NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Inhaled treprostinil for treating pulmonary hypertension associated with interstitial lung disease

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using inhaled treprostinil in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: January 2026

Note that this document is not NICE's final guidance this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using inhaled treprostinil in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 13 February 2026
- Second evaluation committee meeting: To be confirmed
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Inhaled treprostinil should not be used to treat pulmonary hypertension associated with interstitial lung disease (WHO group 3) in adults.

1.2 This recommendation is not intended to affect treatment with inhaled treprostinil that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Inhaled treprostinil is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that inhaled treprostinil offers benefit or is value for money in this population.

Why the committee made these recommendations

Usual treatment for pulmonary hypertension associated with interstitial lung disease is best supportive care.

Clinical trial evidence shows that inhaled treprostinil improves exercise capacity compared with placebo. But this is uncertain because of the trial design.

Results from an indirect comparison of inhaled treprostinil against best supportive care are also uncertain. This is because the study population is not representative of the likely NHS population.

There are uncertainties in the economic model, including the assumptions about how long people live and how long they have treatment with inhaled treprostinil. The model also does not include any implementation costs.

Because of the uncertainties in the economic model and clinical evidence it is not possible to determine the most likely cost-effectiveness estimates for inhaled treprostinil. So, it should not be used.

2 Information about inhaled treprostinil

Anticipated marketing authorisation indication

2.1 Inhaled treprostinil (confidential brand name, Ferrer) does not have a marketing authorisation in the UK yet. The anticipated marketing authorisation for inhaled treprostinil is for 'the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability'.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for inhaled treprostinil.

Price

2.3 The list price of inhaled treprostinil is confidential.

2.4 The company has a commercial arrangement, which would have applied if inhaled treprostinil had been recommended.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Ferrer will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Ferrer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Interstitial lung disease (ILD) encompasses a group of lung disorders characterised by inflammation and fibrosis of the lung parenchyma (the functional tissue of the lung). It can cause progressive scarring of the lung interstitium (the tissue surrounding the air sacs). The patient experts explained that living with ILD is devastating. People can have breathlessness and find it difficult to walk short distances or do daily activities. Other common symptoms are cough and fatigue. People may depend on oxygen therapy, and this can create challenges for daily living. It can be difficult to leave the house or travel because the oxygen equipment may be bulky, and this can have an impact on mental health. As ILD progresses, it can cause chronic hypoxia, fibrosis and inflammation and can lead to pulmonary hypertension (PH). This causes increased pressure in the pulmonary arteries. One clinical expert stated that people can have severe PH (defined haemodynamically as mean pulmonary arterial pressure of more than 20 mmHg, pulmonary arterial wedge pressure of at least 15 mmHg and pulmonary vascular resistance of more than 5 Wood units [WU]). A patient expert explained that developing PH on top of interstitial lung disease (referred to from here as PH-ILD) exacerbates the existing symptoms and can speed up the progression of the disease. People with PH-ILD can have a much worse prognosis than those with ILD alone, and this can exaggerate the symptoms of PH. He explained that people with PH-ILD have a predicted life expectancy of between 3 and 6 years.

Treatments and comparators

3.2 There are no licensed treatment options for PH-ILD. People who do not have severe PH-ILD (defined as pulmonary vascular resistance of between 2 and 5 WU) are usually monitored and may have treatment for ILD at specialist ILD centres. For this, NICE has recommended antifibrotics: nintedanib for progressive fibrosing interstitial lung disease

excluding idiopathic pulmonary fibrosis and pirfenidone for treating idiopathic pulmonary fibrosis. Idiopathic pulmonary fibrosis is a common form of ILD. But the patient experts explained that the side effects of these antifibrotic treatments can be challenging, so some people stop the treatment. The clinical experts said that the underlying phenotype of PH-ILD guides the most suitable treatment, and treatment is considered on an individual basis. People diagnosed with severe PH-ILD may be referred to a specialist PH centre. Phosphodiesterase 5 (PDE-5) inhibitors, such as sildenafil or tadalafil, are prescribed for pulmonary arterial hypertension (PAH). People with PH-ILD are considered for off-label PDE-5 inhibitors. The company stated that advice from its clinical experts noted that only a small number of people with severe PH-ILD would have off-label PAH treatments like PDE-5 inhibitors. It considered best supportive care (BSC) to be the only relevant comparator, with pirfenidone and nintedanib used as background treatments in some people. It explained that the European Society of Cardiology and the European Respiratory Society suggest that treatment options for PAH are not effective for PH-ILD. The company commissioned a UK-based epidemiological study using Clinical Practice Research Datalink (CPRD) linked with Hospital Episode Statistics (HES) data (see section 3.9). This study reported that only 8% of people with PH-ILD had treatment with sildenafil or tadalafil. So, it said that PDE-5 inhibitors were not standard care for the wider population and were not a relevant comparator. The EAG's clinical adviser noted that PDE-5 inhibitor use varied across specialist PH centres, with some centres reporting that up to 60% of people referred with severe PH-ILD would have PDE-5 inhibitors. The clinical experts explained that because treatment options for PH-ILD are limited, most people would try combination treatment, in which case PDE-5 inhibitors may be considered. They estimated that around 20% to 25% of people with PH-ILD may have PDE-5 inhibitors as their disease progresses. The committee agreed that there is a clear unmet need for effective treatments for people with PH-ILD. It also concluded that PDE-5 inhibitors are a relevant comparator and would like

to see cost-effectiveness analyses comparing inhaled treprostinil with PDE-5 inhibitors (see section 3.15).

