NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from **Boehringer Ingelheim**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Action for Pulmonary Fibrosis
   b. Scleroderma & Raynaud's UK
   c. British Thoracic Society (endorsed by Royal College of Physicians)
   d. NHS England

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from **Boehringer Ingelheim**

7. **Technical engagement responses & expert statements from experts:**
   a. Dr Lisa Spencer – clinical expert, nominated by Boehringer Ingelheim
   b. Debbie Roots – patient expert, nominated by Association of Respiratory Nurse Specialists
   c. Stephen Jones – patient expert, nominated by Action for Pulmonary Fibrosis
   d. Dr Voon Ong – clinical expert, nominated by British Society for Rheumatology

8. **Technical engagement response from consultees and commentators:**
   a. Scleroderma & Raynaud's UK
   b. British Thoracic Society (endorsed by Royal College of Physicians)

9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nintedanib for the treatment of adults with progressive fibrosing interstitial lung disease (PF-ILD)

Document B

Company evidence submission

18th December 2020

File name	Version	Contains confidential information	Date
Nintedanib in PF-ILD_final NICE submission	V1	Yes	18th December 2020

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This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication, i.e. adult patients with other chronic fibrosing interstitial lung diseases (ILDs) with progressive phenotype (PF-ILD).

Nintedanib (OFEV®) also has two other licensed indications; for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD) and idiopathic pulmonary fibrosis (IPF). Nintedanib is already recommended by NICE for IPF (TA379), (1) while no submission is planned for the SSc-ILD indication. However, patients with SSc-ILD with the progressing fibrosing phenotype are included in the INBUILD trial and are therefore included in the population considered in this submission, in line with the marketing authorisation for nintedanib.

The decision problem addressed in this submission, as specified in the final NICE scope, is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with progressive-fibrosing interstitial lung disease (excluding idiopathic pulmonary fibrosis)	Adults with progressive-fibrosing interstitial lung disease (excluding idiopathic pulmonary fibrosis)	N/A
Intervention	Nintedanib	Nintedanib	N/A
Comparator(s)	Established clinical management without nintedanib including, but not limited to: • immunosuppressants (such as azathioprine, cyclophosphamide, mycophenolate; do not currently have a marketing authorisation in the UK for this indication) • corticosteroids (do not have currently have a marketing authorisation in the UK for this indication) • infliximab (does not have currently have a marketing authorisation in the UK for this indication) • rituximab (does not have currently have a marketing authorisation in the UK for this indication) • best supportive care	Placebo	At the trial design stage, there were no approved therapies for the treatment of PF-ILD, other than IPF. Currently, the only approved therapy is nintedanib. When diagnosis of ILD is confirmed, patients receive conventional treatment (such as corticosteroids and immunomodulatory agents) based on the specific type of ILD (see the proposed algorithm in Figure 3, page 19). If the disease continues to progress despite use of these conventional treatments, a diagnosis of PF-ILD is then confirmed through pulmonary function tests, as well as radiological and clinical assessments. It is at this stage, once PF-ILD has been confirmed, that nintedanib should be considered as a treatment, as it is the only licensed treatment available for PF-ILD. A consensus of clinical experts have advised that, whilst immunomodulatory agents may still be used to treat the inflammatory component of the disease, there are no randomised controlled trials to suggest that these unlicensed treatments have a positive impact on the chronic fibrotic progression of PF-ILD (i.e. delaying disease progression).[†] Patients were eligible to participate in the trial if their ILD had worsened despite treatment with unapproved medications used in clinical practice to treat ILD. To minimise a potential impact on the efficacy and safety assessments, treatment for ILD with unapproved anti-inflammatory or

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			immunomodulatory medications was required to be discontinued and a wash-out period was to be observed before randomisation of the patient. As there is currently no other targeted anti-fibrotic therapy licensed for the treatment of chronic fibrosing ILD with a progressive phenotype, the use of placebo as a control group was considered justified. However, initiation of concomitant immunomodulatory treatment as medically indicated was allowed for the management of worsening of the disease after the first 6 months of the trial. Some patients received the treatments specified as comparators within the NICE scope, either for treatment of PF-ILD or the underlying condition (see full description on page 51-52). Baseline and concomitant medication use are described in Section B.2.2.
Outcomes	The outcome measures to be considered include: • lung function • physical function • exacerbation rate • progression-free survival • mortality • adverse effects of treatment • health-related quality of life	• Rate of decline in FVC at 52 weeks (primary endpoint) • Absolute change from baseline in total score on K-BILD questionnaire at 52 weeks • Time until acute exacerbation of ILD or death at 52 weeks • Death at 52 weeks • Acute exacerbation of ILD or death up to DBL2 • Death up to DBL2 • AEs, serious AEs and severe AEs	N/A

Abbreviations: AE, adverse event; DBL, database lock 1; FVC, forced vital capacity; ILD, interstitial lung disease; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; N/A, not applicable

† Please see page 84 for details of the Advisory Board held on 11th November 2020, as well as a list of the clinical experts consulted.

B.1.2 Description of the technology being appraised

Nintedanib is a small molecule intracellular inhibitor of tyrosine kinases, including platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3. Nintedanib thereby inhibits several steps in the initiation and progression of lung fibrosis and the proliferation of vascular cells, irrespective of the cause of the underlying lung disease.(2)

Nintedanib has been approved for the treatment of IPF,(3) based on the results of two Phase III trials (INPULSIS-1 and INPULSIS-2)(4) in patients with IPF. As PF-ILDs appear to share pathobiological mechanisms that may represent a common fibrotic response to tissue injury, regardless of the cause, they are potentially responsive to treatment with the same agents.(5-9)

The subsequent Phase III trial, INBUILD,(5, 10) investigated treatment with nintedanib for adult patients with fibrosing interstitial lung diseases with a progressive phenotype, in particular, those forms other than IPF. The efficacy, safety and health-related quality of life (HRQoL) benefits of nintedanib were demonstrated in this broader patient population, similar to its benefits in patients with IPF, over 52 weeks.(5) The results of this study are the basis for the new Marketing Authorisation and provide the primary supportive clinical evidence for the current appraisal of nintedanib in PF-ILD.

Table 2: Technology being appraised

UK approved name and brand name	Nintedanib (OFEV®)
Mechanism of action	Nintedanib is a multi-targeted tyrosine kinase inhibitor that occupies the intracellular ATP-binding pocket of these kinases and blocks the intracellular signalling cascades which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in interstitial lung disease.
Marketing authorisation/CE mark status	Nintedanib was granted EMA marketing approval as specified below: • As VARGATEF®, for the treatment of non-small cell lung cancer in November 2014 • As OFEV®, for the treatment of IPF in January 2015, SSc-ILD in May 2020 and PF-ILD in July 2020
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Nintedanib has four approved marketing authorisations: • As VARGATEF®, it is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology after first-line chemotherapy • As OFEV®, it is indicated in adults for the treatment of: o Idiopathic pulmonary fibrosis (IPF) o Systemic sclerosis associated interstitial lung disease (SSc-ILD) o Other chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD) There are no restrictions in place under the current marketing authorisations.
Method of administration and dosage	Dosing regimen: The recommended dose is 150 mg nintedanib orally twice daily, administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose. In patients with mild hepatic impairment (Child Pugh A), the recommended dose of nintedanib is 100 mg twice daily approximately 12 hours apart. Route of administration: Oral
Additional tests or investigations	None required
List price and average cost of a course of treatment	List price: £2,150.10 Mean cost of treatment (with PAS): [redacted]
Patient access scheme (if applicable)	PAS price: [redacted]

Abbreviations: ATP, adenosine triphosphate; EMA, European Medicines Agency; IPF, idiopathic pulmonary fibrosis; SSC-ILD, systemic sclerosis associated interstitial lung disease

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

Summary

- Interstitial lung diseases (ILDs) are characterised by inflammation and fibrosis of the lung parenchyma.(11) A subset of patients with ILDs will continue to have progressive-fibrosing ILD (PF-ILD), whereby fibrosis and worsening in lung function become independent of the initial cause of disease.(12)
- The definition of PF-ILD used in the INBUILD trial (5) and supported by an expert group of ILD physicians (13) is patients with features of fibrosing lung disease who meet at least one of the following criteria for progression within the past 24 months, despite treatment with unlicensed medications used in clinical practice to treat ILD:
    - Decline in forced vital capacity (FVC) % predicted of ≥10%;
    - Decline in FVC % predicted of ≥5% to <10% with worsening of respiratory symptoms or increasing extent of fibrotic changes on chest imaging;
    - Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging.
- Analysis of patients receiving placebo in the INBUILD trial has shown that individuals with PF-ILD are likely to have a similar clinical disease course to that of patients with idiopathic pulmonary fibrosis (IPF), a type of ILD in which all patients have the progressive fibrosing phenotype, with a similar risk of death.(5, 14) Therefore, it is expected that patients with PF-ILD who do not receive anti-fibrotic therapy would have a median post-diagnosis survival of 2 to 5 years, similar to that of IPF patients. (15, 16)
- Nintedanib is the first licensed drug for adults with chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD) other than IPF.
- Nintedanib represents a step-change in PF-ILD management, allowing patients to receive the same anti-fibrotic treatment currently offered to patients with IPF.

Interstitial lung disease (ILD) is a heterogeneous group of diseases characterised by inflammation and fibrosis of the lung parenchyma,(11) including idiopathic interstitial pneumonias, autoimmune ILDs, hypersensitivity pneumonitis (HP), sarcoidosis and other ILDs.(11, 17) A subset of patients experience self-perpetuating fibrosis, which results in worsening of symptoms with a progressive phenotype, known as progressive-fibrosing ILD (PF-ILD).(12) PF-ILD is a phenotype in which patients continue to progress despite conventional treatments directed at the underlying disease. This phenotype is characterised by a gradual decline in lung function, dyspnoea, worsening of physical performance and quality of life, as well as poor response to immunomodulatory therapies and early mortality.(18) One specific definition, as used in the INBUILD trial, is patients meeting at least one of the following criteria within the past 24 months, despite treatment with unlicensed medications used in clinical practice to treat ILD:(5)

- Decline in forced vital capacity (FVC) % predicted of ≥10%
- Decline in FVC % predicted of ≥5% to <10% with worsening of respiratory symptoms or increasing extent of fibrotic changes on high-resolution chest imaging
- Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on HR-chest imaging.

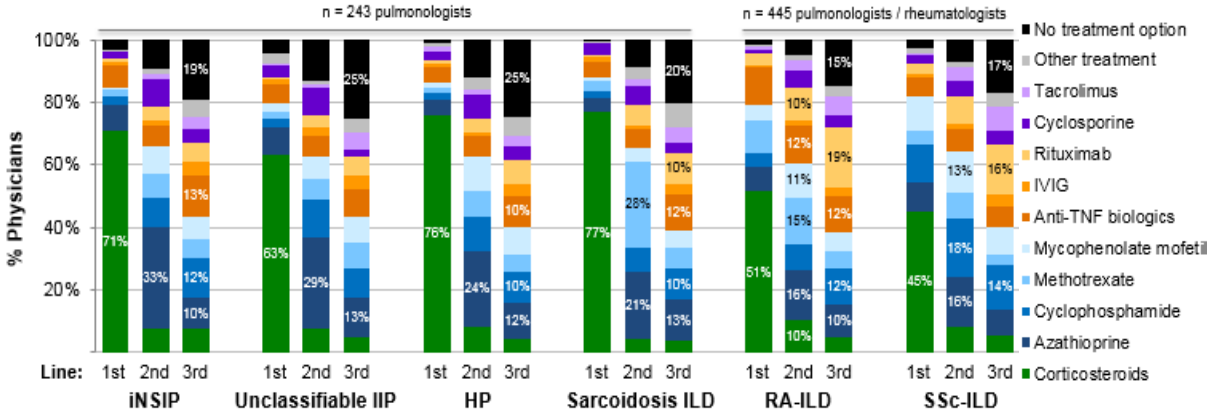
As PF-ILD is a phenotype that has only recently been defined, data on its prevalence and incidence are limited. A retrospective observational study assessing all new referrals to nine tertiary ILD treatment centres in England identified 253 new PF-ILD cases meeting INBUILD criteria over a period of 6 months (1st August 2017 to 31st January 2018), which can be extrapolated to 506 patients over 1 year across these centres.(19) Using the total population of England (56,286,961, 2019 estimate), this corresponds to an incidence and prevalence rate of 0.001% (given we expect PF-ILD patients to present very similarly to IPF where median duration of treatment is around 12 months). Applying this rate to the population of England and Wales gives an estimated 876 patients with PF-ILD who would be eligible for nintedanib.

PF-ILD is associated with considerable clinical, humanistic and economic burden.(14, 20) Patients have poor prognosis, and are expected to have an annual mortality rate similar to that of IPF at approximately 1.4 per 100,000 per year.(21) Patients incur high

direct medical costs and healthcare resource use (HCRU) from emergency room visits, hospital admissions and outpatient services,(22-26) as well as considerable indirect costs, including reduced productivity due to work absenteeism.(27) Furthermore, increases in healthcare expenditures have been linked with disease progression.(23)

The antifibrotics nintedanib and pirfenidone have been established as treatment options for IPF, but until the approval of nintedanib, there were no licensed therapies available for the treatment of other forms of PF-ILD.(28) Patients may be offered unlicensed medicines such as corticosteroids and/or immunosuppressive therapies; however, their efficacy in patients with ILDs other than IPF is supported by limited clinical trial evidence compared to that of nintedanib.(29) In addition, these treatments are often associated with adverse events (AEs) leading to treatment discontinuation.(29) Despite this, a global survey of pulmonologists, rheumatologists and internists (including 41 from the UK) conducted on behalf of Boehringer Ingelheim found that corticosteroids were the standard first-line treatment for non-IPF ILD (Figure 1).(30) Non-steroid immunosuppressants, such as azathioprine and mycophenolate mofetil, were used more frequently as first-line treatments in SSc-ILD, RA-ILD and other autoimmune ILDs.

Figure 1: Surveyed physician treatment lines for non-IPF ILD(30)



Abbreviations: HP, hypersensitivity pneumonitis; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; iNSIP, idiopathic nonspecific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; IVIG, intravenous immunoglobulin; RA, rheumatoid arthritis; SSc, systemic sclerosis; TNF, tumour necrosis factor.

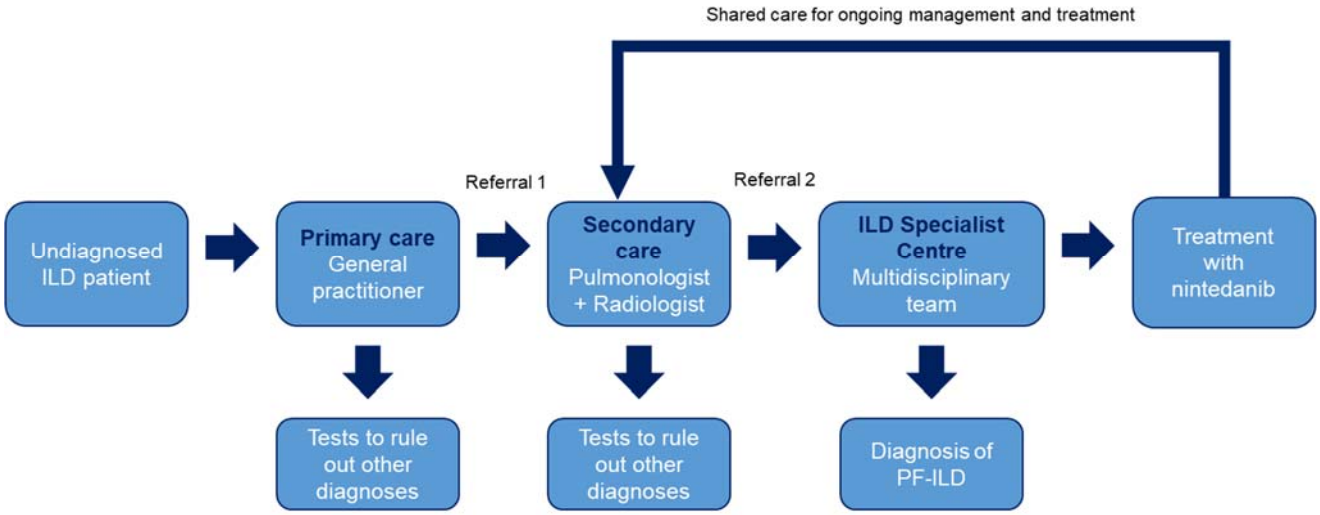
As patients progress, oxygen therapy or pulmonary rehabilitation is usually required and lung transplantation may be considered if appropriate.(31) Although not all

patients will be suitable for lung transplant, this has a significant long-term health and economic impact.(32-35) Overall, there remains a high unmet need for a licensed, cost-effective therapy that can slow disease progression in patients with PF-ILD (other than IPF).

Expected management pathway for patients with PF-ILD

If patients are diagnosed as having IPF, they can be referred to 25 designated tertiary ILD centres in England, where they are offered one of the two licensed and reimbursed antifibrotics, one of which is nintedanib. Patients with other forms of PF-ILD are also referred to these centres, although until recently there were no licensed treatments for diseases other than IPF.(2) Now that nintedanib is licensed for PF-ILD, this broader patient population is expected to follow the same clinical pathway currently in place for those diagnosed with IPF (Figure 2).

Figure 2. Intended pathway for the management of patients with PF-ILD

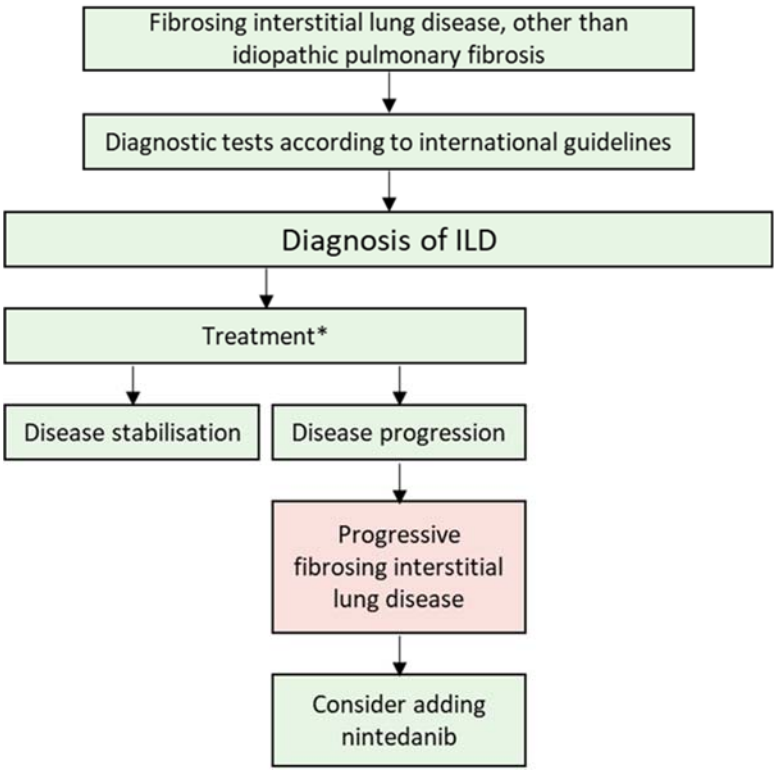


Abbreviations: PF-ILD, progressive fibrosing interstitial lung disease; ILD, interstitial lung disease

There are currently no specific guidelines for interstitial lung diseases with a progressive phenotype (PF-ILD) other than IPF. However, recent publications recognise the use of antifibrotic therapy such as nintedanib as a treatment choice. (13, 36) The proposed diagnosis and management of PF-ILD other than IPF is presented in Figure 3. When diagnosis of ILD is confirmed, patients receive conventional treatment based on the specific type of ILD. If the disease continues to progress, despite use of these conventional treatments, a diagnosis of PF-ILD is then confirmed

by carrying out pulmonary function tests as well as radiological & clinical assessments). It is at this stage of the disease (PF-ILD) that nintedanib should be considered as a treatment as it is the only licensed treatment available for PF-ILD. (13, 36)

Figure 3: Proposed treatment pathway



*Conventional treatments based on the specific interstitial lung disease, including, but not limited to corticosteroids, mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, rituximab. Adapted from: (13).
Abbreviations: ILD, interstitial lung disease

A consensus of clinical experts who manage patients with a confirmed diagnosis of PF-ILD in tertiary ILD specialist centres across England advised that, whilst immunomodulatory treatments may still be used to treat the inflammatory component of the disease, there are no randomised placebo controlled trials to suggest that these unlicensed treatments have a positive impact on the chronic fibrotic progression of PF-ILD – i.e. delaying disease progression. For a list of the clinical experts consulted, please see details of the Advisory Board held on 11th November 2020 (page 84).

B.1.4 Equality considerations

No equality issues are expected.

B.2 Clinical effectiveness

Summary

A systematic literature review, updated in May 2020, identified a single RCT evaluating nintedanib for patients with PF-ILD. The INBUILD trial was a phase III randomised, placebo-controlled, multi-centre phase III study comparing nintedanib with placebo over a minimum of 52 weeks in 663 patients. (5)

The key clinical evidence from the INBUILD trial demonstrating the value of nintedanib for the treatment of PF-ILD is summarised below.

- Nintedanib 150 mg twice daily significantly slowed the decline in FVC over 52 weeks in patients with PF-ILD vs. placebo (difference 107.0; 95% CI: 65.4, 148.5; p<0.001).(5)
    - The slower relative decline in FVC was consistent in patients with usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT (difference 128.2; 95% CI: 70.8, 185.6; p<0.001) and those with other fibrotic patterns (difference 75.3; 95% CI: 15.5, 135.0; nominal p=0.0137).(5)
- The annual rate of decline in FVC in the placebo group in all populations in the INBUILD trial was similar to that observed in the placebo groups in the INPULSIS trials, supporting the hypothesis that patients with a progressive phenotype have similar disease progression, regardless of the clinical diagnosis.(4, 5)
- The treatment effect of nintedanib vs. placebo was consistent across secondary lung function endpoints and subgroup analyses, further supporting the primary endpoint results.(5, 37)
- Over the whole trial period (up to database lock [DBL] 2), fewer patients treated with nintedanib (n=46) experienced an acute exacerbation or death compared with those in the placebo group (n=65; HR: 0.67; 95% CI: 0.46, 0.98).(37)
- Treatment with nintedanib resulted in a numerical improvement in health-related quality of life (HRQoL) in the overall population and patients with UIP-like patterns, as measured by the K-BILD questionnaire.(5)
- Safety results for nintedanib in patients with PF-ILD were consistent with those seen in IPF patients previously. (4, 5) The most frequent adverse event (AE) was diarrhoea, however all episodes were grade 3 or lower.(5, 37) Nausea, vomiting,

abdominal pain, decreased appetite and weight loss were also more frequent in the nintedanib group than the placebo group, although common AEs were mostly mild or moderate in intensity. (5, 37)

- Safety results in patients with UIP-like fibrotic pattern, including AEs, serious AEs and clinical laboratory values, were consistent with the safety profile in the overall population.(37)

Consistent with nintedanib being the only licensed treatment for PF-ILD, it was not possible to perform an indirect comparison with any other treatments. The SLR identified five other studies in relevant patient populations but lack of connection or comparability in patient populations prevented indirect comparison.

