Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease

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This is a single technology appraisal topic

Highly specialised technology evaluations committee 18 December 2025 assessing ID6459 as a single technology evaluation

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Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on pulmonary hypertension and interstitial lung disease

Condition and causes

- Interstitial lung disease (ILD) is a group of disorders causing progressive scarring of the lung interstitium (tissue surrounding air sacs)
- Caused by autoimmune disease, environmental exposure, medication, or unknown factors, such as idiopathic pulmonary fibrosis
- Chronic hypoxia, fibrosis and inflammation from ILD can lead to pulmonary hypertension (PH). PH causes increased pressure within the pulmonary arteries
- Estimates for people with ILD with pulmonary hypertension (PH-ILD) may be as high as 86% depending on type of ILD and disease; annual prevalence and incidence is 0.36 and 0.19 per 10,000 people respectively (Kiely, et al, 2019)

Classification

- WHO classify PH into five clinical groups : PH-ILD is classified as WHO Group 3*
- WHO Group 3 can include PH associated with chronic obstructive pulmonary disease, sleep-disordered breathing or ILD. Proposed indication for inhaled treprostrinil is anticipated to be specifically for PH-ILD

Symptoms and prognosis

- Symptoms overlap between ILD and PH-ILD- include dyspnoea (shortness of breath), cough and fatigue
- Company note PH-ILD have exacerbated respiratory symptoms compared with ILD alone
- Prognosis worsens with severe PH (mPAP ≥35 mmHg or PVR >5 Wood units)

Abbreviations: ILD, interstitial lung disease; mPAP, mean pulmonary arterial pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance WHO, World Health Organisation

*see appendix for WHO classification

Patient perspectives

There is currently no treatment available for PH-ILD on the NHS

Submissions from 2 patient experts

- There is a clear and urgent unmet need for effective therapies for people living with PH-ILD. Many of the drugs used carry a high side effect profile that impacts on people's experiences.
- Therapies include: cough therapies, pulmonary rehabilitation, psychological support and supplementary oxygen can be effective in improving quality of life. The burden of symptoms / level of disability in PH-ILD patients makes accessing services problematic.

Inhaled treprostinil

- 4 times daily dose is a burden and most patients are not accustomed to inhaling medicines. The preparation of inhaled medication may be difficult for those with dexterity issues. It is still seen as a welcome addition given the lack of other treatment options. But there is a current lack of data around the impact on aspects such as quality of life, improvement in work, education.
- The cost of delivering treatment needs to be considered from the perspective of infrastructure and capacity as well as the cost of the therapy itself.

There is a lack of clarity around where the management of these patients will sit. This group must be regarded as an entirely separate cohort and managed in addition to current services

This group of patients currently fall outside the remit of the PH expert centres. Accurate diagnosis, phenotyping and appropriate expert follow-up to measure treatment efficacy will need careful consideration

Abbreviations:; PH-ILD, pulmonary hypertension associated with interstitial lung disease;

Patient and professional perspectives

PH-ILD is underdiagnosed in the NHS and there is a lack of current treatments

Submissions from Action for Pulmonary Fibrosis, British Thoracic Society and Association of Respiratory Nurse Specialists

Diagnosis and pathway of care

- RHC is required to assess eligibility for treatment. But patients are not routinely referred as there are no therapeutic options.
- Limited access to diagnostic tests or PH specialist centres suggests PH-ILD is underdiagnosed

Current treatment is supportive and there is no pathway of care

- Treatment tailored to an individual, guided by clinical evaluation of condition, functional class, and haemodynamic state
- PDE5is can be offered but there is no real benefit from other agents used to treat pulmonary arterial hypertension

Inhaled treprostinil

- Could significantly improve quality of life
- 4 times daily dose is a burden. But this is still seen as a welcome addition given the lack of other treatment options

There is no licensed therapy for PH-ILD in the UK. Often only palliative approaches are available.

Centres will have to offer RHC to allow eligibility for treatment. But RHCs are not provided in all secondary care centres

Abbreviations:; PH-ILD, pulmonary hypertension associated with interstitial lung disease; RHC, right heart catheterisation

Clinical perspective

There is a high unmet need for treating PH-ILD. Inhaled treprostrinil represents a step change in treatment

Submission from 1 clinical expert

High unmet need

- Group 3 PH-ILD is an area of high unmet need, with a poor prognosis
- A UK PH audit identified median survival is less than 2 years in PH-ILD

Assessments for starting treatment

- Current assessments include a measure of symptoms; measure of exercise capacity and assessing right ventricular function

Inhaled treprostinil is a step change in treatment

- It is the first treatment that has shown improvement in measures of exercise capacity. If introduced there is a need for:
    - staff to train patients in administration of drug and provide support
    - access to diagnostics (imaging, exercise testing and RHC)
    - MDT discussion to ensure that only suitable people start treatment

Health related quality of life

- Complexity of dose titration, administering the treatment, and side effects of treatment may be challenging for some people and could impact overall HRQoL

Given the poor prognosis of people with PH-ILD an improvement with treatment represents a very significant achievement

Introducing inhaled treprostinil for treating PH-ILD would require additional infrastructure support to allow equitable delivery of this treatment in the UK

Abbreviations: HRQoL, health related quality of life; MDT, multi disciplinary team; PH-ILD, pulmonary hypertension associated with interstitial lung disease; RHC, right heart catheterisation

NHS England perspective

Inhaled treprostinil will be the first licensed treatment for this indication and expected to have a significant impact on use of resources.

Submission from NHS England

Inhaled treprostinil becoming available is expected to change the pathway of care and increase referrals to specialised services for ILD and PH

Clinical leads have started to discuss with NHS England how services will need to develop to increase capacity and ensure appropriate access to treatment.

People with PH-ILD are typically older so a local/network approach is favoured.

Home treatment or homecare supply would be beneficial.

It is expected that treatment will start in specialised services with ongoing prescribing and supply will be through secondary care utilising hub/spoke model or 'shared care' to increase capacity and ensure care closer to patient's.

The pathway of care will vary depending on access and referral to specialist centres.

Patients are 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.

Abbreviations: HRQoL, health related quality of life; MDT, multi disciplinary team; PH-ILD, pulmonary hypertension associated with interstitial lung disease

Equality considerations

- A clinical expert noted people may have disabilities that limit their exercise capacity so safeguards would need to be in place to ensure that these people would not be excluded:
    - Especially if a recommendation relied upon criteria based upon exercise capacity over a threshold to access treatment or improvement in exercise capacity to allow continued use of therapy
- A patient expert, professional organisation and patient organisation noted there is limited access to specialist ILD or PH centres.
    - Many ILD specialist centres do not have easy access to RHC so many people who would benefit from having inhaled treprostrinil would not be able to access it
    - People living in remote areas, away from RHC centres will find it difficult to access and people from socially deprived groups may find the cost and effort of getting to an RHC centre is prohibitive. If access to a Pulmonary Hypertension Specialist Centre is needed for diagnosis/prescribing, it could limit people who find travel difficult

NICE comment: this would not normally be considered an equalities issue for the committee to address within its recommendation.

Abbreviations: ILD, interstitial lung disease; RHC, right heart catheterisation

inhaled treprostinil ([redacted] Ferrer)

Marketing authorisation	• Inhaled treprostinil does not yet have marketing authorisation for any indication in the UK • It is expected to be indicated for "treatment of pulmonary hypertension associated with interstitial lung disease" (PH-ILD) • Expected date of MHRA approval is [redacted]
Mechanism of action	• Treprostinil widens blood vessels (vasodilation) of the pulmonary and systemic arterial vascular beds and prevents blood platelets sticking together (platelet aggregation)

Administration	• Solution for oral inhalation administered through ultrasonic, pulsed-delivery nebuliser
	  • Initial dose 3 breaths per session, 4 sessions daily,
	  • Titrated up to target dose 9 breaths per session, 4 sessions daily
	  • Maximum dose 12 breaths per session, 4 sessions daily

