR to state [redacted].	The value currently presented for the DLCO change from baseline for the placebo group at week twelve is incorrect and needs to be updated to align with the OLE CSR.	The EAG amended the figure.
Page 76: "Taken together, while median values at the group level do not indicate a clear trend"	Change to "Taken together, while median values at the group level **from the OLE** do not indicate a clear trend"	Added wording for clarity.	The EAG has amended the text for clarity.
Page 77, Table 17 of the EAG report presents the LS mean difference in SGRQ at Week 16 from the INCREASE RCT underneath the columns for both INCREASE and INCREASE OLE.	Present the LS mean difference in SGRQ at Week 16 from the INCREASE RCT underneath the columns for INCREASE only and report N/A underneath the columns for INCREASE OLE.	The LS mean difference in SGRQ at Week 16 from the INCREASE RCT is reported underneath the columns for both INCREASE and INCREASE OLE, so it is not clear which study this is from.	The EAG has amended table 14 for clarity.
Page 83, Table 16 of the EAG report states that the median (min, max) duration (in days) of hospitalisations due to cardiopulmonary	Update the median (min, max) duration of hospitalisations due to cardiopulmonary indications for placebo patients to [redacted].	The value currently presented for the median (min, max) duration of hospitalisations due to cardiopulmonary indications for placebo	The EAG has replaced the reported values (interquartile) with the

indications for placebo patients during the INCREASE RCT was [redacted].		patients in the INCREASE RCT is incorrect and needs to be updated to align with the INCREASE CSR.	min-max reported in Table 14.2.3.2.

Page 85, Table 18 of the EAG report states that is presents a summary of the TEAEs by system organ class and preferred term. However, only 2 system organ classes are included in the table and the rest have not been included. Also, Table 18 seems to present the TEAEs occurring in >10% of patients in any treatment group. However, not all relevant TEAEs occurring in >10% of patients from Table12-4 of the INCREASE CSR and Table12-4 of the OLE CSR are included.	Update Table 18 to align with Table12-4 of the INCREASE CSR and Table12-4 of the OLE CSR to include details of system organ class and TEAEs occurring in 10% of patients in any treatment group. Also, make sure the CIC marking aligns with data presented Table 3 of the Waxman et al. 2021 publication and Table 2 of the Waxman et al. 2023 publication.	Currently, Table 18 does not include all of the relevant data and needs to be amended to align with the INCREASE and OLE CSRs.	The EAG has chosen to report events based on their frequency for all patients where data is available. To avoid confusion, Table 18 has been updated to ensure consistency in reporting events from similar sources wherever possible, except in cases where preferred groupings, such as infections and infestations or neoplasms, were used.
Page 85, Table 18 of the EAG report states that, in the INCREASE RCT, the percentage of patients who experienced diarrhoea [redacted] for those receiving inhaled Treprostinil, and [redacted] for those receiving placebo. These data are incorrect	Update the percentage of patients who experienced diarrhoea in the INCREASE RCT to 13.5 for those receiving inhaled Treprostinil, and 11.7 for those receiving placebo and unmark the data.	The percentage of patients who experienced diarrhoea in the INCREASE RCT is incorrect and need to be updated to align with the CS document. Also, the data should not be marked as confidential.	Following the previous query, the EAG has updated Table 18 to report events from similar sources.

and should also not be marked as confidential.			
Page 106, “The EAG prefers to use a log-logistic model for both arms which is among the best fitting models for both arms and is consistent with guidance from Technical Support Document 14 which suggests using models of the same type”	Add “, although results in 1.5% of patients in the BSC arm being free of any clinical worsening event after 3 years, which is contrary to expert clinical opinion.”	Expert clinical input solicited during model development indicated that no patients would be free of any clinical worsening event after 3 years.	Not a factual error. The EAG’s clinical experts did not raise this objection.
Page 109, omission of goodness-of-fit statistics indicating that the EAG preferred model has the worst statistical fit to the OS data in the BSC, and consistently ranks poorly	Add AIC and BIC rankings of the generalised gamma and Gompertz models, particularly in the BSC arm where both models are ranked as the fourth to sixth best fit (of six) by both AIC and BIC.	The generalised gamma model, while preferred by the EAG, has the worst statistical fit of all models to the OS data in the BSC arm by BIC, and ranks fifth (of six) in the inhaled treprostinil arm by BSC. By AIC, the same model ranks fourth and fifth (of six) in the BSC and inhaled treprostinil arms, respectively.	Not a factual error. The EAG is unclear how the fit to BSC is relevant given that the EAG implements a hazard ratio applied to the treprostinil extrapolation, and does not use models fitted to BSC data provided. Information on goodness-of-fit statistics is already reported in the company submission,

			and the EAG avoids unnecessary repetition. The EAG notes that the Gompertz model is the best fitting model according to AIC for treprostinil OS, whilst the fit of the generalised gamma model is not meaningfully different from the company's preferred Weibull model.

Issue 8 Minor typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Table 1: "Error! Reference source not found"	Update cross-referencing	Minor cross-referencing error	The cross-reference has been updated.
Page 17: "Error! Reference source not found"	Update cross-referencing	Minor cross-referencing error	The cross-reference has been updated.

Page 28: “Below 2.5 liters”	2.5 litres	Align with UK spelling	In response to Issue 1, this part of text has been removed.
Page 29: “efficacy and tolerability in PAH patients[17] Although”	“efficacy and tolerability in PAH patients**.**[17] Although”	Minor typographical error: period missing between patients and reference 17	The typographical error has been resolved.
Page 31: “Treprostinil or Tyvaso is a type of …” Repeated several times on pages 30, 42, 53 (section 3.2.4, Table 7), pages 78, 81, 82, 84, 85 (including Table 18), 86, 105 (throughout section 4.2.5), 112 (throughout section 4.2.5.3), pages 121,134 ,145 (Table 42), 148, 152	Inhaled treprostinil or Tywazo	Correct brand (only page 30) and non proprietary name across cited pages	All brand names and instances of ‘treprostinil’ have been replaced with ‘inhaled treprostinil’.
Page 51-52: “ILD-PH”	Update to PH-ILD	Align acronym with the rest of the EAG report and CS documents	This is not a factual error. The statement aligns with the source under discussion and uses phrasing taken directly from Dawes et al.