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

The phase III INBUILD trial provided evidence for nintedanib in the treatment of patients with PF-ILD. A summary of the methodology of this study is given in Table 3.

Table 3: Clinical effectiveness evidence – the INBUILD trial

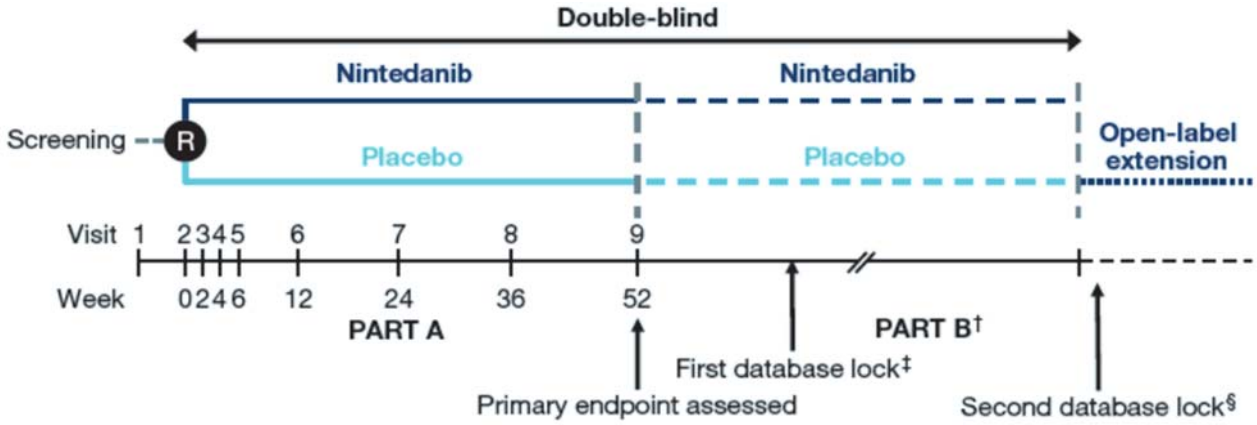
Study	INBUILD (Flaherty et al 2017(10); Flaherty et al 2019(5))				
Study design	Phase III, multicentre, prospective, randomised, double-blind, placebo-controlled study				
Population	Patients with PF-ILD				
Intervention(s)	Nintedanib				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	INBUILD is the pivotal trial for nintedanib in PF-ILD				
Reported outcomes specified in the decision problem	**Rate of decline in FVC at 52 weeks (primary endpoint)**; absolute change from baseline in total K-BILD questionnaire at 52 weeks; **acute exacerbation of ILD or death at 52 weeks**; **death at 52 weeks**; acute exacerbation of ILD or death up to DBL2; death up to DBL2; **AEs**, serious AEs and severe AEs				
All other reported outcomes	Not applicable				

Abbreviations: AE, adverse event; DBL1, database lock 1; FVC, forced vital capacity; ILD, interstitial lung disease; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; PF-ILD, progressive fibrosing interstitial lung disease

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The INBUILD trial was a phase III, multicentre, randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of nintedanib in patients with progressive-fibrosing lung disease over a minimum of 52 weeks.(10) Eligible patients were randomised in a 1:1 ratio to either oral nintedanib 150 mg twice daily or matching placebo. The initial period of the study (part A) was followed by a variable treatment period (part B) (see Figure 4). In part B, patients continued on blinded, randomised assigned treatment (nintedanib or placebo) until the end of the trial or until a reason for treatment withdrawal was met. The blinded trial period ended once the last randomised patient reached the week 52 visit and the benefit-risk profile of nintedanib over this time had been assessed. If the benefit-risk assessment were deemed positive, all patients were to have the option of receiving open-label nintedanib in an extension study known as INBUILD-ON. Database lock 1 (DBL1) occurred on 3rd June 2019 with 565 patients ongoing in the trial while database lock 2 (DBL2) was on 11th September 2019 with all patients completing the trial.

Figure 4: Design of the INBUILD trial



†Visits occurred every 16 weeks until end of treatment. ‡After last subject had completed week 52 visit. §After all patients had completed follow-up visit or entered open-label extension study.
Abbreviations: EOT, end of trial; R, randomisation

The study was conducted in specialised ILD referral centres in 15 countries, including 5 sites in the UK, from which 22 patients were recruited. Other countries included in the study were Argentina, Belgium, Canada, Chile, China, France, Germany, Italy, Japan, Korea, Poland, Russia, Spain and the US.

An enrichment design was planned, with stratification of the trial population so that two thirds of the patients had a usual interstitial pneumonia (UIP)-like pattern on high-resolution CT (HRCT) and one third had other fibrotic patterns. The protocol-defined HRCT criteria were based on those used in the INPULSIS studies, the phase III trials for nintedanib in IPF (see Table 4).(4) However, stratification caps were not implemented, since recruitment led to a ratio close to 2:1 without the need for active management.

Table 4: HRCT criteria for UIP-like fibrotic patterns in patients who meet the protocol criteria defined for PF-ILD†

Category	Description (patients meeting either criteria A, B and C, criteria A and C, or criteria B and C are considered to have UIP-like fibrotic patterns)
A	Definite honeycomb lung destruction with basal and peripheral predominance.
B	Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance.
C	Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern.

Abbreviations: HRCT, high-resolution computed tomography; PF-ILD, Progressive Fibrosing Interstitial Lung Disease; UIP, usual interstitial pneumonia.
† Patients with fibrosing interstitial lung disease who meet diagnostic criteria for idiopathic pulmonary fibrosis, according to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association 2011 guidelines were excluded.

Patients aged ≥18 years were eligible if they had a physician-diagnosed fibrosing ILD (such as connective tissue disease (CTD)-associated ILD, rheumatoid arthritis-associated ILD, systemic sclerosis – associated ILD , chronic fibrosing hypersensitivity pneumonitis (HP), idiopathic non-specific interstitial pneumonia (iNSIP), unclassifiable idiopathic interstitial pneumonia (IIP), environmental/occupational lung disease, sarcoidosis and other ILDs) present with features of diffuse fibrosing lung disease of ≥10% extent on HRCT, and met the protocol criteria for progression within 24 months of screening as assessed by the investigator. The criteria for evidence of disease progression are given in Table 5, in addition to the full list of inclusion and exclusion criteria.

Table 5: Inclusion and exclusion criteria in the INBUILD trial

Inclusion criteria	Exclusion criteria
• Written informed consent consistent with ICH-GCP and local laws signed prior to entry in the study population • Aged ≥18 years at Visit 1 • Physician-diagnosed ILD with at least one of the following criteria for PF-ILD within 24	• AST, ALT >1.5 × ULN at Visit 1 • Bilirubin >1.5 × ULN at Visit 1 • CrCl <30 mL/min calculated by the Cockcroft-Gault formula at Visit 1‡ • Patients with underlying chronic liver disease (Child Pugh A, B or C hepatic impairment

Inclusion criteria	Exclusion criteria
months of screening despite treatment with unlicensed medications used in clinical practice to treat ILD, as assessed by the investigator: o Clinically significant decline in FVC % predicted based on a relative decline of ≥10% o Marginal decline in FVC % predicted based on a relative decline of ≥5 –<10% combined with worsening respiratory symptoms o Marginal decline in FVC% predicted based on a relative decline of ≥5 – <10% combined with increasing extent of fibrotic changes on chest imaging o Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging† • Fibrosing lung disease on HRCT, defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10%, performed within 12 months of Visit 1 as confirmed by central readers • For those with underlying connective tissue disease (CTD), stable CTD as defined by no initiation of new therapy or withdrawal of therapy for CTD within 6 weeks prior to Visit 1 • Carbon monoxide diffusing capacity (DL_{CO}) corrected for Hb ≥30% predicted of normal at Visit 1 and <80% predicted of normal at Visit 2 • FVC ≥45% predicted at Visit 2 (randomisation)	• Previous treatment with nintedanib or pirfenidone • Other investigational therapy received within 1 month or 6 half-lives (whichever was greater) prior to Visit 1 • Use of any of the following medications for the treatment of ILD: AZA, cyclosporin, mycophenolate mofetil, tacrolimus, OCS >20 mg/day and the combination of OCS+AZA+NAC within 4 weeks of Visit 2, cyclophosphamide within 8 weeks of Visit 2, rituximab within 6 months of Visit 2§ • Diagnosis of IPF based on ATS/ERS/JRS/ALAT 2011 guidelines • Significant PAH defined by any of the following: o Previous clinical or echocardiographic evidence of significant right heart failure o History of right heart catheterisation showing a cardiac index ≥2 l/min/m2 o PAH requiring parenteral therapy with epoprostenol/treprostinil o Primary obstructive airway physiology (pre-bronchodilator FEV1/FVC <0.7 at Visit 1) o In the opinion of the Investigator, other clinically significant pulmonary abnormalities • Major extrapulmonary physiological restriction (e.g. chest wall abnormality, large pleural effusion) • CVD, any of the following: o Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 months of Visit 1 o MI within 6 months of Visit 1 o Unstable cardiac angina within 6 months of Visit 1 • Bleeding risk, any of the following: o Known genetic predisposition to bleeding o Patients who require: fibrinolysis, full-dose anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin); high-dose antiplatelet therapy o History of haemorrhagic CNS event within 12 months of Visit 1 o Any of the following within 3 months of Visit 1: haemoptysis or haematuria; active GI bleeding or GI ulcers; major injury or surgery (Investigator's judgement) o Coagulation parameters: INR >2, prolongation of PT and aPTT by 1.5 × ULN at Visit 1 • History of thrombotic event (including stroke and transient ischaemic attack) within 12 months of Visit 1

Inclusion criteria	Exclusion criteria
	• Known hypersensitivity to the trial medication or its components • Peanut allergy • Other disease that may interfere with testing procedures or in the judgement of the Investigator may interfere with trial participation or may put the patient at risk when participating in the trial • Life expectancy for disease other than ILD <2.5 years (Investigator assessment) • Planned major surgical procedures • Women who are pregnant, nursing, or who plan to become pregnant while in the trial • Women of childbearing potential not willing or able to use highly effective methods of birth control that result in a low failure rate of less than 1% per year when used consistently and correctly as well as one barrier method for 28 days prior to and 3 months after nintedanib administration • In the opinion of the Investigator, active alcohol or substance abuse • Not able to understand or follow trial procedures including completion of self-administered questionnaires without help

Abbreviations: ALAT, Latin American Thoracic Association; ALT, alanine aminotransferase; aPTT, activate partial thromboplastin time; AST, aspartate aminotransferase; ATS, American Thoracic Society; AZA, azathioprine; CNS, central nervous system; CrCl, creatinine clearance; CTD, Connective Tissue Disease; CVD, cardiovascular diseases; DL_{CO}, diffusing capacity of the lung for carbon monoxide; ERS, European Respiratory Society; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GI, gastrointestinal; HRCT, high-resolution computed tomography; ICH-GCP, International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice; ILD, interstitial lung disease; INR, international normalised ratio; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; MI, myocardial infarction; NAC, n-acetylcysteine; OCS, oral corticosteroids; PAH, pulmonary arterial hypertension; PF-ILD, Progressive Fibrosing Interstitial Lung Disease; PT, prothrombin time; ULN, upper limit of normal.

† Changes attributable to comorbidities (e.g. infection, heart failure) must be excluded. Unapproved medications used in clinical practice to treat ILD include, but are not limited to, corticosteroid, azathioprine, mycophenolate mofetil, n-acetylcysteine, rituximab, cyclophosphamide, cyclosporin, tacrolimus.

‡ Laboratory parameters from Visit 1 have to satisfy the laboratory threshold values as shown above. Visit 2 laboratory results will be available only after randomisation. If results no longer satisfy the entry criteria at Visit 2, the decision of whether the patient remained on the study drug was at the discretion of the Investigator. Documentation was required for this decision. Laboratory parameters that were found to be abnormal at Visit 1 were allowed to be re-tested (once), if it was thought to be a measurement error (i.e. there was no abnormal result of this test in the recent history of the patient and there were no related clinical signs) or the result of a temporary and reversible medical condition, once that condition is resolved.

§ Patients whose rheumatoid arthritis (RA)/CTD is managed by these medications were not considered for participation in the study unless change in RA/CTD medication is medically indicated (see inclusion criteria).

Restricted and disallowed concomitant medications

Due to the lack of availability of specific targeted therapies, immunomodulatory treatments (including azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids) have routinely been used in clinical practice for the treatment of ILD. However, their benefit-risk

profiles in PF-ILD have not been established and they are not licensed for the treatment of PF-ILD. In order to avoid the potential impact of these drugs on the assessment of nintedanib in PF-ILD, their use was not allowed at randomisation and during the first 6 months of the treatment period. Patients who had taken these drugs could only participate in the trial if a wash-out period was observed before randomisation (Table 6). As the clinical trial protocol required that eligible patients progressed despite treatment with these medications, this prohibition was considered justified. In cases of worsening ILD and/or a CTD, the use of any of these drugs were allowed after 6 months study treatment as assessed by the treating clinician. Patients treated with a combination of oral corticosteroids + azathioprine + N-acetylcysteine within 4 weeks of randomisation were excluded, as were those receiving pirfenidone, full-dose therapeutic anticoagulation or high-dose antiplatelet therapy (e.g. aspirin >325 mg/day, clopidogrel >75 mg/day or equivalent doses of other therapy).

Table 6: Wash-out schedule for medications that were not permitted at baseline

Medication used to treat ILD	Wash-out period
Azathioprine Cyclosporin Tacrolimus Mycophenolate mofetil Oral corticosteroids >20 mg/day	4 weeks before randomisation
Rituximab	6 months before to randomisation
Cyclophosphamide	8 weeks before randomisation
Investigational drugs	4 weeks or 6 half-lives (whichever is longer) before randomisation

Abbreviations: ILD, interstitial lung disease

Treatment of underlying diseases associated with ILD

Investigators were encouraged to maintain the baseline treatment of CTD, including rheumatoid arthritis (RA), throughout the trial unless change was medically indicated. All RA/CTD medications were allowed at stable doses at baseline (visit 2) and during the trial with the exception of the following, less frequently used medications which were not allowed: azathioprine, cyclosporin, tacrolimus, high dose steroids, rituximab. In addition, cyclophosphamide and mycophenolate mofetil were not allowed for the off-label treatment of RA/CTD throughout the trial.

Initiation of these medications in addition to study medication was permitted after 6 months of trial treatment if deemed clinically necessary in the event of severe deterioration of CTD or ILD, as summarised in Table 7.

Table 7: Medication restrictions

	For ILD	For CTD
Baseline	Not allowed at Visit 2[1]	Not allowed
Within first 6 months of trial treatment	Not allowed	Not allowed
After 6 months of trial treatment	Allowed in case of significant deterioration[2]	Allowed in case of significant deterioration
After end of treatment	Allowed	Allowed

[1]Wash-out periods to be observed as described in Table 6.
[2]All could be used in case of clinically significant deterioration of PF-ILD or worsening CTD at the discretion of the investigator, except for investigational drugs. Introduction of new therapy for CTD was to be minimised.
CTD, connective tissue disease; ILD, interstitial lung disease
Restricted medications: azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, or oral corticosteroids (>20 mg per day), investigational drugs.

Study endpoints

A list of the study endpoints is given in Table 8. The primary endpoint was annual rate of decline in forced vital capacity (FVC; mL/year) over 52 weeks.

Table 8: Study endpoints in the INBUILD trial

Endpoint	Description
Efficacy	
Primary endpoint	Annual rate of decline in FVC as assessed over 52 weeks
Main secondary endpoints†	Change from baseline K-BILD questionnaire total score at week 52 (HRQoL) Time until first acute ILD exacerbation or death over 52 weeks Time until death over 52 weeks
Other secondary endpoints	Time to death due to respiratory cause over 52 weeks Time to progression (≥10% absolute decline in FVC % predicted) or death over 52 weeks Proportion of patients with a relative decline in FVC % predicted of >10% vs. baseline at week 52 Proportion of patients with a relative decline in FVC % predicted of >5% vs. baseline at week 52 Change from baseline L-PF symptoms, dyspnoea domain score at week 52 Change from baseline L-PF symptoms, cough domain score at week 52
Other model-relevant endpoints	Patient reported EQ-5D data collected to determine HSUV
Safety	
Safety endpoints	AEs over 52 weeks‡ Physical examination over 52 weeks‡ Vital signs over 52 weeks‡ Bodyweight over 52 weeks‡

Abbreviations: AE, adverse event; FVC, forced vital capacity; HRQoL, health-related quality of life; HSUV, health state utility values; ILD, interstitial lung disease; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; L-PF, living with pulmonary fibrosis.
† Main secondary endpoints were not powered to show statistical significance
‡ 52 weeks refers to the primary safety assessment. Selected safety analyses will be repeated to include data collected beyond 52 weeks (part B of the study).

Please see Table 9 for a summary of the trial methodology.

Table 9: Summary of trial methodology

Trial acronym	INBUILD
Location	15 countries, including Argentina, Belgium, Canada, Chile, China, France, Germany, Italy, Japan, Korea, Poland, Russia, Spain, UK and US.
Trial design	Phase III, multicentre, prospective, randomised, double-blind, placebo-controlled study.
Eligibility criteria for participants	**Inclusion criteria** • Written informed consent • Age ≥18 years • Physician-diagnosed ILD with ≥1 of the following criteria for PF-ILD within 24 months of screening despite treatment with unlicensed medications used to treat ILD in clinical practice: o Clinically significant decline in FVC %pred (relative decline of ≥10%) o Marginal decline in FVC %pred (relative decline of ≥5 – <10%) combined with worsening respiratory symptoms o Marginal decline in FVC %pred (relative decline of ≥5 – 10%) combined with increasing extent of fibrotic changes on chest imaging o Worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging† • Fibrosing lung disease on HRCT (within 12 months of screening and confirmed by central readers), defined as reticular abnormality with traction bronchiectasis with or without honeycombing, with disease extent of >10% • For those with underlying CTD: stable CTD (defined as no initiation of new CTD therapy or withdrawal of CTD therapy within 6 weeks before screening) • DL_{CO} corrected for haemoglobin ≥30% and <80% of predicted normal at randomisation • FVC ≥45% predicted at randomisation **Exclusion criteria** • AST, ALT >1.5 × ULN at screening • Bilirubin >1.5 × ULN at screening • CrCl <30 mL/min • Chronic liver disease (Child Pugh A, B or C hepatic impairment) • Previous treatment with nintedanib or pirfenidone • Other investigational therapy received within 1 month or 6 half-lives (whichever is greater) before screening • Use of any of the following medications to treat ILD: AZA, cyclosporin, mycophenolate mofetil, tacrolimus, OCS >20 mg/day or the combination of OCS+AZA+NAC (within 4 weeks of randomisation); cyclophosphamide (within 8 weeks of randomisation); or rituximab (within 6 months of randomisation) • Diagnosis of IPF based on ATS/ERS/JRS/ALAT 2011 guidelines • Significant PAH defined by any of the following:

Trial acronym	INBUILD
	o Previous clinical or echocardiographic evidence of significant right heart failure o History of right heart catheterization showing a cardiac index ≤2 l/min/m2 o Requirement for parenteral therapy with epoprostenol/treprostinil • Primary obstructive airway physiology (pre-bronchodilator FEV_1/FVC <0.7 at screening) • Other clinically significant pulmonary abnormalities (in the opinion of the investigator) • Major extra-pulmonary physiological restriction (e.g. chest wall abnormality, large pleural effusion) • Any of the following CV diseases within 6 months of screening: o Severe hypertension, uncontrolled by treatment (≥ 160/100 mmHg) o Myocardial infarction o Unstable cardiac angina • Bleeding risk as a result of any of the following: o Known genetic predisposition to bleeding o Patients requiring fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin) or high-dose antiplatelet therapy o History of haemorrhagic CNS event within 12 months of screening o Haemoptysis or haematuria, active GI bleeding or ulcers, major surgery or injury (in the opinion of the investigator) within 3 months of screening o INR >2, prolongation of prothrombin time and aPTT >1.5 × ULN at screening • History of a thrombotic event (including stroke and transient ischaemic attack) within 12 months of screening • Known hypersensitivity to the trial medication or its components • Peanut allergy • Other disease that may interfere with the testing procedures or (in the opinion of the investigator) with trial participation or may put the patient at risk when participating in the trial • Life expectancy for disease other than ILD <2.5 years (investigator's assessment) • Planned major surgical procedures • Women who are pregnant, nursing or who plan to become pregnant during the trial • Women of childbearing potential not willing or able to use highly effective methods of birth control that result in a low failure rate of less than 1% per year (when used consistently and correctly) and one barrier method for 28 days before and 3 months after nintedanib administration • Active alcohol or drug abuse (in the opinion of the investigator) • Patients not able to understand or follow trial procedures (including completion of self-administered questionnaires) without help
Settings and locations where the data were collected	Specialist referral centres experienced in the management of ILD
Trial drugs (the interventions for each group with sufficient details to allow replication, including	**Intervention:** oral nintedanib 150 mg bid (n=332) **Comparator:** matched placebo (n=331) **Restricted medication‡:** azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, oral corticosteroids.

Trial acronym	INBUILD
how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x]) Permitted and disallowed concomitant medication	**Permitted concomitant medication:** Approved RA/CTD medications at stable doses with the exception of restricted and disallowed medications. **Disallowed concomitant medication:** pirfenidone, full dose therapeutic anticoagulation or high dose antiplatelet therapy (e.g. acetyl salicylic acid >325 mg/day, clopidogrel >75 mg/day, equivalent doses of other antiplatelet therapy); cyclophosphamide, mycophenolate mofetil for the treatment of RA/CTD.
Primary outcomes (including scoring methods and timings of assessments)	**Primary endpoint:** annual rate of decline in FVC (mL/year) over 52 weeks in two co-primary populations (overall population and patients with UIP-like pattern on HRCT). **Main secondary endpoints**: change from baseline K-BILD total score at week 52; time to first acute ILD exacerbation or death over 52 weeks; time to death over 52 weeks.
Other outcomes used in the economic model/specified in the scope	Acute exacerbation of ILD or death up to DBL2 Death up to DBL2 AEs, serious AEs and severe AEs
Pre-planned subgroups	Overall population: gender, age group, race, baseline FVC % predicted, underlying clinical ILD diagnosis Patients with UIP-like fibrotic patterns: gender, age group, race

Abbreviations: AE, adverse event; ALAT, Latin American Thoracic Association; ALT, alanine aminotransferase; aPTT, activate partial thromboplastin time; AST, aspartate aminotransferase; ATS, American Thoracic Society; AZA, azathioprine; bid, twice daily; CNS, central nervous system; CrCl, creatinine clearance; CTD, Connective Tissue Disease; CV, cardiovascular; DBL1, database lock 1; DL_{CO}, diffusing capacity of the lung for carbon monoxide; ERS, European Respiratory Society; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FVC %pred, forced vital capacity % predicted; GI, gastrointestinal; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; INR, international normalized ratio; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; NAC, n-acetylecysteine; OCS, oral corticosteroids; PAH, pulmonary arterial hypertension; PF-ILD, Progressive Fibrosing Interstitial Lung Disease; RA, rheumatoid arthritis; ULN, upper limit of normal.
† Changes attributable to comorbidities (e.g. infection, heart failure) were excluded. Unapproved medications used to treat ILD in clinical practice include, but are not limited to, corticosteroids, azathioprine, mycophenolate mofetil, n-acetylcysteine, rituximab, cyclophosphamide, cyclosporin and tacrolimus.
‡ Use of restricted medications was not allowed at randomization and during the first 6 months of the treatment period.