Diagnosis and implementation

3.3 PH-ILD is classified by the European Society of Cardiology and the European Respiratory Society as group 3, based on World Health Organization (WHO) functional class. Their guideline recommends that diagnosis of PH-ILD is by right heart catheterisation (RHC) at specialist PH centres. But the clinical experts confirmed that there is regional variation in referral and management of people with PH-ILD across the UK. Referrals to specialist PH centres will typically only occur if severe PH-ILD is suspected, and referral rates tend to be low. In its submission, the company stated that this is mainly because of a lack of approved treatment options for PH-ILD and limited capacity and resources in specialist PH centres. The patient experts agreed that this is why PH-ILD is largely underdiagnosed. A clinical expert explained that people with PH are assessed in one of 7 adult specialist PH centres. A patient expert highlighted the geographical variation in accessing services. The burden of symptoms and level of disability in people with PH-ILD makes it challenging to access these services. In their submission, another patient expert explained that people living in remote areas, far from specialist PH centres, will find it difficult to access RHC diagnosis at these centres. They also noted that some groups may be limited by the cost and effort involved in getting to a specialist PH centre for RHC. A clinical expert explained that although the guidelines recommend RHC is used, in practice it is not always needed to diagnose PH-ILD. Other diagnostic tests, including echocardiography, computed tomography (CT) and lung function tests, are typically used. But RHC is usually needed to identify people with more severe lung disease, so it would be used if treatment is being considered. A patient expert was concerned that if RHC is needed to be eligible for treatment, it would need to be done in PH centres. He explained that these centres are at high capacity because some PH centres already do RHC for cardiac and lung transplants. He emphasised

the need to avoid putting additional pressure on these centres and affecting the clinical services they already provide. The company explained that the European guidelines are due to be updated soon, and this could help to be more precise about who should be referred to PH centres. The clinical experts estimated that adding a new group of people who need RHC and treatment for PH-ILD could increase work capacity in PH centres by 10% to 15%. The committee agreed that the need for increased capacity should be considered. The company explained that it had not included the costs of RHC in its economic analysis because RHC is already needed before treatment starts. The committee concluded that the cost and impact of introducing an RHC diagnosis need to be considered in this evaluation (see section 3.18).

Implementation of inhaled treprostinil

3.4 Inhaled treprostinil is used with an ultrasonic, pulsed-delivery nebuliser that is prepared with a solution each day. Inhaled doses are increased from a starting dose of 3 breaths per session to 12 breaths per session, 4 times a day. The solution cannot be used with other inhalation systems and the inhalation sessions are individually programmed. So, people need to be trained and supervised before they start treatment, then monitored to ensure proper dosing and inhalation technique. A patient expert was concerned about whether treatment would be started in PH centres and explained the challenges relating to increased infrastructure that would be needed (see section 3.3). They added that introducing treprostinil could change the demographic of people seen at PH centres. The clinical experts explained that various approaches are used in practice to limit the impact on specialist services. These include shared-care pathways and multidisciplinary team approaches that provide coordination between diagnostic teams, and staff training in PH centres to deliver treatment and follow up on people having treatment. The committee considered where treatment with inhaled treprostinil would start and be delivered. The clinical experts explained that, based on their experience of prescribing a similar inhaled product used with a nebuliser to treat PAH, treatment

would start in hospital or a specialist PH centre, but with sufficient training could be used at home in the long term. A patient expert highlighted the challenges some people may have when using the device, especially with increased dosing. The patient experts were concerned about the practical demands of treatment. The EAG noted that challenges included mastering breathing techniques, adhering to treatment frequency, and preparing and cleaning the device. A clinical expert highlighted the need for coordination and support across care teams, and the importance of a clear infrastructure for training people in using the device. The company explained that it provides support by a phone line to anyone having inhaled treprostinil in countries where it is already being used. It explained that it intended to support the service delivery of inhaled treprostinil by training nurses to teach patients to use the nebuliser, so that the treatment can be used at home. But it confirmed that it had not included the costs of nurse time and other training in its economic analysis. The committee concluded that it would need to see an exploration of these costs to help inform its decision making.