Page 61: “Figure 3: Change in baseline 6-minute walking distance from INCREASE. (CS Figure 12b)”	Update Figure title to “Figure 3: Change in baseline 6-minute walking distance from INCREASE RCT to end of the OLE (CS Figure 12b)”	Not clear which study the figure is related to	Not a factual error. The studies are identified in the figure with specified follow-up points. Furthermore, the figure does not include all follow-up from the OLE as suggested by the company.
Page 61: Figure 4: Mean change from baseline in 6MWD (metres) by visit (CSR OLE Figure 14.2.1)	Update Figure title to “Figure 4: Mean change from baseline 6MWD (metres) in the OLE by visit (CSR OLE Figure 14.2.1)	Not clear which study baseline data the figure is related to	This is not a factual error; the source of the data is clearly noted in the parentheses.
Page 63: Figure 5: Kaplan-Meier plot of overall survival from INCREASE	Update Figure title to “Figure 5: Kaplan-Meier plot of overall survival from INCREASE RCT and the OLE	Not clear which study the figure is related to	The changes have been made as suggested.
Page 64: Missing cross referencing “(see Figure 3)”	Add cross-referencing	Add cross-referencing to correct figure, currently no cross reference included	The cross-reference has been updated.
Page 68: Missing cross referencing “The EAG presents graphical representation of the CW outcome, which uses data	Add cross-referencing to Figure 8 updating the text to: “The EAG presents graphical representation of the CW outcome, which uses data from the trial and OLE periods of INCREASE (Figure 8).	Add cross-referencing to correct figure	The cross-reference has been updated.

from the trial and OLE periods of INCREASE."			
Page 70: "Table 10: Number of disease progression events by treatment arms (copied from Table 2 of Nathan et al. 2021 by 16 weeks follow-up)"	Update Table title to "Table 10: Number of disease progression events by treatment arms in the INCREASE RCT (copied from Table 2 of Nathan et al. 2021 by 16 weeks follow-up)"	Not clear which study the Table is related to	The table's title was updated for clarification.
Page 72, "Figure 9 Kaplan–Meier estimates of time to first and second disease progression (≤16 Weeks): inhaled treprostinil vs. placebo (copied from company Figure 11)"	Update Figure title to "Figure 9 Kaplan–Meier estimates of time to first and second disease progression in the INCREASE RCT (≤16 Weeks): inhaled treprostinil vs. placebo (copied from CS Figure 11)"	Not clear which study the figure is related to and which document the figure was copied from	Figure 9's title has been revised to improve clarity.
Page 81, Table 15: the footnote [a] is included in the 'total' row of the 'overall' column for the INCREASE OLE.	Move the footnote [a] to the 'other' row of the 'overall' column to align with the INCREASE OLE CSR.	The footnote relates to the other row not the total row	The footnote has been amended.
Page 101: "Key baseline characteristics are directly derived from the INCREASE trial. (see Table 22)."	Amend to "Key baseline characteristics are directly derived from the INCREASE trial (see Table 22)."	Remove full stop	The changes have been made as suggested.

Page 101: “nice guidelines”	Update to: **NICE**	Change to capitals	The changes have been made as suggested.
Page 104: “However, the EAG acknowledges that any comparison would be reliant on MAIC or similar methodology due a lack of direct evidence”	Change to “or similar methodology due **to** a lack of direct evidence”	Missing word	The changes have been made as suggested.
Page 114: “SGRQ data were stratified by clinical worsening (CW) health states: clinical worsening free (CWF), one event (CW1), and two or more events (CW≥2).(see Table 29)”	Amend to “SGRQ data were stratified by clinical worsening (CW) health states: clinical worsening free (CWF), one event (CW1), and two or more events (CW≥2) (see Table 29).”	Move full stop to end of sentence	The changes have been made as suggested.
Page 117: “The EAG criticised the univariate approach for several reasons”	“The EAG criticised the choice of the SGRQ for several reasons”	This sentence is a prelude to critique of the SGRQ, not the choice of a univariate model	This is not a factual error. No change made.
Page 119: “To ensure consistency with population-level HRQoL trajectories, EQ-5D values were adjusted for age and gender using estimates from the Health Survey for England and	Amend to: “To ensure consistency with population-level HRQoL trajectories, EQ-5D values were adjusted for age and gender using estimates from the Health Survey for England and methods described by Hernández-Alava (2022).[60]”	Move full stop to end of sentence	The changes have been made as suggested.

methods described by Hernández-Alava.(2022)[60]"			
Page 122 of the EAG report, Section 4.2.7.1, second paragraph is missing a table reference "The company stated that patients in the BSC arm (placebo) received no treatment other than background medications for ILD management, with a higher baseline use of pirfenidone and nintedanib compared to the treprostinil arm (see Table **xx**), reflecting INCREASE trial data."	Missing table reference	Add cross-referencing to correct table	The changes have been made as suggested.
Page 131: "The company included the wheelchair costs due to NHS funding, cover non-powered (£712.34 upfront, £3.76/week maintenance) and powered wheelchairs (£1,219.12 upfront, £16.08/week maintenance), applied after the first clinical worsening event (e.g., 30% non-	Missing table reference and full stop not at the end of the sentence	Add cross-referencing to correct table and move full stop to end of sentence	The changes have been made as suggested.

powered, 20% powered for 6MWD ≥15% or exacerbation).(see table xx)”			
Page 143: “Table and Table present the revised version of the company’s base case, with the misapplication of the severity modifier and the inconsistency in PSA results resolved”	Update cross-references to relevant tables.	Update cross-referencing error	The changes have been made as suggested.
Page 158: Summary of QALY shortfall analysis (obtain from the CS, section 3.7)”	Update cross-reference to ‘**section 3.6’**	Update cross-referencing error	The changes have been made as suggested.
Page 160 of the EAG report, Line 17, update cross-referencing, currently reads “**Error**! Reference source not found”	Cross-reference error	Update cross-referencing error	The changes have been made as suggested.

Issue 9 Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 48	The EAG report currently states "[redacted]% (68/326) of subjects in the randomized phase had at least one major protocol deviation, compared to [redacted]% (21/242) in the OLE phase (CSR INCREASE, p. 304; CSR OLE, p. 572), with the total number of subjects with any protocol deviation declining from [redacted] to [redacted]." The total number of subjects who had at least one major protocol deviation in both the INCREASE RCT and the OLE need to be marked confidential.	Update the marking to "[redacted]% ([redacted]/326) of subjects in the randomized phase had at least one major protocol deviation, compared to [redacted]% ([redacted]/242) in the OLE phase (CSR INCREASE, p. 304; CSR OLE, p. 572), with the total number of subjects with any protocol deviation declining from [redacted] to [redacted]".	The confidentiality markings have been updated.
Page 49	The EAG report currently states "Precisely, 47 deviations deemed major in INCREASE were reclassified as non-major in the unblinded OLE phase". The number of deviations	Update the marking to "Precisely, [redacted] deviations deemed major in INCREASE were reclassified as non-major in the unblinded OLE phase" and confirm where the number is from or delete from the report.	The confidentiality markings have been updated.

	needs to be marked confidential.		
Page 53, Table 7	Table 7 of EAG report currently states that, in the INCREASE RCT, the mean (SD) age of patients at baseline was [redacted] for inhaled Treprostinil and [redacted] for placebo. The mean age for patients in both groups is presented in Waxman et al. 2021 so does not need to be marked confidential.	Update the marking for mean (SD) age of patients at baseline to "65.6 [redacted] for inhaled Treprostinil and 67.4 [redacted] for placebo"	The confidentiality markings have been updated.
Page 53, Table 7	Table 7 of EAG report currently states that, in the INCREASE RCT, the mean (SD) PCWP (mmHg) of patients was 10.1 (3.4) for inhaled Treprostinil and 9.6 (3.5) for placebo. The SD for both groups is not published and needs to be marked confidential.	Update the marking for the mean (SD) PCWP (mmHg) to "10.1 ([redacted]) for inhaled Treprostinil and 9.6 ([redacted]) for placebo"	The confidentiality markings have been updated.
Page 62, Table 8	Table 7 of EAG report currently presents the Hodges-Lehmann estimator (week 16) as 21.0 [95% CI 7.0-37.0, p-value 0.0043]. This is not published	Update the marking Hodges-Lehmann estimator (week 16) to "[redacted]"	The confidentiality markings have been updated.