Study population and baseline characteristics

A summary of patient demographics and baseline characteristics are presented in Table 10. Overall, 663 patients were treated in a 1:1 ratio between the nintedanib group and placebo group. Patient demographics were similar in both groups and efficacy variables were balanced across the groups at baseline.(5)

Treatment discontinuation over 52 weeks was greater in the nintedanib group (24.1%) than the placebo group (14.8%), with AEs accounting for the majority of discontinuations. Most patients in the nintedanib and placebo groups remained in the

trial until week 52 (94.6% and 94.0%, respectively). 69.6% of patients in the nintedanib group and 74.0% of the placebo group continued follow-up for the entire trial period.(5)

Table 10: Baseline characteristics in the INBUILD trial

	Nintedanib (n=332)	Placebo (n=331)
Male – no. (%)	179 (53.9)	177 (53.5)
Age – yr	65.2±9.7	66.3±9.8
Former or current smoker – no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on HRCT – no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in 24 months before screening (grouped) – no. (%)		
Relative decline in FVC ≥10% predicted	160 (48.2)	172 (52.0)
Relative decline in FVC ≥5–<10% predicted combined with worsening of respiratory symptoms and/or increased extent of fibrosis on HRCT	110 (33.1)	97 (29.3)
Worsened respiratory symptoms and increased extent of fibrosis on HRCT only	62 (18.7)	61 (18.4)
FVC		
Mean value – mL	2,340±740	2,321±728
% of predicted value	68.7±16.0	69.3±15.2
DLco, mmol/min/kpa†	3.5±1.2	3.7±1.3
DLco, % of predicted value†	44.4±11.9	47.9±15.0
K-BILD questionnaire total score‡	52.5±11.0	52.3±9.8

Abbreviations: DLco, diffusion capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; K-BILD, King's Brief Interstitial Lung Disease; UIP, usual interstitial pneumonia. * Plus–minus values are means ± SD. † The DLco value was corrected for the haemoglobin level. ‡ K-BILD questionnaire total score ranges from 0–100, with higher scores representing better health status.
Sources: Flaherty 2019 (5)

Baseline and concomitant medications

Baseline medication use was well balanced between treatment groups (Table 11).

Table 11: Baseline restricted therapies

	Nintedanib (n=332)	Placebo (n=331)
Patients taking ≥1 restricted therapy at baseline	57 (17.2)	59 (17.8)
Biologic disease-modifying antirheumatic drugs	14 (4.2)	17 (5.1)
Denosumab	3 (0.9)	8 (2.4)
Abatacept	3 (0.9)	3 (0.9)
Etanercept	3 (0.9)	1 (0.3)
Tocilizumab	2 (0.6)	2 (0.6)
Adalimumab	2 (0.6)	1 (0.3)
Infliximab	0 (0.0)	2 (0.6)

	Nintedanib (n=332)	Placebo (n=331)
Rituximab	1 (0.3)	0 (0.0)
Ascorbic acid; collagen	0 (0.0)	1 (0.3)
Other†	0 (0.0)	1 (0.3)
Glucocorticoids‡	3 (0.9)	5 (1.5)
Meprednisone	1 (0.3)	2 (0.6)
Prednisone	2 (0.6)	2 (0.6)
Prednisolone	0 (0.0)	1 (0.3)
Immunomodulatory medications for ILD	3 (0.9)	4 (1.2)
Mycophenolate mofetil	2 (0.6)	1 (0.3)
Ciclosporin	0 (0.0)	2 (0.6)
Rituximab	1 (0.3)	0 (0.0)
Tacrolimus	0 (0.0)	1 (0.3)
Non-biologic disease-modifying antirheumatic drugs	35 (10.5)	42 (12.7)
Hydroxychloroquine	13 (3.9)	9 (2.7)
Leflunomide	10 (3.0)	8 (2.4)
Methotrexate	5 (1.5)	10 (3.0)
Sulfasalazine	5 (1.5)	5 (1.5)
Hydroxychloroquine sulfate	5 (1.5)	3 (0.9)
Methotrexate sodium	1 (0.3)	3 (0.9)
Mycophenolate mofetil	2 (0.6)	1 (0.3)
Ciclosporin	0 (0.0)	2 (0.6)
Doxycycline	0 (0.0)	2 (0.6)
Chloroquine phosphate	0 (0.0)	2 (0.6)
Penicillamine	0 (0.0)	2 (0.6)
Bucillamine	0 (0.0)	1 (0.3)
Iguratimod	0 (0.0)	1 (0.3)
Tacrolimus	0 (0.0)	1 (0.3)
Minocycline hydrochloride	1 (0.3)	0 (0.0)

Data are n (%) of patients. Medications based on customised drug grouping category. †Ascorbic acid; boswellia serrata resin; chondroitin sulfate; collagen; glucosamine hydrochloride; hyaluronic acid; manganese sulfate; methylsulfonylmethane; sodium; sodium borate. ‡Only included in customized drug grouping if high dose and route of administration was oral, intravenous, or intramuscular.

During the course of the trial (over 52 weeks) 70 patients (21.1% in the placebo arm and 36 patients (10.8%) in the nintedanib arm received at least one restricted therapy (Table 12). Important protocol deviations, defined as initiation of treatment with azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, or oral corticosteroids (>20 mg per day) for the treatment of ILD or CTD within the first 6 months of study treatment were reported for 19 patients (5.7%) in the placebo group and 7 patients (2.1%) in the nintedanib group.

Table 12: Restricted therapies initiated between first and last trial drug intake over 52 weeks

	Nintedanib (n=332)	Placebo (n=331)
Patients with ≥1 restricted therapy over 52 weeks	36 (10.8)	70 (21.1)
Biologic disease-modifying antirheumatic drugs	2 (0.6)	2 (0.6)
Rituximab	2 (0.6)	2 (0.6)
Glucocorticoids*	33 (9.9)	57 (17.2)
Prednisone	20 (6.0)	27 (8.2)
Prednisolone	8 (2.4)	15 (4.5)
Methylprednisolone sodium succinate	5 (1.5)	14 (4.2)
Methylprednisolone	4 (1.2)	9 (2.7)
Hydrocortisone	1 (0.3)	2 (0.6)
Meprednisone	1 (0.3)	1 (0.3)
Steroids	2 (0.6)	0 (0.0)
Betamethasone sodium phosphate	1 (0.3)	0 (0.0)
Deflazacort	1 (0.3)	0 (0.0)
Dexamethasone	0 (0.0)	1 (0.3)
Dexamethasone sodium phosphate	0 (0.0)	1 (0.3)
Immunomodulatory medications for ILD	9 (2.7)	21 (6.3)
Mycophenolate Mofetil	3 (0.9)	7 (2.1)
Azathioprine	1 (0.3)	5 (1.5)
Tacrolimus	3 (0.9)	3 (0.9)
Ciclosporin	0 (0.0)	4 (1.2)
Rituximab	2 (0.6)	2 (0.6)
Cyclophosphamide	0 (0.0)	2 (0.6)
Non-biologic disease-modifying antirheumatic drugs	7 (2.1)	19 (5.7)
Mycophenolate mofetil	3 (0.9)	7 (2.1)
Tacrolimus	3 (0.9)	3 (0.9)
Azathioprine	1 (0.3)	5 (1.5)
Ciclosporin	0 (0.0)	4 (1.2)
Cyclophosphamide	0 (0.0)	2 (0.6)

Data are n (%) of patients. Medications based on customized drug grouping category. *Only included in customized drug grouping if high dose and route of administration was oral, intravenous, or intramuscular.

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

The analysis considered two co-primary analysis populations, the overall population (including all patients) and all patients with HRCT with UIP-like fibrotic pattern only (see Table 4 for the definition of this group). The sample size was calculated to provide adequate power to detect a clinically meaningful treatment difference in either of the co-primary populations, based on several scenarios (see Table 13). No key secondary endpoints were planned but the main secondary endpoints were chosen to provide the most relevant supportive evidence to the primary endpoint assessment. The trial was

not powered to demonstrate a statistically significant reduction in mortality over 52 weeks (one of the main secondary endpoints).

Sample size was calculated assuming annual rates of decline in FVC of 150–200 mL/year for patients with UIP-like fibrotic pattern and 120–150 mL/year for patients with other HRCT fibrotic patterns. An approximate 50% reduction in the annual rate of decline in FVC was expected in patients treated with nintedanib, based on data from IPF patients in the IMPULSIS trial. The treatment effect was therefore expected to be in the range of 75–100 mL/year for PF-ILD patients with UIP-like HRCT pattern and 60–75 mL/year in PF-ILD patients with other HRCT fibrotic patterns. For patients with other HRCT fibrotic patterns, the variability was assumed to be larger than in IPF, with a standard deviation (SD) of 400 mL/year. For patients with UIP-like HRCT pattern, a more homogeneous group, the variability was assumed to be the same as observed in IPF with a SD of 300 mL/year. Therefore, the proposed sample size of 300 patients randomised per treatment group (600 patients in total, including 400 patients with UIP-like HRCT pattern) was expected to provide adequate power to demonstrate a clinically important treatment benefit on the primary endpoint. This was also expected in scenarios where the annual rate of decline in both co-primary patient populations was lower than observed in the phase III trials for IPF patients.

Table 13: Power properties for varying treatment differences in the two co-primary populations

	Patients with HRCT with UIP-like pattern only (co-primary)	Patients with other HRCT fibrotic patterns	Overall patient population (co-primary)
Scenario 1			
Assumed treatment difference in absolute change in FVC in mL/year (SD)	100 (300)	75 (400)	92 (337)
Individual test power	90.2%	-	90.3%
Overall power†	92.6%		
Scenario 2			
Assumed treatment difference in absolute change in FVC in mL/year (SD)	75 (300)	60 (400)	70 (337)
Individual test power	67.2%	-	68.2%
Overall power†	72.4%		
Scenario 3			

	Patients with HRCT with UIP-like pattern only (co-primary)	Patients with other HRCT fibrotic patterns	Overall patient population (co-primary)
Assumed treatment difference in absolute change in FVC in mL/year (SD)	75 (300)	75 (400)	75 (337)
Individual test power	68.2%		73.4%
Overall power†	75.8%		

Abbreviations: FVC, forced vital capacity; HRCT, high-resolution computed tomography; SD, standard deviation; UIP, usual interstitial pneumonia.
† Equals the probability of concluding statistical significance for either of the co-primary populations.

Efficacy and safety analyses were conducted using data from patients who were randomised to treatment (nintedanib or placebo) and received at least one dose of study medication (known as the treated set [TS]). The primary assessment of the benefit/risk was based on efficacy and safety data over 52 weeks. To reduce the amount of missing data, patients who discontinued the trial drug for any reason prior to completing the 52 week treatment period were asked to attend all visits and undergo all examinations as previously planned. In addition, for patients who prematurely discontinued trial medication and were unable to complete the scheduled visits, every attempt was made to collect information on vital status at week 52, at the time of data cut-off for the primary analysis and at the end of the trial. Data collected beyond 52 weeks (i.e. during part B) provided supportive longer term information on the effect of nintedanib. Part B was a variable treatment period beyond 52 weeks, during which patients continued on blinded, randomised treatment. Data from Part B, DBL, are included in the submission as supportive information.

Dose reduction from 150 mg BID to 100 mg BID or treatment interruption were considered to manage AEs. No further dose reduction was possible for patients on the 100 mg BID regimen because of possible lack of efficacy. Treatment discontinuation was considered where persistent AEs were observed at the 100 mg BID dose or where there were severe effects at 150 mg BID.

Similarly to the INPULSIS trials, a random coefficient regression (random slopes and intercepts) model was used for the primary endpoint. Mixed Effects Models for Repeated Measures (MMRM) were used for continuous secondary endpoints, whereas Cox proportional hazards models and Kaplan-Meier plots were used for time-to-event secondary endpoints and logistic regressions for binary secondary endpoints.

Formal statistical testing was performed using data from the two co-primary populations (the overall population and all patients with HRCT with UIP-like fibrotic pattern only). To maintain an overall type 1 error rate of 5%, a Hochberg procedure was used for multiplicity adjustment. (38) For the primary endpoint, statistical significance was to be declared if the analysis in both co-primary populations was significant at the two-sided 5% level, or if the analyses in either co-primary population were statistically significant at the two-sided 2.5% level. It was not expected that there would be sufficient power to achieve statistical significance in the subgroup of patients with other HRCT fibrotic patterns. However, results in this subgroup were also assessed and presented descriptively. The primary analysis used all available data from baseline (excluded) up to week 52, including visits done after premature treatment discontinuation, end of trial visits, and follow-up visits done before week 52 (i.e. including all measurements after first drug intake and before or on Day 373).

No interim analyses were planned or performed, but the conduct of the trial was monitored by a Data Monitoring Committee until database lock 1.

Missing data

The statistical model used for the primary analysis allowed for missing data, assuming they were missing at random. Patients were included in the model if they had at least one post-baseline assessment. The statistical model assumed that patients who prematurely discontinued trial participation would have behaved similarly to those who remained in the trial. Sensitivity analyses using alternative assumptions were conducted to investigate the potential effect of missing data on the results of the primary analysis.

Secondary analyses of continuous endpoints also allowed for missing data by assuming they were missing at random. Missing item-level data in quality of life questionnaires were handled according to the instructions provided by the instrument developer. For time-to-event endpoints, missing or incomplete data were managed by standard survival analysis techniques (i.e. censoring). A missing or incomplete date of death was imputed as the earliest time point a patient may have been dead (worst case for time-to-event analysis). For binary endpoints, two analyses were performed.

Patients with missing data were considered as non-responders (worst case analysis) and missing values were imputed based on a multiple imputation approach.

For a description of the subgroup analyses conducted, please see Section B.2.7 and Appendix E.

A summary of statistical analyses in the INBUILD trial is given in Table 14.

Table 14: Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
INBUILD (study 1199.247, NCT02999178)(10)	**Null hypothesis:** There is no difference in either of the co-primary populations (all patients and patients with HRCT with UIP-like fibrotic pattern only) in the annual rate of decline in FVC from baseline until 52 weeks between nintedanib 150 mg bid and placebo. **Alternative hypothesis:** There is a difference in the annual rate of decline in FVC between nintedanib 150 mg bid and placebo over 52 weeks, in either or both co-primary populations.	Primary analysis of the primary endpoint was based on all measurements taken over 52 weeks using a random coefficient regression model. Continuous secondary endpoints were analysed using Mixed Effects Models for Repeated Measures. Time-to-event secondary endpoints were analysed using Cox proportional hazards models and Kaplan-Meier plots; binary secondary endpoints were analysed using logistic regressions. Formal statistical testing was performed on both co-primary populations, and statistical significance declared if the analysis in both populations was significant at the two-sided 5% level, or if the analyses in either population were statistically significant at the two-sided 2.5% level. A Hochberg procedure was used to maintain an overall type 1 error rate of 5%.	A sample size of 600 patients (300 per randomised treatment group with 400 patients with UIP-like HRCT pattern) was expected to provide adequate power to demonstrate a clinically important treatment benefit on the primary endpoint, according to three scenarios (see Table 13). This included a scenario where the effect on the primary endpoint in both co-primary populations is lower than observed for IPF patients in the INPULSIS trials.	To reduce the amount of missing data, patients who discontinued the trial drug prior to completing the 52 week treatment period were asked to attend all visits as planned. In addition, for patients who prematurely discontinued trial medication and were unable to complete the scheduled visits, every attempt was made to collect information on vital status at week 52, at the time of data cut-off for the primary analysis and at the end of the trial. All aspects of data handling were performed according to guidelines and safety procedures established by BI for safety, completeness, consistency, accuracy, plausibility, legibility and adherence to the Clinical Trial Plan.

Abbreviations: bid, twice daily; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia

Please see Appendix D for the participant flow in the INBUILD trial, including the number of patients screened, randomised and allocated to treatment.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Please see Appendix D for a full quality assessment of the INBUILD trial. Overall, we consider this trial to be of high quality, with a low risk of bias.

B.2.6 Clinical effectiveness results of the relevant trials

The results presented here have been taken from two published manuscripts (Flaherty et al, 2019 (5), Wells et al, 2020 (39) and the clinical trial report. (37) Data from database lock 2 (DBL2) of INBUILD have been taken from a poster developed for the European Respiratory Society International Congress, 7-9th September 2020.(40)

Primary endpoint

The primary endpoint, annual rate of decline in FVC over 52 weeks, was met in both co-primary populations (see Table 15). Treatment with nintedanib reduced the adjusted annual rate of decline in FVC by 107.0 mL (p<0.001) in the overall population and by 128.2 mL (p<0.001) in patients with UIP-like fibrotic pattern vs. placebo. Consistent results were observed in the complementary population of patients with other fibrotic patterns.

The treatment effect between populations according to the imaging pattern was consistent (Figure 5) and all sensitivity analyses relating to the handling of missing data were supportive of findings in the primary analysis. Furthermore, the curves of observed change from baseline in FVC in the nintedanib and placebo groups separated early and continued to diverge (Figure 6).

Table 15: Efficacy endpoint results

Endpoint	Nintedanib (N = 332)	Placebo (N = 331)	Difference vs. placebo (95% CI; p-value)
Primary endpoint			
Rate of decline in FVC at 52 weeks (mL/year)†			
Overall population	−80.8±15.1	−187.8±14.8	107.0 (65.4, 148.5; p<0.001)
Patients with UIP-like fibrotic pattern	−82.9±20.8	−211.1±20.5	128.2 (70.8, 185.6; p<0.001)

Endpoint	Nintedanib (N = 332)	Placebo (N = 331)	Difference vs. placebo (95% CI; p-value)
Patients with other fibrotic patterns	−79.0±21.6	−154.2±21.2	75.3 (15.5, 135.0; nominal p=0.0137)‡
Annual rate of decline in FVC (mL/ year) over the whole trial period up to DBL2			
Overall population	−118.14±11.4	−175.67±11.2	57.5 (26.1–89.0)
Patients with UIP-like fibrotic pattern	−130.3±15.5	−204.2±15.3	73.9 (31.0–116.8)
Patients with other fibrotic patterns	−101.3±16.7	−134.9±16.3	33.7 (−12.3–79.6)
Main secondary endpoints			
Absolute change from baseline in total score on K-BILD questionnaire at 52 weeks§			
Overall population	0.55±0.60	−0.79±0.59	1.34 (−0.31, 2.98; p=0.1115)‡
Acute exacerbation of ILD or death at 52 weeks (no. with event/total no. [%])			
Overall population	26/332 (7.8)	32/331 (9.7)	0.80 (0.48, 1.34; p=0.3948)‡¶
Time to first acute ILD exacerbation or death over the whole trial period up to DBL2 (no. with event/total no. [%])			
Overall population	46/332 (13.9)	65/331 (19.6)	0.67 (0.46 to 0.98)¶
Death at 52 weeks (no. with event/total no. [%])			
Overall population	16/332 (4.8)	17/331 (5.1)	0.94 (0.47, 1.86; p=0.8544)‡¶
Time to death over the whole trial period up to DBL2 (no. with event/total no. [%])			
Overall population	36/332 (10.8)	45/331 (13.6)	0.78 (0.50 to 1.21)¶
Other secondary endpoints assessed until DBL2 in the overall population (no. with event/total no. [%])			
Time to progression (≥10% absolute decline in FVC % predicted) or death	134/332 (40.4)	181/331 (54.7)	0.66 (0.53 to 0.83¶
Time to death due to a respiratory cause	21/332 (6.3)	30/332 (9.1)	0.68 (0.39 to 1.18)¶

Abbreviations: FVC, forced vital capacity; ILD, interstitial lung disease; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; NR, not reported; UIP, usual interstitial pneumonia.

† For the primary end point, the patients with a UIP-like fibrotic pattern included 206 in each treatment group. The patients with other fibrotic patterns included 126 in the nintedanib group and 125 in the placebo group.

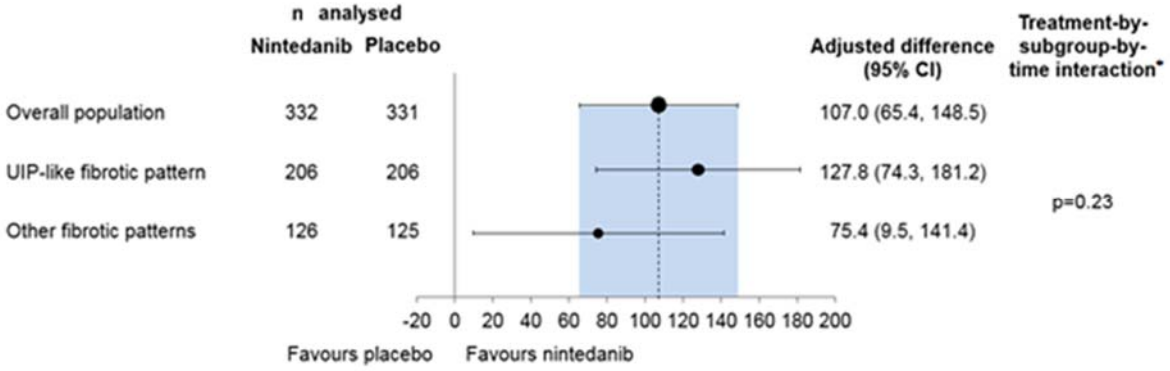
‡ The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

§ For the analysis of the scores on the K-BILD questionnaire, 332 patients were included in the nintedanib group and 330 in the placebo group in the overall population; among the patients with a UIP-like fibrotic pattern, included were 206 patients and 205 patients, respectively.

¶ The difference was assessed as a hazard ratio.