Clinical effectiveness

INCREASE study

3.5 Clinical-effectiveness data came from the INCREASE trial. This was a phase 3, multicentre, randomised controlled trial comparing inhaled treprostinil (n=163) with placebo (n=163). The inhaled treprostinil solution was administered using an ultrasonic nebuliser (0.6 mg/ml) in up to 12 breaths (total 72 micrograms), 4 times daily. The trial included adults who had:

- a confirmed diagnosis of WHO group 3 PH based on CT imaging and any form of ILD or combined pulmonary fibrosis and emphysema
- diffuse parenchymal lung disease confirmed with CT imaging within 6 months before starting the trial

- RHC diagnosis in the past year that was greater than 3 WU, pulmonary capillary wedge pressure of at least 15 mmHg and mean pulmonary arterial pressure of at least 25 mmHg
- a baseline 6-minute walking distance (6MWD) of at least 100 metres and a stable dose of any chronic lung medication for at least 30 days.

The randomised controlled period had a 16-week follow up. After this, participants could be enrolled on a single-arm, open-label extension (OLE) to have only inhaled treprostinil for a further 108 weeks. A total of 242 people enrolled on the OLE and 70 completed the study period.

The EAG highlighted several concerns with the randomised trial:

- It thought that a high number of participants did not complete the study period. Of 163 people randomised to have inhaled treprostinil, 130 (79.8%) completed the 16-week randomised period and of the 163 people having placebo, 128 (78.5%) completed this period. This could affect the study's statistical robustness and interpretability.
- People were selected by unblinded investigators, which may have introduced selection bias. Also, several outcomes were investigator reported, which introduced subjectivity. The EAG also noticed that participants were encouraged to complete assessments up to week 16 because of the high dropout rate, to preserve statistical power. This could have introduced bias.
- The randomisation to treatment groups was based only on baseline 6MWD and did not consider other prognostic factors. There were imbalances in baseline factors, including sex, age, ethnicity and cause of lung disease. The company did not do statistical tests to assess these differences.
- Some participants in INCREASE and the OLE stopped treatment early or missed doses because of adverse events or disease progression. Upon clarification, the company had considered that this could have

affected functional outcomes, but confirmed that it had not done statistical tests to assess these differences.

Clinical-effectiveness results

3.6 The primary outcome of INCREASE was the change in exercise capacity assessed by change in 6MWD from baseline to week 16. This was later evaluated as the primary outcome in the OLE. In INCREASE, 258 of the 326 people completed the 16-week randomised study period (see section 3.5). So, the company did analyses to account for the missing data. Its primary analysis used a mixed model for repeated measures approach and assumed that the data was missing at random. Using this statistical model, the least-squares mean difference in peak 6MWD from baseline to week 16 between people having inhaled treprostinil and people having placebo was statistically significant (31.12 metres; 95% confidence interval [CI] 16.85 to 45.39 metres; p<0.001). The change from baseline in INCREASE to week 52 in the OLE 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. The EAG thought that the company's imputation strategy (approach to replacing the missing data) of not assigning subsequent measurements for people who died, had clinically worsened or were too unwell may have introduced bias because people having inhaled treprostinil had a lower clinical worsening rate (22.7%) than people having placebo (33.1%). So, this could have increased the treatment effect of treprostinil because the disease did not appear to worsen as much for those having inhaled treprostinil as for those who had placebo. It thought the mean change from baseline showed people who were originally randomised to have inhaled treprostinil had increased exercise capacity in the 16-week randomised period, which continued into the early stages of the OLE. But by week 64 of the OLE, there was a decline in exercise capacity and this continued to the end of the OLE. The EAG suggested that people having inhaled treprostinil may not maintain improvements in exercise capacity in the long term. People having placebo had a gradual decline in exercise

capacity, and this continued into the OLE. The clinical experts and company expressed their surprise at these results. The company explained that, apart from those who discontinued treatment, all those having placebo during the randomised period (121 out of 128 people) switched to inhaled treprostinil in the OLE. The EAG preferred to source the analysis of peak 6MWD from data in the clinical study report (the exact results are confidential so cannot be included here). These show that exercise capacity (mean change from baseline at 16 weeks) for people having inhaled treprostinil or placebo declined. But the decrease from baseline in exercise capacity was larger for people who had placebo than for those who had inhaled treprostinil. The committee agreed that the data was difficult to interpret. It did not suggest a treprostinil benefit in the long term. It was uncertain about how long the treatment effect would last when considering the OLE data. It would like the company to provide further rationale and analysis to explain the observations in the OLE for the people in the placebo arm who crossed over.