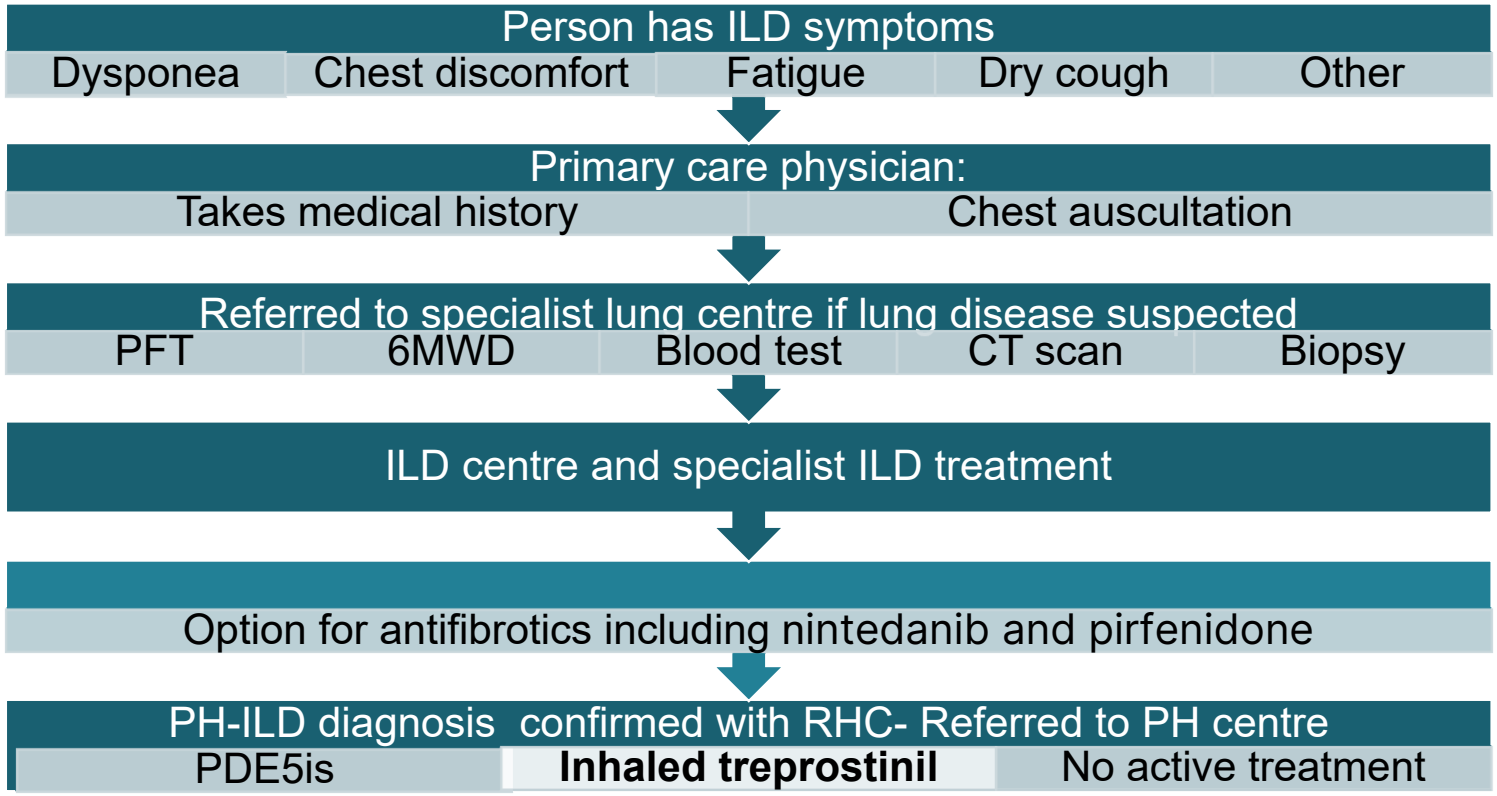
Price	• [redacted] per starter kit, [redacted] per refill kit • Company has a simple patient access scheme discount approved

Is there a timeframe for titrating the dose of inhaled treprostinil?

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency;

Pathway and positioning of inhaled treprostinil

Company: Currently no approved treatment and no treatment guidelines for management of PH-ILD in England
- Referral to PH centre for PH-ILD diagnosis and treatment is low: Only if severe PH suspected (PVR ≥5 WU)
- ESC/ ERS guidelines (2022) PDE5i may be used after referral to PH centre. But recommendations based on conflicting and limited evidence



Abbreviations: 6MWD, 6-minute walk distance; CT, computed tomography; European Society of Cardiology/European Respiratory Society PDE5i, phosphodiesterase type 5 inhibitors; PFT, pulmonary function test; PVR, pulmonary vascular resistance RHC, right heart catheterisation, WU, wood unit

In INCREASE only pirfenidone and nintedanib were given at baseline
Pirfenidone:11.7% treatment arm, 15.3% control arm
Nintedanib: 6.7% treatment arm, 11.7% control arm

- Will people have background medicines in clinical practice?
- Are they treatment effect modifiers?
- Is the proportion having background medicines in INCREASE representative of clinical practice?

Unknown impact

Key issues Implementation and impact of inhaled treprostinil (1)

Background

- EAG noted several challenges with implementing inhaled treprostinil. It could not explore impact of these due to limitations in the submitted evidence but suggest the impact of these should be considered

Theme	Description
Diagnosis	• Referrals to PH centres in severe PH (PVR ≥5 WU) only, so many people undiagnosed or managed in ILD services • Regional variation in referral rates and diagnosis for different ILD subtypes
RHC	• RHC is gold standard but only used if strong clinical suspicion of PH. This limits early detection
Proportion having RHC	• RHC is routinely used for transplant-eligible population • If RHC is used to diagnose PH-ILD this may lead to earlier diagnoses at a younger age
Impact of having RHC	• CPRD/HES data show better outcomes for RHC diagnosed Non RHC-confirmed (n=1561) had poor survival compared with RHC-confirmed NHS population may have higher mortality than RHC-confirmed dataset • Diagnosis in younger age may have more life-years gain and improved quality of life but may mean baseline population is less severely ill than the current population • RHC diagnosis needed to start inhaled treprostinil so increased diagnosis will lead to greater volumes of people and the number of PH centres may need to be expanded

What is the age and severity at diagnosis of PH-ILD? Would this change if treprostinil was recommended? How many PH centres diagnose using RHC? How would implementation impact upon PH centres?

Unknown impact

Key issues Implementation and impact of inhaled treprostinil (2)

Theme	Description
Design	• Inhaled treprostinil is for inhalation and is designed to be used with an ultrasonic pulsed-delivery nebuliser prepared daily for programmed individual inhalation • Solution for oral inhalation administered through a unique ultrasonic, pulsed-delivery nebuliser
Patient training and monitoring treatment	• Patients should be trained and supervised before starting treatment to ensure proper dosing and inhalation technique • Concerns of inconsistent instruction by healthcare providers, • Monitoring is recommended during dose adjustment because inhaled treprostinil may cause hypotension in patients with low blood pressure and reduced systemic arterial pressure, as well as risk of bleeding, acute bronchospasm, and airway hyperresponsiveness
Challenges of administration	• Patient-dependent administration could result in dosing errors and minor deviations may result in hypotension or rebound pulmonary hypertension • Practical demands such as mastering breathing techniques, adhering to treatment frequency, and managing daily preparation, assembly, and cleaning of the device • Inhalation techniques distinct from other devices, and overall burden of managing complex regimens

- Is inhaled treprostinil intended for home treatment?
- How often will people having treatment be monitored?
- How will care teams be co-ordinated to ensure safe delivery and treatment monitoring to mitigate adverse effects?

Unknown impact

Key issues: Comparators

Company: BSC is the only comparator; EAG: PDE5is likely to be a relevant comparator

Background

- Company: Consider BSC is only relevant treatment comparator.
- EAG: PDE5i are justified as a comparator because some people do have these therapies

Company: Do not consider PDE5is are a relevant comparator

- European guidelines recommend PDE5i use in severe PH-ILD only but quality of evidence supporting use of PDE5is is considered very low
- UK advisory board: PDE5is are not considered standard of care in the overall patient population
  - Small percentage with very severe PH-ILD use off-label (in absence of any licensed treatment) but low expectations of effectiveness
- UK-based epidemiological study (commissioned by Ferrer): only 8% of people with PH-ILD use PDE5is
- Included MAIC analyses of inhaled treprostinil compared with PDE5is after EAG report (see later slides)

EAG: PDE5is are likely to be a relevant comparator

- Concurs with comparators in NICE scope: Includes PDE5is (sildenafil and tadalafil).
- EAG's clinical advice: excluding PDE5i may be challenging due to limited treatment alternatives but people with mild disease are not referred to PH centres.
- Clinical adviser report PDE5i use varies. But in some centres up to 60% of people referred are having PDE5i

- What proportion have PDE5is in clinical practice?
- Are PDE5is only given in severe cases?

Abbreviations: BSC, best supportive care; MAIC, matched adjusted indirect comparison PDE5i, phosphodiesterase type 5 inhibitors; PH-ILD, pulmonary hypertension with interstitial lung disease

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Key issues

Issue	ICER impact
Implementation: • Is there a timeframe for titrating the dose of inhaled treprostinil? Will people have background medicines in clinical practice? Are they treatment effect modifiers? • Is the proportion having background medicines in INCREASE representative of clinical practice? • What is the age and severity at diagnosis of PH-ILD? How many PH centres diagnose using RHC? How would implementation impact upon PH centres? • Is inhaled treprostinil intended for home treatment? How often will people having treatment be monitored? How will care teams be co-ordinated to ensure safe delivery and treatment monitoring to mitigate adverse effects?	Unknown
Comparators: • What proportion have PDE5is in clinical practice? Are PDE5is given in severe cases?	Large
Clinical effectiveness: • Is the modelled approach or the observed approach the most appropriate method to interpret the results of exercise capacity? • Should data be adjusted for crossover? If so, is the IPCW or RPSFT approach preferred? Should a scenario of re-censoring data also be explored? • Is Dawes an appropriate source or should a MAIC including the CPRD dataset be explored? • Which data source and approach should be used to compare inhaled treprostinil with PDE5is? • Do these results align with the results comparing inhaled treprostinil with BSC?	Unknown
Modelling overall survival: • Which is the most appropriate extrapolation for modelling OS with inhaled treprostinil? • How should OS for BSC be extrapolated considering the crossover?	Large
Modelling time to treatment discontinuation: • Should a constraint be applied to model the treatment duration of inhaled treprostinil?	Medium
Utilities: • IS the SGRQ tool appropriate to capture HRQoL in PH-ILD? • Should a univariate or multivariate approach be used to analyse utilities?	Small