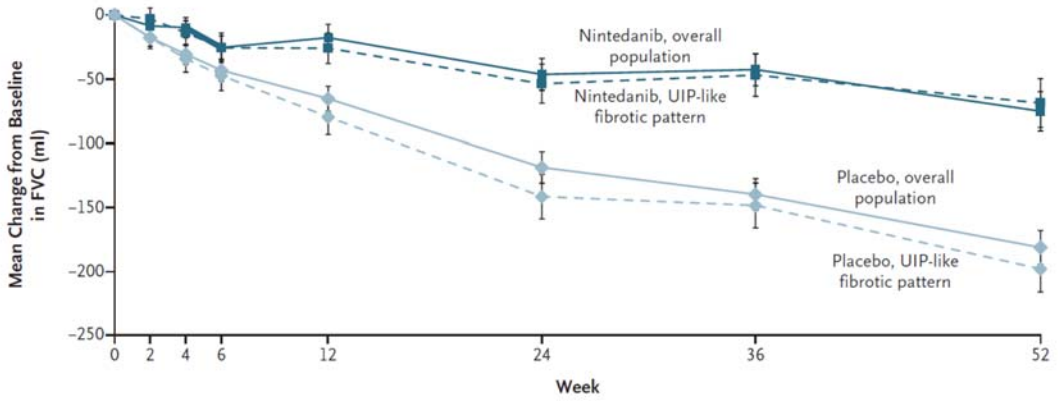
Data are taken from Flaherty 2019(5) and the Clinical Trial Report (37). DBL2 data have been taken from the Clinical Trial Report (37) and a poster developed by Flaherty et al for the European Respiratory Society International Congress, 7-9th September 2021.(40)

Figure 5: Between-group adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks in populations by HRCT pattern(5)



Abbreviations: bid, twice daily; CI, confidence interval; FVC, forced vital capacity; SE, standard error.
*Estimated based on a random coefficient regression model with fixed effects for baseline FVC, random effect of patient specific intercept and time, and including baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interactions.

Figure 6: Decline from baseline in FVC at 52 weeks



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

Abbreviations: FVC, forced vital capacity; UIP, usual interstitial pneumonia

Main secondary endpoints

The results of the main secondary endpoints are presented in Table 15. In the overall population, treatment with nintedanib resulted in a numerical improvement in HRQoL as measured by the King's Brief Interstitial Lung Disease (K-BILD) questionnaire compared with placebo (adjusted mean difference 1.34; 95% CI -0.31, 2.98; nominal p=0.1115), although the change from baseline total score was small in both treatment groups. A lower proportion of patients in the nintedanib group (7.8%) than in the

placebo group (9.7%) had an event of first acute ILD exacerbation or death over 52 weeks. The hazard ratio (HR) for time to first acute ILD exacerbation or death was numerically in favour of nintedanib vs. placebo (HR 0.80; 95% CI 0.48, 1.34; nominal p=0.3948). The HR for time to death over 52 weeks was 0.94 (95% CI 0.47, 1.86; nominal p=0.8544). Over the whole trial (up to DBL2), in the overall population, a lower proportion of patients in the nintedanib group (13.9%) than in the placebo group (19.6%) had an event of first acute ILD exacerbation or death (Table 15). Treatment with nintedanib reduced the risk of first acute ILD exacerbation or death by 33% compared with placebo, as indicated by the HR of 0.67 (95% CI 0.46, 0.98; Table 15).

In the overall population, the percentage of patients who died over 52 weeks was similar between treatment groups (%; n/N, nintedanib: 4.8%; 16/332, placebo: 5.1%, 17/331). The HR for time to death over 52 weeks was 0.94 (95% CI: 0.47, 1.86; nominal p=0.8544). Over the whole trial (up to DBL2), in the overall population, a lower proportion of patients died in the nintedanib group (10.8%) than in the placebo group (13.6%). The HR indicated that the risk of death was 22% lower in the nintedanib group than in the placebo group (HR 0.78; 95% CI 0.50, 1.21).

Other secondary endpoints (37)

In the overall population, over the whole trial period (up to DBL2), a lower proportion of patients in the nintedanib group (40.4%; n/N, 134/332) than in the placebo group (54.7%; n/N, 181/331) progressed (defined as ≥10% absolute decline in FVC % predicted) or died. Most of these patients had an event of progression (34.3% nintedanib vs. 48.3% placebo). Treatment with nintedanib reduced the risk of progression or death by 34% compared with placebo, as indicated by the HR of 0.66 (95% CI 0.53, 0.83). In the overall population, over the whole trial period (up to DBL2), a lower proportion of patients died due to respiratory cause in the nintedanib group (6.3%; n/N, 21/332) than in the placebo group (9.1%; n/N, 30/331). The HR indicated that the risk of death due to respiratory cause was 32% lower in the nintedanib group than in the placebo group (HR 0.68; 95% CI 0.39, 1.18).

The analysis of the proportions of patients with a relative decline from baseline in FVC % predicted of >10% (adjusted odds ratio [OR] 0.70; 95% CI 0.52, 0.96) or >5% (adjusted OR 0.50; 95% CI 0.36, 0.68) in the overall population at 52 weeks were

numerically in favour of nintedanib vs. placebo. Treatment with nintedanib in the overall population also numerically improved the Living with Pulmonary Fibrosis (L-PF) symptoms dyspnoea score at week 52 (adjusted mean difference -3.53; 95% CI -6.14, -0.92) and the L-PF symptoms cough domain score (adjusted mean difference -6.09; 95% CI -9.65, -2.53) compared with placebo.

B.2.7 Subgroup analysis

Subgroup analyses for the description of the trial population, the primary endpoint and safety endpoints were performed in the following pre-planned groups: gender, age (<65 years vs. over 65 years), race, baseline FVC % predicted (≤70% vs >70%) and underlying clinical ILD diagnosis in groups.

For each subgroup analysis of the primary endpoint, the heterogeneity of the subgroup treatment effect on the slope was estimated. A random slope and intercept mixed model was fitted based on the statistical model for the primary analysis, but parametrised using the treatment-by-subgroup and the treatment-by-subgroup-by-time interaction terms. A contrast statement, with appropriate contrasts, was used to conduct an F-test of heterogeneity across all expression levels of the subgrouping.

The primary endpoint was also analysed in the overall population by subgroups based on HRCT pattern (UIP-like pattern only vs. other HRCT fibrotic patterns). The model excluded the term for the HRCT pattern in this analysis, and the obtained interaction p-value served as an objective measurement of whether the results of the primary endpoint were consistent between the co-primary population of patients with UIP-like fibrotic pattern and the complementary population of patients with other fibrotic patterns. A pre-specified additional analysis of the impact of underlying ILD diagnoses on the primary endpoint results was also carried out by excluding ILD diagnosis groups one by one, however it should be noted that these are exploratory analyses.(39)

The efficacy of nintedanib vs. placebo in these subgroups can be found in Appendix E. None of the demographics or clinical characteristics had a substantial influence on the treatment effect of nintedanib vs. placebo in the overall population or the population with UIP-like fibrotic pattern on HRCT. All point estimates were in favour of nintedanib vs. placebo. An additional analysis investigated the impact of the underlying

ILD diagnoses by employing the method of excluding ILD diagnosis groups one by one, thus exploring the influence of the excluded ILD diagnosis group on the overall treatment effect. The point estimates and CIs were very similar in these analyses, showing that the treatment effect was not driven by one of the ILD diagnosis groups. The results were similar in both the overall population and the population with UIP-like fibrotic pattern by HRCT.

B.2.8 Meta-analysis

As stated earlier in the submission, nintedanib is the only licensed treatment for PF-ILD other than IPF. Although immunomodulatory agents may be used to treat the inflammatory component of patients' underlying disease, there are no randomised controlled trials to suggest that these unlicensed treatments have a positive impact on the chronic fibrotic progression of PF-ILD.

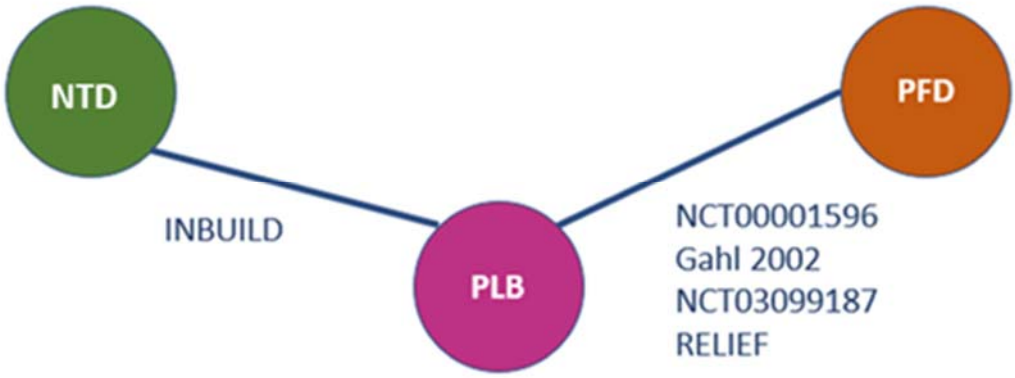
However, as an exercise of due diligence, the feasibility of a quantitative evidence synthesis, such as an NMA or Bucher's indirect comparison with available treatments used in clinical practice, was assessed based on evidence identified in the SLR described in Appendix D. The possibility of forming a connected network comparing the treatments of interest for each outcome of interest was assessed. Potential treatment effect modifiers were then identified, which could introduce heterogeneity and lead to bias in the analysis. These included different treatment doses and schedules, outcome definitions or time points, patient characteristics, baseline risks and observed treatment effects.

Six studies were explored in the feasibility assessment as they met the criteria for inclusion in the SLR and reported results (Table 75). Wyser 1997(41) was immediately excluded from the feasibility analysis as this study did not form a connected network with any of the other included studies.

A potentially feasible network indirectly comparing nintedanib to pirfenidone via placebo was identified (Figure 7). One study (INBUILD) informed the nintedanib vs. placebo comparison and four studies informed the pirfenidone vs. placebo comparison. However, three of the four studies informing pirfenidone vs. placebo (RELIEF, NCT00001596 and Gahl 2002)(42-44) were not considered suitable due to

differences in patient and trial characteristics compared to INBUILD(5) (the only study informing nintedanib versus placebo) and lack of outcome reporting (see Table 16, Table 17 and Table 18). An indirect comparison at 24 weeks was technically possible between nintedanib and pirfenidone, based on INBUILD(5) and NCT03099187.(45) However, since PF-ILD is a chronic condition, this comparison is expected to be immature. As a result, no indirect treatment comparisons were undertaken. It should also be noted that pirfenidone is not licensed for the treatment of PF-ILD, which further suggests that this is not an appropriate comparison. Pirfenidone is also not included as a comparator in the decision problem specified in Table 1.

Figure 7: Potential network plot



Abbreviations: NTD, nintedanib; PFD, pirfenidone; PLB, placebo

Table 16: Trial characteristics in indirect comparison feasibility assessment

Trial	Publication year	Phase	Country	Results timepoint
NCT00001596 (42)	2011	2	USA[a]	12 months
Gahl 2002(43)	2002	NR	USA[a]	Various (up to 44 months)
NCT03099187(45)	2019	2	International	24 weeks
INBUILD(5)	2019	3	International	52 weeks[b]
RELIEF(44)	2019	2	Germany	NR

[a] patients were predominantly from Puerto Rico; [b] change in FVC from baseline also reported at 2, 4, 6, 12, 24, 36 weeks in figure
Abbreviations: NR, not reported

Table 17: Patient baseline characteristics for studies included in the feasibility assessment

Trial	Intervention	N randomised	Age, mean (SD)	Gender (% male)	Former/ current smoker (%)	UIP-like fibrotic pattern on HRCT
NCT00001596 (42)	Pirfenidone	23	39.2 (10.8)	35%	NR	NR
	Placebo	12	43.4 (7.7)	50%	NR	NR
Gahl 2002(43)	Pirfenidone	11	41.5 (12.1)	*45%*	*18%*[a]	NR
	Placebo	10	34.0 (9.2)	*40%*	*20%*[a]	NR
NCT03099187 (45)	Pirfenidone	127	70.0 (61.0–76.0)[b]	55%	NR	NR
	Placebo	126	69.0 (63.0–74.0)[b]	55%	NR	NR
INBUILD(5)	Nintedanib	332	65.2 (9.7)	54%	54%	62%
	Placebo	331	66.3 (9.8)	54%	51%	62%
RELIEF(44)	Pirfenidone	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR

[a] current smokers only (greater than one pack a year); [b] median (IQR)
Baseline characteristics similar to INBUILD are highlighted in **green**, differences are highlighted in **red**. Calculated values are shown in *italics*.
Abbreviations: HRCT, high-resolution computed tomography; NR, not reported; SD, standard deviation; UIP, usual interstitial pneumonia.

Table 18: Outcome baseline values for studies included in the feasibility assessment

Trial	Intervention	FVC (% predicted), mean (SD)	FEV1/FVC ratio	DLCO (% predicted)	6MWD, m	K-BILD score
NCT00001596 (42)	Pirfenidone	72.9 (7.9)	108 (11.3)[a]	68.0 (16.6)	504 (120)	NR
	Placebo	73.5 (9.7)	111 (6.7)[a]	66.8 (15.9)	525 (94)	NR
Gahl 2002(43)	Pirfenidone	58.5 (12.9)	NR	60.0 (24.5)	NR	NR
	Placebo	59.7 (10.5)	NR	66.6 (25.4)	NR	NR
NCT03099187 (45)	Pirfenidone	71.0 (59.0–87.3)[b]	0.82 (0.78–0·86)[b]	44.6 (36.9–53.5)[b]	372 (303–487)[b]	NR
	Placebo	71.5 (58.0–88.0)[b]	0.84 (0.78–0.87)[b]	48.0 (38.4–59.0)[b]	395 (325–472)[b]	NR
INBUILD(5)	Nintedanib	68.7 (16.0)	0.83 (0.07)	44.4 (11.9)	NR	52.5 (11.0)
	Placebo	69.3 (15.2)	0.83 (0.07)	47.9 (15.0)	NR	52.3 (9.8)
RELIEF(44)	Pirfenidone	NR	NR	NR	NR	NR
	Placebo	NR	NR	NR	NR	NR

[a] these results are likely reported in a different unit to the other studies due to the large discrepancy in between-study values; [b] median (IQR)
Baseline characteristics similar to INBUILD are highlighted in **green**, differences are highlighted in **red**.

Abbreviations: 6MWD, 6-minute walking distance; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; K-BILD; King's Brief Interstitial Lung Disease; NR, not reported

B.2.9 Indirect and mixed treatment comparisons

As described above, it was not possible to conduct any indirect or mixed treatment comparisons due to lack of published evidence for comparator treatments. For this reason, these sections in Appendix D have not been completed.

B.2.10 Adverse reactions

Safety over 52 weeks

An overall summary of AEs reported over 52 weeks is given in Table 19. In the overall population, the percentages of patients with any AEs and serious AEs were similar in the nintedanib and placebo groups. The most frequently reported AEs by system organ class (SOCs with a frequency >20% in either treatment group) were gastrointestinal disorders (nintedanib: 80.7%; placebo: 45.0%); infections and infestations (53.3% vs. 55.9%); respiratory, thoracic and mediastinal disorders (38.6% vs. 43.5%); investigations (34.3% vs. 16.9%); general disorders and administration site conditions (25.9% vs. 25.7%); musculoskeletal and connective tissue disorder (23.2% vs. 26.3%); nervous system disorders (20.8% vs. 16.3%); and metabolism and nutrition disorders (20.8% vs. 11.5%).

Table 19: AEs in the INBUILD trial (overall population, 52 weeks)

AE	Nintedanib	Placebo
Any (n [%])	317 (95.5)	296 (89.4)
Any except for progression of interstitial lung disease	317 (95.5)	295 (89.1)
Most frequent AEs		
Diarrhoea	222 (66.9)	79 (23.9)
Nausea	96 (28.9)	31 (9.4)
Bronchitis	41 (12.3)	47 (14.2)
Nasopharyngitis	44 (13.3)	40 (12.1)
Dyspnoea	36 (10.8)	44 (13.3)
Vomiting	61 (18.4)	17 (5.1)
Cough	33 (9.9)	44 (13.3)
Decreased appetite	48 (14.5)	17 (5.1)
Headache	35 (10.5)	23 (6.9)
Alanine aminotransferase increased	43 (13.0)	12 (3.6)

AE	Nintedanib	Placebo
Progression of ILD	16 (4.8)	39 (11.8)
Weight loss	41 (12.3)	11 (3.3)
Aspartate aminotransferase increased	38 (11.4)	12 (3.6)
Abdominal pain	34 (10.2)	8 (2.4)
Severe AEs	60 (18.1)	73 (22.1)
Serious AEs	107 (32.2)	110 (33.2)
Fatal AE		
Any	11 (3.3)	17 (5.1)
Any except for progression of ILD	10 (3.0)	14 (4.2)
AE leading to discontinuation	65 (19.6)	34 (10.3)
AE leading to permanent dose reduction	110 (33.1)	14 (4.2)

Abbreviations: AE, adverse event; ILD, interstitial lung disease

Overall, the most frequently reported AEs leading to premature treatment discontinuation were diarrhoea (nintedanib: 5.7%, placebo: 0.3%), alanine aminotransferase increased (1.8% vs. 0.3%) and ILD (0.6% vs. 3.0%). The most frequently reported AEs leading to permanent dose reduction were diarrhoea (nintedanib: 16.0%, placebo: 0.9%), alanine aminotransferase increased (5.4% vs. 0.6%), and aspartate aminotransferase increased (4.8% vs. 0.3%). These were also the most common other significant AEs (diarrhoea: 19.9% vs. 1.2%, alanine aminotransferase increased: 6.6% vs. 0.6%, and aspartate aminotransferase increased: 5.4% vs. 0.3%).

The most common investigator-defined drug-related AEs were diarrhoea (nintedanib: 59.0%, placebo: 17.8%), nausea (23.8% vs. 5.7%), and vomiting (12.3% vs. 2.1%). Overall, the most frequently reported severe AEs were acute respiratory failure (nintedanib: 2.7%, placebo: 0.6%), pneumonia (2.4% vs. 1.8%), diarrhoea (2.4% vs. 0.9%), interstitial lung disease (1.5% vs. 5.1%), and respiratory failure (0.9% vs. 2.4%). The most frequently reported serious adverse events (SAEs) were pneumonia (nintedanib: 3.6%, placebo: 3.3%), interstitial lung disease (3.3% vs. 9.4%), acute respiratory failure (3.0% vs. 0.6%), respiratory failure (1.8% vs. 2.7%), and drug-induced liver injury (1.8% vs. 0%). AEs leading to death were reported for 3.3% of patients in the nintedanib group and for 5.1% of patients in the placebo group.

AEs, serious AEs and clinical laboratory safety results over the whole trial period (Part A + B) were generally in line with the results over 52 weeks. In addition, safety results

in patients with UIP-like fibrotic pattern, including AEs and serious AEs and clinical laboratory values, were consistent with the safety profile in the overall population.

B.2.11 Ongoing studies

There are no ongoing studies.

B.2.12 Innovation

Until the recent approval of nintedanib for SSc-ILD and PF-ILD, there were no licensed treatments for patients with PF-ILD other than IPF. Patients with PF-ILD may continue to receive unlicensed corticosteroids and/or immunosuppressive therapies for the treatment of the inflammatory component of their underlying disease; however there are no randomised controlled trials to suggest that these unlicensed treatments have a positive impact on the chronic progression of PF-ILD (i.e. delaying disease progression). Nintedanib is the first pharmacological treatment to show clinical evidence of slowing disease progression in patients with PF-ILD, through the dedicated INBUILD trial, showing a statistically significant difference in the primary endpoint in both co-primary populations.(5) This treatment effect was seen across all patients, regardless of the underlying ILD diagnosis.(39) Nintedanib also showed a numerical improvement in HRQoL as measured by the K-BILD questionnaire, although the difference was small in both groups. As such, nintedanib represents a step-change in the treatment of patients with PF-ILD other than IPF, providing a much needed treatment option for patients with no approved therapies for their condition.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Key findings for nintedanib are listed below:

- Nintedanib 150 mg twice daily significantly slowed the decline in FVC over 52 weeks in patients with PF-ILD vs. placebo (difference 107.0; 95% CI 65.4, 148.5; p<0.001).(5) The slower relative decline in FVC was consistent in patients with UIP-like fibrotic pattern (difference 128.2; 95% CI 70.8, 185.6; p<0.001) and those with other fibrotic patterns (difference 75.3; 95% CI 15.5, 135.0; nominal p=0.0137).(5)
- The annual rate of decline in FVC in the placebo group in all populations was similar to that observed in the placebo groups in the INPULSIS trials, supporting the

hypothesis that patients with a progressive phenotype have similar disease progression, regardless of the clinical diagnosis.(4, 5)

- Over the whole trial period (up to DBL2), fewer patients treated with nintedanib (n=46) experienced an acute exacerbation or death compared with those in the placebo group (n=65; HR: 0.67; 95% CI: 0.46, 0.98).(37)
- Treatment with nintedanib resulted in a numerical improvement in HRQoL in the overall population and patients with UIP-like fibrotic patterns, as measured by the K-BILD survey.(5, 37)
- Safety results for nintedanib in patients with PF-ILD were consistent with those seen in IPF patients.(4, 5) The most frequent AE was diarrhoea, however all episodes were grade 3 or lower.(5, 37) Nausea, vomiting, abdominal pain, decreased appetite and weight loss were also more frequent in the nintedanib group than the placebo group, although common AEs were mostly mild or moderate in intensity.(5, 37)
- Safety results in patients with UIP-like fibrotic pattern, including AEs, serious AEs and clinical laboratory values, were consistent with the safety profile in the overall population.(37)

Strengths and limitations of the evidence base

The INBUILD trial has high internal validity, as an adequately randomised, controlled trial. Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained blinded with regard to treatment assignments until after database lock. There were no unexpected imbalances in drop-out between groups, and all outcomes have been reported in the published literature or the clinical trial report. Please see Appendix D for a more detailed quality assessment.

The trial also has high external validity, with a study design that is relevant to clinical practice in England and Wales.

The primary endpoint, FVC % predicted, is a validated and well-recognised endpoint for studies investigating patients with IPF,(46) having been the primary endpoint for the pivotal studies for nintedanib and pirfenidone in this indication.(46) It has also been

used in studies of patients with SSc-ILD, such as the Scleroderma Lung Studies and the SENSCIS trial.(47, 48) The K-BILD questionnaire, a main secondary endpoint, is validated in IPF and has been found to provide additional information on the burden of living with IPF compared with pulmonary function tests alone.(49) Assessments of this endpoint within the INBUILD trial also demonstrated high internal consistency, as well as good cross-sectional validity.(50) The remaining main secondary endpoints (acute exacerbation of ILD or death at 52 weeks and death at 52 weeks) are also of relevance to clinical practice in England and Wales, as these represent the major burden of disease for ILD, both in terms of burden to the patient and the healthcare system.