Potential treatment effect modifiers

3.7 The committee considered whether the baseline characteristics of participants in INCREASE reflected real-world clinical settings. The company explained that in INCREASE 13.5% of people had pirfenidone and 9.2% had nintedanib. But most (77%) of the participants were not having a background antifibrotic medicine at baseline. A clinical expert estimated that in clinical practice around 60% of people with PH-ILD would have an antifibrotic medicine. He explained that because inhaled treprostinil has an antifibrotic effect, the background treatments may be treatment effect modifiers. He explained that the INCREASE trial had recruited people before antifibrotic medicines had become standard clinical practice. The committee noted that pirfenidone and nintedanib use were not completely balanced across arms (11.7% of the treatment arm compared with 15.3% of the control arm had pirfenidone, and 6.7% of the treatment arm compared with 11.7% of the control arm had nintedanib). In terms of PDE-5 inhibitor treatments, the company confirmed that people

who had had any PAH treatment within 60 days of randomisation were not allowed to participate in the trial. This meant that nobody in the trial would have had PDE-5 inhibitor treatment. The committee thought that this was not in line with clinical practice. The clinical experts confirmed that, in practice, people with PH-ILD would need more treatment as their symptoms progressed. The clinical experts estimated that 20% to 25% of people with PH-ILD would have a concurrent PDE-5 inhibitor. The committee thought that the population in INCREASE may have been fitter than the group that would have inhaled treprostinil in clinical practice. It thought that there were potential effect modifiers that had not been explored and these were problematic because of imbalances in baseline characteristics between the arms. It would like to see a statistical analysis that explores the impact of all potential effect modifiers, including background treatments and the severity of disease at baseline. It would prefer to see this statistical analysis appropriately adjusted to incorporate potential treatment effect modifiers. It would like this analysis to be included in the cost-effectiveness model to ensure that the people starting treatment in the model are in line with the population that is likely to have inhaled treprostinil in clinical practice.

Adjusting for treatment crossover in the OLE for overall survival

3.8 The company thought the overall survival (OS) results for people previously having inhaled treprostinil were confounded by people switching from placebo to inhaled treprostinil. So, it explored crossover adjustment in a post-hoc analysis of INCREASE and the OLE. The intention-to-treat (ITT) analysis showed a hazard ratio (HR) of 0.71 (95% CI 0.46 to 1.10, p=0.1227). The company explored 2 adjustment methods: randomised-based rank-preserving structural failure time (RPSFT), which produced an HR of 0.26 (95% CI 0.07 to 0.98, p=0.0473); and inverse probability of censoring weighting (IPCW), which produced an HR of 0.62 (95% CI 0.39 to 0.99, p=0.0483). Both adjustment methods are recommended by NICE technical support documents 16 and 24. It thought the RPSFT was a more robust approach to adjusting survival estimates

and that the IPCW could be susceptible to bias because of the high crossover. So, it applied the RPSFT method in its base-case cost-effectiveness model (see section 3.13). The EAG noted that the HR using the RPSFT method was markedly different from the ITT analysis and the Kaplan–Meier estimates for OS. The confidence intervals surrounding the HR were wide, suggesting high imprecision and uncertainty in the point estimate. It thought the HR estimate using the RPSFT may not be realistic and did not have face validity. The EAG noted that only a few people did not switch to inhaled treprostinil. It did not consider either adjustment approach to be reliable. So, it preferred the ITT analysis as the only appropriate option. It noted that the observed data from the clinical trial suggested that both study arms showed an equal rate of decline in 6MWD across the OLE period. The company said the ITT approach assumed that there had been no benefit to people who switched from having placebo to inhaled treprostinil during the OLE. But the randomised period had shown a difference in effect between the 2 treatment groups (see section 3.6). The EAG noted that the RPSFT method did not adjust for the possibility that people having higher doses may have additional benefits beyond those having lower doses. The committee thought that there were uncertainties with both the RPSFT and the ITT approach. The trial design made it challenging to understand what impact the treatment had during the OLE period (see section 3.5). The committee noted that everyone had inhaled treprostinil upon crossing over, and it was unsure how much impact this may have had on the results. It thought there was some uncertainty in understanding the prognostic factors in the people who switched from placebo to inhaled treprostinil (see section 3.7). The committee requested further rationale for the observations in the OLE for people who crossed over from placebo (see section 3.13). The committee's preferred approach to capturing OS for people having BSC is discussed in section 3.13.

Indirect treatment comparisons

Indirect treatment comparison with best supportive care

3.9 To provide additional evidence, the company did a matching-adjusted indirect comparison (MAIC) to establish the relative efficacy of inhaled treprostinil (from the trial) compared with BSC. The source for the BSC data was a single-centre, retrospective observational study of 128 people with PH-ILD (50 people in the MAIC after exclusions applied) in the UK (Dawes et al., 2023). The company matched the data of people having inhaled treprostinil from INCREASE and the OLE to the population of the untreated group from Dawes. It assumed there were no unmeasured confounding variables. But it did note that there was insufficient data for body mass index and smoking history to determine the sufficiency of overlap and the need for adjustment. It excluded variables from its analysis for the following reasons:

- In Dawes, people were assumed to have a time since diagnosis of 0, but in INCREASE there was a delay from diagnosis to study entry of up to 13 years. So, people with a time since diagnosis of more than 2 years in the INCREASE studies were excluded to allow for meaningful comparisons.
- To align with the population in Dawes people with connective tissue disease in INCREASE were also excluded from the analysis.