	and needs to be marked confidential.		
Page 84, Table 17	Table 17 of the EAG report presents the percentage of patients who have had at least one AE as [redacted] for inhaled Treprostinil and [redacted] for placebo in the INCREASE RCT and as [redacted] for all patients in INCREASE OLE. These data are published and do not need to be marked confidential.	Update the marking for the percentage of patients who have had at least one AE to "93.3 for inhaled Treprostinil and 91.4 for placebo in the INCREASE RCT and 94.6 for all patients in INCREASE OLE"	The confidentiality markings have been updated.
Page 84, Table 17	Table 17 of the EAG report presents the percentage of patients who have had at least one SAE as [redacted] for inhaled Treprostinil and [redacted] for placebo in the INCREASE RCT and as [redacted] for all patients in INCREASE OLE. These data are published and do not need to be marked confidential.	Update the marking for the percentage of patients who have had at least one SAE to "23.3 for inhaled Treprostinil and 25.8 for placebo in the INCREASE RCT and 55.0 for all patients in INCREASE OLE"	The confidentiality markings have been updated.
Page 84, Table 17	Table 17 of the EAG report states that, in INCREASE OLE, the percentage of patients who had at least one AE leading to withdrawal was [redacted]. This data	Update the marking for the percentage of patients who had at least one AE leading to withdrawal to "22.3"	The confidentiality markings have been updated.

	is published and does not need to be marked confidential.		
Page 85, Table 18	Table 18 of the EAG report states that, in the INCREASE RCT, the percentage of patients who experienced headache [redacted] for those receiving inhaled Treprostinil, and [redacted] for those receiving placebo. The table also states that, in the INCREASE OLE, the percentage of patients who experienced at least one AE was [redacted]. These data are published and do not need to be marked confidential. The table also states that, in the INCREASE OLE, the percentage of patients who experienced chest pain was 9.9%. This is not published and needs to be marked confidential.	Update marking for the percentage of patients who experienced headache in the INCREASE RCT to “27.6 for those receiving inhaled Treprostinil, and 19.6 for those receiving placebo” Update marking for the percentage of patients who experienced at least one AE in the INCREASE OLE to “94.6” Update the marking for the percentage of patients who experienced chest pain in the INCREASE OLE to “9.9%”	The confidentiality markings have been updated.

Page 109, Figure 13	Figure 13: Time to second clinical worsening event for people who had a first clinical worsening event – this figure was provided as response to clarification question A13. This is not published and needs to be marked confidential.	Update the confidential marking for Figure 13	The confidentiality markings have been updated.
Page 122 Table 31. Table 31 of the EAG report states that [redacted] and [redacted] patients received pirfenidone and nintedanib as background medication.	The proportion of patients was marked confidential in the submission but not in the EAG report. It needs to be marked as confidential.	Update the confidential marking for the percentage and number of patients receiving pirfenidone "[redacted]" and nintedanib "[redacted]"	The confidentiality markings have been updated.

References

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Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name: **Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease**
Topic ID: **ID6459**
Managed Access Lead: **Sarika Paul**
Date of assessment(s): **07/10/2025**

Feasibility of successful managed access	Comments / Rationale	
Committee judgement required	**Rationale for rating**	The company have submitted a managed access proposal that may help resolve some uncertainties identified by the EAG. The committee will need to discuss if a period in managed access would be helpful in resolving uncertainties, or if this can be managed during committee discussion.
	Previous ratings and rationale for change	

Managed Access Proposal	Yes	
Managed Access Team input at Committee meeting	High	Managed access team will be present at the committee meeting and will be available to provide information during committee discussions about managed access.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	This is a severe disease with no approved treatments. There is a managed access proposal, which focuses on using an NHS registry for data collection on HRQoL, and clinical outcomes.
Are there outstanding uncertainties that could be resolved with further data collection?	Medium	The company has submitted a managed access proposal which would provide addittional data to help resolve the uncertainties around overall survival, clinical worsening, and health related quality of life. These are a number of key uncertainties identified by the EAG, but other uncertainties remain which cannot be resolved with further data collection. Committee discussion will be required to determine if the uncertainties that remain after committee meetings can be resolved by the proposed data collection.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Yes	There are no onging studies for this technology. The company submitted a managed access proposal listing a NHS based UK registry from the Royal Brompton Hospital pulmonary hypertension centre. The data items collected will provide further information on time to next clinical worsening and health related quality of life. The registry data can be linked to HES and NHS spine data to obtain overall survival information. The registry is in current use, and has agreed with the company to be part of a managed access agreement. It is likely that further data collection will help resolve some of the uncertainties identified.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	High	The company have submitted a managed access proposal which includes using data from the Royal Brompton Hospital pulmonary hypertension registry, and have gotten agreement from the registry to be involved in a managed access agreement. The registry has not got experience with managed access, but the data items collected are relevant, and linkages to HES and NHS spine data are possible to obtain mortality data at the end of the managed access period.

Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	The company has confirmed with the data registries that they are willing to be part of an MAA, and while they are new to managed access, the data items collected are relevant.

Key questions for committee if Managed Access is considered	
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Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
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Commissioner Ops Briefing

Explanation

This page guides the discussion between the Managed Access Team and partner organisations at Managed Access Operational meetings. It provides a summary of the MAT's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. It is updated with key issues raised by either MAT or the other participants in those meetings. This page is not aimed at the Committee or other readers, and may make points that seem irrelevant outside of the target audience, but should contain no confidential information. As with the overall feasibility assessment, it does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, or use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation.

Topic name: **Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease**
Topic ID: **ID6459**
Managed Access Lead: **Sarika Paul**
Date of assessment(s): **07/10/2025**

Feasibility of successful managed access	Comments / Rationale	
Committee judgement required	**Rationale for rating**	The company have submitted a managed access proposal that may help resolve some uncertainties identified by the EAG. The committee will need to discuss if a period in managed access would be helpful in resolving uncertainties, or if this can be managed during committee discussion.
	Previous ratings and rationale for change	

Managed Access Proposal	Yes	
Managed Access Team input at Committee meeting	High	Managed access team will be present at the committee meeting and will be available to provide information during committee discussions about managed access.

Area	Rating	Comments / Rationale
Is this technology eligible for managed access through the CDF or IMF?	Yes	This is a severe disease with no approved treatments. There is a managed access proposal, which focuses on using an NHS registry for data collection on HRQoL, and clinical outcomes.
What is the likelihood that further data collection could sufficiently resolve key uncertainties?	Medium	The company has submitted a managed access proposal which would provide addittional data to help resolve the uncertainties around overall survival, clinical worsening, and health related quality of life. These are a number of key uncertainties identified by the EAG, but other uncertainties remain which cannot be resolved with further data collection. Committee discussion will be required to determine if the uncertainties that remain after committee meetings can be resolved by the proposed data collection.
Are data sources are available for data collection during a managed access period? Will these sources feasibly resolve the key uncertainties?	Yes	There are no onging studies for this technology. The company submitted a managed access proposal listing a NHS based UK registry from the Royal Brompton Hospital pulmonary hypertension centre. The data items collected will provide further information on time to next clinical worsening and health related quality of life. The registry data can be linked to HES and NHS spine data to obtain overall survival information. The registry is in current use, and has agreed with the company to be part of a managed access agreement. It is likely that further data collection will help resolve some of the uncertainties identified.