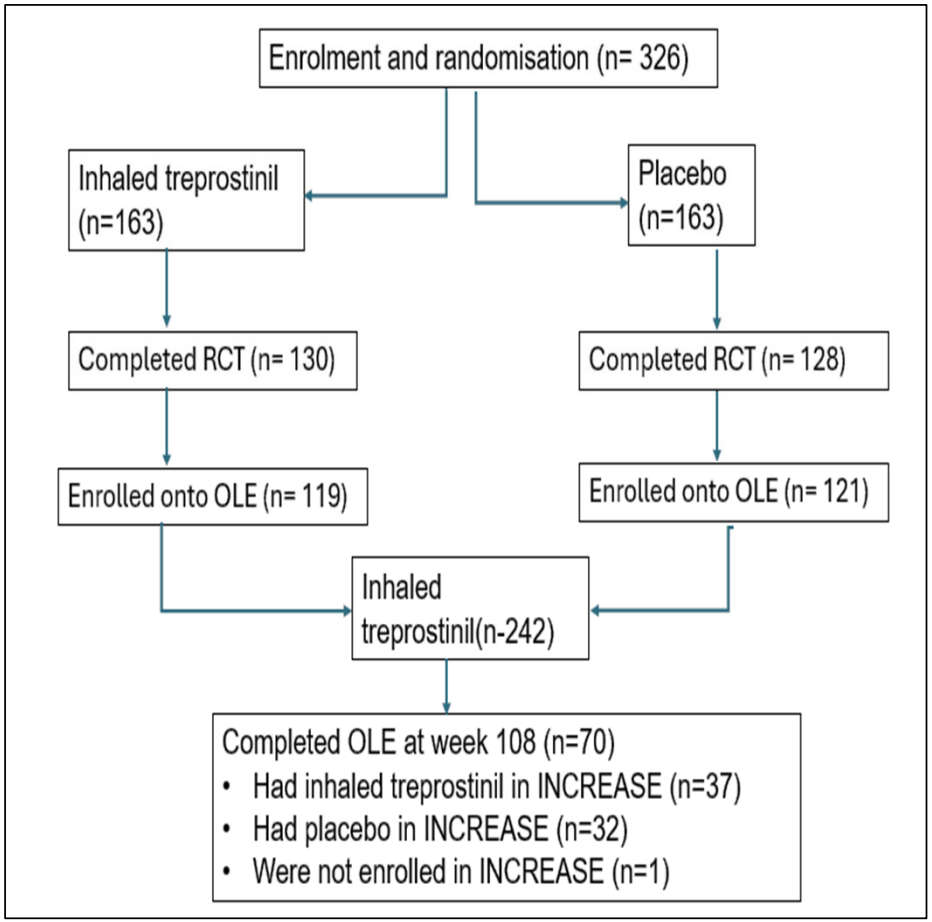
INCREASE and INCREASE OLE study design

EAG: Risk of bias

INCREASE had some concerns with bias

INCREASE OLE had high risk of bias

- Baseline imbalances in lung disease aetiology without statistical adjustment
- Unblinded investigators involved in enrolment in RCT (n=136 of 462 excluded at enrolment). But extent of bias is unclear
- OLE high attrition (29% complete week 108)
- OLE eligibility based on prior participation Exclusions relied on investigator judgement without clearly defined criteria and raise concerns about consistency, selectivity, and interpretability of long-term outcomes



See baseline characteristics in INCREASE
See INCREASE and OLE study characteristics

Abbreviations: OLE, open label extension; RCT, randomised controlled trial

INCREASE baseline characteristics

link

	Characteristic	Inhaled treprostinil (n=163)	Placebo (n=163)
Demographics	Female sex, n (%)	85 (52.1)	68 (41.7)
	Age at randomisation, mean (SD) years	65.6 [redacted]	67.4 [redacted]
Cause of lung disease%	Idiopathic interstitial pneumonia	39.9%	49.7%
	Connective tissue disease	24.5%	19.6%
	Idiopathic pulmonary fibrosis	22.7%	33.7%
	Hypersensitivity pneumonitis	6.1%	5.5%
	Non-specific interstitial pneumonia	12.9%	9.8%
Background therapy %	None	81.6%	73.0%
	Pirfenidone only	11.7%	15.3%
	Nintedanib only	6.7%	11.7%
Pulmonary function tests	FEV1 % predicted median	63.0%	63.0%
	FVC % predicted median	60.0%	61.0%
	DLCO % Predicted median	29.0%	26.0%
6MWD (meters)	Mean (SD)	254.1 [redacted]	265.1 [redacted]

Are the baseline characteristics representative of PH-ILD?

Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PH-ILD, pulmonary hypertension with interstitial lung disease; 6MWD, six minute walking distance

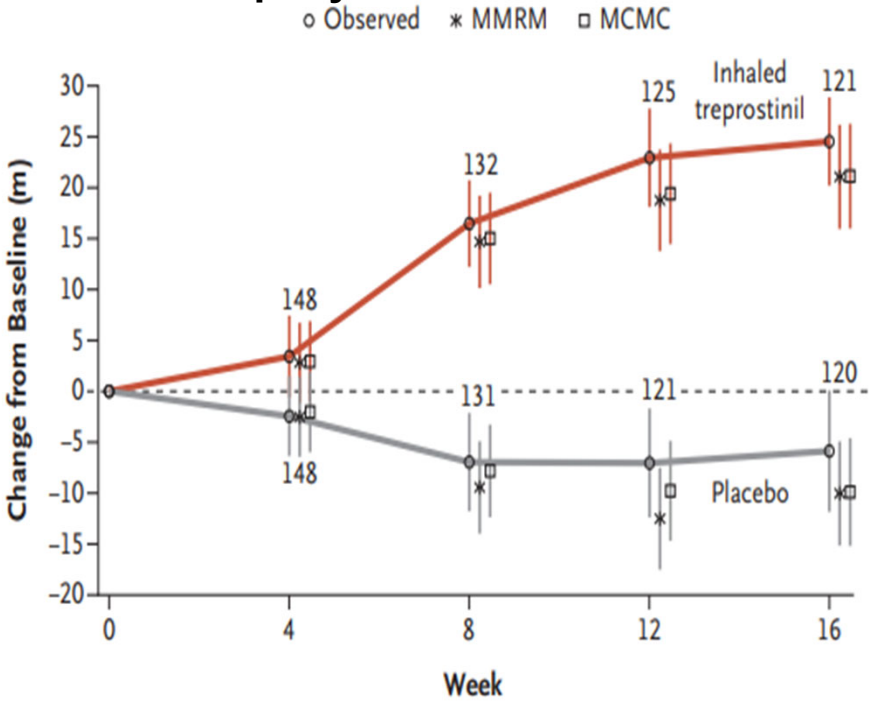
Primary outcome: Exercise capacity measured by 6MWD (1)

Data include observed, and 2 modelled analysis approaches to account for missing data- mixed model repeated measurement (MMRM) and Markov chain Monte Carlo method. Company chose MMRM

Company: Absolute change from baseline to end of INCREASE (week 16) showed statistically significant improved 6MWD for inhaled treprostinil compared with placebo

EAG: Mean change from baseline suggests marginal clinical benefit in 6MWD for inhaled treprostinil

Mean change from baseline 6MWD in INCREASE based on company's modelled methods



Mean change from baseline 6MWD in INCREASE modelled and naïve results

	Change in 6MWD (metres) baseline to week 16 (n=163 each arm)	
	Inhaled treprostinil	Placebo
Company- MMRM change in peak 6MWD (SE)	+21.08 (5.12)	-10.04 (5.12)
EAG- Mean change from baseline (SD) at week 16	[redacted]	[redacted]
Company- Mean difference (MMRM)	+31.12 metres (95% CI, 16.85, 45.39) p<0.0001	
EAG- Mean difference (naïve)	[redacted]	

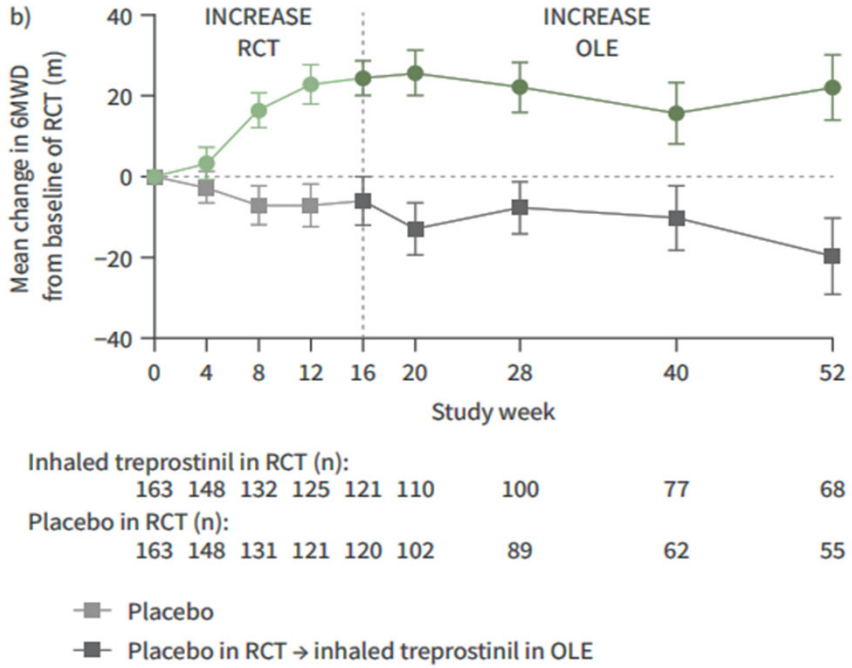
Abbreviations: OLE, open label extension; 6MWD, six minute walking distance

Primary outcome: Exercise capacity measured by 6MWD (2)

EAG: Mean change from baseline most relevant measure. Modest effect size, broad confidence intervals, and similar rate of decline in 6MWD in OLE between study arms raise questions about long-term clinical value from inhaled Treprostinil. Small sample sizes so uncertain

Change from baseline (MMRM method) in INCREASE and early stages of OLE

The MMRM estimate reflects a modelled trajectory and not the raw mean.