The EAG had several concerns with using the Dawes data that would limit the applicability and generalisability to clinical practice:

- Some of the tools used for measuring outcomes were not fully validated for use in ILD-PH. The Composite Physiologic Index had not been validated outside idiopathic pulmonary fibrosis, and emPHasis-10 was developed for PAH.

- RHC was applied only cautiously to minimise procedural risk. Selectively applying RHC may have limited the completeness of data and generalisability to UK clinical practice.
- The EAG's clinical experts noted that male predominance is typical in idiopathic pulmonary fibrosis, but only 20% of people with idiopathic pulmonary fibrosis in Dawes were male.

The company's results showed an incremental benefit in median OS with inhaled treprostinil compared with BSC (HR=0.16; 95% CI 0.09 to 0.28). It also did the MAIC using only outcomes for people originally randomised to inhaled treprostinil. This produced an HR of 0.16 (95% CI 0.06 to 0.41) and an unweighted naive comparison (HR=0.28; 95% CI 0.19 to 0.40). The EAG noted that all results suggested a clear benefit associated with the INCREASE population. The EAG was concerned that the impact of unadjusted differences between INCREASE and Dawes could bias the results. It thought that the company's CPRD linked with HES data could provide a comprehensive dataset for comparing the impact of inhaled treprostinil with BSC. It suggested that a naive comparison of INCREASE data with the CPRD study data would be an appropriate way to explore using this alternative source. But, overall, the EAG was content with a comparison of data based on the randomisation ITT period within INCREASE. A clinical expert explained that prospective evidence in PH-ILD is limited. In addition to the CPRD dataset, the GoDeep registry is a large ongoing global PH registry. As of April 2025, it included 34,482 people with PH-ILD, in 25 centres, including 2 in the UK. It could be an appropriate source for indirect comparisons. The committee agreed this would be a reliable source. It concluded that data from either the GoDeep registry or the CPRD dataset would be helpful to validate the results obtained using the company's comparison with Dawes. This data should validate the committee's requested adjusted analysis using the INCREASE trial data (see section 3.8).

Indirect treatment comparison with PDE-5 inhibitors

3.10 In its submission, the company said it did not consider PDE-5 inhibitors to be an appropriate comparator (see section 3.2). To provide more evidence supporting the effectiveness of inhaled treprostinil, it later did a MAIC to assess the comparative effectiveness in PH-ILD of inhaled treprostinil against PDE-5 inhibitors. It used this to support scenario analyses in the cost-effectiveness model. The company's MAIC compared people having inhaled treprostinil in INCREASE and the OLE with people having PDE-5 inhibitor treatment in Dawes (2022), and generated weights to match covariate distributions in INCREASE and the OLE to the population in Dawes. The results produced an HR of 0.44 (95% CI 0.24 to 0.80), which suggested a larger effect size than a naive comparison (HR 0.58; 95% CI 0.36 to 0.95). The EAG noted that a similar pattern between the naive comparison and MAIC HRs was shown in the company's MAIC against BSC, and suggested that the outcomes for inhaled treprostinil improved when the MAIC weights apply. So, it questioned the face validity of the company's MAIC. The EAG had noted concerns with using the Dawes data, based on its retrospective, single-centre design and generalisability to UK clinical practice (see section 3.9). It sourced a larger multicentre study (Yogeswaran et al. 2025) with a large sample that was based on data from the GoDeep registry (see section 3.9). This included 940 adults with PH-ILD, of whom 511 had PDE-5 inhibitor treatment (Yogeswaran et al. 2025). The EAG thought the study population was more similar than the Dawes population to the INCREASE population. It suggested that a MAIC comparing INCREASE data with the GoDeep data reported in Yogeswaran would be appropriate. But the company thought that a MAIC would not be appropriate because of missing data and greater heterogeneity in baseline characteristics. The EAG did a naive comparison of OS for people in INCREASE who were randomised to treprostinil and people in Yogeswaran with PH-ILD who had treatment with a PDE-5 inhibitor. This produced an HR of 0.63 (95% CI 0.45 to 0.89). The committee agreed that the data from Yogeswaran (informed by

the GoDeep registry) was more reliable than the data from Dawes at informing the indirect comparison between inhaled treprostinil and PDE-5 inhibitors. The committee concluded that it would prefer to see a MAIC using Yogeswaran as the source of data for PDE-5 inhibitors.

Economic model

Company's model structure

3.11 The company presented a partitioned survival model with 4 health states:

- no clinical worsening event, or clinical worsening free
- first clinical worsening event
- 2 or more clinical worsening events
- death.