Is RWE data collection within managed access feasible?	High	The company have submitted a managed access proposal which includes using data from the Royal Brompton Hospital pulmonary hypertension registry, and have gotten agreement from the registry to be involved in a managed access agreement. The registry has not got experience with managed access, but the data items collected are relevant, and linkages to HES and NHS spine data are possible to obtain mortality data at the end of the managed access period.
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	The company has confirmed with the data registries that they are willing to be part of an MAA, and while they are new to managed access, the data items collected are relevant.

Points raised by MAT	
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Points raised by managed access Ops Group	
1	EAG2 - Rates of right heart catheterisation to investigate for PH-ILD could be collected and reported. Will need to be clarified.
2	Service delivery and implementation - no service in place therefore may be delay in getting access to patients while this is set up.
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Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for managed access.

Date agreed with NHSE	13/10/2025

Is this technology eligible for managed access through the CDF or IMF?	
Rating	**Rationale**
Yes	This is a severe disease with no approved treatments. There is a managed access proposal, which focuses on using an NHS registry for data collection on HRQoL, and clinical outcomes.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	Pulmonary hypertension with interstitial lung disease has a poor prognosis and high patient burden. Currently, there are no approved treatment options for patients with PH-ILD, though treatments do exist for each condition separately and clinicians may use PDE5 inhibitors (PDE5i). These treatments are given to some patients, with the proportion varying considerably across centres, with expert estimates ranging from 8% to 60%.
Is there any evidence for the technologies to provide significant clinical benefits to patients	The technology causes a small increase QALYs compared to BSC alone in the company base case. However the company excluded PDE5is as a comparator, so it unknown how great a clinical benefit the technology delivers in relation to those. The technology causes very small increase in QALYs compared to BSC in the EAG report.
Represents a step-change in medicine for patients and clinicians	This is the first licenced treatment for a condition which has poor prognosis. It will be used in addition to existing treatments. How patient training to use the nebuliser and adverse events affect patient experience can be explored with patient experts at the committee meeting.
Could new evidence be generated that is meaningful and would sufficiently reduce uncertainty	The company found the utility data was a key uncertainty and provided a managed access proposal to allow for further utilities data collection. However, EAG scenario analyses find that survival assumptions, particularly for BSC and treprostinil, are the most influential drivers of cost-effectiveness results. An updated managed access proposal was submitted by the company to address these uncertanties.

System implementation	Supporting Evidence
Has the technology has been flagged as a potential IMF candidate to NICE by NHSE horizon scanning?	

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify its decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

What is the likelihood that further data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Medium	The company has submitted a managed access proposal which would provide addittional data to help resolve the uncertainties around overall survival, clinical worsening, and health related quality of life. These are a number of key uncertainties identified by the EAG, but other uncertainties remain which cannot be resolved with further data collection. Committee discussion will be required to determine if the uncertainties that remain after committee meetings can be resolved by the proposed data collection.

Key Uncertainties

Number	Title	Summary of issue	Impact on ICER	Data available to resolve uncertainty	Data collection in company proposal	Resolvable with managed access	Managed Access Team view on feasibility
EAG1	Choice of comparator: Are PDE5i's a relevant comparator?	The company has excluded a group of treatments known as PDE5 inhibitors (PDE5i). These treatments are given to some patients, with the proportion varying considerably across centres, with expert estimates ranging from 8% to 60%. The EAG considers PDE5is are likely to be a relevant comparator.	Unknown - The EAG has not been able to adapt the economic model to compare to PDE5is.	No	No data collection on comparators is possible as part of a managed access agreement	Low	Committee discussion required
EAG2	Concerns around implementation and impact of treprostinil.	The EAG understands that at present, some people with suspected or confirmed pulmonary hypertension interstitial lung disease (PH-ILD) are turned away from specialist centres as their disease is not severe enough, and there is a lack of treatment options. The availability of treprostinil would transform care for PH-ILD, with specialist centres likely managing greater volumes of patients, possibly requiring expansion. Furthermore, treprostinil treatment will likely require disease confirmation through right-heart catheterisation (RHC) or other clear diagnostic criteria. The availability of treprostinil may cause an increase in the number of people undergoing RHC and shift the baseline characteristics of the treated population to be on average, less severely ill than the current population.	Not quantified	No	The company managed access proposal includes a registry which has key clinical outcome measures and HRQoL data. They also propose HES and NHS spine linkages to calculate overall survival.	Medium	The registry population includes people with RHC diagnosed PH. So the population numbers may be able to be ascertained from this. There is also a national registry component that captures a retrospective snapshot of patients from all UK pulmonary hypertension centres. This dataset includes cases collected over the past 20 years and focuses on patients with PH-ILD and sarcoidosis-associated PH. This could potentially be used to determine the increase in RHC rates following the introduction of this technology.
EAG3	Crossover adjustment for INCREASE comparator arm	The company applies a rank-preserving structural failure time (RPSFT) adjustment to the open-label extension (OLE) of INCREASE, to account for the fact that all people entering the OLE received treprostinil. The EAG does not consider that the assumption of a common treatment effect is supported by the data, nor that the magnitude of the RPSFT adjustment holds any face validity. The EAG prefers to apply no adjustment, as it is unclear whether any benefit was received by switching, and explores the impact of applying an alternative adjustment (inverse probability of censoring weighting (IPCW)).	This has a large effect on the ICER and would impact decision making	No	This study is completed, committee discussion on the appropriate adjustment will be needed to resolve this uncertainty	Low	Committee discussion required
EAG4	Uncertain efficacy of best supportive care	The company presents analyses comparing treprostinil to the control arm of INCREASE, and an indirect comparison to the untreated arm from Dawes et al. The company have not implemented a comparison to other potential sources, including a CPRD study commissioned by the company; however, there are concerns about the classification of patients in this source. The EAG is content with a comparison of data based on the randomisation within INCREASE. A naïve comparison of INCREASE to the CPRD study is the only way to explore using this alternative source, as the company did not complete a MAIC.	This is likely to have a large impact on cost effectiveness, however has not been fully explored by the EAG.	No	No data collection on comparators is possible as part of a managed access agreement	Low	Committee discussion required
EAG5	Choice of extrapolation for treprostinil overall survival	The company selected a Weibull extrapolation, which is the model with the most optimistic predictions from models which capture an increasing hazard rate. The EAG selected a generalised gamma extrapolation for the EAG base case, which also models an increasing hazard rate, and explored the impact of using a Gompertz model, which is the only other plausible extrapolation.	This has a large effect on the ICER and would impact decision making	Yes	The company managed access proposal includes a registry which has key clinical outcome measures and HRQoL data. They also propose HES and NHS spine linkages to calculate overall survival.	High	The company proposes linkages with HES and NHS spine which allows for calculation of OS data, this will be completed by the company following the 48 months of data collection in the MA.
EAG6	Approach to extrapolation for treprostinil time to treatment discontinuation	Within the observed follow-up, a comparison of time to discontinuation (TTD) for treprostinil and second clinical worsening (CW2) suggests that people remain on treatment beyond CW2. However, in the company's extrapolations into the future, TTD is shorter than CW2. The EAG considers there is no rationale for this change, and so the company's model is likely to be underestimating the true duration of treatment with treprostinil. The EAG adds a constraint to the modelling of TTD so that it cannot fall below the extrapolation for CW2.	This has a moderate effect on the ICER, but would still impact decision making.	Yes	The company managed access proposal includes a registry which has key clinical outcome measures and HRQoL data. They also propose HES and NHS spine linkages to calculate overall survival.	High	From the company managed access proposal it appears possible to collect data on time to clinical worsening. However discussion with the registries would be needed to ensure data about treatment discontinuation is recorded.