Change from baseline (no formal analysis) in INCREASE OLE. Taken from CSR

[redacted]

Is the modelled approach or the observed approach the most appropriate method to interpret the results of exercise capacity?

Abbreviations: CSR, clinical study report; MMRM, mixed model repeated measures; OLE, open label extension; 6MWD, six minute walking distance

Key issues: Overall survival: Adjusting for crossover from INCREASE to OLE (1)

Background

- All people entering the OLE received inhaled treprostinil, including those who had been in the placebo arm of INCREASE RCT

Company: Explored IPCW but applied RPSFT in line with NICE TSD 16 and 24

- RPSFT is most appropriate adjustment because all control patients switched to inhaled treprostinil. It is a robust method for adjusting survival estimates if switching is extensive but IPCW prone to bias
- See link for HRs from the analyses adjusted with IPCW, RPSFT and conventional ITT analysis

EAG: Explored impact of IPCW approach but prefers to apply no adjustment

- Consider OS data immature, with the median OS not reached and unclear if survival benefit needs adjusting
- RPSFT assumes a constant treatment effect regardless of timing or duration, but in PH-ILD, starting treatment early and dose escalation of inhaled treprostinil appear influential
- Hazard ratio for RPSFT diverges markedly from hazard ratio for ITT analysis and Kaplan Meier estimates lacks face validity
- IPCW may be more plausible estimate: covariates included were comprehensive but only a few people did not switch to inhaled treprostinil so estimates may be unreliable and biased
- A recensoring scenario (NICE TSD 16) may also be required
- 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.

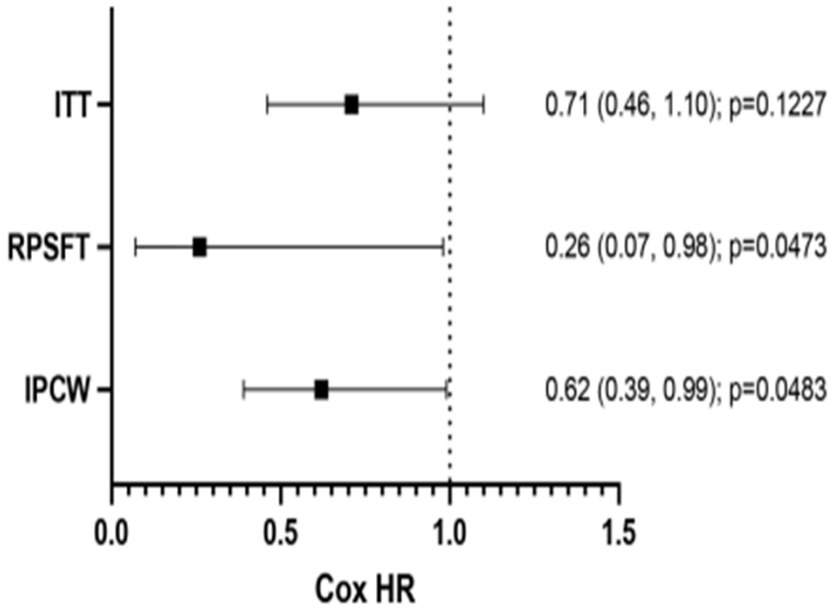
NICE

Abbreviations: IPCW, inverse probability of censoring weighting; OLE, open label extension; PH-ILD; pulmonary hypertension with interstitial lung disease; RPSFT, rank-preserving structural failure time;

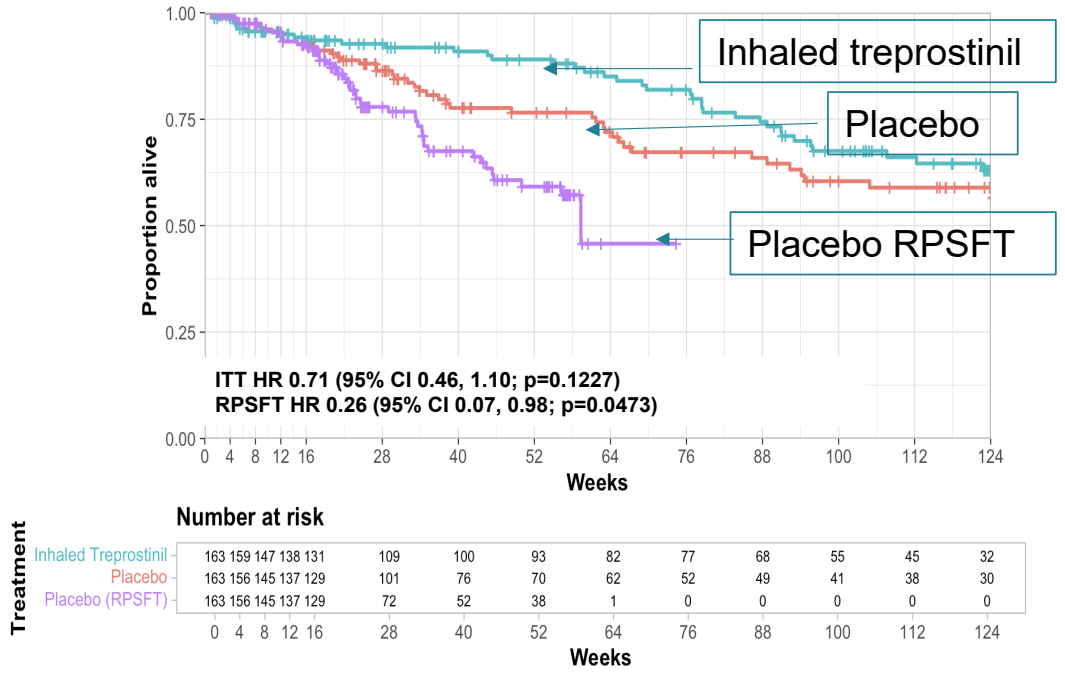
Key issues: Adjusting for crossover from INCREASE to OLE (2)

EAG: Results across other outcomes do not show a clear benefit of treprostinil in people who switched from placebo. So unclear if a survival benefit needs adjusting.

OS HR estimates in INCREASE and OLE comparing ITT population with crossover adjusted analyses



Kaplan-Meier plot of OS in INCREASE and OLE



- Should data be adjusted for crossover?
- If so, is the IPCW or RPSFT approach preferred?
- Should a scenario of re-censoring data also be explored?

Abbreviations: IPCW, inverse probability of censoring weighting; ITT, intention go treat; OLE, open label extension; RPSFT, rank-preserving structural failure time;

Link*

Key issues: Indirect comparison

Distribution in INCREASE, Covariates in MAIC, and characteristics from Dawes and Yogeswaran Taken from table 1 in EAG report addendum

Effect modifier	Original distribution in INCREASE (N=163)	MAIC population in INCREASE (un-weighted)	MAIC population in INCREASE (weighted)	Distribution Dawes et al. (2022) (N=50)	Yogeswaran N=511
Mean age in years [median]	65.6	68.36	65.0	65.0	Not reported [67.0]
Sex (proportion male)	0.48	0.59	0.42	0.42	0.52
6MWD in 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 % predicted (median)	63.0	67.0	59.0	59.0	NR
FVC % predicted (median)	60.0	NA	NA	57.0	58 (24% 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

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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

Key issues: MAIC: uncertain efficacy of best supportive care

Background

- Company's SLR only identified the INCREASE trials and a study by Dawes et al (2022)
- EAG consider other studies could have been more relevant for inclusion in a MAIC

Company: MAIC: statistically significant OS benefit for inhaled treprostinil vs BSC

- Sourced Dawes et al. (2022), as comparator study;
  - Retrospective cohort in people with PH-ILD treated with or without PDE5is;
- Carried out analysis on people treated with inhaled treprostinil in INCREASE and OLE and people treated with PDE5i in Dawes et al. n= 128 had PH-ILD

EAG: Limitations with Dawes so results not reliable. Suggested alternative source for ITC

- Retrospective design of Dawes introduces potential confounding and selection bias.
- Measurement tools not fully validated for PH-ILD (CPI, emPHasis-10), and selective use of RHC may limit generalisability
  - EAG clinical experts note male predominance in IPF but in Dawes only 20% (15 of 74) were male
  - Excluded connective tissue disease patients so limits generalisability to NHS clinical practice
- Results suggest benefit. But uncertain if this this can be attributed to inhaled treprostinil:
- UK database of primary care and hospital data in group 3 PH-ILD patients (CPRD) is an alternative source
  - Naïve comparison of CPRD study suggest cost effectiveness of inhaled treprostinil is dominated by RHC population so company could implement MAIC adjusting for age and sex differences between sources

Is Dawes an appropriate source or should a MAIC including the CPRD dataset be explored?