Although the INBUILD trial was placebo controlled, this was considered justified as there are no currently no disease-modifying treatments indicated for the treatment of ILD. However, initiation of concomitant immunomodulatory treatment as medically indicated was allowed for the management of worsening of the disease after the first 6 months of the trial. Concomitant medications at baseline were well balanced between the treatment groups. While treatments commonly used for ILD were prohibited at baseline and subject to a wash-out period, stable treatment for underlying CTD was permitted. A small proportion of patients in both treatment groups were receiving immunomodulatory medication (biologic or non-biologic DMARDs) or high-dose corticosteroids at baseline, reflecting a pattern of treatment expected in UK clinical practice. During the 52 weeks of the trial, a small proportion of patients received medications which are used off-label for treatment of PF-ILD, including those treatments listed as potential comparators in the final NICE scope. This initiation reflects clinical opinion that treatment for worsening CTD or ILD was required and is reflective of the underlying treatment that would be seen in UK clinical practice. Use of these medications was initiated more frequently in the placebo group than the nintedanib group. The placebo treatment in the INBUILD trial therefore reflects standard treatment for the PF-ILD as well as underlying conditions. Overall, 68.6% of trial participants received systemic corticosteroids at baseline or during the 52-week trial period (placebo, 70.1% vs nintedanib, 67.2%). Non-steroid anti-rheumatic or anti-inflammatory treatments were received by 39.8% of patients at baseline or during the

52-week trial period (placebo, 38.1% vs. nintedanib, 41.6%).Treatments listed in the final NICE scope were initiated during the 52 week trial period as follows:

- Azathioprine: 5 patients (1.5%) in the placebo group vs 1 (0.3%) in the nintedanib group
- Cyclophosphamide: 2 (0.6%) vs 0
- Mycophenolate mofetil: 7 (2.1%) vs 3 (0.9%)
- High-dose (oral, intravenous, or intramuscular) corticosteroids: 57 (17.2%) vs 33 (9.9%)
- Infliximab: not initiated in either trial group
- Rituximab: 2 (0.6%) in each treatment group.

Real-world data on UK patients with PF-ILD are very scarce; the only registry is the BTS ILD registry which includes the UK IPF Registry.(51) Differences between the trial population and registry populations are therefore to be expected, however the baseline characteristics in the INBUILD trial were broadly similar to those reported in this registry in terms of race, age, rates of smoking and UIP-like pattern on HRCT (see Table 20). The INBUILD trial also included 5 sites in the UK. Therefore, we expect the population of the INBUILD trial to be broadly representative of UK patients in clinical practice. Subgroup analysis from the INBUILD trial also showed a consistent effect of nintedanib across gender, age group and race (see Appendix E), further demonstrating that the benefits of nintedanib are likely to be generalisable across the population.

Table 20: Comparison of the INBUILD trial population and the BTS ILD registry (UK IPF)

	INBUILD (total)	UK IPF Registry(51)
Male (%)	54%	79%
Mean age (yr ± SD)	66 ± 10	73.5 ± 8.3
Race	White – 74% Asian – 25% Black or African American – 1.5%	Not available
Weight (mean kg ± SD)	77 ± 17	Not available
BMI (mean)	28 ± 5	Not available
Former or current smoker (%)	51%	70%
Current	2%	4%
Former	49%	66%
UIP-like fibrotic pattern on HRCT (%)	62%	**Most recent visit** 55% (definite UIP) 37% (possible UIP)

Abbreviations: BMI, body mass index; HRCT, high resolution computed tomography; IPF, idiopathic pulmonary fibrosis; SD, standard deviation; UIP, usual interstitial pneumonia

Overall, the design of the INBUILD trial is well aligned to the decision problem agreed with NICE (see Table 1 for further details).

The consistency of treatment effect across subgroups defined by underlying cause of ILD in the INBUILD trial (39) is supported by the consistency in effect seen between the INBUILD trial and trials for SSc-ILD (SENSCIS) and IPF (INPULSIS-1 and INPULSIS-2). The SENSCIS trial included some patients with SSc-ILD who had the PF-ILD phenotype, while the INPULSIS trials included patients with IPF, the archetypal form of PF-ILD.

Life expectancy of people with PF-ILD in England

Analysis of patients receiving placebo in the INBUILD trial has shown that individuals with PF-ILD are likely to have a similar clinical disease course to that of patients with IPF, with a similar risk of death.(14) Therefore, it is expected that patients with PF-ILD who are not receiving an anti-fibrotic therapy would have a median post-diagnosis survival of 2 to 5 years. (15, 16)

The prevalence and incidence of PF-ILD is difficult to estimate due to a paucity of data. A retrospective observational study assessing all new referrals to nine tertiary ILD

treatment centres in England identified 253 new PF-ILD patients meeting INBUILD criteria over a period of 6 months (1st August 2017 to 31st January 2018), which can be extrapolated to 506 patients over 1 year across these centres. (19) Using the total population of England (56,286,961, 2019 estimate), this corresponds to an incidence and prevalence rate of 0.001% (given we expect PF-ILD patients to present very similarly to IPF where median duration of treatment is around 12 months). Applying this rate to the population of England and Wales gives an estimated 876 patients with PF-ILD who would be eligible for nintedanib.

The prevalence estimates for the other licensed indications for nintedanib (OFEV®) are given in Table 21.

Table 21: Estimated prevalence for other licensed indications for nintedanib

Indication	Estimate prevalence in England	Estimated number of patients in England†
IPF	0.0230%(52)	12,946
SSc-ILD	24.8–70.4 per million‡	1,396–3,963

Abbreviations: IPF, idiopathic pulmonary fibrosis; NSCLC, non-small cell lung cancer; SSc-ILD, systemic sclerosis-associated interstitial lung disease
† Based on a total population in England of 56,286,961 (53)
‡ Based on an estimated prevalence for SSc of 31–88 per million in the UK and up to 80% of people with SSc developing ILD (54)

Nintedanib is not expected to meet the criteria for end-of-life use.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review was conducted in June 2020, as described in Appendix G. No relevant cost-effectiveness studies were identified. Therefore, a *de novo* economic model was developed. This is described further in Section B.3.2.

B.3.2 Economic analysis

Patient population

Nintedanib has marketing authorisation for adults with chronic fibrosing ILD with a progressive phenotype, i.e. PF-ILD. The marketing authorisation was based on the results of the INBUILD phase III trial. Thus, the model population was based on this trial and included patients within the marketing authorisation.

Model structure

A Markov model was developed in Microsoft Excel, with the overall structure shown in Figure 8, in order to undertake a cost-utility analysis of nintedanib versus best supportive care (BSC). This model is commercial-in-confidence.

Design and definition of health states

The economic model was designed with the objective to accommodate available evidence from the INBUILD trial (10, 37, 55) to depict an accurate representation of the patient condition, and to allow easy adaptation for sensitivity analysis of the main inputs.

As described in Section B.3.1, no previous economic evaluations within the indication of PF-ILD were identified following a literature review. However, a number of relevant economic analyses within the area of IPF have been undertaken in recent years. Therefore, given the similarities in the clinical manifestations between the two conditions it was determined that the methods adopted for previous economic analyses of IPF treatments could inform the current submission. More information on economic analyses within the IPF indication are provided below.

Cost-utility analyses of nintedanib for the treatment of IPF were previously undertaken as part of formal submissions to the SMC, NCPE and NICE. The model structure for these analyses were informed by a targeted review of the literature, undertaken in March 2015, to identify other economic analyses within IPF. The UK NICE clinical guidelines for IPF (56) were also consulted, and the meeting for the UK NICE technology appraisal for pirfenidone attended (NICE TA 282 (57)), meeting held in Manchester on 29th January 2013). No relevant economic analyses, other than the pirfenidone NICE submission, were found at this time. Furthermore, Irish clinicians were consulted during an advisory board meeting on 18th June 2015, at which the assumptions and structure of the IPF model were discussed. The model assumptions and structure were validated by the clinical experts present (Professor Jim Egan, Professor Seamas Donnelly, Professor Anthony O'Regan and Dr. Emmet McGrath). (58) Please note that the model structure for PF-ILD was validated at an Advisory Board of UK clinicians held on 11th November 2020 (see page 84 for further details).

When the original nintedanib IPF model was being developed, different outcomes that could impact disease progression were considered in order to determine the most appropriate model health states. A targeted review of the literature identified studies that considered a single parameter (59-67) or a risk scoring system (multiple parameters). (68, 69) Most studies analysed predictors of mortality rather than disease progression. Although this could be an indication of patient health status, it was possible that the definition of health states could come from a finer examination of these predictors. The literature was consulted for parameters that were considered relevant for the economic model, in order to identify the minimal clinically important difference (MCID) (albeit with reference to survival). A limitation identified in risk scoring systems was potential collinearity of the parameters considered; for example, age and FVC % predicted (FVC%Pred). Therefore, a risk scoring system was not considered appropriate for the model.

FVC was selected to be the main factor of disease progression in the previous IPF analyses because it is a widely used measure of disease status and a common endpoint in clinical trials in IPF and ILD patients. (46) In particular, FVC%Pred was considerate more appropriate for incorporation into a Markov model health state when

compared with FVC (in mL), as it reflected the absolute state of patient condition and adjusted for body capacity, age, gender, and height.

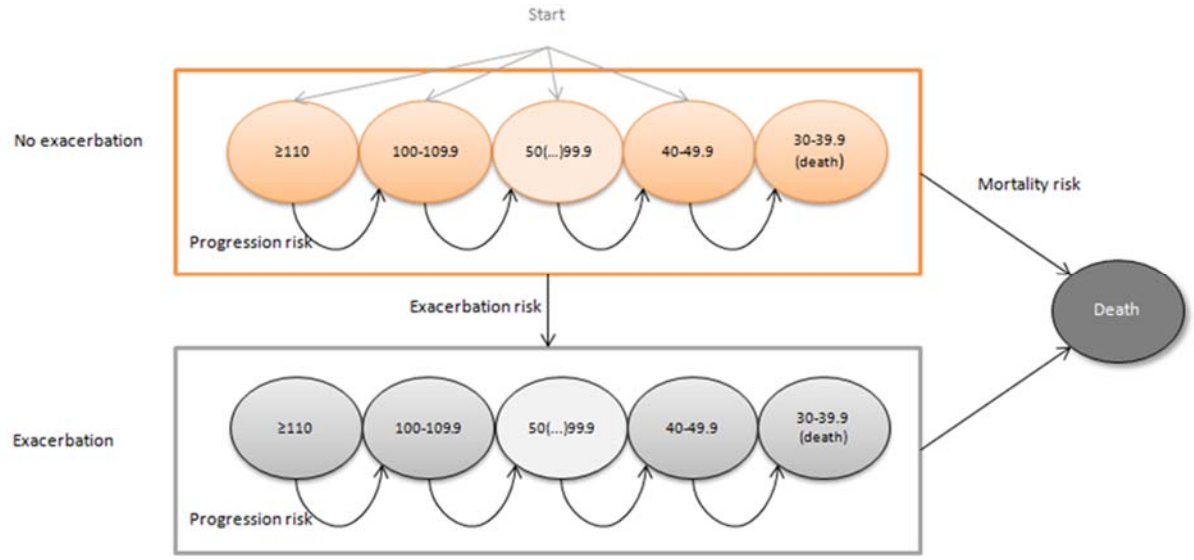
This removed some of the heterogeneity between the patients within each health-state and adhered to Markov model conventions.

According to many studies the MCID for FVC%Pred ranged between a 2 to 6% change, or a 10% change. (46) A 5 to 10% change has also been suggested for predicting long-term outcomes including survival. After consultation with clinical experts (58), and consideration of available evidence from the trial and in the literature, a 10-point categorization of FVC%Pred was considered most appropriate for use in the previous IPF analysis.

In addition to lung function, acute exacerbations of ILD are dramatic, singular events that are often fatal and a major cause of mortality and morbidity in ILD. Therefore, the final IPF model structure was designed with health states that described the patient condition as a combination of both lung function (FVC%Pred) and exacerbation (Figure 8). This structure was adopted for the submissions of nintedanib in IPF to NICE, the SMC and the NCPE.

The model structure described above was judged to be appropriate by both the NICE committee and Evidence Review Group (ERG) during the nintedanib submission for IPF. (52) Additionally, as described previously, IPF and PF-ILD are considered to have equivalent disease trajectories. Therefore, the model structure presented in Figure 8 was also adopted for this analysis (i.e. the health states, and possible transitions between these health states, were the same). More details on the overall model approach are provided in the subsequent section. It should be noted, however, that the values that were applied for the model input parameters were updated for this analysis, such that they were specific to PF-ILD and the application of nintedanib in this specific population. More details on these input parameters are provided in Section B.3.3 Clinical parameters and variables.

Figure 8: Schematic representation of Markov model



Note: numbers in diagram relate to FVC%Pred.

Cohort transitions

A Markov model was analysed by cohort analysis using time-dependent and constant transition probabilities to describe decline in lung function and incidence of first acute exacerbations over the cohort's lifetime. A set of mutually exclusive health states was defined. It was assumed that each state represented the full health condition of its members. Possible transitions were defined between each of the health states and the probability of each transition occurring within a set period of time (a cycle) was assigned to each possible transition.

The cohort entered the model at different FVC%Pred health states without exacerbation. The possible transitions were:

- Death
- Loss of lung function (progression to a health state with lower FVC%Pred)
- Exacerbation
- Loss of lung function combined with exacerbation
- Remaining in the same health state

Transitions were evaluated over a three-month period. This cycle length was chosen to match the nintedanib pack usage size. Half-cycle correction was applied to all costs and health benefits.

It was assumed that once progressed to a lower FVC%Pred the cohort could not regress back to health states with an improved lung function (higher FVC%Pred). Moreover, once an exacerbation occurred, the cohort could not move back to a health state without exacerbation and would remain in the health states with exacerbation history for the remainder of the time horizon.

Loss of lung function was defined as a 10-point decrease in FVC%Pred within three months, which aligns with clinical expert opinion and the literature. (16, 46)

Death could occur in two ways:

a) At any point in the model (and from any health state) based on the survival analysis of the clinical trial data.
b) At the point patients reached a level of FVC%Pred of <40%, which was assumed to be an unsustainable level of lung function. (56)

The relationship of health states and interdependence of events and transitions was studied through different analyses of the clinical trial data. In particular, the dependencies of mortality and exacerbation, and mortality and lung-function status (FVC%Pred category), were explored. The final structure of the model transitions, with overall survival and exacerbation risks being dependent on treatment allocation and lung function being dependent on a number of predictors, was deemed to provide the most appropriate balance between the available evidence, and flexibility of the model for sensitivity analysis. The structure takes account of a patient's risk of decline in lung-function over time and their risk of exacerbation. The resulting costs and QoL associated with this could then be captured.

The model was constructed from the perspective of the NHS and Personal Social Services (PSS) in England and Wales.

A lifetime horizon was adopted to capture all relevant costs and health-related utilities, with all costs and utilities discounted at a rate of 3.5% per year in alignment with the NICE guide to methods of technology appraisal. (54)

A full list of assumptions for the model, including input parameters and their justifications, can be found in Table 22 and Table 23 below.

Table 22: Model transitions and inputs

Transition	Input	Source
Mortality	Survival analysis of time to death and conditional to progression to FVC%Pred of 40%	Phase III clinical trial (INBUILD) clinical trials data for PBO and nintedanib risk
Loss of lung function (disease progression)	Survival analysis of time to progression of FVC%Pred (progression defined as a 10% point decline)	Phase III (INBUILD) clinical trial data for PBO risk and OR value for nintedanib
Exacerbation	Survival analysis of time to exacerbation (investigator reported and adjudication committee exacerbations, see section 3 for definitions)	Phase III (INBUILD) clinical trial data for PBO and nintedanib risk

Abbreviations: FVC, Forced Vital Capacity; PBO, Placebo; NDB, nintedanib; PFN, pirfenidone; OR, odds ratio.

Table 23: Features of the economic analysis

Current appraisal	Chosen values	Justification
Model structure	Markov model	The model structure captures the impact of distinct resource use and patient HRQoL associated with each health state and allows for a cost-utility analysis over an extended time horizon.
Time horizon	Lifetime	Set to cover the lifetime of the patients, in order to fully incorporate the costs and health outcomes of PF-ILD.
Half-cycle correction	Half-cycle correction was applied to all costs and health benefits	Half cycle correction applied to minimise bias and is a commonly accepted method in economic evaluations.
Cycle length	The model cycle length was three months	The cycle length was selected to be consistent with the clinical trial intervals between observations and was considered a balanced interval for the model outcomes.
Source of utilities	Patient level EQ-5D measured directly from the INBUILD trial	The adoption of EQ-5D data is consistent with the NICE reference case.
Source of costs	NHS Reference costs, PSSRU, NICE CG, Rincoig *et al* (2007)	Consistent with the NICE reference case
Treatment-related adverse events (TRAE)	Diarrhoea, nausea and vomiting were included in the model	The inclusion of adverse events was determined by a criterion based on severity and incidence within the INBUILD trial.

Current appraisal	Chosen values	Justification
Baseline mortality risk	It was assumed that death could occur at the point that patients reached a level of FVC%Pred of 30-39.9%	A discussion with clinical experts held regarding the point at which life becomes unsustainable with low FVC%Pred values. (58) A similar assumption was made in the NICE IPF Clinical Guideline (CG163) for a threshold of 35% FVC%Pred. (56) To fit with the 10-percentage-points categories 40% was used. The impact of this to the incremental cost-effectiveness results was tested in sensitivity analysis and it was minimal.
Definition of baseline disease progression / loss of lung function	Baseline disease progression was defined as a 10-point drop in FVC%Pred every three months (constant risk)	According to many studies the MCID for FVC%Pred ranged between a 2-6% change (68) or a 10% change. (16, 68) After consultation with the clinical experts (58), it was decided that a 10-point categorisation of FVC%Pred was a balanced range to capture granularity of outcomes without overcomplicating the model.
Progression / loss of lung function	It was assumed that once progressed to a lower FVC%Pred the cohort could not regress back to health states with improved lung function (higher FVC%Pred)	Similar assumptions were made in submissions of both nintedanib and pirfenidone to NICE technology appraisal programmes. (52, 57) Clinical expert opinion validated the assumptions.
Exacerbation risk	Exacerbation was assumed to be a constant hazard every three months (exponential model)	Several parametric models were considered based on INBUILD trial data. Considering the AIC values and model parsimony, the exponential model was selected.
Discount for outcomes and costs	3.5%	Consistent with the NICE reference case

Abbreviations: AIC, Akaike Information Criterion; CG, clinical guideline; FVC, forced vital capacity; HRQoL, health-related quality of life; QALYs, quality-adjusted life years; MCID, minimal clinically important difference; NICE, The National Institute for Health and Care Excellence; NHS, National Health Service; PF-ILD, Progressive fibrosing interstitial lung disease; PFN, pirfenidone; PSSRU: Personal Social Services Research Unit; TRAE: treatment-related adverse events.

Intervention technology and comparators

Details on nintedanib are summarised in Table 24.

Table 24: Description of nintedanib

Item	Description
Approved name	Nintedanib
Drug class/pharmaco-therapeutic group	Antineoplastic agents, protein kinase inhibitors
ATC code	L01XE31
Brand name	Ofev®
Pharmaceutical form(s)	Soft capsules containing nintedanib (as esilate)

Item	Description
Strengths available	100 mg and 150 mg
Route of administration	Oral
Licensed dose & frequency	Recommended dose for nintedanib (Ofev®) is 150 mg twice daily, approximately 12-hour apart. The 100 mg twice daily dose is only recommended for use in patients who do not tolerate the 150 mg twice daily dose
Duration of use	Continuous daily treatment unless unacceptable adverse events are experienced

Abbreviations: ATC, Anatomical Therapeutic Chemical classification system.

As there are no relevant comparators for the treatment of PF-ILD in the UK, the model implements a comparison of nintedanib vs BSC (best supportive care) for adults with PF-ILD. The dose and frequency of nintedanib is continuous treatment of 150 mg twice daily (300 mg per day). BSC is the best comparator with the INBUILD comparator arm closely matching UK clinical practice in treating patients with progressive phenotype.

B.3.3 Clinical parameters and variables

It should be noted that the INBUILD trial was the main data source for the economic model, being as it was used to populate the following parameters: overall survival, time-to-first acute ILD exacerbation, loss of lung function, time-to-treatment discontinuation, utility values and health-care resource use. The 52-week analysis from INBUILD has previously been published, based on DBL1 from the trial (which is an interim analysis as the trial is ongoing) (5). However, a second database lock (DBL2) was undertaken approximately three months after DBL1. Given that DBL2 provides longer-term follow-up data this dataset was used to populate all of the parameters just listed. This longer-term follow-up period is expected to be particularly pertinent for the survival curve analysis as it slightly reduces the immaturity of the data.

Treatment efficacy transition probabilities

Source of evidence

The model captured three types of transitions related to treatment efficacy: mortality, acute ILD exacerbations and decline of lung function (progression based on FVC%Pred). Therefore, the inputs for these transitions were all estimated based on data from the INBUILD trial.

In terms of BSC, these transitions were based on the placebo arm of this trial. As is usual for a placebo-controlled clinical trial, the protocol of the INBUILD clinical trials provided rules for the use of concomitant medication during the trial period. In general, patients were allowed to use a range of background medication that closely resembled BSC in this disease.

The risk of mortality and acute exacerbations were extrapolated beyond the observed trial follow-up period using a statistical analysis presented in the following sections with separate survival curves fitted to the INBUILD trial data for placebo (i.e. BSC) and nintedanib.

Survival analysis

Using the individual patient data (IPD) from the phase III INBUILD trial, parametric models were fitted to determine the transition probabilities for both the BSC and nintedanib arms from the start of the model. The use of parametric modelling is common when there is a need to extend beyond the clinical trial observational period. The base-case analysis assumed that the parametric model was applied for the full duration of the economic model; that also included the first year of the analysis where clinical trial data were available. This allowed for a more robust representation of uncertainty from the trial results and a formal exploration via a probabilistic sensitivity analysis (PSA). More details on the survival analyses that were undertaken are provided below.