EAG7	Inappropriate choice of utility values and analysis of health-related quality of life data.	No EQ-5D data was collected in INCREASE. Hence the company rely on mapping data from the St George's respiratory questionnaire. The company prefers to use utility values from a univariate analysis, however, the EAG considers this prone to bias. The EAG prefers to use utility values obtained from a generalised linear model analysis.	This has a moderate effect on the ICER, but would still impact decision making.	Yes	The company managed access proposal includes a registry which has key clinical outcome measures and HRQoL data. They also propose HES and NHS spine linkages to calculate overall survival.	Medium	The managed access proposal from the company focuses on collecting HRQoL data from the emPHasis-10 tool, and mapping this to the EQ-5D. While they will collect EQ-5D data, they state that this is only for validation of their mapping algorithm. The committee will need to decide if this mapped utilities data is appropriate for decision making, and if a period of time in managed access is valuable to help resolve this uncertainty.
EAG8	Potential for bias from difference in definition of clinical worsening used across clinical and cost-effectiveness sections	The company's definitions for clinical worsening in the cost-effectiveness section adds two additional types of events, compared to the definition of clinical worsening as defined in the INCREASE trial. These are: acute lung disease exacerbation and decrease in FVC of ≥ 10% from baseline. The EAG has compared the Kaplan-Meier functions for these outcomes and considers the potential for bias and impact on the ICER to be small.	This is likely to have a small efffect on the ICER and unlikely to impact decision making.	No	N/A	Low	Committee discussion required on need for further economic analyses from the company with unified definitons of clinical worsening.
EAG9	Choice of extrapolation for first clinical worsening (CW1)	The company selects two separate types of parametric model to extrapolate CW1 data for treprostinil and BSC. The EAG is concerned the choice of models may be influenced by the differing lengths of follow-up and could be a source of bias. The EAG uses log-logistic extrapolations for both arms.	This is likely to have a small efffect on the ICER and unlikely to impact decision making.	Yes	The company managed access proposal includes a registry which has key clinical outcome measures and HRQoL data. They also propose HES and NHS spine linkages to calculate overall survival.	Medium	In the company managed access proposal includes the collection of clinical outcomes for a period of 48 months. The OLE study has approximately 2 years of follow up. Increased duration of RWE about clinical worsening could help with the choice of extrapolation and help resolve this uncertainty.
EAG10	Inappropriate application of discounting in first year of the model	The company apply discounting on a weekly basis, beginning from the start of the model time horizon. The EAG understands discounting rates should be applied from after one year has passed within the model.	This has a small efffect on the ICER and unlikely to impact decision making.	N/A	No further data collection necessary	Low	Committee discussion can resolve this uncertainty
EAG11	Inaccuracies in dosing and costing assumptions for background medications	The EAG noted discrepancies in the pack sizes, dosing and prices used by the company for pirfenidone and nintedanib. These overestimate costs for BSC. The EAG uses pricing and pack sizes using eMIT prices and corrects the dosing error for nintedanib.	This has a small efffect on the ICER and unlikely to impact decision making.	N/A	No further data collection necessary	Low	Committee discussion can resolve this uncertainty
EAG12	Underestimation and simplification of ongoing resource use and costs	The company's choice of inputs for representing resource use appears to underestimate use compared to data included in the company's CPRD report. The EAG prefers to use the CPRD as the source for a range of inputs to represent NHS resource use for people with PH-ILD.	This has a small efffect on the ICER and unlikely to impact decision making.	No	No further data collection possible	Low	Committee discussion required.
EAG13	Costs relating to lung transplant	The company does not include costs relating to lung transplant, though a small number of people do receive lung transplants in the INCREASE study, the efficacy of which is included for overall survival. The EAG includes costs of lung transplant for the small proportion of people who received them within the INCREASE study.	This has a small efffect on the ICER and unlikely to impact decision making.	N/A	No further data collection necessary	Low	Committee discussion can resolve this uncertainty

Data Collection

Explanation

This tab collects information on the data sources that could be available for further data collection during a period of managed access, including any ongoing clinical trials, NHS registry data sets, and non-registry data sets. Analysts should assess the availability of this data to answer key uncertainties.

Are data sources are available for data collection during a managed access period? Will these sources feasibly resolve the key uncertainties?	
Rating	**Rationale**
Yes	There are no onging studies for this technology. The company submitted a managed access proposal listing a NHS based UK registry from the Royal Brompton Hospital pulmonary hypertension centre. The data items collected will provide further information on time to next clinical worsening and health related quality of life. The registry data can be linked to HES and NHS spine data to obtain overall survival information. The registry is in current use, and has agreed with the company to be part of a managed access agreement. It is likely that further data collection will help resolve some of the uncertainties identified.

Existing or proposed clinical trials	
Name and registry ID of trial	Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE (INCREASE) ClinicalTrials.gov ID NCT02630316
Is trial proposed for managed access?	No
Link to clinicaltrial.gov	https://clinicaltrials.gov/study/NCT02630316
Start date	03/02/2017
Anticipated completion date	Dec-19
Data cut presented to committee	Complete results
Data collection timeline	N/A
Description of trial	INCREASE was a Phase 3, multicentre, randomised, double-blind, placebo controlled, 16-week, parallel-group study designed to investigate the safety and efficacy of inhaled treprostinil versus placebo in patients with PH-ILD. The study was conducted at 119 sites in the US and Puerto Rico. However the outcomes assessed in the trial and background anti-fibrotic treatments received in patients at baseline are considered consistent with standard practice in the NHS England at the time of trial. For inclusion in INCREASE, patients had to be ≥ 18 years of age with a confirmed diagnosis of WHO group 3 PH based on computed tomography imaging, performed within 6 months prior to randomisation demonstrating evidence of diffuse parenchymal lung disease. Patients could have any form of ILD or combined pulmonary fibrosis and emphysema (CPFE). Patients were also required to have a RHC within 1 year prior to randomisation to confirm a PVR >3 WU, a PCWP of <15 mmHg, and a mPAP of >25 mmHg. Patients with WHO group 3 PH due to connective tissue disease were required to have a baseline FVC of less than 70%. Eligible patients also had to walk at least 100 metres during a 6MWT.