Clinical worsening was a composite endpoint defined as any of the following events:

- a decrease in 6MWD of 15% or more from baseline
- a decrease in forced vital capacity of 10% or more from baseline
- cardiopulmonary hospitalisation (an episode of care needing hospital admission directly caused by an indication related to the heart and lungs)
- acute lung disease exacerbation (a clinically significant respiratory deterioration characterised by new widespread alveolar abnormality)
- lung transplant
- death.

This approach simulated a cohort of people with PH-ILD transitioning over time based on time-to-event data taken from INCREASE and the OLE. It assumed that people can only progress and do not transition back to earlier health states. The committee noted that there was some heterogeneity in health states. This meant that some people started

within a health state with more severe worsening than others. But it concluded that the model was appropriate for decision making.

Extrapolating overall survival for inhaled treprostinil

3.12 The company fitted parametric models to the INCREASE and OLE data for those who were originally randomised to inhaled treprostinil. The company selected the Weibull distribution in its base case to extrapolate beyond the end of the OLE. It fitted the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised-gamma parametric models to the individual patient survival data. It visually inspected the curve fits and consulted with clinical experts to identify the best fitting and most clinically plausible parametric model. It said the Weibull ranked third in its statistical analysis. Its clinical experts had said that the distributions with the best statistical fit (exponential and Gompertz) had underestimated and overestimated mortality, respectively. The EAG considered the Weibull distribution to be too optimistic because it showed that some people would still be alive at 15 years. It noticed that the Kaplan–Meier data showed an increasing hazard rate, whereas the Weibull model captured only a small increase in the hazard rate over time. The company said the exponential distribution was excluded because it did not represent the steep early decline seen in the Kaplan–Meier curves. The EAG preferred to use the generalised-gamma distribution in its base case. This led to lower survival estimates than those predicted by the Weibull distribution. It showed that a small proportion of people would live to 10 years, but no one would be alive at 15 years. This was in line with clinical estimates. The committee noted that the company's clinical experts had ruled out the exponential for being too optimistic, but the Weibull was not dissimilar. The committee agreed that the generalised gamma was the most appropriate distribution to model OS for people having inhaled treprostinil. The committee recalled that the trial data and resulting extrapolations may be affected by treatment effect modifiers, including background antifibrotic treatments and the severity of disease at baseline (see section 3.7). It also recalled that it may not be appropriate to adjust the treprostinil data for those who

switched to treprostinil for the OLE (see section 3.8). Overall, the committee would prefer for the extrapolated inhaled treprostinil survival to be informed only by people originally randomised to treprostinil, after these data had been explored and adjusted for any treatment effect modifiers to reflect the population expected in the NHS.

Extrapolating overall survival for best supportive care

3.13 Overall survival for BSC in the company's model was based on placebo-arm data from INCREASE and OLE data adjusted for the placebo crossover using the RPSFT approach (see section 3.8). This was extrapolated using the Weibull distribution, which was the second-best-fitting model statistically. This distribution also produced extrapolations showing low survival at 5 years, which aligned to its clinical experts' expectations. So, the company selected this distribution. The EAG had previously noted concerns with the adjusted analysis (see section 3.8). It preferred to generate the BSC arm by applying the ITT OS HR from the INCREASE and OLE (unadjusted for crossover) and extrapolating this with the generalised-gamma distribution. The company explored extrapolating using the 16-week randomised follow up from INCREASE for inhaled treprostinil and BSC as a scenario analysis. The EAG noted that the company's model had included functionality to derive the BSC arm by applying an HR to the treatment arm, but this had not been used to populate any parameters. The committee recalled its concerns with interpreting the clinical effectiveness for people who crossed over in the trial, and it was uncertain about the impact of treatment effect modifiers (see section 3.7). The committee would prefer the BSC OS curve to be derived using a measure of relative effect that is neither impacted by nor adjusted for crossover, but has been adjusted for potential treatment effect modifiers (see section 3.7). This OS modelling approach should use the appropriately extrapolated inhaled treprostinil arm (see section 3.8).

Extrapolating time to treatment discontinuation

3.14 Modelling time to treatment discontinuation (TTD) applied only to the inhaled treprostinil arm of the model because people in the BSC arm did not have an active treatment. In the company's base case, TTD was informed by survival analysis using the OLE data. The company used the generalised-gamma distribution to extrapolate TTD. This was the second-best-fitting model and reflected a fast rate of stopping treatment. The company's clinical experts believed this was in line with the high mortality rates expected for people with PH-ILD. The EAG thought that the company's modelling approach underestimated the number of people who stayed on treatment. It explained that the company's modelling assumed that some people would stop treatment before having a clinical worsening event. It noticed that the Kaplan–Meier data showed a relationship between TTD and clinical worsening events. But in the extrapolated models the extrapolation for TTD fell below people having 2 or more clinical worsening events (CW2). So, people would discontinue treatment before having a second clinical worsening event. The EAG thought this lacked face validity. It included a constraint in its modelling, so that the TTD extrapolated using its preferred generalised-gamma distribution did not fall below the CW2 Kaplan–Meier curve. Based on the OLE data, the EAG noticed that the company's modelling estimated that at 30 years only 7% of people would continue having inhaled treprostinil. But the EAG had calculated that approximately 37% of people would continue treatment with inhaled treprostinil at the end of the OLE period (after 124 weeks). A clinical expert explained that because there are limited treatment options, people would be unlikely to stop treatment even after 2 or more clinical worsening events. Another clinical expert estimated that around 50% of people would still be having treatment with inhaled treprostinil at 3 years, and a patient expert explained that people would only choose to stop treatment because of side effects. The company explained that its modelling had not explored a link between clinical worsening and stopping treatment. The committee concluded that both the company's and the