NICE

Abbreviations: CPI, Composite Physiologic Index; CPRD, Clinical Practice Research Datalink; IPF, , Idiopathic pulmonary fibrosis; MAIC, matched adjusted indirect comparison; PH-ILD, pulmonary hypertension with interstitial lung disease; RHC right heart catheterisation;

Key issues: MAIC analysis compared with PDE5is: Methods

Background

- EAG deemed PDE5is a relevant comparator
- Company conducted MAIC after EAG report (Dawes et al 2022). But maintains PDE5is not relevant

Company: MAIC methodology

- Did unanchored MAIC against PDE5is to assess OS from inhaled treprostinil in PH-ILD
- Inhaled treprostinil from INCREASE and INCREASE OLE vs PDE5is from Dawes et al.
- In Dawes time since diagnosis was zero but in INCREASE diagnosis could have been up to 13 years before study entry. So analyses:
  - assumed no unmeasured confounding variables
  - excluded people in INCREASE with time since diagnosis of more than 2 years and people with connective tissue disease to allow meaningful comparisons with Dawes population
- Presented ICERs with PDE5i proportions:
  - 8% based on CPRD data
  - 10% based on NHSE estimate

EAG: Critique of MAIC methodology

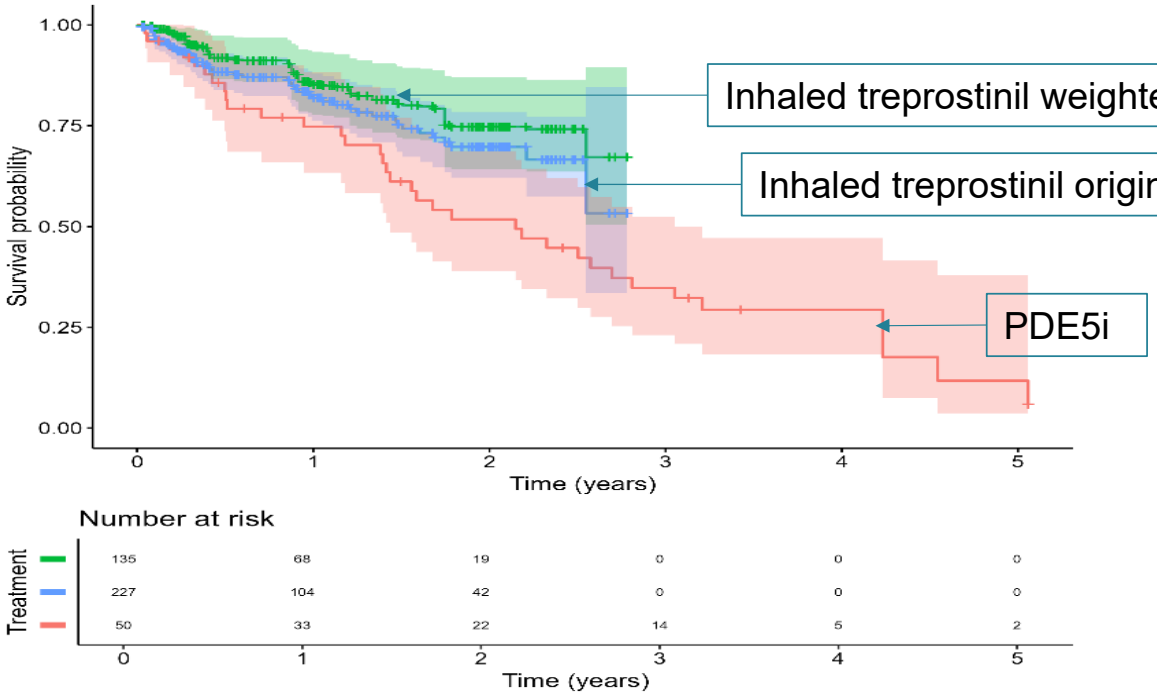
- Note limitations with Dawes (retrospective, risk of selection bias, unclear reporting on covariates- smoking status and BMI). Identified alternative source: Yogeswaran et al (2025)
  - N= 511 of 940 adults with PH-ILD (WHO group 3.2) had PDE5is. Global, multi-centre (including UK)
- Potential MAIC with Yogeswaran- population appropriate but has limitations
  - missing data and potential for bias
  - data collection spans 30+ years (PH definitions and management strategies have evolved in that time)
- EAG clinical experts support generalisability of Yogeswaran et al.
- Naïve comparison with Yogeswaran is more reliable than a MAIC with Dawes and INCREASE population appears to be more similar to Yogeswaran than Dawes

NICE

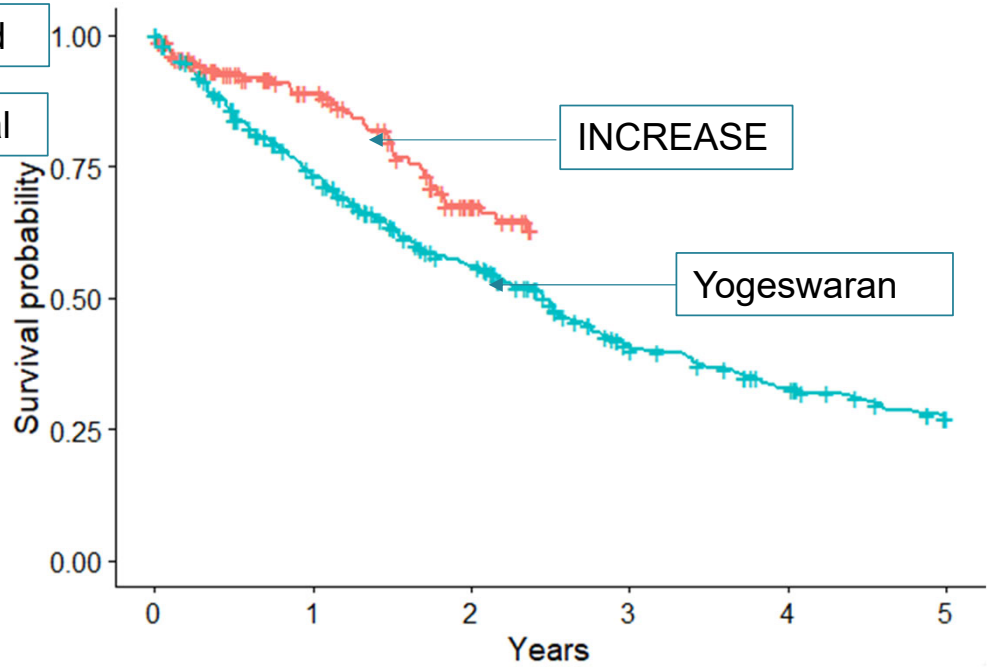
Abbreviations: ICER, Incremental cost-effectiveness ratio; MAIC, matched adjusted indirect comparison; OLE, open label extension; PDE5i, PDE5 inhibitors; PH pulmonary hypertension; PH-ILD, pulmonary hypertension with interstitial lung disease .

Key issues: ITC: MAIC analysis compared with PDE5is: Results

Kaplan Meier for inhaled treprostinil, weighted treprostinil (INCREASE) and PDE5i (Dawes et al.)



Naïve comparison of overall survival from INCREASE and Yogeswaran (EAG preferred approach)



Results

Company: MAIC show more people having inhaled treprostinil vs those having PDE5is alive at 2 and a half years

EAG: Cautious in interpreting MAIC from Dawes et al: a naïve comparison of Yogeswaran is more relevant

Abbreviations: ITT, intention to treat; MAIC, matched adjusted indirect comparison; PDE5i, phosphodiesterase type 5 inhibitors

Key issues: ITC: MAIC analysis: Results compared with all comparators

PDE5is vs Treprostinil- OS relative efficacy

Source	HR (95% CI)	Preference
MAIC INCREASE vs Dawes	0.44 (0.24, 0.80)	Company
Naive INCREASE vs Dawes	0.58 (0.36, 0.95)	
Naïve INCREASE vs Yogeswaran	0.63 (0.45, 0.89)	EAG

BSC vs Treprostinil- OS relative efficacy

Source	HR (95% CI)	Preference
ITT INCREASE	0.71 (0.46, 1.10)	EAG
RPSFT INCREASE	0.26 (0.07, 0.98)	Company
IPCW INCREASE	0.62 (0.39, 0.99)	
MAIC INCREASE vs Dawes	0.16 (0.09, 0.28)	
Naive INCREASE vs Dawes	0.28 (0.19, 0.40)	

Company: incremental benefit vs PDE5is. This was more favourable than EAG's preferred comparison vs BSC (unadjusted ITT analysis). So EAG's BSC comparison likely inappropriately conservative.

EAG: High degree of uncertainty due to varying estimates by source and statistical adjustment. Pattern of MAIC HRs more favourable than naïve even when comparing to RWD- may lack face validity

Naïve comparison with PDE5i is limited due to being a naïve comparison of a real-world and trial dataset and may explain the unexpected implied difference that PDE5is are inferior to BSC

- Which data source and approach should be used to compare inhaled treprostinil with PDE5is?
- Do these results align with the results comparing inhaled treprostinil with BSC?