Link(s) to published data	
Existing or proposed clinical trials	
Name and registry ID of trial	An Open Label Extension Study to Evaluate Inhaled Treprostinil in Adult PH With ILD Including CPFE (INCREASE OLE) ClinicalTrials.gov ID NCT02633293
Is trial proposed for managed access?	No
Link to clinicaltrial.gov	https://clinicaltrials.gov/study/NCT02633293
Start date	01/09/2016
Completion date	Aug-21
Data cut presented to committee	Data up until study termination in 2021.
Data collection timeline	N/A
Description of trial	INCREASE OLE was a Phase 3, multicentre, OLE study designed to assess the long-term safety and efficacy of inhaled treprostinil in patients with PH-ILD. The study was conducted at 119 sites in the US and Puerto Rico and completed on 1 August 2021. Eligible patients discontinued the treatment received during the INCREASE RCT and received inhaled treprostinil (6µg/breath) regardless of their previously assigned treatment arm. To preserve prior blinding, all patients initiated inhaled treprostinil at three breaths per session (18µg) four times daily. Recommended dose escalations were an additional one breath per session four times daily every three days, per the investigator's discretion, to a maximum of 15 breaths per session (90µg) four times daily as tolerated. There were no prespecified analyses as the objective of INCREASE OLE was to provide inhaled treprostinil to study patients and capture observational long-term safety and efficacy data in the open-label setting. In the OLE, patients were assessed at week 20 (i.e. 4 weeks into the OLE), week 28 and then every 12 weeks up to week 124. There were 24 (9.9%) patients who discontinued when the study was terminated by the Sponsor when FDA approval was reached. Total median inhaled treprostinil exposure duration in the OLE was 62.1 weeks (77.3 and 47.0 weeks in patients from the inhaled treprostinil group and placebo group of the RCT, respectively).
Link(s) to published data	https://pmc.ncbi.nlm.nih.gov/articles/PMC10307984/

NHS registry data	
Name of registry	The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB) https://www.rbht.nhs.uk/ourservices/heart/pulmonary-hypertensionservice
Is registry proposed for managed access?	Yes
Mandated data collection?	No - the increased frequency of patient reported outcomes may be a burden for patients, though these data items do already exist in the data set. The company considers that the clinician burden will be low due to clinicans already collecting and recording the majority of the measures.
Available to use?	Yes, the company have been in contact with the registry and have confirmed with them that they would be willing to participate in a managed access agreement.

Data items already collected	1. 6-minute walk distance (6MWD) 2. Forced vital capacity (FVC) 3. Cardiopulmonary hospitalisation - derived from linking with HES 4. Lung exacerbation - derived from linking with HES 5. NT-proBNP 6. Patient Reported Outcomes (emPHasis-10, EQ-5D-3L) The company also highlight in their proposal that registry data could be linked to HES and NHS spine records at the end of the managed access agreement to obtain overall survival data.
Issues raised by committee or stakeholders	While the registries are available for data collection, and are considered to have good data completeness (as reported by the company), committee will need to discuss if the data items proposed for collection are able to resolve the uncertainties identified.
Data collection timeline (future data cuts, proposed end of data collection.)	Following recommendation into the Innovative Medicines Fund, Ferrer anticipates that a timeframe of four years would be sufficient to address uncertainties about OS and HRQoL. The proposed study is expected to have a 48-month timeframe. This is sufficient to obtain OS/mortality data and HSUVs for clinical worsening (CW) events (deterioration in 6MWD and/or FVC; cardiopulmonary hospitalisation, lung exacerbations).

Data collected in clinical practice

Non-SACT

Explanation on criteria

This tab collects more detailed information on the data within registries, and on the registries themselves. It will only be important to fill these firelds in if a managed access agreement is likely to happen.

Is RWE data collection within managed access feasible?		
Overall Rating	**Rationale/comments**	
High		The company have submitted a managed access proposal which includes using data from the Royal Brompton Hospital pulmonary hypertension registry, and have gotten agreement from the registry to be involved in a managed access agreement. The registry has not got experience with managed access, but the data items collected are relevant, and linkages to HES and NHS spine data are possible to obtain mortality data at the end of the managed access period.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Adapted	Existing data sources with addittional HES and NHS spine linkage
Prior experience with managed access	Low	The proposed registry has not had experience with MA before, but has been contacted by the company and is aware and willing to be involved if necessary.
Relevance of existing data items	High	It will be necessary to ensure that information on medications taken, and when they're discontinued, is recorded in the registry.
If required, ease that new data items can be created / modified	Not applicable	Not known at this stage - but not likely to be necessary based on current uncertainties.
How quickly could the data collection be implemented	Normal timelines	Company has been in contact with the registry and they are willing to engage with a managed access agreement. The registry is already in existence and collects relevant data items.
Data quality		
Population coverage	Medium	The registry proposed includes patients referred to the Royal Brompton Hospital, one of the 7 specialist centres covering England and Wales. The committee will need to discuss if having a London registry provides data that can be extrapolated.
Data completeness	Medium	Not known at this stage.
Data accuracy	Medium	Not known at this stage.
Data timeliness	Medium	Not known at this stage.
Quality assurance processes	Medium	Not known at this stage.
Data availability lag	Medium	Not known at this stage.
Data sharing / linkage		
New data sharing arrangements required?	Yes	The company has previously licenced data from the registry for a RWE study. New data sharing arrangements will be able to be established, and the registry is aware of this.
New data linkages required?	Yes	Yes, new HES linkages are proposed by the company, and NHS spine data will be used to determine overall survival.
If yes, has the governance of data sharing been established	Unclear	Not known at this stage.

Analyses		
How easily could collected data be incorporated into an economic model	High	Data collection proposed includes overall survival and utility data, which can easily be included in the existing economic model.
Existing methodology to analyse data	Yes	The data can be incorporated into the existing model
If no, is there a clear process to develop the statistical analysis plan	Not applicable	
Existing analytical capacity	High	The registry believe they will have sufficient capacity, as long as they recieve ongoing funding.
Governance		
Lawful basis for data collection	Yes	Not known at this stage.
Privacy notice & data subject rights	Yes	Not known at this stage.
Territory of processing	Yes	Not known at this stage.
Data protection registration	Yes	Not known at this stage.
Security assurance	Yes	Not known at this stage.
Existing relevant ethics/research approvals	Yes	Not known at this stage.
Patient consent	No	There is not yet patient consent, but there is a plan in place to amend the ethics, which would enable collection of patient consent.
Funding		
Existing funding	Yes	The registry is supported by the NHS
Additional funding required for MA	No	
If yes, has additional funding been agreed in principle	Not applicable	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	
Are any of the clinical assessments not validated for use or accepted clinical practice	No	
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Yes, the registry is currently in use in NHS hospitals
Burden		
Additional patient burden	Unclear	Patient reported outcomes are currently collected in the NHS registry proposed for data collection, but the increased frequency of these may increase patient burden.
Additional clinical burden	Unclear	Company states that clinicians typically already use the instruments and registries proposed for data collection
Other additional burden	No	

Other issues

Non SACT

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
No	The company has confirmed with the data registries that they are willing to be part of an MAA, and while they are new to managed access, the data items collected are relevant.

Burden		**Rating**	**Rationale / comments**
	Expected overall additional patient burden from data collection?	Medium	While patient reported outcomes are included in normal care, there may be an addittional burden if clinicians increase focus on obtaining these records more frequently.
	Expected overall additional system burden from data collection?	Medium	Company states that clinicians typically already use the instruments and registries proposed for data collection
	Do stakeholders consider any additional burden to be acceptable	Unclear	Not known at this stage
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	No	

Patient Safety		**Rating**	**Rationale / comments**
	Have patient safety concerns been identified during the evaluation?	Unclear	While there were high level of AEs in the OLE, patient safety concerns were not highlighted by the EAG or company.
	Is there a clear plan to monitor patient safety within a MA?	No	
	Are additional patient safety monitoring processes required	No	

Patient access after MAA		**Rating**	**Rationale / comments**
	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Unclear	Not known at this stage
	If yes, have NHS England and the company agreed in principle to the exit strategy	Not Applicable	

Service implementation		**Rating**	**Rationale / comments**
	Is the technology disruptive to the service	Unclear	Implementation of this technology will likely increase the number of diagnostic right heart cathetrisations needed. It is unclear how disruptive this will be.
	Will implementation subject the NHS to irrecoverable costs?	Unclear	Not known at this stage - currently there is no active treatment for the condition, and therefore patients may only recieve a formal diagnosis using right heart catheterisation, when it is clinically necessary. Introduction of this technology is expected to increase use of right heart catheterisation, necessary for a formal diagnosis.
	Is there an existing service specification which will cover the new treatment?	No	NHSE say a new service will have to be set up to deliver this technology.