Overall survival

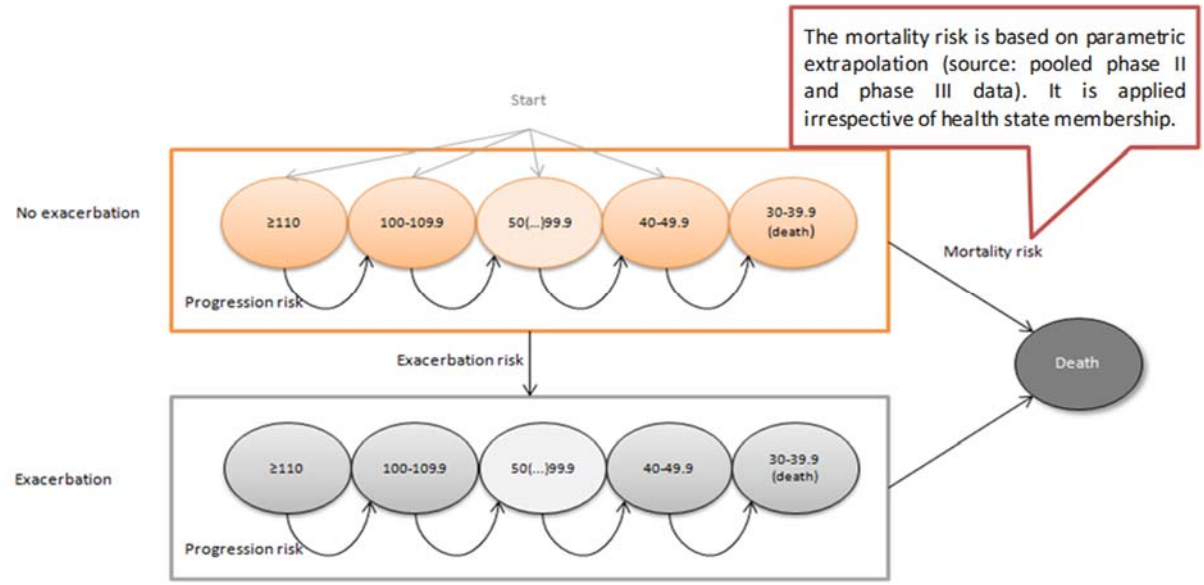
Several different standard parametric models have been explored for mortality, TTD and TTFAE probabilities including: exponential, Gompertz, generalised gamma, log-normal, log-logistic, and Weibull. All of these standard parametric models were fit using the “flexsurv” package in R (data analysis and statistics software). (70, 71) Additionally, a Bayesian survival analysis approach was also conducted for overall survival. This Bayesian approach is discussed further in below.

Goodness of fit was assessed using the Akaike Information Criterion (AIC). In general, the smallest AIC value represents the best-fit parametric model. The magnitude of the absolute AIC value is not meaningful in itself as it depends on the set of data. However, relative differences are meaningful; parametric models are seen as suitable candidates for inclusion in the economic model if they are within three points of the parametric model with the lowest AIC or BIC.

As a second step the results of the parametric modelling were compared with evidence from the literature (visual inspection/face validity). Altogether, the following criteria were considered when choosing the parametric model for the economic analysis:

a) The AIC/BIC value (smallest value preferred)
b) Face validity/visual inspection and comparison with published cohorts
c) Precedent in the literature (where evidence was available)
d) Clarity of understanding and computation

Figure 9: Model structure – OS



The extrapolation of overall survival was undertaken using two approaches: a typical frequentist method and an exploratory Bayesian analysis. For the frequentist approach, six parametric distributions were explored to extrapolate overall survival.

Of these six distributions, the exponential, lognormal and Generalised gamma were found to have a poor fit to the data and, therefore, were not pursued further in this analysis. Therefore, the loglogistic, Gompertz and Weibull distributions were adopted for the frequentist approach. The goodness of fit for six parametric models for OS is presented in Table 25, separated by treatment arm.

Table 25: Goodness of fit (AIC and BIC) – OS

Treatment arm	Distribution	AIC	BIC	Decision
Placebo	Exponential	842.1154	845.9175	Excluded from model
	Weibull	822.3554	829.9597	
	Lognormal	825.7844	833.3886	Excluded from model
	Loglogistic	822.5821	830.1864	
	Gompertz	823.3835	830.9878	
	Generalised gamma	824.2238	835.6302	Excluded from model
Nintedanib	Exponential	690.9068	694.712	Excluded from model
	Weibull	687.0584	694.6687	
	Lognormal	690.5765	698.1868	Excluded from model
	Loglogistic	687.4335	695.0438	
	Gompertz	685.4074	693.0177	
	Generalised gamma	688.7022	700.1176	Excluded from model

Briefly, the aim of the Bayesian analysis was to improve the accuracy and precision of the extrapolated OS estimates for the PF-ILD population. The analysis was conducted to inform the INBUILD survival data using IPF data from the following trials: TOMORROW (NCT00514683) (72), INPULSIS (NCT01335464 and NCT01335477) (73), INPULSIS-ON (NCT01619085) (74). More information on the Bayesian analysis is provided below.

Bayesian analysis – overall survival

While IPF is the classic fibrosing ILD, PF-ILD patients demonstrate a number of similarities to IPF, with their disease being defined by the presence of progressive pulmonary fibrosis, worsening respiratory symptoms, declining lung function, resistance to immunomodulatory therapies and, ultimately, early mortality. (11, 75, 76) Due to these similarities across IPF and PF-ILD, it was hypothesised that the trajectory of the survival of IPF patients could be used to inform survival estimates for PF-ILD patients.

Data on the long-term survival of IPF patients are available from several trials, including two phase 3 IPF trials (INPULSIS I and INPULSIS II) (73) and a combined long-term extension of these studies, known as INPULSIS-ON. (74) This extension study monitored OS for over eight years in IPF patients taking nintedanib.

The IPF data were used to generate an informative prior, utilising data from several IPF RCTs and long-term extensions of these trials. This prior was then used to inform the Bayesian survival analysis of the PF-ILD data. Before synthesising the evidence using a Bayesian framework, the individual patient data were cleaned and linked across databases. The IPF patients were matched to PF-ILD patients using propensity score matching to ensure that these patients had similar baseline characteristics. Survival data were then generated for the matched, weighted IPF patients.

Following data pre-processing, there were two components to the analysis. The first component of the analysis involved generating an informative prior using data from the IPF patients that had been matched to the PF-ILD patients.

The second component of the analysis involved using the best fitting models to synthesise informative priors to inform a Bayesian survival analysis of the PF-ILD patient data. These pre-processing steps, and the subsequent methodology used to conduct the Bayesian survival analysis, are described in further detail below.

Study linking and data cleaning

Data from the following IPF trials were used in this analysis:

- **TOMORROW (phase II) study** (72): patients receiving nintedanib (300mg) or placebo; patients from TOMORROW who did not receive the 300mg dose of nintedanib were excluded.
- **INPULSIS 1 and 2 (phase III studies)** (73): all patients.
- **INPULSIS-ON (open-label extension [OLE] from phase II and III studies)** (74): patients previously receiving nintedanib (300mg) who continue treatment; patients who were on placebo and then went on to receive nintedanib in the OLE were censored on initiation of nintedanib.

The phase II/III data and OLE data were merged for the purpose of this analysis using the following censorship rules:

- Placebo patients were censored at the last contact date recorded in the phase II/III studies, or on the date they entered the OLE study, whichever happened first.
- Nintedanib patients who did not enter the OLE study were censored at the last contact date recorded in phase II/III.
- Nintedanib patients who entered the OLE study were censored at the last contact date recorded in the OLE.

A total of 1,239 IPF patients have been included in this global dataset; 726 patients were treated with nintedanib and 513 with placebo.

Data from the phase 3 INBUILD trial were used in this analysis to incorporate PF-ILD patients. The INBUILD data were provided by Boehringer Ingelheim on 8th May 2020. This dataset contained 663 patients with PF-ILD; 332 patients were treated with nintedanib and 331 with placebo.

Propensity score matching

Patients from the IPF dataset were matched to PF-ILD patients from the INBUILD trial using propensity score matching. The aim of this pre-processing step was to ensure that the IPF patients used to inform the Bayesian prior had similar baseline characteristics and disease severity compared to the PF-ILD patients. The following matching algorithms were considered:

- **Kernel matching:** This is a non-parametric matching estimator. For each PF-ILD patient, IPF patients with a closer propensity score are given more weight than IPF patients that are further away.
- **Radius matching:** A threshold is applied to the maximum possible propensity score distance, known as a caliper. All IPF patients that match to a PF-ILD patient within the caliper radius are equally weighted and included in the analysis.

For both types of matchings, two radii were tested, one of 0.1 and one of 0.05. The matchings were performed using the "psmatch2" command in Stata. The propensity score itself was created using the "pscore" command, using a logit model. Balance was checked across main and control groups.

The common support assumption was assessed after patients' propensity scores had been generated to determine whether there was overlap between the scores generated by the IPF patients and the PF-ILD patients. If a patient in the PF-ILD group had a propensity score that was not similar to any patients in the IPF group, then it would not be possible to match that patient to an IPF patient.

As radius matching uses a caliper, similarity was assessed by determining all IPF patients that fell within a PF-ILD patient's radius. If a PF-ILD patient was very dissimilar from all IPF patients then they were not excluded in radius matching due to the nature of the method. Given this, it was not deemed necessary to restrict the selection of controls to the common support area.

Baseline characteristics were explored to determine which could be used in the matching analysis. The impact of missing data or large differences between trial populations was also explored.

The validity of the matching was assessed using common diagnostic statistics and plots. The balance of covariates after the matching and weighting of control observations was checked using the "pstest" command in Stata. This displays standardised differences and a summary of the mean and median bias across all covariates before and after matching, as well as Rubin's B (absolute standardised difference of the means of the linear index of the propensity scores between the two groups) and Rubin's R (ratio of the variances of the propensity score index in the two groups) indicators. Ideally, the bias (expressed as a percentage) should be below 5, Rubin's B less than 25 and Rubin's R between 0.5 and 2. The distribution of the propensity scores was also plotted.

The propensity score matching was performed using Stata IC (version 14.2) (77) and separate analyses were conducted for each treatment arm.

Generating survival data

IPF patients who received nintedanib in both a clinical trial and (optionally) an open-label extension were of interest in this analysis. IPF patients who received placebo at the start of a clinical trial and then went on to receive nintedanib in an open-label extension were censored on initiation of the open-label extension when they started treatment with nintedanib.

Overall survival was estimated by finding the duration of time from a patient's first baseline visit to the date of the last recorded visit. A patient was censored on their last visit if they had not been recorded as having died during the trial period.

Once OS was estimated for all patients the data were reformatted in order to be analysed using BUGS programming software. The survival analysis was performed using OpenBUGS (version 3.2.3 rev 1012). (78)

Generating the informative prior

This analysis followed similar methodology outlined in Soikkeli 2019. (79) Standard frequentist survival models were fit to the matched, weighted IPF patient data using the "flexsurv" package in R (version 3.6.1). (70, 71) Seven survival models were generated: exponential, Weibull, log normal, log logistic, generalised gamma, gamma and Gompertz. The Akaike information criterion (AIC), Bayesian information criterion (BIC) and visual inspection were used to select the best fitting model.

The three models with the lowest AIC and BIC (i.e. the best fitting models of the matched IPF data) were used to generate informative priors for the shape parameter of the Bayesian PF-ILD model. The best fitting model of the IPF data also dictated the model that was fit to the PF-ILD data. For example, if the Weibull model was the best fitting model for the matched IPF data then a Weibull model was also fit to the PF-ILD patient data.

Generating the PF-ILD parameter estimate

The distribution of the shape parameter generated using the matched IPF data was used to inform the shape parameter of the PF-ILD model. Following the methodology outlined in Soikkeli 2019 (79), the Bayesian shape parameter prior was modelled using a gamma (α,β) distribution. The estimates of the mean (μ) and standard deviation (SD) of the shape parameter produced by the frequentist analysis of the matched IPF data were used to inform the gamma distribution of the informative prior using the following equations:

$$\alpha = \mu\beta$$

$$\beta = \frac{\mu}{SD^2}$$

A noninformative prior was used for the scale parameter throughout all analyses.

For the log-logistic model, the logistic distribution was fit to the log-transformed survival data. The informative prior distribution was used to inform the location parameter of this logistic distribution.

Convergence was assessed, and a sufficient burn-in selected, for all analyses conducted in OpenBUGS. Autocorrelation was also evaluated and a thinning factor was applied when required.

Propensity score matching results

Baseline characteristics were assessed to determine which patient characteristics reported across the PF-ILD and IPF trials would be most relevant in the propensity score matching analysis. Baseline characteristics were assessed according to whether they were widely reported and clinically meaningful. The following baseline characteristics were used in the patient matching:

- Age.
- Sex.
- Race (coded in this analysis as Asian versus other).
- Time since IPF or PF-ILD diagnosis.

- Percent predicted diffusing capacity for carbon monoxide (DLco) corrected for haemoglobin.
- Percent predicted forced vital capacity (FVC) at baseline.
- Smoking status (coded in this analysis as never smoked, used to smoke, currently smokes).

Information on usual interstitial pneumonia pattern at baseline and diagnosis via honeycombing were also available. However, these characteristics were not used in the matching analysis as they were not widely reported across patients and their use would have resulted in a large number of patients being excluded from the matching analysis.

This selection of variables led to the upfront exclusion of nine PF-ILD patients with a missing baseline percent predicted DLco, and 140 IPF patients (129 had missing race, three missing baseline percent predicted DLco and eight had no baseline characteristics). The final analysis dataset therefore contained 654 PF-ILD patients (326 nintedanib patients and 328 placebo patients) and 1099 IPF patients (640 nintedanib patients and 459 placebo patients).

The radius matching algorithm with a radius of 0.1 produced the best results of all the matching algorithms tested across both the nintedanib matching analysis and the placebo matching analysis. For the nintedanib and placebo analyses, this resulted in a Ruben's B score of 13.3 and 12.8 and a Ruben's R score of 0.96 and 0.89, respectively, suggesting that the samples were sufficiently balanced. The IPF patient baseline characteristics before and after matching are shown in Table 26 (placebo) and Table 27 (nintedanib). An arbitrary threshold of 5% was selected to show potential characteristics which still presented some bias after matching. For placebo, two characteristics (percent predicted DLco and percent predicted FVC) presented a small bias after matching. Percent predicted FVC also presented a small bias after matching for nintedanib. However, actual differences across the PF-ILD and matched IPF datasets were very small and so the matching was deemed appropriate. For example, the largest percentage bias was 10.6% for percent predicted FVC in the nintednaib dataset. However, this only corresponded to a 1.8% difference between the PF-ILD and matched IPF datasets.

Table 26: Placebo patient baseline characteristics before and after matching

Baseline characteristic	PF-ILD	Unmatched IPF	Matched IPF	% bias	% bias reduction
Age (continuous)	66.4	66.6	66.4	-0.7	73.2
Gender (% female)	46.0%	22.0%	46.5%	-0.9	98.2
Race (% Asian)	24.4%	32.0%	25.4%	-2.2	87.1
Percent predicted DLco	47.9	46.9	46.7	8.6*	-24.9
Percent predicted FVC	69.2	79.8	70.2	-6.4*	90.1
Smoking (% ex smokers)	48.8%	65.1%	49.1%	-0.6	98.3
Smoking (% current smokers)	2.4%	5.0%	2.5%	-0.2	98.2

*absolute percentage bias greater than 5%

Table 27: Nintedanib patient baseline characteristics before and after matching

Baseline characteristic	PF-ILD	Unmatched IPF	IPF	% bias	% bias reduction
Age (continuous)	65.3	66.4	65.2	0.4	97
Gender (% female)	46.0%	21.6%	47.2%	-2.6	95.1
Race (% Asian)	25.5%	33.8%	26.1%	-1.4	92.4
Percent predicted DLco	44.4	47.3	44.3	0.4	98.2
Percent predicted FVC	68.6	79.3	70.4	-10.6*	83.4
Smoking (% ex-smokers)	50.6%	68.3%	49.0%	3.3	91
Smoking (% current smokers)	0.9%	3.6%	1.2%	-2.1	88.2

*absolute percentage bias greater than 5%

Figure 10 shows the distribution of propensity scores across the PF-ILD and IPF datasets for both nintedanib and placebo after matching. As shown, it appears that there is a sufficient overlap between the propensity score distributions in the PF-ILD and matched IPF datasets across both treatments. Figure 11 shows the reduction in standardised percentage bias across covariates after matching for both the nintedanib and placebo cohorts.

Figure 10: Propensity score distribution of the IPF and PF-ILD datasets after matching for nintedanib (left) and placebo (right)

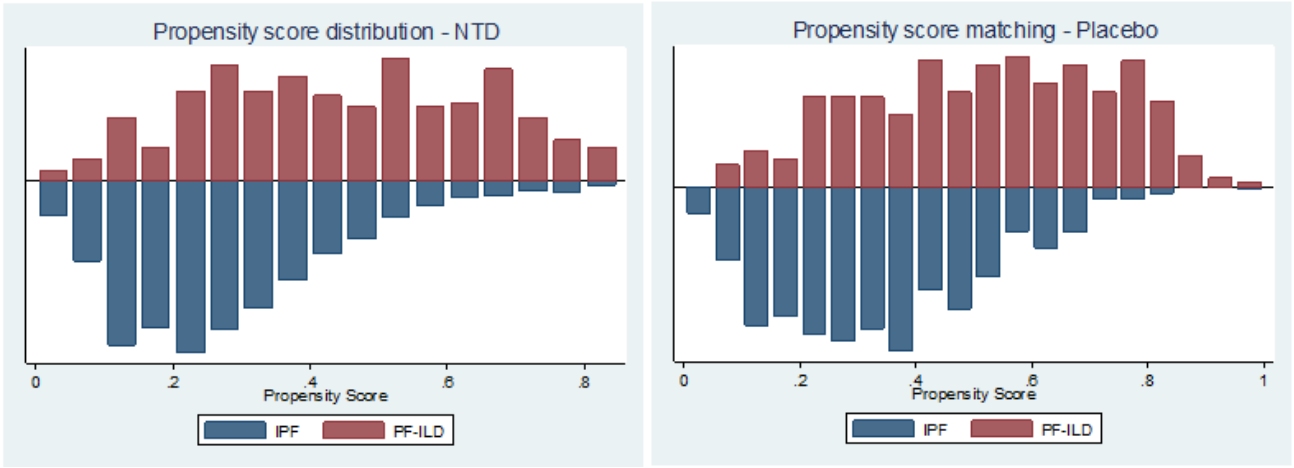
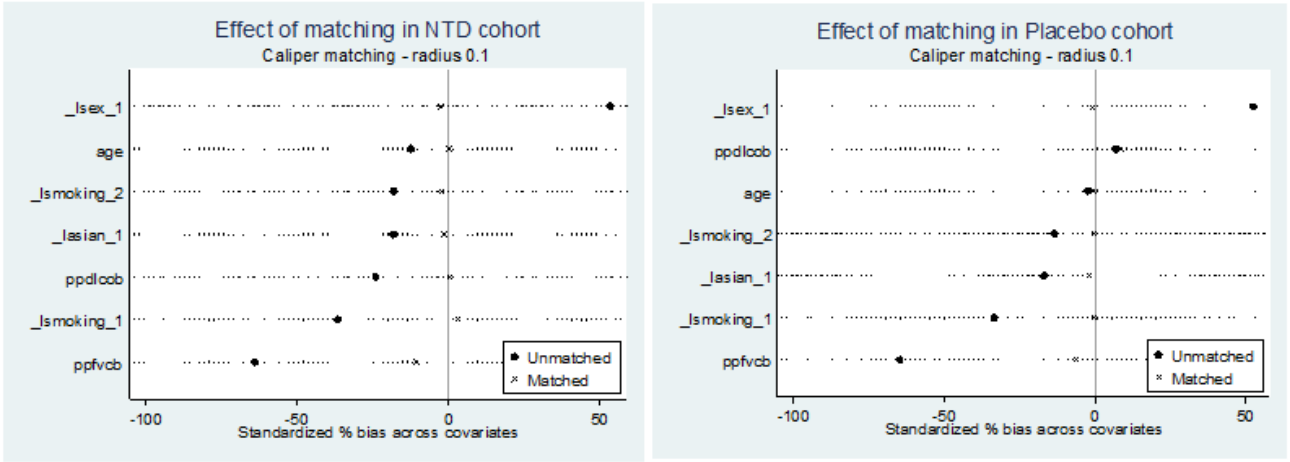


Figure 11: Standardised percentage bias across covariates after matching for the nintedanib (left) and placebo (right) cohorts



Overall survival estimates informing Bayesian prior

Seven survival models were fit to the matched IPF data for both the nintedanib and placebo cohorts. The survival models were visually inspected and the models with the lowest AIC and BIC were selected to inform the shape parameter of the prior distribution.

The AIC and BIC of the IPF survival models are presented in Table 28. Across the nintedanib and placebo cohorts, the Weibull, log-logistic and gamma distributions produced the lowest overall AICs and BICs. However, there was little difference between these models in terms of AIC and BIC. Therefore, all three models were considered in the Bayesian survival analysis.

For the nintedanib cohort, the gamma distribution produced the lowest AIC and the second lowest BIC values. The exponential distribution produced the lowest BIC value for the nintedanib dataset; however, the exponential distribution produced unrealistic long-term survival estimates for the placebo cohort. It is recommended that, when comparing results across treatments, the same survival model is used for all treatments. Therefore, the exponential model was not considered further due to the unrealistic survival estimates it produced for placebo.

For the placebo cohort, the best survival model was log-logistic which produced both the lowest AIC and BIC values.

Table 28: AIC and BIC values for matched IPF survival models used to generate analysis prior

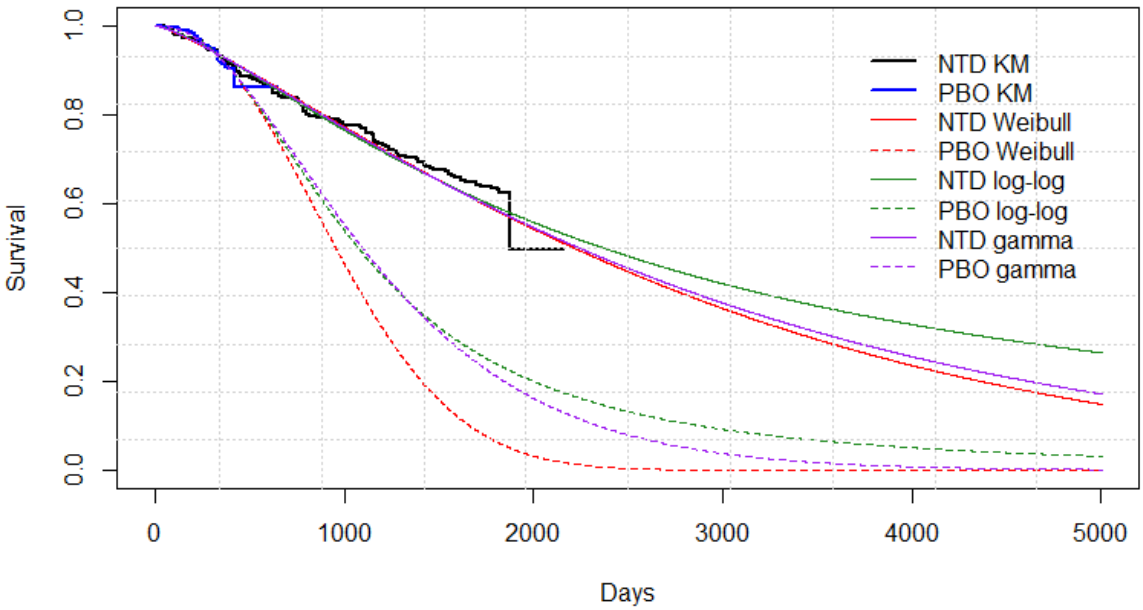
Distribution	Nintedanib		Placebo	
	AIC	BIC	AIC	BIC
Weibull	1468.961	1476.535	567.0736	574.6227
Exponential	1471.934	1475.721	580.1805	583.9613
Generalised gamma	1470.677	1482.037	569.1665	580.4714
Log-logistic	1469.346	1476.920	567.0456	574.5948
Log-normal	1470.437	1478.010	568.6821	576.2312
Gompertz	1470.285	1477.859	568.4749	576.0240
Gamma	1468.814	1476.388	567.2287	574.7778

The three lowest AIC and BIC values for each treatment cohort are shaded in yellow

The three survival models that produced the lowest overall AIC and BIC across the nintedanib and placebo cohorts were plotted against the corresponding Kaplan-Meier curves produced by the matched IPF data in Figure 12. For nintedanib, the log-logistic model produced the highest long-term survival estimate (median OS: 6.48 years) while the gamma (median OS: 6.13 years) and Weibull (median OS: 6.06 years) models produced similar, lower survival estimates.