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Abbreviations: ITT, intention to treat; MAIC, matched adjusted indirect comparison; PDE5i, phosphodiesterase type 5 inhibitors

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Other considerations
- ❑ Summary

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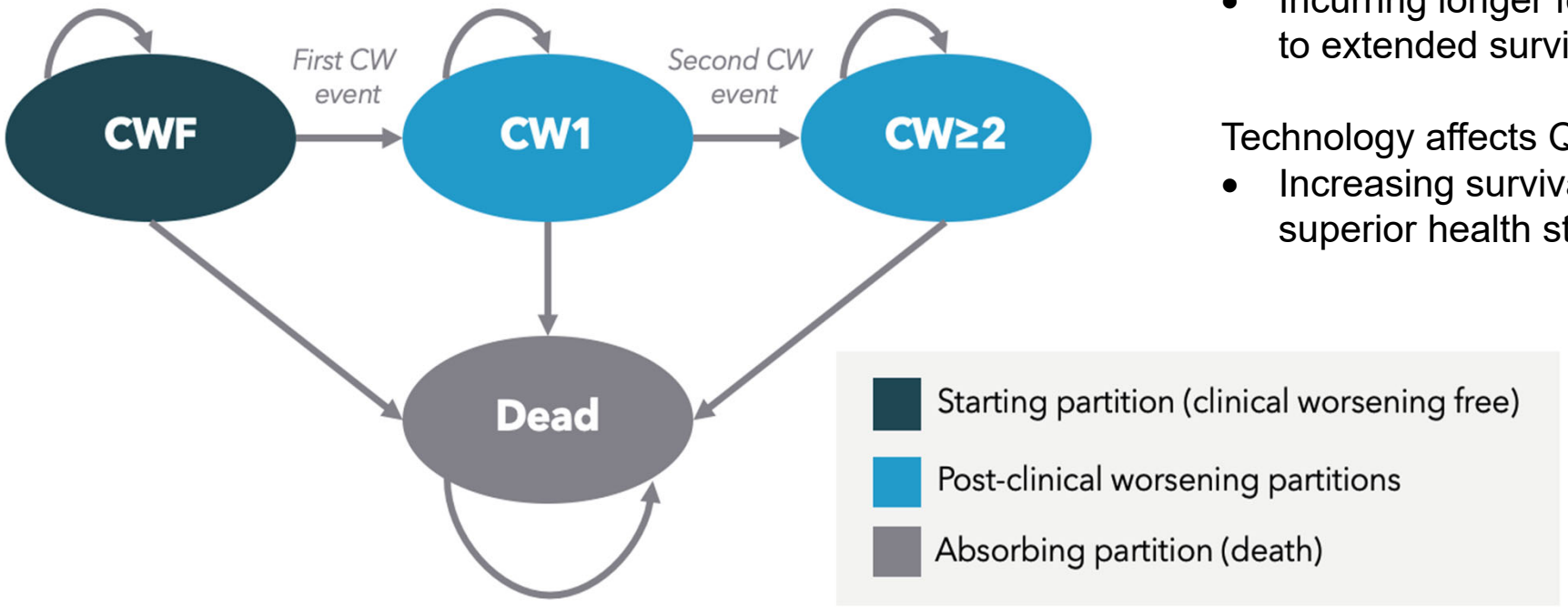
Company's model overview

De novo partitioned survival model with four health states



Technology affects costs by:

- Having a higher acquisition cost than current care.
- Incurring longer follow-up costs due to extended survival time.

Technology affects QALYs by:

- Increasing survival and time spent in superior health states

See link to baseline characteristics in model

Abbreviations: BSC, best supportive care; CW1, first clinical worsening event; CW≥2, two or more clinical worsening events; CWF, clinical worsening-free; ICER, incremental cost- effectiveness ratio; OLRE open label extension; OS, overall survival; PH-ILD, pulmonary hypertension with interstitial lung disease; QALY, quality adjusted life year; TTD, time to treatment discontinuation;

Large impact

Key Issue: Extrapolating overall survival for inhaled treprostinil (1)

Background

- Company fit a Weibull model to extrapolate OS in the inhaled treprostinil arm in its base case.
- EAG consider this too optimistic and prefers the generalised gamma model in its base case

Company

- Held a workshop with UK clinicians (N=2) in April 2025 and discussed extrapolations
- Used INCREASE and OLE data to inform OS in the inhaled treprostinil arm
- Weibull distribution fits best practice. It ranked third by BIC and AIC
  - Exponential provided best statistical fit based on BIC but UK clinicians considered it too optimistic
  - Gompertz distribution ranked second by BIC but UK clinicians considered it overestimated mortality

EAG

- Agrees INCREASE data is most appropriate to inform OS in the inhaled treprostinil arm
- Weibull extrapolation is too optimistic. It assumes a constant hazard so only captures a small increase in the hazard rate over time, but Kaplan Meier function shows an increasing hazard rate.
- Gompertz and Generalised gamma best capture the increasing hazard rate, though neither represent the observed period very well
- Base case uses generalised gamma, Scenario analysis using Gompertz

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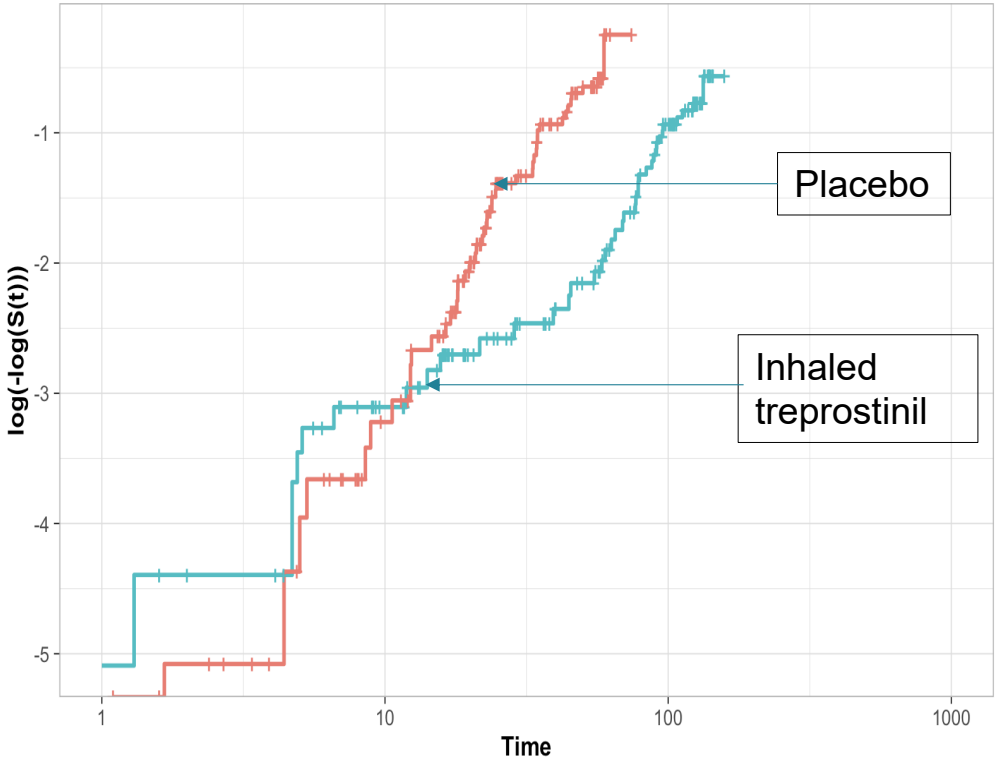
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OLE, open label extension; OS overall survival ,

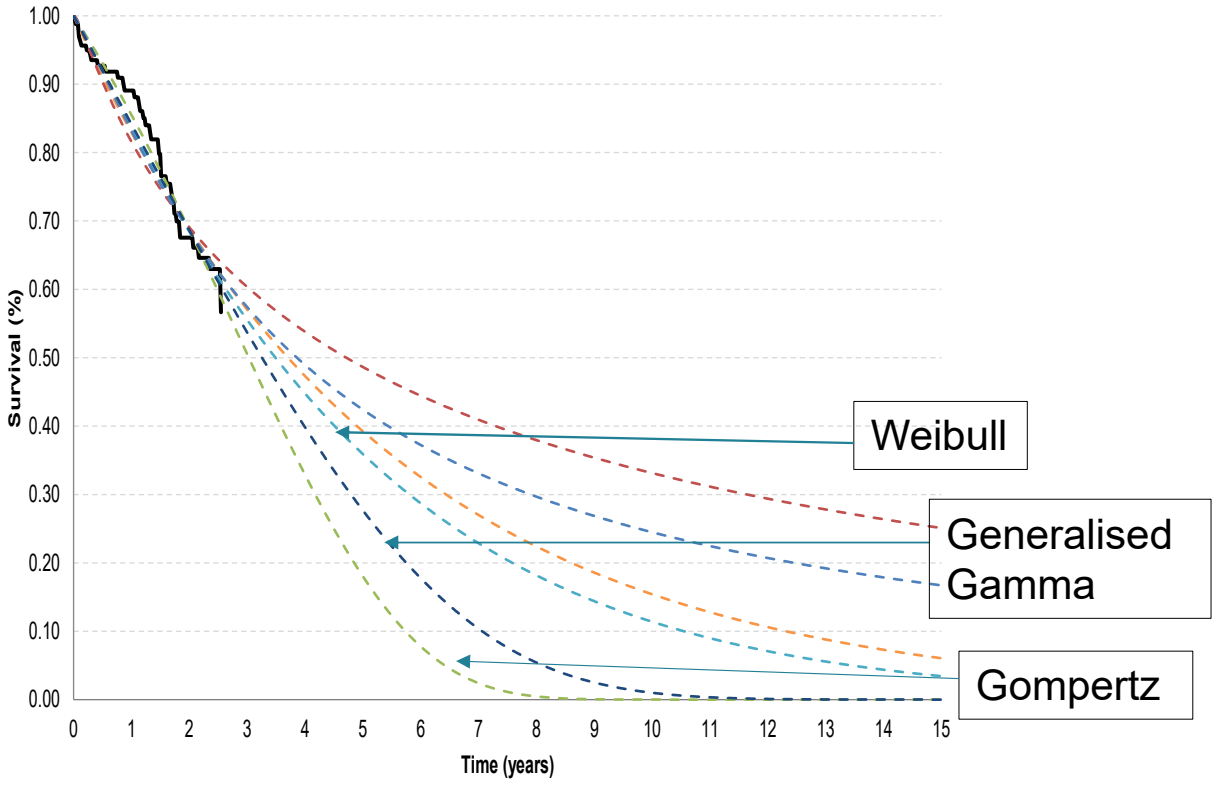
Large impact

Key Issue: Extrapolating overall survival for inhaled treprostinil (2)

Log-log hazard plot based on survival data underpinning base case (inhaled treprostinil vs RPSFT-adjusted placebo).