Patient eligibility		**Rating**	**Rationale / comments**
	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	

Patient eligibility	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not Applicable	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Unclear	Not known at this stage.

3.8 Managed access proposal

3.8.1 Eligibility for the Innovative Medicines Fund

Ferrer considers that routine commissioning is the most appropriate route for inhaled treprostinil. However, it acknowledges uncertainty in the long-term overall survival (OS) for inhaled treprostinil due to the comparatively short follow-up period of INCREASE OLE relative to the time horizon of the economic model. Ferrer also recognises that there is some uncertainty regarding the utility values used within the health economic model. This is due to the use of the St George's Respiratory Question (SGRQ) instrument in the INCREASE trial, which may not have fully captured the specific pulmonary hypertension associated with interstitial lung disease (PH-ILD) impacts on health-related quality of life (HRQoL).

Should NICE's technology appraisal committee deem the evidence too uncertain to support a recommendation for routine commissioning, Ferrer is open to exploring a managed access agreement within the Innovative Medicines Fund.

To resolve the uncertainty around OS, Ferrer proposes collecting longer term mortality data for inhaled treprostinil from a UK-based registry (UKRB) linked to Hospital Episode Statistics (HES) data. This will provide more robust estimates of OS to reduce uncertainty in the economic model.

With regards to the utility values, the SGRQ was designed for use in obstructive pulmonary disease such as asthma and Chronic Obstructive Pulmonary Disease (COPD); therefore, the majority of its content reflects symptoms typical of these conditions. It assesses impact of symptoms such as cough, sputum production and wheezing, while the clinical features of PH-ILD such as dyspnoea, fatigue and even pre-syncope are underrepresented or absent. The SGRQ also does not reflect the specific psychological and functional burden associated with PH-ILD, such as the need for long-term oxygen therapy, anxiety related to progressive hypoxaemia, or limitations on exertion that result in social withdrawal and dependency.

Additionally, the 50-item length of the SGRQ can also be burdensome for patients with PH-ILD. Fatigue is a key symptom of PH-ILD, and this can lead to missing HRQoL data due to patients not completing the entire questionnaire (item nonresponse) or their lack of participation in data collection (unit nonresponse). Unit nonresponse can be a particular issue during hospital admissions. Since inhaled

treprostinil is associated with fewer hospitalisations than best supportive care, this could result in differential levels of missing data between the treatment arms, introducing bias into the HRQoL-related model inputs.

To address this uncertainty Ferrer proposes collecting additional HRQoL data using the emPHasis-10 from patients in the aforementioned UKRB registry. This instrument is shorter, simpler to complete, and specifically developed for pulmonary hypertension (PH), making it more sensitive to PH-specific HRQoL impacts. Furthermore, it is widely used in routine clinical practice at PH clinics. The most recent National Audit of Pulmonary Hypertension (2023) reported that nearly all patients (92%) who have had at least one consultation in the last year have had an emPHasis-10 quality of life score recorded. Incorporating emPHasis-10-based data into the health economic model is therefore anticipated to reduce uncertainty by improving the accuracy of the health state utility values (HSUVs).

A managed access agreement would be appropriate for inhaled treprostinil given its potential to address the substantial high unmet need in patients with PH-ILD and to deliver clinically meaningful benefits (see Table 53 within Section 3.10, Company Submission). Inhaled treprostinil demonstrates improvements in exercise capacity and reductions in disease progression.

3.8.2 Uncertainties that could prevent the committee from making a recommendation for routine use

Table 1. List of uncertainties and potential data collection

Clinical uncertainty	Outcome data	Data source
Overall survival	• Overall survival (mortality; NHS Spine linkage and HES linkage)	• The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)
Accuracy of the utility values within the health economic model	• HRQoL scores from emPHasis-10 • Health state utility values mapped from emPHasis-10 to EQ-5D	• The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)

Abbreviations: EQ-5D: EuroQol 5-Dimensions; HES: Hospital Episode Statistics; HRQoL: Health-Related Quality of Life; NHS: National Health Service; UKRB: The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom.

3.8.3 Data collection

For OS, through the proposed prospective study Ferrer plans to collect mortality data through linkage of the UKRB registry with NHS Spine and HES data. This will

provide longer term estimates of OS compared with INCREASE, which will reduce uncertainty in the economic model.

To inform the utility values in the economic model, Ferrer plans to develop and validate an algorithm that predicts EQ-5D utilities from emPHasis-10 in patients with PH-ILD. Baseline utility values for the health economic model will be updated by HSUVs derived from a mapping of emPHasis-10 scores to EQ-5D-3L.

The proposed prospective study here will assess the impact of inhaled treprostinil on HRQoL using emPHasis-10 and EQ-5D-3L. EQ-5D data is collected solely to support the development of a mapping algorithm rather than directly generate utilities since this generic patient-reported outcome measure (PROM) is not considered to fully capture PH-specific impacts on HRQoL (see Section 2.6.1.5, Company Submission).

3.8.4 Overview of the data sources: UK Royal Brompton registry

Ferrer has explored the feasibility of using the UKRB registry to address the uncertainty around the accuracy of the utility values within the economic model, as well as to validate the long-term survival of patients having inhaled treprostinil.

In a previous version of this proposal, the ASPIRE (Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre), patient registry based in Sheffield Pulmonary Vascular Unit, had been included as a potential data source. However, as ASPIRE can only provide retrospective data, Ferrer has decided to remove it from the managed access proposal. Collecting prospective OS data from patients who are yet to receive inhaled treprostinil would not be feasible within ASPIRE; therefore, it is not considered an appropriate source for addressing this uncertainty.

The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)

The UKRB registry is a disease-specific patient registry and was established in 2023.[1] It aims to understand the pathophysiology of PH related to chronic lung disease (WHO Group 3 PH patients). This registry contains anonymised patient data from the records of consecutive incident patients referred to the Royal Brompton Hospital National Pulmonary Hypertension Service. Treating clinicians or other healthcare professionals manually transcribe data from electronic health records.

As of August 2024, this registry includes approximately 900 patients who have been referred to the Royal Brompton Pulmonary Hypertension Service.

The following outcomes are routinely collected: emPHasis-10 score, six-minute walk distance (6MWD), and levels of B-type natriuretic peptide (BNP). In the proposed study, additional data collection includes an increased number of emPHasis-10 assessments over time, as well as measurements on EQ-5D-3L, and cardiopulmonary hospitalisation and lung exacerbations occurrence. Data quality is assessed through medical review of the data. Highly skilled professionals (e.g., clinical research fellows) are trained to enter the data under close supervision from the senior physicians. Ad-hoc data verification may occur via discussion between the data-entry professional and senior physicians. The UKRB data are linked to NHS Spine; therefore, mortality data collection is possible. Linking to HES data will be feasible at the end of the designated follow-up period, with OS analyses to be conducted thereafter.