For placebo, the gamma and log-logistic curves produced the most realistic survival estimates for the matched IPF data (median OS: 2.93 – 3.00 years; OS at 5 years: 20 – 23%). The Weibull placebo curve may underestimate survival (median OS: 2.6 years; survival at 5 years: 6%).

Figure 12: Matched IPF Kaplan-Meier curves for placebo and nintedanib plotted alongside the three best survival models



Abbreviations: KM, Kaplan-Meier; log-log, log-logistic; NTD, nintedanib; PBO, placebo

PF-ILD parameter estimates from Bayesian survival analysis

The three best fitting survival models of the matched IPF data were used to inform the shape parameter priors in the Bayesian analysis of the PF-ILD data for both nintedanib and placebo. For each IPF model, the same survival model was fit to the PF-ILD data.

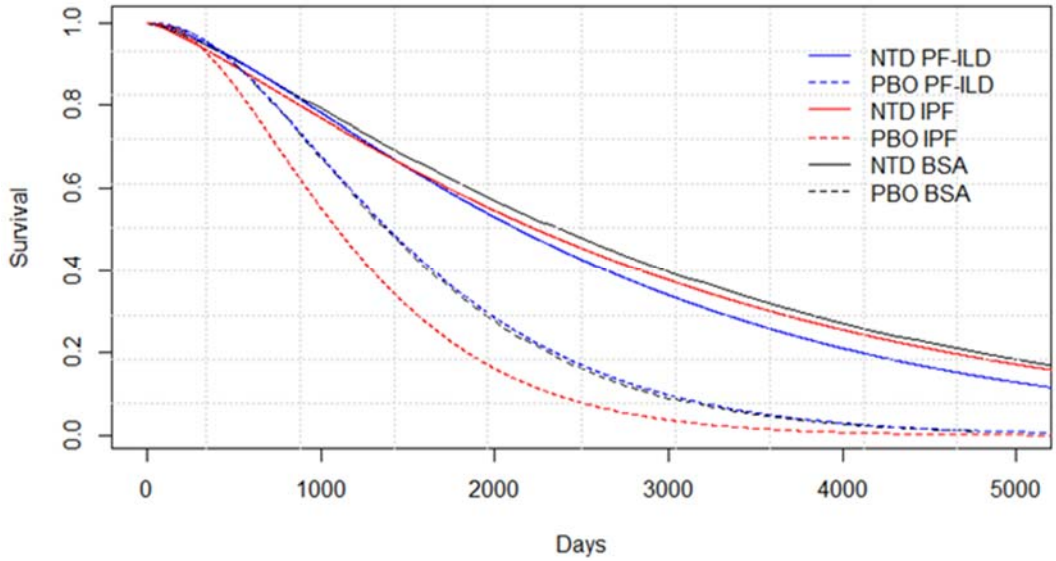
The results from fitting the gamma, log-logistic and Weibull models are described below. The standard frequentist results produced by modelling survival using the matched IPF data and the PF-ILD data (with no informative prior) were also plotted against the Bayesian survival analysis results for comparison.

The results of the Bayesian survival analysis for the gamma distribution are presented in Figure 13. For the nintedanib cohort, the Bayesian survival model initially appears to follow the PF-ILD model; however, long-term estimates are more aligned with the matched IPF model results. For the placebo cohort, the survival estimates produced by the Bayesian analysis are very similar to those produced by the frequentist analysis of the PF-ILD data. The median OS Bayesian estimates for patients taking nintedanib and placebo are 6.50 years and 3.76 years, respectively. Survival estimates at 5 years are approximately 60% for patients treated with nintedanib and 32% for patients treated with placebo.

The results of the Bayesian survival analysis for the log-logistic distribution are presented in Figure 14. For the nintedanib cohort, the Bayesian survival model appears to produce similar results to the frequentist PF-ILD survival model. For placebo, the Bayesian survival model produces results that lie between the IPF and PF-ILD survival estimates. The median OS Bayesian estimates for patients taking nintedanib and placebo are 6.39 years and 3.51 years, respectively. Survival estimates at 5 years are approximately 59% for patients treated with nintedanib and 30% for patients treated with placebo.

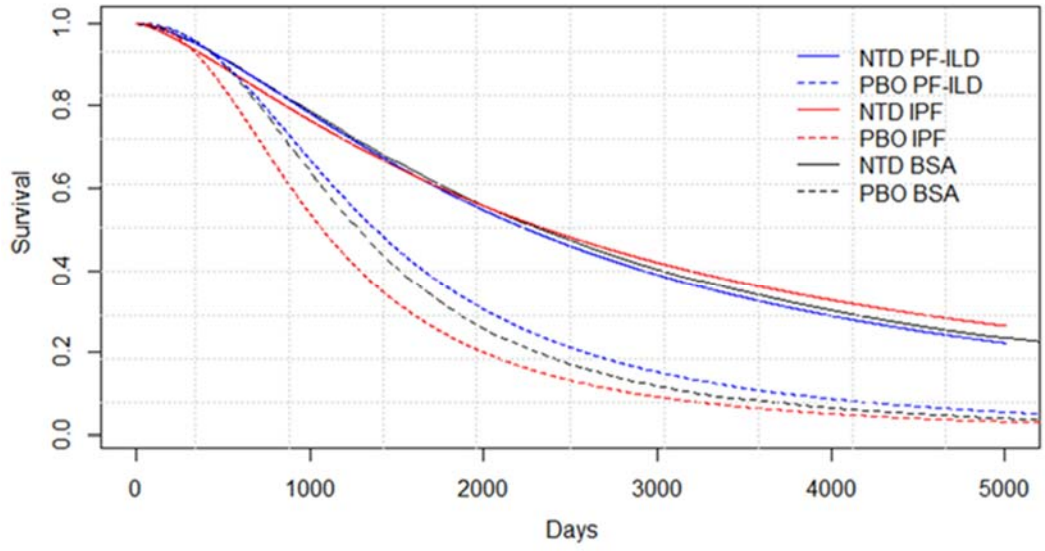
The results of the Bayesian survival analysis for the Weibull distribution are presented in Figure 15. For the nintedanib cohort, the Bayesian survival model appears to follow the frequentist matched IPF model more closely than the PF-ILD model. However, for placebo the Bayesian survival model produces very similar results to the frequentist PF-ILD model. The median OS Bayesian estimates for patients taking nintedanib and placebo are 6.45 years and 3.42 years, respectively. Survival estimates at 5 years are approximately 60% for patients treated with nintedanib and 21% for patients treated with placebo.

Figure 13: Gamma Bayesian analysis (plotted against the frequentist matched IPF and PF-ILD models for comparison)



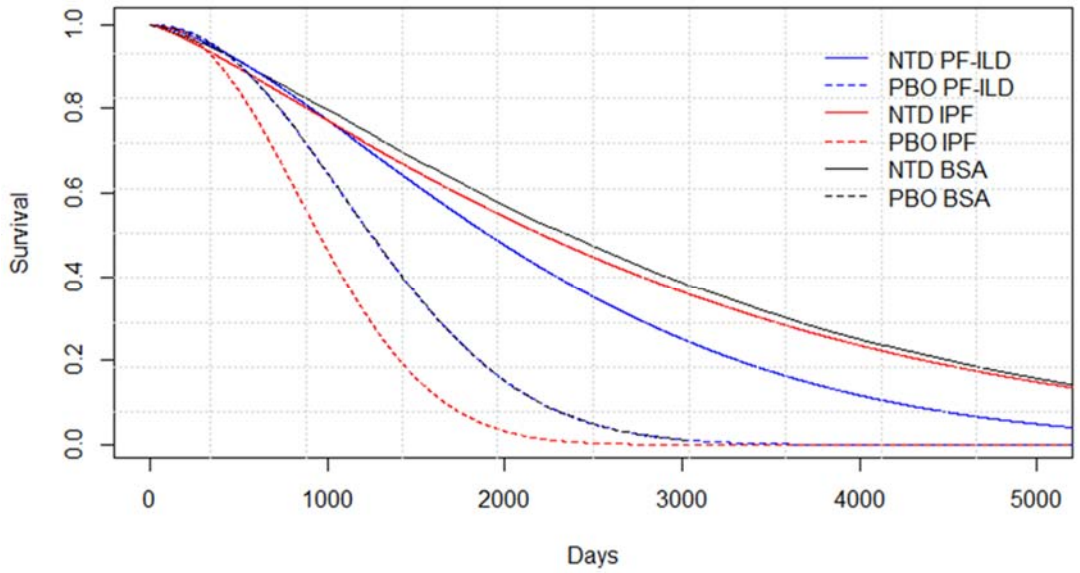
Abbreviations: NTD/PBO BSA, nintedanib/placebo survival model produced by Bayesian survival analysis; NTD/PBO IPF, nintedanib/placebo survival model produced by frequentist matched IPF survival model; NTD/PBO PF-ILD, nintedanib/placebo survival model produced by frequentist PF-ILD survival model

Figure 14: Log-logistic Bayesian analysis (plotted against the frequentist matched IPF and PF-ILD models for comparison)



Abbreviations: NTD/PBO BSA, nintedanib/placebo survival model produced by Bayesian survival analysis; NTD/PBO IPF, nintedanib/placebo survival model produced by frequentist matched IPF survival model; NTD/PBO PF-ILD, nintedanib/placebo survival model produced by frequentist PF-ILD survival model

Figure 15: Weibull Bayesian analysis (plotted against the frequentist matched IPF and PF-ILD models for comparison)



Abbreviations: NTD/PBO BSA, nintedanib/placebo survival model produced by Bayesian survival analysis; NTD/PBO IPF, nintedanib/placebo survival model produced by frequentist matched IPF survival model; NTD/PBO PF-ILD, nintedanib/placebo survival model produced by frequentist PF-ILD survival model

The OS estimates produced by the three selected Bayesian survival models are reported in Table 29. Overall, median OS estimates and 5-year survival estimates are consistent across the three Bayesian models. The Weibull model produces a lower 5-year survival estimate for placebo compared to the other Bayesian models (21% vs 30-32%); however, the median OS for placebo is similar to other model estimates (3.42 years vs 3.51-3.76 years).

The gamma model produces the highest median OS and 5-year survival estimates for both nintedanib and placebo. The log-logistic model produces the lowest survival estimates for nintedanib; whereas the Weibull model produces the lowest survival estimates for placebo.

Table 29: OS estimates produced by Bayesian survival models

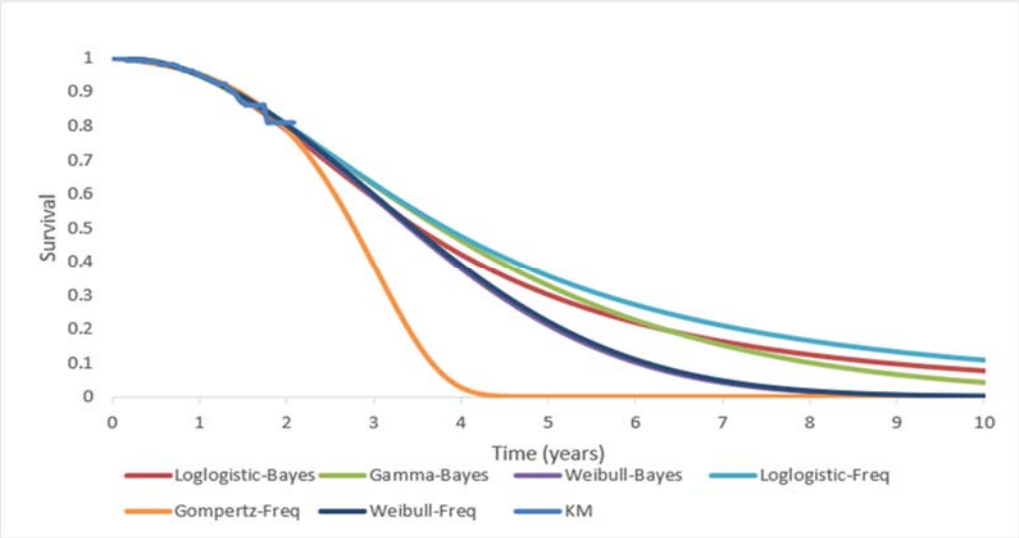
Distribution	Median OS (years)		5-year survival (%)	
	Nintedanib	Placebo	Nintedanib	Placebo
Log-logistic	6.39	3.51	59	30
Gamma	6.50	3.76	60	32
Weibull	6.45	3.42	60	21

Abbreviations: OS; overall survival.

Summary of overall survival analysis

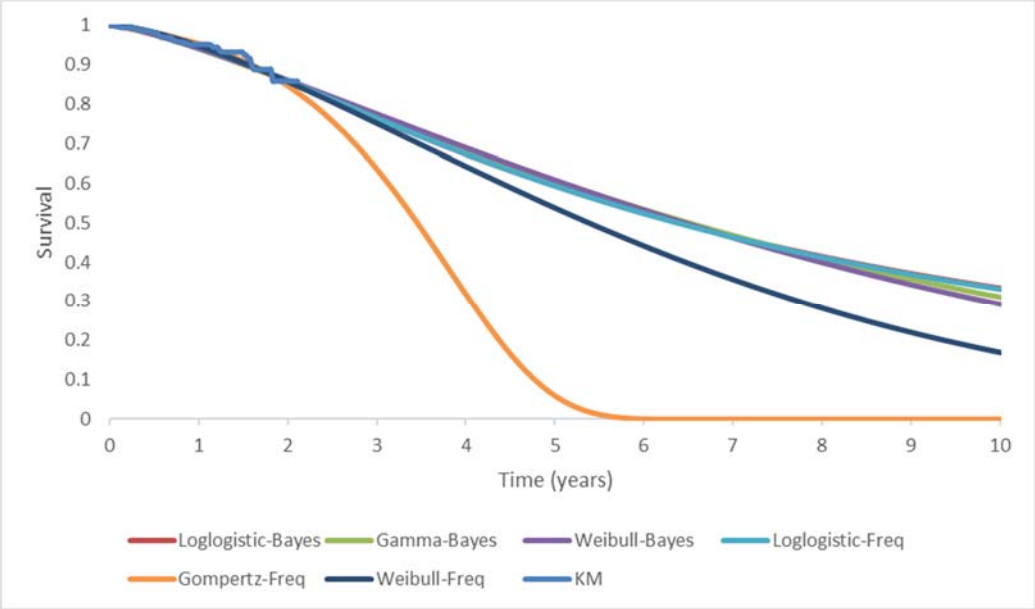
Altogether, three frequentist distributions (i.e. based on PF-ILD data alone) and three Bayesian survival curve distributions were plotted. Figure 16 and Figure 17 present all six distributions, and the KM curves from the INBUILD trial, for placebo and nintedanib respectively.

Figure 16: OS models fit versus INBUILD clinical trial KM – placebo arm



*Curves are overlapping and may not be entirely distinguishable.
Abbreviations: Bayes; Bayesian, Freq; frequentist, KM; Kaplan-Meier, OS; overall survival.

Figure 17: OS models fit versus clinical trial KM – nintedanib arm



*Curves are overlapping and may not be entirely distinguishable.
Abbreviations: Bayes, Bayesian; Freq, frequentist; KM, Kaplan-Meier; OS, overall survival.

The coefficients for all six parametric models are presented in Table 30 and Table 31.

Table 30: Coefficients for OS parametric models - placebo arm

Model		Variable	Coefficient	Std. Dev	95% Conf. Interval	
Frequentist	Loglogistic	Shape	0.786	2.510	0.515	1.056
		Scale	7.243	2.539	6.969	7.516
	Gompertz	Shape	0.004	0.014	0.002	0.005
		Rate	-9.650	6.727	-10.374	-8.925
	Weibull	Shape	0.744	2.528	0.471	1.016
		Scale	7.315	2.622	7.033	7.598
Bayesian	Loglogistic	Shape	0.855	2.110	0.624	1.078
		Scale	7.155	1.847	6.979	7.377
	Generalised Gamma	Shape	2.476	6.187	1.874	3.207
		Rate	-6.459	4.469	-6.983	-6.020
	Weibull	Shape	0.752	1.940	0.534	0.952
		Scale	7.303	1.707	7.146	7.513

Abbreviations: Conf, confidence; Std Dev; standard deviation.

Table 31: Coefficients for OS parametric models – nintedanib arm

Model		Variable	Coefficient	Std. Dev	95% Conf. Interval	
Frequentist	Loglogistic	Shape	0.443	2.887	0.133	0.754
		Scale	7.753	4.481	7.271	8.235
	Gompertz	Shape	0.002	0.016	0.001	0.004
		Rate	-9.398	6.824	-10.132	-8.664
	Weibull	Shape	0.416	2.912	0.103	0.730
		Scale	7.826	4.612	7.330	8.322
Bayesian	Loglogistic	Shape	0.436	1.779	0.244	0.626
		Scale	7.755	2.022	7.543	7.978
	Generalised Gamma	Shape	1.400	2.491	1.149	1.685
		Rate	-7.692	4.660	-8.239	-7.237
	Weibull	Shape	0.267	1.456	0.103	0.417
		Scale	8.046	2.140	7.839	8.300

Abbreviations: Conf, confidence; Std Dev, standard deviation.

The variance-covariance matrices corresponding to each placebo and nintedanib model for OS are presented in Table 32 and Table 33.

Table 32: Variance-covariance matrix for OS – placebo arm

Model		Variable	Rate	Shape	Scale
Frequentist	Weibull	Shape	NA	0.019	-0.017
		Scale	NA	-0.017	0.021
	Log-logistic	Shape	NA	0.019	-0.016
		Scale	NA	-0.016	0.019
	Gompertz	Shape	0.000	0.000	NA
		Rate	0.137	0.000	NA
Bayesian	Weibull	Shape	NA	0.011	-0.006
		Scale	NA	-0.006	0.009
	Generalised Gamma	Shape	0.080	0.116	NA
		Rate	0.060	0.080	NA
	Log-logistic	Shape	NA	0.010	-0.009
		Scale	NA	-0.009	0.013

Table 33: Variance-covariance matrix for OS – nintedanib arm

Model		Variable	Rate	Shape	Scale
Frequentist	Weibull	Shape	NA	0.026	-0.036
		Scale	NA	-0.036	0.064
	Log-logistic	Shape	NA	0.025	-0.035
		Scale	NA	-0.035	0.060
	Gompertz	Shape	0.000	0.000	NA
		Rate	0.140	0.000	NA
Bayesian	Weibull	Shape	NA	0.006	-0.008
		Scale	NA	-0.008	0.014
	Gamma	Shape	0.030	0.019	NA
		Rate	0.065	0.030	NA
	Log-logistic	Shape	NA	0.012	-0.007
		Scale	NA	-0.007	0.010

The model uses the coefficients reported in Table 32 and Table 33 above and the following functions to estimate the cycle before a patient died. The functions for all parametric distributions are reported in Table 34 below.

Table 34: Functions used to generate last cycle before death for each parametric distribution

Parametric distribution		Function
Frequentist	Weibull	1-(1-EXP(-((time_in_days/EXP(scale))^EXP(shape))))
	Log-logistic	1-(1-1/(1+(time_in_days*EXP(-1*scale))^(1/EXP(-1*shape))))
	Gompertz	MAX(EXP(-EXP(rate)*1)/shape*(EXP(shape*times_in_days)-1)),(1E-307))
Bayesian	Weibull	1-(1-EXP(-((time_in_days/EXP(scale))^EXP(shape))))
	Gamma	1-GAMMADIST(time_in_days,shape,1/EXP(rate),TRUE)
	Log-logistic	1/(1+(time_in_days*EXP(-1*scale))^(1/EXP(-1*shape)))

Abbreviations: EXP, exponential.

The same functions were used to estimate the cycle before a patient discontinues from active treatment (time to treatment discontinuation) and the cycle during which a patient experiences an acute ILD exacerbation (time to first acute ILD exacerbation; TTFAE). These two outcomes are discussed further later in this section.

Fit of parametric model

Figure 18 and Figure 19 compare the fit of the parametric models to the Kaplan-Meier curves from the INBUILD clinical trial for both the placebo and nintedanib arms. This allows for a visual inspection of each distribution and corroborates the findings from the AIC scores (i.e. that all presented distributions appear to offer a robust fit to the available data).