Overall survival extrapolation for inhaled treprostinil arm



Which is the most appropriate extrapolation for modelling OS with inhaled treprostinil?

Key Issue: Extrapolating overall survival for BSC

Large impact

Background

- People in the placebo arm of INCREASE crossed over to inhaled treprostinil for the OLE
- Company base case- adjusted trial data using RPSFT and used Weibull distribution
- EAG used INCREASE OLE ITT data (unadjusted) due to uncertainty if OS benefit was obtained by switching

Company

- INCREASE crossover-adjusted data most appropriate source for informing OS in BSC arm
  - Both inhaled treprostinil and BSC arms are based on INCREASE and RPSFT is commonly used and in line with TSD 24
- Weibull distribution for BSC arm:
  - Second-best fitting model based on AIC and BIC and extrapolations more aligned with clinical expectations, showing low survival at five years
  - TSD 14 recommended applying separate parametric models of the same type in each arm.

EAG

- Previously noted concerns with RPSFT so preferred to use INCREASE OLE ITT data due to uncertainty whether any OS benefit was obtained by switching
- Applied ITT hazard ratio (assuming proportional hazards), to inhaled treprostinil and extrapolated with Generalised Gamma distribution

How should OS for BSC be extrapolated considering the crossover?

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Abbreviations, AIC, AIC: Akaike Information Criterion; BIC, Bayesian Information Criterion; BSC, best supportive care; ITT, intention to treat; OLE, open label extension; OS, overall survival; RPSFT, rank preserving rank-preserving structural failure time model

Medium impact

Key Issue: Extrapolating time to treatment discontinuation (1)

Background

- Company used Generalised Gamma to extrapolate TTD in the inhaled treprostrinil arm of its base case
- EAG consider company's model underestimates treatment duration with inhaled treprostinil so applied a constraint to modelling TTD

Company Applied generalised gamma to TTD informed by INCREASE–OLE data

- TTD only directly impacts the drug cost component because efficacy for people stopping treatment had already been captured

EAG Company's TTD modelling underestimates number staying on treatment:

  - proportion staying on treatment at 30 years is 7.4%
  - Based on final data cut of the OLE EAG calculated treatment persistence in surviving patients is 37% KM data for inhaled treprostinil shows the TTD curve closely aligns with proportion having 2 or more clinical worsening events (CW2) but TTD extrapolation is below CW2 so inconsistent with trial

- May lead to implausibly low treatment duration estimates and underestimated drug cost
- EAG's clinical adviser confirmed that discontinuation after a second clinical worsening event is a reasonable and clinically plausible assumption.
- Preferred base case: generalised gamma but with a constraint that TTD does not fall below CW2 and a scenario that proportion of surviving people having treatment stays at or above 37%

Abbreviations: CW, clinical worsening, KM Kaplan Meier, OLE, open label extension TTD, time to treatment discontinuation

Medium impact

Key Issue: Extrapolating time to treatment discontinuation (2)

Relationship of time-to-event outcomes for company's modelling of inhaled treprostinil

EAG: In the plot CW2 and TTD are similar but in the extrapolated models, the extrapolation for TTD falls below CW2

Should a constraint be applied to model the treatment duration of inhaled treprostinil?

Link*

Abbreviations: CW2, 2 or more clinical worsening events; TTD, time to treatment discontinuation

Key issue: Choice of utility values

Small impact

Background: Company used a univariate analysis of INCREASE SGRQ data mapped to EQ5D utilities but EAG considers a multivariate analysis ensures more reliable HRQoL estimates

Company: Did not identify studies to inform HRQoL in model but used SGRQ from INCREASE to capture HRQoL - unvalidated for PH-ILD but experts agreed most appropriate tool

- Mapped SGRQ values to EQ-5D utilities using Freemantle and Starkie algorithms
  - but excluded HRQoL data from week 108 INCREASE due to small sample size
- Carried out a univariate descriptive analysis and multivariate regression analyses
- Base case: univariate mapped using Freemantle Multivariate showed smaller differences between health states than the univariate analysis and experts deemed clinically plausible to use univariate analysis so adopted this in base case

EAG: Lack of validation of SGRQ- result in measurement uncertainty;

- May overestimate HRQoL and risk inaccurate estimates for severe health states but agree no better alternative
- Suggest long term approach to validate HRQoL tools in PH-ILD population and incorporate utility data beyond Week 48

Prefers multivariate approach

- Accounts for covariates (age, sex and baseline SGRQ) and repeated measures and statistical adjustments makes this more robust Base case: multivariate mapped using Freemantle
- but 2 scenario analyses had small impact
  - Company's univariate approach
  - Starkie algorithm to less relevant disease population

- IS the SGRQ tool appropriate to capture HRQoL in PH-ILD?
- Should a univariate or multivariate approach be used to analyse utilities?

Abbreviations: HRQoL, health related quality of life;; PH, pulmonary hypertension; ILD, interstitial lung disease: SGRQ ,Saint George's Respiratory Questionnaire

HRQoL inputs mapped to EQ5D

Key Issue Inhaled treprostinil compared with PDE5i (1)

Large impact

Background

- Company provided scenario analyses after EAG report comparing inhaled trepostinil to mixed comparator of BSC and PDE5is
- EAG noted methodological concerns with the company's approach

Company

- Assume 8% or 10% had PDE5is, (based on CPRD and NHSE estimates)
- Compared each proportion with BSC and extrapolated OS using base case and EAG preferred distribution
- Results based on weighted average of ICERs across people having PDE5i and those not having PDE5is.

EAG:

- Standalone analysis using PDE5is as the comparator may be more appropriate (100% weighting), but scenario analyses including 54% (proportion in Yogeswaran et al.) and 8% (CPRD data)
- Company included benefit of PDE5i treatment (sildenafil) but not drug costs so likely to bias results
- Company use PDE5i OS HR from MAIC with Dawes. EAG prefer naïve comparison with Yogeswaran
  - Yogeswaran- multi-centre dataset, larger UK sample (n=138) than Dawes (n=128); emerging data and analyses in Yogeswaran likely influence onwards prescribing practices
- Weighted approach is mathematically invalid : ICERs cannot be combined arithmetically magnitude of bias increases with a higher proportion of people having PDE5s
- Applying weights at the end of the model ignores time-dependent effects. It is more appropriate to apply weights across all model cycles to OS, PFS, costs, and QALYs- but difference between method's is minor

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Abbreviations: BSC, best supportive care; CPRD, clinical practice research datalink; HR, hazard ratio; MAIC, matched adjusted indirect comparison; OS, overall survival; PDE5i, PDE5 inhibitor

Large impact

Key Issue Inhaled trepostrinil compared with PDE5i (2)

Assumption 1: Indirect comparison approach

Option 1:
Company analyses:
MAIC based on Dawes

Option 2:
EAG analyses:
Naïve comparison with Yogeswaran

Assumption 2: Proportion having PDE5is

Option 1:
Company analyses
PDE5i costs excluded:
- 8% having PDE5is
- 10% having PDE5is
- Noone having PDE5is

Option 2:
EAG analyses
PDE5i cost of sildenafil only included:
- 54% having PDE5is
- 8% having PDE5is
- Noone having PDE5is

Assumption 3:OS HR from INCREASE data

Option 1:
Company analyses:
based on INCREASE data adjusted with RPSFT

Option 2:
EAG analyses:
Based on INCREASE unadjusted data

- Which data source and approach should be used to compare inhaled treprostinil with PDE5is?
- Should costs of PDE5is be included? If so, is the cost of sildenafil only appropriate?
- What proportion is most representative of PDE5i use in clinical practice?
- Should data be adjusted for crossover? If so, is the RPSFT approach preferred?