EAG's modelling did not align with the clinical experts' predictions and both extrapolations underestimated the proportions of people who would be having treatment at 3 years. So, neither approach would be appropriate. It suggested that evidence from real-world use in the US might inform appropriate TTD estimates. But, it concluded that it would like to see an approach that was in line with clinical experts' views that, in practice, people would not discontinue treatment as their disease progresses and they would expect 50% of people to still be having treatment at 3 years.

Comparison with PDE-5 inhibitors

3.15 The company conducted a MAIC to compare inhaled treprostinil with PDE-5 inhibitors. The company extrapolated the inhaled treprostinil OS INCREASE and OLE data that had been adjusted for crossover and applied the OS HR from its MAIC to establish the relative efficacy of inhaled treprostinil with PDE-5 inhibitors (see section 3.10). Instead of cost-effectiveness results compared with PDE-5 inhibitors alone, it presented cost-effectiveness scenarios, in which the comparator was a mixed population of people having either BSC or PDE-5 inhibitors. The cost-effectiveness results for each population were weighted in a post-hoc approach to reflect the proportion of people having each treatment. The company provided scenarios that assumed that 8% and 10% of people would have PDE-5 inhibitors, based on its UK epidemiological CPRD, and said these estimates were reflective of PDE-5 inhibitor use in the NHS. The EAG noted several concerns with the company's approach:

- Applying weights only at the end of the model oversimplified the modelling and did not consider any time-dependent effects. This could contribute to structural bias.
- Applying a standalone analysis without proportional weighting may be more appropriate, for example comparing with 100% of people having PDE-5 inhibitors.

- The proportions of PDE-5 inhibitor use had not been validated.

The committee recalled its uncertainty in the survival extrapolations for inhaled treprostinil (see section 3.12) and its preferred approach for establishing the relative efficacy compared with PDE-5 inhibitors (see section 3.10). It concluded that it would need to see additional standalone cost-effectiveness analyses showing separate comparisons without proportional weighting of treatments that compared inhaled treprostinil with BSC and inhaled treprostinil with PDE-5 inhibitors.

Utility values

Source of utility values

3.16 The company's literature search did not identify any evidence relating to health-related quality of life (HRQoL) in people with PH-ILD. Its clinical experts had explained that it was not appropriate to use HRQoL values related only to ILD or PH because these would not accurately depict the impact of PH with ILD. INCREASE and the OLE collected HRQoL data using the St George's respiratory questionnaire (SGRQ). The company's clinical experts advised that the SGRQ was the most appropriate measure to inform the company's economic model because there were no alternative tools. The company considered 2 different approaches to applying the SGRQ data from INCREASE and the OLE. In its base case it applied univariate, treatment-independent SGRQ values taken from week 48 of the OLE and excluded data from the end of the OLE because there was a large amount of missing data and it did not show statistical significance. It explained that this was because it showed larger HRQoL differences between health states, which were considered clinically plausible by its clinical experts. But it did a multivariate regression analysis that included baseline SGRQ, age and gender and accounted for repeated measures as covariates. The EAG had several concerns with the univariate approach:

- it did not adjust for selection bias and exaggerated health state differences, which potentially inflated cost-effectiveness outcomes
- it limited how long-term HRQoL impacts were captured because of missing data from the OLE
- it relied on descriptive statistics and considered relying on subjective clinical opinion for choosing that approach, which could introduce uncertainty
- the SGRQ did not capture HRQoL during exacerbations, which may have overestimated utilities and cost-effectiveness outcomes.

The EAG thought that the multivariate approach was more robust in coping with any bias and small sample sizes and applied this in its base case. The committee thought that the univariate analysis had not controlled for sources of bias or overestimation of utilities, so the multivariate approach would ensure more reliable estimates. The committee concluded that the multivariate approach was the most reliable approach to estimating HRQoL.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs, a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The EAG agreed that a severity weighting of 1.2 was appropriate. But the committee will need to consider the absolute and proportional QALY shortfall estimates in the light of its requested analyses. Both the company's and EAG's base-case ICERs applied a QALY weighting of 1.2. The exact cost-effectiveness estimates are confidential and cannot be reported here. The deterministic and

probabilistic incremental cost-effectiveness ratios (ICERs) for inhaled treprostinil compared with BSC in the company's base case were within the range normally considered an acceptable use of NHS resources. But in the EAG's base case these ICERs were considerably higher than the range normally considered an acceptable use of NHS resources.