Table 2. Overview of the Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)

Registry	The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB) https://www.rbht.nhs.uk/ourservices/heart/pulmonary-hypertensionservice
Type of registry	Disease-specific patient registry
Population	Adult patients (aged ≥18 years at index date) diagnosed with PH associated with ILD of various aetiologies, documented by an RHC UKRB is Royal Brompton, Guy's and St Thomas' and all satellite centres (covering a large area of London and surrounding counties: Oxford, Reading, Southampton, UCH, St George's, Surrey and Sussex), within the population covered by Royal Brompton PH centre. In addition, there is a national registry component that captures a retrospective snapshot of patients from all UK pulmonary hypertension centres. This dataset includes cases collected over the past 20 years and focuses on patients with PH-ILD and sarcoidosis-associated PH.
Relevant data items collected	Clinical outcomes: 1. 6MWD 2. FVC 3. Cardiopulmonary hospitalisation

	4. Lung exacerbation 5. NT-proBNP 6. **Overall survival** 7. **PROs (emPHasis-10, EQ-5D-3L)**
Data analysis	The analysis will be devised based on the following study: **Proposed study:** Prospective study to collect overall survival outcomes and evaluate the impact of inhaled treprostinil on HRQoL using emPHasis-10 and EQ-5D-3L.
Governance	The Royal Brompton Hospital research governance department is the controller of the UKRB registry data. The registry is supported by the NHS and Ferrer have previously licenced data from this registry to support a RW research study. Additional funding was awarded in 2023 by Ferrer pharmaceuticals to support a research fellow for a prospective PH-ILD registry.
Indicate if registry previously used within a NICE managed access	No.
Abbreviations: 6MWD: 6-Minute Walk Distance; EQ-5D-3L: EuroQol 5-Dimensions 3-Level; FVC: Forced Vital Capacity; HRQoL: Health-Related Quality of Life; NHS: National Health Service; NT-proBNP: N-terminal pro b-type Natriuretic Peptide; PH: Pulmonary Hypertension; PH-ILD: Pulmonary Hypertension associated with Interstitial Lung Disease; PROs: Patient-Reported Outcomes; UCH: University College Hospital; UKRB: Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom.	

Mortality data are currently collected through linkage with NHS Spine, which provides accurate information and can be updated at the designated censoring date.

During the managed access period, linkage to HES data will be incorporated following REC approval. HES linkage will be undertaken once at the end of the registry follow-up period, with subsequent analyses performed thereafter.

The additional data collection would include an increased number of emPHasis-10 assessments over time as well as measurements on the EQ-5D-3L and determining cardiopulmonary hospitalisation and lung exacerbations occurrence.

During the managed access period, emPHasis-10 and EQ-5D will be self-administered by patients at baseline and at every 3 months thereafter. Patients will also be encouraged to complete these PROMs during hospitalisation.

Cardiopulmonary hospitalisation and lung exacerbations occurrence will be derived from linking registry data to the HES database.

3.8.5 Prior approach to the registry for the data specified in the managed access proposal

Ferrer has had collaborations with stakeholders from the UKRB registry and it has approached registry owners regarding the data collection, analysis and sharing specified in this managed access proposal.

3.8.6 Timeframe of data collection

Following recommendation into the Innovative Medicines Fund, Ferrer anticipates that a timeframe of four years would be sufficient to address uncertainties about OS and HRQoL.

The proposed study is expected to have a 48-month timeframe. This is sufficient to obtain OS/mortality data and HSUVs for clinical worsening (CW) events (deterioration in 6MWD and/or FVC; cardiopulmonary hospitalisation, lung exacerbations).

Based on the INCREASE trial, modelling of time to first and second CW events shows that by the end of 18 months, approximately 90% and 60% of patients have had their first and second CW event, respectively (Company submission, Sections 3.3.3 and 3.3.4). Additionally, a recent analysis of HES data showed the mean annualised rate of all-cause hospitalisations for patients newly diagnosed with PH-ILD was approximately 3 per person-years within the first year of follow-up.[2]

In 2029, Ferrer anticipates incorporating the additional OS and HRQoL data collected during the managed access period into an evidence submission and updated economic model (Table 3).

Table 3. Duration of proposed managed access activities

Activity	Duration	Provisional study title
Proposed study	48 months	Prospective study to collect OS data for inhaled treprostinil based on the registries linking with the HES and to assess the impact on HRQoL
Resubmission	6 months	Revise the evidence submission and economic model to incorporate OS and HRQoL data.
Abbreviations: HES: Hospital Episode Statistics; HRQoL: Health-Related Quality of Life; OS: overall survival.		

The study timeframe also includes the time needed to:

- Link mortality data with HES and conduct analyses after the designated period of time.
- Define a validated mapping algorithm between emPHasis-10 and EQ-5D-3L utility values.

3.8.7 Additional considerations that may impact feasibility of data collection

Ferrer has a good relationship with key opinion leaders and stakeholders at the UKRB registry. UKRB has confirmed their willingness to participate in a managed access agreement. Therefore, Ferrer does not anticipate any barriers to obtaining an OS data collection agreement with UKRB or the use of emPHasis-10.

Listed below are specific considerations that may impact the feasibility of data collection within the managed access period:

UKRB REC approval: Amendments to the existing ethical approvals are currently in progress, and a prospective component will be submitted for Research Ethics Committee review. A potential challenge is that any delay in obtaining REC approval could impact on the initiation of additional data collection activities.

Informed consent: Lack of patient consent to give access to their clinical data.

PRO data collection for patients and clinicians: PRO collection facilitates monitoring of patients' symptoms with PH-ILD and supports tailoring of treatment to patient needs. However, the proposed frequency of administration of PRO measurements over the data collection period is a potential burden to patients and

clinicians. This may lead to poor data quality due to non-response or incomplete responses by patients. Ferrer aims to address this potential burden by having patients complete electronic PROs (ePROs) versions of emPHasis-10 and EQ-5D-3L. ePROs are considered easier and faster to complete than traditional pen and paper versions.

The interpretation of emPHasis-10 scores by clinicians over the course of the managed access period is unlikely to significantly burden clinicians. This is based on clinicians routinely collecting and using emPHasis-10 in patients attending PH clinics.[3]

To ensure adherence to HRQoL data collection, Ferrer will produce supportive educational materials for patients to explain the importance of data collection in PH-ILD.

Demographic characteristics of PH-ILD patients: In the UK, patients with PH-ILD have a mean age of 71 years,[2] therefore age-related physical or cognitive decline may be a barrier for elderly patients to complete the PROMs.

Ferrer will include interview support (telephone) for patients if needed to facilitate the collection of HRQoL data (such as those who are unable to complete ePROs).

References

1. Guy's and St Thomas' NHS Foundation Trust. New national pulmonary hypertension database gets greenlight 2023 [Available from: https://www.rbht.nhs.uk/research/new-national-pulmonary-hypertension-database-gets-greenlight.
2. Ferrer International. Characterization of the epidemiology and burden of Pulmonary Hypertension WHO Group 3 in the UK: a retrospective study from Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) database. 2024.
3. NHS England. National Audit of Pulmonary Hypertension, 13th Annual Report 2023 [Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-pulmonary-hypertension-audit/13th-annual-report.