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case considered as key issues

Assumption	Company base case	EAG preferred base case	Impact
OS for inhaled treprostinil	Source: INCREASE-OLE ITT Distribution: Weibull	Source: INCREASE-OLE ITT Distribution: Generalised gamma	large
OS for BSC	Source: Crossover analysis adjusted INCREASE data Distribution: Weibull	Source: Using the INCREASE-OLE ITT HR (BSC vs inhaled treprostinil) Distribution: Gen. gamma	large
TTD for inhaled treprostinil	Source: INCREASE-OLE Distribution: Generalised gamma	Source: INCREASE-OLE Distribution: Generalised gamma, (constraint: TTD does not fall below CW2)	medium
HRQoL- type of utility	Univariate analysis of INCREASE OLE treatment-independent SGRQ data	Multivariate analysis of INCREASE OLE treatment-independent SGRQ data	small
PDE5i comparison	Not relevant. MAIC vs Dawes. 8% or 10% PDE5i scenarios	Relevant. Naïve comparison with Yogeswaran. Up to 54% PDE5i	large

see link for other differing assumptions between company and EAG base case.
These had a small impact on ICER

Abbreviations: BSC, best supportive care; CW2, proportion having 2 or more clinical worsening events; HR, hazard ratio; OLE open label extension; OS overall survival; PDE5i, PDE5 inhibitor; SGRQ, Saint George's Respiratory Questionnaire

All ICERs are reported in PART 2 because they include confidential discounts

Company presented base case comparing inhaled treprostinil with BSC only. ICER was within the range normally considered an effective use of NHS resources.
Scenario analyses comparing inhaled treprostinil with PDE5 inhibitors (with 8% or 10% PDE5i use and remaining proportion having BSC)

The EAG preferred base case comparing inhaled treprostinil with BSC substantially increased the ICER above the range normally considered an effective use of NHS resources.
Scenario analyses explored 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.

Both company and EAG analyses apply a severity modifier of 1.2
Assumptions with the greatest effect on the ICER include:

- extrapolation for inhaled treprostinil OS;
- choice of hazard ratio for modelling BSC
- approach to modelling TTD for inhaled treprostinil

The most influential drivers of cost-effectiveness results are survival assumptions for BSC and inhaled treprostinil

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.
    - company noted plans to develop and validate an algorithm that predicts EQ-5D utilities from emPHasis-10 in people 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.
    - company stated it is exploring the feasibility of using the UKRB registry to address the uncertainty around the accuracy of the utility values within the economic model.

Abbreviations: ASPIRE, Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre Registry; HSUV, health state utility value; PH-ILD, pulmonary hypertension with interstitial lung disease; UKRB, Royal Brompton hospital pulmonary hypertension registry in the United Kingdom

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Key issues

Issue	ICER impact
Implementation: • Is there a timeframe for titrating the dose of inhaled treprostinil? Will people have background medicines in clinical practice? Are they treatment effect modifiers? • Is the proportion having background medicines in INCREASE representative of clinical practice? • What is the age and severity at diagnosis of PH-ILD? How many PH centres diagnose using RHC? How would implementation impact upon PH centres? • Is inhaled treprostinil intended for home treatment? How often will people having treatment be monitored? How will care teams be co-ordinated to ensure safe delivery and treatment monitoring to mitigate adverse effects?	Unknown
Comparators: • What proportion have PDE5is in clinical practice? Are PDE5is given in severe cases?	Large
Clinical effectiveness: • Is the modelled approach or the observed approach the most appropriate method to interpret the results of exercise capacity? • Should data be adjusted for crossover? If so, is the IPCW or RPSFT approach preferred? Should a scenario of re-censoring data also be explored? • Is Dawes an appropriate source or should a MAIC including the CPRD dataset be explored? • Which data source and approach should be used to compare inhaled treprostinil with PDE5is? • Do these results align with the results comparing inhaled treprostinil with BSC?	Unknown
Modelling overall survival: • Which is the most appropriate extrapolation for modelling OS with inhaled treprostinil? • How should OS for BSC be extrapolated considering the crossover?	Large
Modelling time to treatment discontinuation: • Should a constraint be applied to model the treatment duration of inhaled treprostinil?	Medium
Utilities: • IS the SGRQ tool appropriate to capture HRQoL in PH-ILD? • Should a univariate or multivariate approach be used to analyse utilities?	Small

Inhaled treprostinil for treating pulmonary hypertension caused by interstitial lung disease

Supplementary appendix

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Background on pulmonary hypertension (PH) and interstitial lung disease (ILD) WHO classification

World Health Organisation classification of pulmonary hypertension

Group 1: Pulmonary arterial hypertension	Group 2: PH associated with left heart disease	Group 3: PH associated with ILD and/or hypoxia	Group 4: PH associated with chronic pulmonary artery obstructions	Group 5: PH with unclear and/or multifactorial mechanisms

*see link for background to ILD-PH

Abbreviations: ILD, interstitial lung disease; PH, pulmonary hypertension; WHO, World Health Organisation

INCREASE and INCREASE OLE study characteristics

link

	INCREASE			INCREASE OLE

Inclusion criteria	• People aged 18 years or over
	• WHO group 3 PH and evidence of parenchymal lung disease
	• Baseline 6MWD ≥100m
	• Baseline FVC <70 % and PH due to connective tissue disease
	• Right heart catheterisation showing
	  • PVR>3 wood units
	  • PCWP≤ 15mmHg
	  • Mean PAP≥ 25mmHg
				Adults with PH-ILD who either
				• Stayed on study drug and completed all scheduled visits in INCREASE or
				• Permanently stopped having the study drug due to clinical worsening and completed all scheduled visits in INCREASE or
				• Enrolled in INCREASE at trial discontinuation

Outcomes	Primary outcome: • 6MWD at 16 weeks	Secondary outcomes: • NT-ProBNP at 16 weeks; • Time to clinical worsening; • 6MWD at 12 weeks and 15 weeks	Exploratory outcomes: • 6MWD at 4 weeks; • QoL at 16 weeks; • Distance saturation product at 16 weeks	• 6MWD • NT-ProBNP concentration • SGRQ • Distance saturation product • Optional biomarkers

Company's model overview- Baseline characteristics

Table: Baseline characteristics used in the company's cost-effectiveness model based on INCREASE

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)

*No UK patients were included in INCREASE, but company's clinical experts considered the study population to be broadly generalisable to people in NHS clinical practice.

EAG: Heterogeneous population at baseline.
One person may be healthier than another after two worsening events

Company: modelled cohort reflects heterogeneity in INCREASE and includes varying forms of ILD, and different levels of disease severity

Abbreviations: CPFE, Combined pulmonary fibrosis and emphysema; PVR, Pulmonary vascular resistance.

Link*

Key issue: Choice of utility values

Small impact

Company base case- HRQoL inputs mapped to EQ5D with Freemantle algorithm and univariate analysis

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]					

univariate, treatment-independent SGRQ values were taken from INCREASE OLE (week 48) and mapped to EQ-5D utilities using Freemantle algorithm
BSC values were assumed to be equivalent to those for inhaled treprostinil across all health states.

EAG base case- HRQoL inputs mapped to Freemantle algorithm and multivariate 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]					

Multivariate included 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.

link

Abbreviations: AF, adjustment factor; CW, clinical worsening; CWF, clinical worsening-free; SGRQ, Saint George's Respiratory Questionnaire.;

Small impact

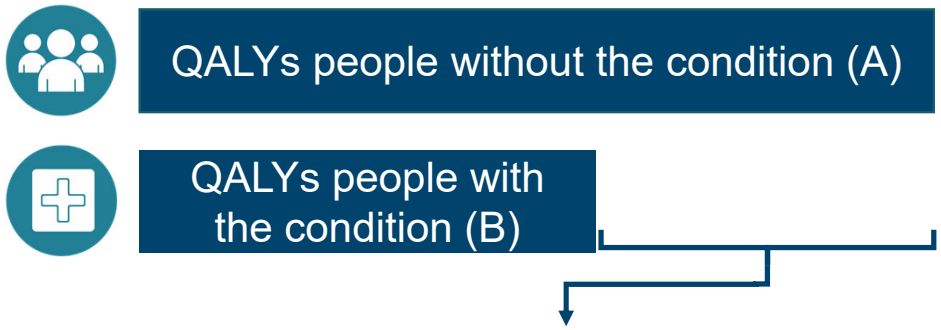
Other assumptions contributing to company and EAG base case

Assumptions in company and EAG base case with only a small impact on cost-effectiveness results link

Assumption	Description	Company base case	EAG preferred base case
Time to first CW1 for inhaled treprostinil	EAG: Company chose separate models for inhaled treprostinil and BSC. This may be influenced by different follow-up lengths and could be a source of bias	Source: INCREASE-OLE Distribution: Log-normal	Source: INCREASE-OLE Distribution: log-logistic
Time to first CW1 for BSC		Source: INCREASE 16 weeks Distribution: Exponential	Source: INCREASE 16 weeks Distribution: log-logistic
Discount factor	EAG: per-cycle discount rate splits annual discount rate into smaller intervals. Company (7 days) applies discounting earlier than annual approach	Per-cycle (weekly) discount factor- applying for first year (start of model time horizon)	Per-year discount factor- no discount for first year
Dosing and pricing for background medications	EAG: discrepancies in pack sizes, dosing and prices used by company for pirfenidone and nintedanib overestimate BSC cost	Weekly dose of 4,200 mg for nintedanib and applied an eMIT price of £106 per 84-tablet pack of pirfenidone (801 mg)	Used lower weekly dose of 2,100 mg for nintedanib and applied most recent eMIT price of £61.45 per 84-tablet pack of pirfenidone (801 mg).
Ongoing resource use and cost	EAG: Company's inputs underestimate use compared with data in CPRD report	Ongoing costs were mainly specialist outpatient visits, with assumptions such as 50% oxygen use post-CW	Replaced ongoing resource use with UK-specific values from CPRD report and updated assumptions for higher supplemental oxygen use
Cost of lung transplants	EAG: A small number had lung transplants in INCREASE	Excluded costs of lung transplant	Included costs for proportion having lung transplants in INCREASE

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

see link for *