Costs

Costs of implementing inhaled treprostinil

3.18 The company had included the costs of an ampule of inhaled treprostinil but explained that it had not included the additional costs involved with diagnosing PH-ILD and implementing inhaled treprostinil within its economic model. The committee agreed there would be implementation costs relating to the introduction of inhaled treprostinil in terms of RHC diagnosis and resource use (see sections 3.3 and 3.4). For example, one of the clinical experts noted an increase in workload of 10% to 15%. The committee requested that these costs are included in the company's model.

Acceptable ICER

3.19 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects, including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- the proportions of people who would have PDE-5 inhibitors in clinical practice (see section 3.2)
- interpreting the clinical-effectiveness results, particularly:
  - consideration of any treatment effect modifiers (see section 3.7)

  - adjusting for those who crossed over from the placebo arm of the randomised period to inhaled treprostinil in the OLE (see section 3.8)

- the data used to source the indirect treatment comparison with BSC (see section 3.9)
- the extrapolation of OS for inhaled treprostinil and BSC (see section 3.13)
- the time to discontinuation for those having inhaled treprostinil (see section 3.14).

So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Committee's preferred assumptions

3.20 The committee agreed that its preferred modelling included the following assumptions:

- Background treatments with antifibrotics should be considered. This is based on the expert opinion that in clinical practice 60% of people with PH-ILD are likely to be using antifibrotic medicines (see section 3.2).
- The BSC OS curve obtained using a measure of relative effect that is neither impacted by nor adjusted for crossover, but has been adjusted for potential treatment effect modifiers (see section 3.7).
- PDE-5 inhibitors are a relevant comparator (see section 3.2), and cost-effectiveness results should be presented compared with PDE-5 inhibitors alone (see section 3.15).
- The costs of introducing inhaled treprostinil should be included (see section 3.18) and these should account for the impact on service provision and number of RHCs (see sections 3.3 and 3.4).
- 50% of people will still be having treatment with inhaled treprostinil at 3 years (see section 3.14).

- The multivariate analysis should be applied to interpret utility values (see section 3.16).

Requests for additional analyses

3.21 The committee agreed that because of the high level of uncertainty (see section 3.19) it could not determine the most plausible ICER without further analyses. It requested the following:

- the cost of any additional RHCs needed for diagnosing people who need treatment (see section 3.3)
- including additional costs of starting treatment with inhaled treprostinil in the economic model (see section 3.4). These should include:
  - the cost of the inhalation device (nebuliser)
  - resource costs for training staff to start treatment
  - the cost of any hospital stay, monitoring and follow up
  - the cost of training and support for people having treatment
- analyses exploring all variables that could be treatment effect modifiers, including background antifibrotic treatments and severity of disease at baseline, and these used in the model to reflect the population expected in NHS practice (see section 3.7)
- additional analysis to explain the observations in the OLE for people who crossed over from the placebo arm (see sections 3.8 and 3.13)
- using the adjusted treprostinil INCREASE and OLE treatment arm (for treatment effect modifiers) to derive the extrapolated OS BSC arm by applying a relative measure of effect (see section 3.7)
- analysis using data from the CPRD registry or the GoDeep registry to inform indirect comparative evidence for inhaled treprostinil compared with BSC (see section 3.9)
- a MAIC using the GoDeep registry (Yogeswaran) to establish the relative efficacy between inhaled treprostinil and PDE-5 inhibitors (see section 3.10)

- analysis to support the clinical experts' estimates for TTD that 50% of people would still be having treatment with inhaled treprostinil at 3 years (see section 3.14)
- standalone cost-effectiveness analyses showing separate comparisons without proportional weighting of treatments that compared inhaled treprostinil with BSC and inhaled treprostinil with PDE-5 inhibitors (see section 3.16).

Managed access

3.22 Having concluded that inhaled treprostinil could not be recommended for routine use in the NHS, the committee then considered if it could be recommended for use during a managed access period. Although the company provided a managed access proposal, the committee had not seen evidence that inhaled treprostinil had the plausible potential to be cost effective. So, it concluded that a recommendation with managed access was not an option at this time.

Other factors

Equality

3.23 The committee did not identify any equality issues but discussed potential equality issues raised by stakeholders. The equality impact assessment provides a summary of these issues.

Conclusion

Recommendation

3.24 The committee agreed that further information was needed before it could decide on all its preferred modelling assumptions and understand the full impact of the uncertainties. So, it was unable to establish that inhaled treprostinil was a cost-effective use of NHS resources. It concluded that inhaled treprostinil should not be used for treating PH-ILD.

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Iolo Doull

Vice chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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