Figure 18: OS model fit vs Kaplan-Meier for placebo

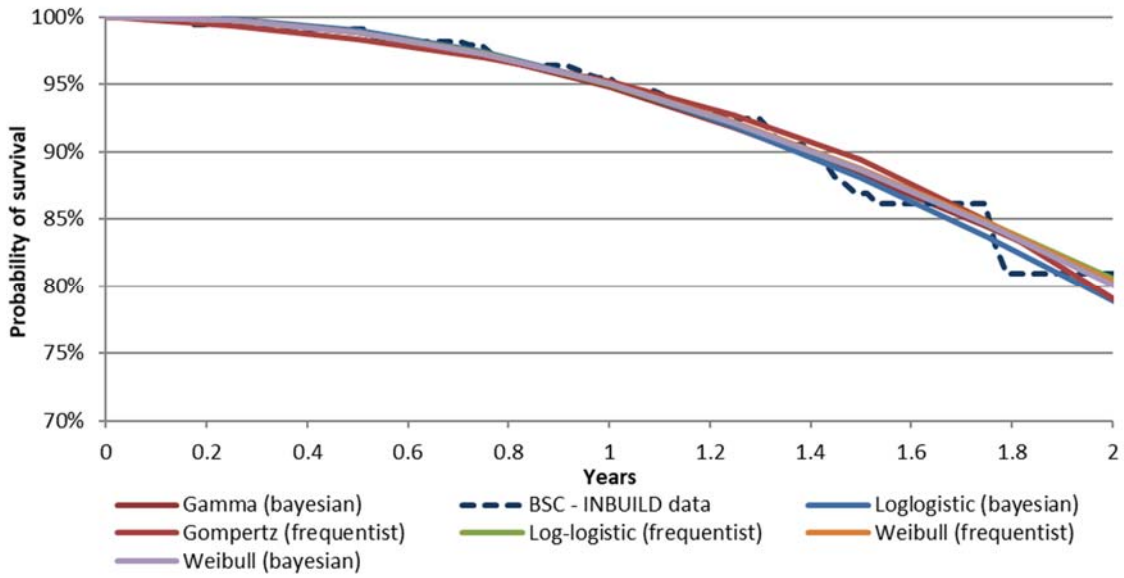
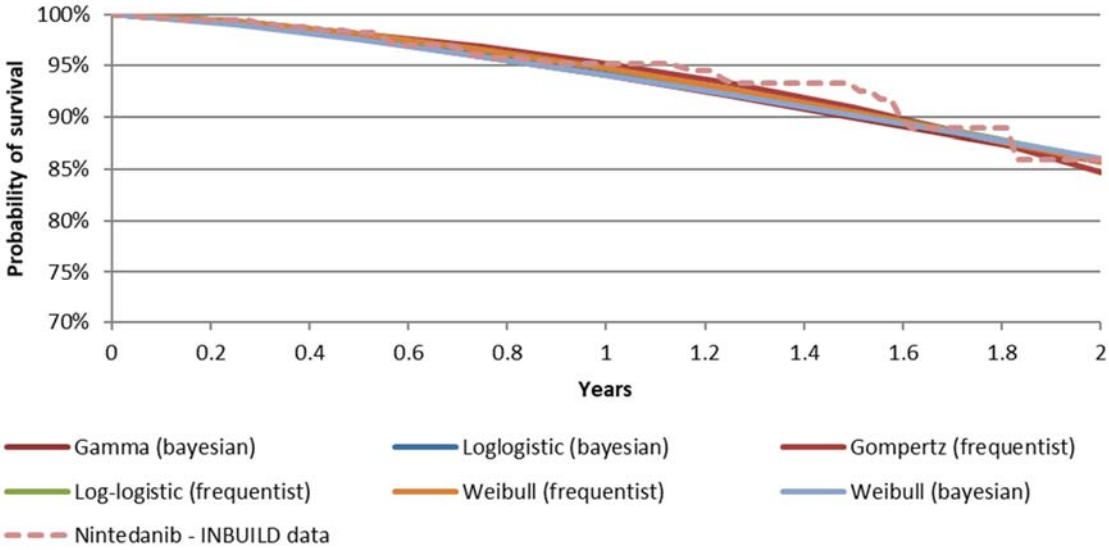


Figure 19: OS model fit vs Kaplan-Meier for nintedanib



External validation

Boehringer Ingelheim selected clinical experts to review assumptions within the model on the basis that they had a vast range of previous publications and were involved in clinical trials and guidelines/guidance development. Five clinical experts were approached to validate the assumptions within the model during a 2-hour teleconference held on the 11th November 2020. The advisory board was facilitated by Boehringer Ingelheim representatives. The clinicians were:

- Dr Nazia Chaudhuri (NC) (Advisor Wythenshaw Hospital)
- Dr Peter George (PG) (Advisor Royal Brompton Hospital, London)
- Dr Michael Gibbons (MG) (Advisor, Exeter)
- Dr Lisa Spencer (LS) (Advisor, University of Liverpool Hospital)
- Dr Helen Parfrey (HP) (Advisor, Papworth, Cambridge)

The clinicians were aware that the purpose of the teleconference was to discuss aspects of the nintedanib for PF-ILD health technology assessment (HTA) submission, and they were familiar with the nintedanib clinical trials. During the teleconference, the clinical assumptions of the model were checked and discussed between the clinicians, with a particular focus on the long-term overall survival predictions of the model for PF-ILD patients.

The clinicians were presented with the overall survival extrapolations presented in Figure 16 and Figure 17 and were able to provide more commentary on the curves for BSC given the limited knowledge on the long-term impact of nintedanib in the PF-ILD population. The clinicians agreed that for both curves the frequentist Gompertz curve was likely to underestimate survival as they would expect a proportion of patients to live beyond 5 years; these were therefore removed from further consideration.

Similarly, it was agreed that a number of the extrapolations appeared to be too optimistic in terms of long-term survival. In particular, it would be expected that nearly all ILD patients with the progressive fibrosing phenotype would be dead by 10 years without any anti-fibrotic treatment.

Therefore, it was agreed that the logistic curves (both frequentist and Bayesian) would likely overestimate survival in both arms. The clinicians could not confirm which specific distribution is likely to be valid for nintedanib patients but it was agreed that either of the Weibull curves could be plausible for BSC.

Given the advice of the clinicians it was judged that either of the Weibull curves (either frequentist or Bayesian) should be adopted in the base case for both nintedanib and BSC. It is expected that the Bayesian analysis should provide more robust estimates of long-term survival, given the inclusion of longer-term IPF data to support to use of immature PF-ILD data. Therefore, the Bayesian Weibull curves were adopted for both nintedanib and BSC in the base case. The adoption of alternative parametric distributions were explored within a scenario analysis.

An attempt was also made to validate the survival curves using real-life data. Firstly, the clinicians were asked to confirm whether it was appropriate to use IPF data as a proxy for longer-term outcomes within the PF-ILD. They agreed this was appropriate given the similar pathophysiologies of the two diseases and also referenced the Brown et al study as confirmation of this.(14) A number of potentially relevant studies were identified following the targeted literature review. (66, 80-86) The study by Lancaster et al. was judged to be the most useful for the general validation of the model. (80) This is because the authors reported data from six clinical trials to characterise the long-term safety and efficacy profile of nintedanib in IPF patients. In total, there were 1,126 and 565 patients in the pooled nintedanib and placebo arms respectively, with data on overall survival available for over eight years. However, as described in Section 6.3.1.1, these data were used as a prior in the Bayesian analysis. Therefore, it would not be appropriate to use these data to validate the overall survival curves in the model. Therefore, the other data sources were used.

To inform the validation process, the Kaplan-Meier (KM) data from the identified studies were recreated in the economic model using appropriate digitalisation software (WebPlotDigitizer, https://automeris.io/WebPlotDigitizer/).

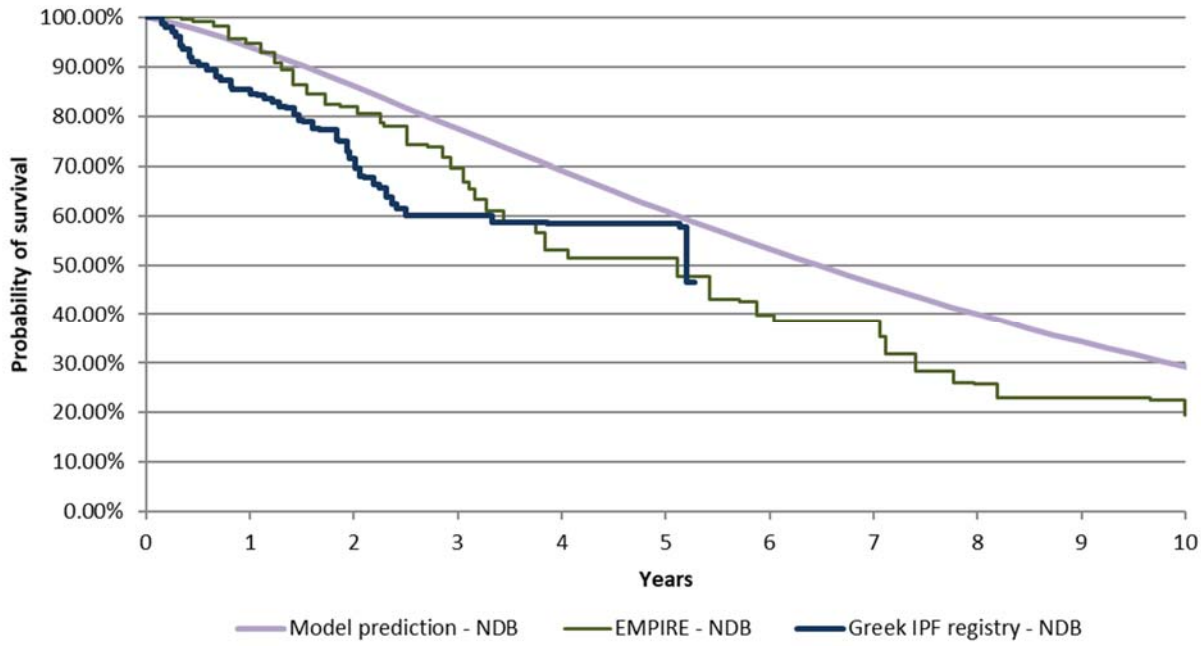
Two data sources that provide longer term data on the efficacy of nintedanib were identified, both within the IPF population. Firstly, the EMPIRE study (n=637), which

provides much longer-term data than is available from the nintedanib clinical trials in either PF-ILD or IPF (approximately 10 years) (81). Secondly, a study by Antoniou et al (2020) who reported 5-year survival data for patients receiving nintedanib (n=244) in Greece (83). This was a retrospective observational study based on the Greek IPF registry.

A comparison of the data from the EMPIRE study and Greek IPF registry with the model extrapolations using a Weibull Bayesian distribution are presented in Figure 20. This figure indicates, in terms of the EMPIRE study, the model predictions are well matched during the first two years and then is a slight diversion whereby survival with nintedanib in the model slightly exceeds both study. It should be noted that these data are only available in the form of poster presented at the European Respiratory Society Annual Meeting 2019 and, therefore, this analysis has not been peer-reviewed.

For comparison with the Greek IPF registry, the model predictions for overall survival consistently exceed the registry data.

Figure 20: Comparison of data on long-term survival with nintedanib in the IPF population (EMPIRE study and Greek IPF registry) versus the model predictions



Abbreviations: NDB, nintedanib

More data are available to validate the BSC predictions for overall survival. The KM data from the treatment arms with no antifibrotic treatment in the EMPIRE study, Australian IPF registry, European IPF registry and Finnish IPF registry are presented

in Figure 21 (81, 82, 85, 86). This graph indicates that each study was associated with quite distinct survival outcomes with no consistency shown. It is expected that this variation will be largely explained by variations in study design, in particular the enrolled patient populations. The key baseline characteristics for the study are presented in Table 35.

The UK clinicians were asked to comment on the appropriateness of each study to validate the model predictions. It was noted that there were limitations associated with each study but it was raised that the Australian registry may be the most appropriate due to similarities between UK and Australian clinical practice (82). It should be noted, as presented in Table 35, that there are important differences in the baseline characteristics of patients in the INBUILD study and Australian registry, namely that patients in INBUILD were younger but with lower FVC%.

If it is judged that the Australian registry provides the most appropriate data source to validate the model predictions then, as presented in Figure 21, the Weibull Bayesian curve appears to align relatively closely with the available KM data from this study.

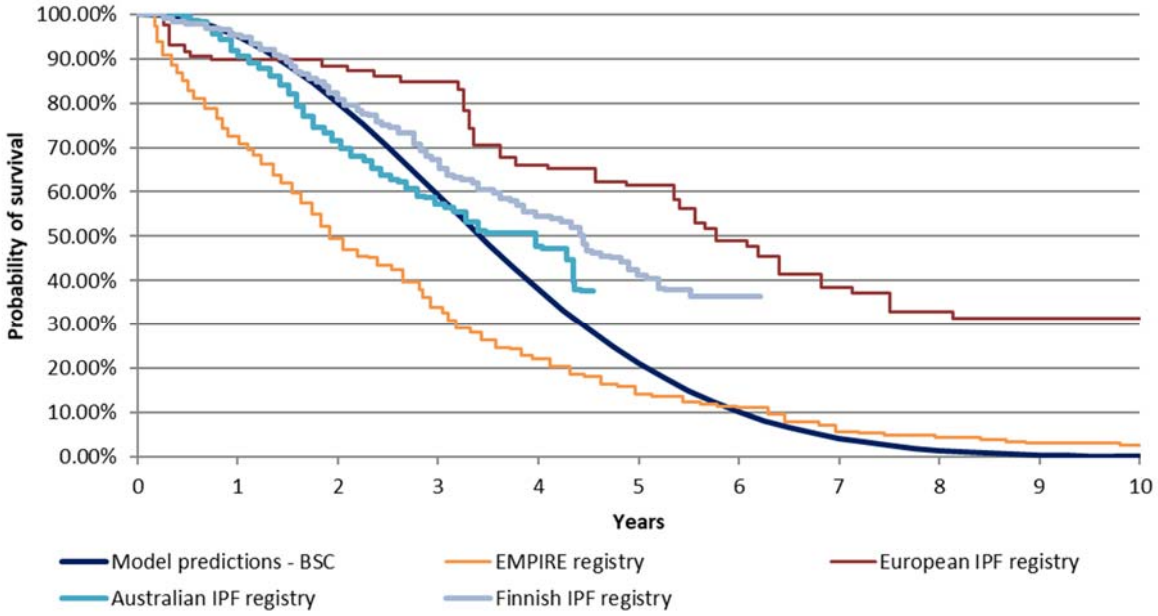
Another two studies, by Nathan et al and Wuyts et al, were also identified that present long-term survival data within IPF (44, 66, 84). However, the study by Nathan and colleagues was judged to not be generalisable to current UK clinical practice as it covered the period of 2000 to 2009 and in a US setting. Alternatively, the study by Wuyts and colleagues only presented survival data on patients who received pirferidone and, therefore, these data were judged not to be representative of BSC in the UK for PF-ILD. Therefore, the data from these studies were not used to validate the model predictions.

Table 35: Summary of key characteristics of participants in INBUILD study and IPF registries with relevant mortality data

Data source	Mean age	Male	Smoker	UIP	FVC	DC
INBUILD trial (37)	65.75	53.75%	51%	62.10%	69.00%	46.15%
European IPF registry (86)	68.10	73.30%	64.70%	63.70%	68.40%	42.10%
EMPIRE registry (81)	67.28	68%	NR	67.59%	77.08%	NR
Australian registry (82)	70.90	67.70%	71.10%	NR	81.00%	48.40%
Greek IPF registry (83)	71.80	79.10%	78.20%	NR	73.30%	42.60%
Finnish IPF registry (85)	73.00	65.10%	55.00%	NR	80.20%	55.60%

Abbreviations: DC, diffusing capacity; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia

Figure 21: Comparison of data on long-term survival with placebo in the IPF population (EMPIRE study, European IPF registry and Australian IPF registry) versus the model predictions

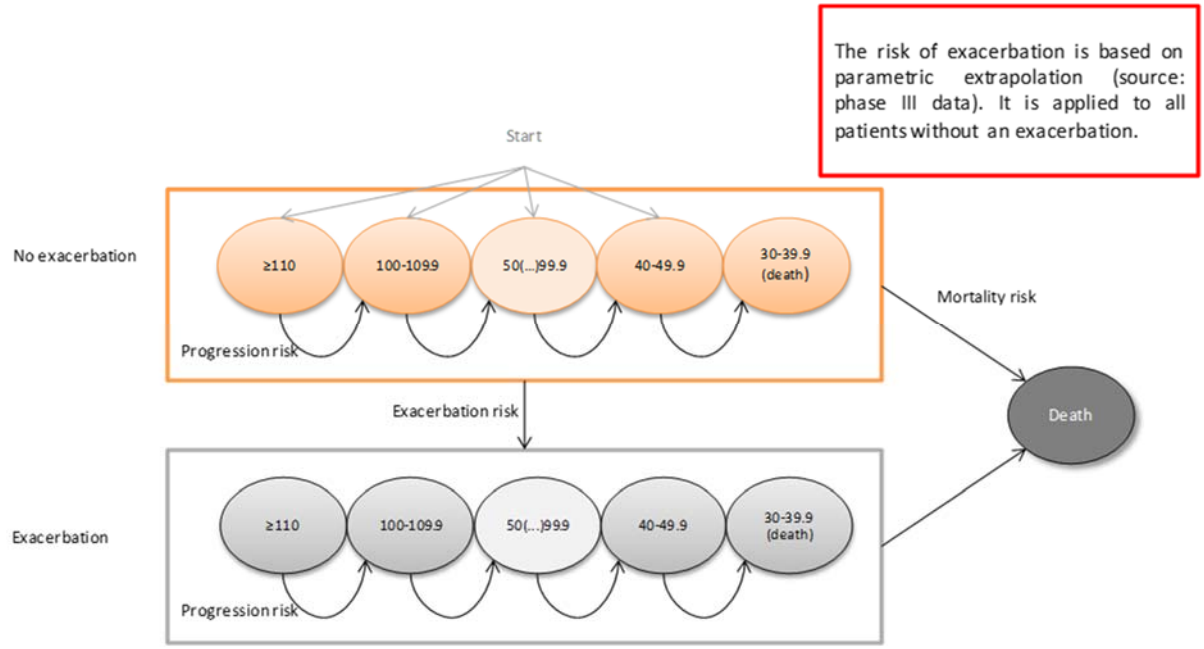


Overall, based on the feedback from the UK clinicians, and a visual comparison of the BSC curve in the model to data from EMPIRE study, Greek IPF registry and Australian registry (82, 83), it was judged that the Weibull Bayesian distribution generated the most valid long-term extrapolations for the BSC arm. The Weibull curve also produces one of the lower AIC and BIC scores thereby indicating a good statistical fit to the data. Therefore, the Weibull Bayesian distribution was also selected for the nintedanib arm. The choice of distribution was examined further in the scenario analyses.

Time to first acute exacerbation

Time to first acute exacerbation is relevant to the following transitions presented in Figure 22.

Figure 22: Model structure – exacerbations



Available clinical evidence

According to the INBUILD trial design, time to first acute exacerbation of ILD, or death over 52 weeks, was a secondary endpoint in the phase III clinical trial. (10) The trial statistical analysis plan defines acute ILD exacerbation as an acute, clinically significant, respiratory deterioration characterised by evidence of new widespread alveolar abnormality with all of the following:

- Previous or concurrent diagnosis of ILD.
- Acute worsening or development of dyspnoea typically less than one-month duration.
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with fibrosing ILD.
- Deterioration not fully explained by cardiac failure or fluid overload.

Only events that were considered to fulfil all the criteria depicted above were taken into account and contributed to the endpoint. Similar to the overall survival analysis, several parametric models were considered for modelling the TTFAE variable.

The goodness of fit for time to first acute exacerbation is presented in Table 36.

Table 36: Goodness of fit: time to first acute exacerbation

Treatment arm	Exponential	GenGamma	Gompertz	Log logistic	Log normal	Weibull
Nintedanib	461.81	458.98	463.48	463.64	462.02	463.79
Placebo	670.14	673.82	672.14	672.15	671.82	672.11

As with the OS curves, the AIC scores presented in Table 36 indicate there was little difference between each distribution in terms of statistical fit. However, the exponential curve was associated with the lowest AIC score for the placebo arm and the second lowest fit for the nintedanib arm. Additionally, the adoption of the exponential curve facilitates a simpler modelling approach. This is because this distribution incorporates a constant hazard, which allowed for a fixed transition probability for acute exacerbations to be included in the model. Each of the other distributions would have required time-varying transition probabilities (i.e. the probability of an exacerbation could change for each cycle in the model) to be incorporated, leading to a more complex analysis. Any additional complexity in the model increases the risk of errors that may lead to the model producing misleading results. For these two reasons, the exponential distribution was selected to predict the time to first acute exacerbation for both treatment arms in the model. The coefficients for the exponential model are presented in Table 37.

Table 37: Coefficients for exponential model - acute exacerbation

Treatment	Variable	Coefficient	Std. Dev.	95% Conf. Interval	
Placebo	Rate	8.545	3.075	8.214	8.876
Nintedanib		8.996	3.799	8.587	9.405

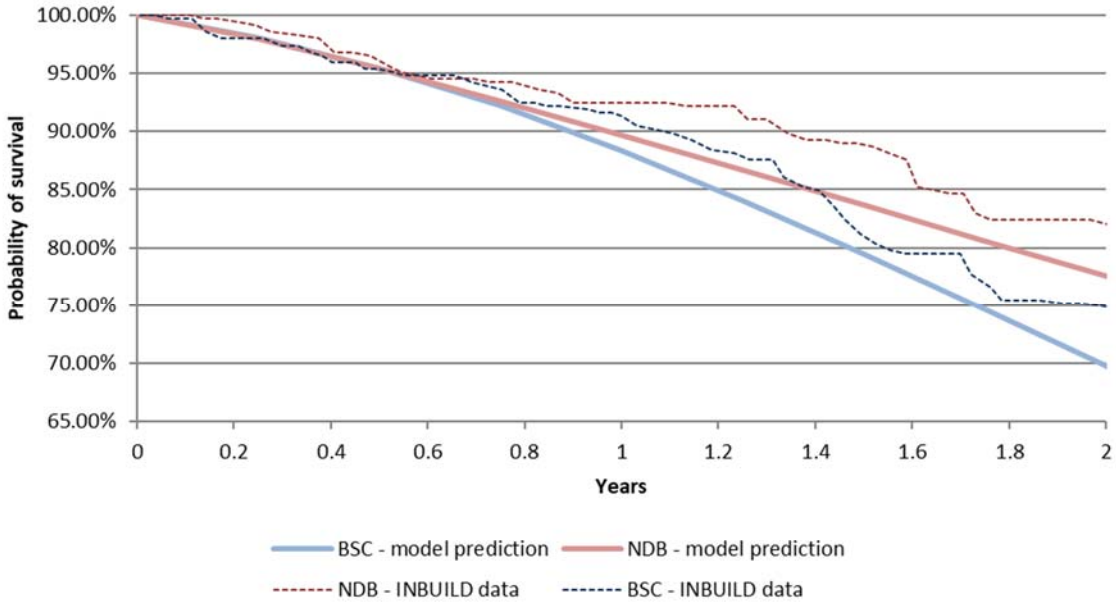
Abbreviations: Conf, confidence; Std Dev, standard deviation

The estimated exacerbation risks applied in the model for placebo and nintedanib per three-month cycles were 1.76% and 1.12% respectively.

Fit of parametric models

Similarly, to the overall survival curves, Figure 23 compares the exponential parametric models for both types of exacerbations to the Kaplan-Meier curves from the clinical trial (study period: two years) for time to exacerbation.

Figure 23: Exacerbation model fit vs. clinical trial Kaplan-Meier



Abbreviations: BSC, best supportive care; NDB, nintedanib

Recurrent exacerbations

By default, the model assumed a patient could experience one acute exacerbation, although the model can allow for recurrent exacerbations. Given that in general the outlook of patients with an acute ILD exacerbation is very poor, this is probably a conservative assumption. Furthermore, the low overall frequency of exacerbations combined with the limited remaining lifetime of the patients in the model results in a very low risk for recurrent exacerbation.

Loss of lung function

Patient disposition at start of the model

For a more accurate reflection of the clinical trial setting, the cohort entered the model at different FVC%Pred health states. The disposition of the cohort at the start of the model is presented in Table 38 and is based on Phase III clinical trial data. The model structure for loss of lung function is presented in Figure 24.

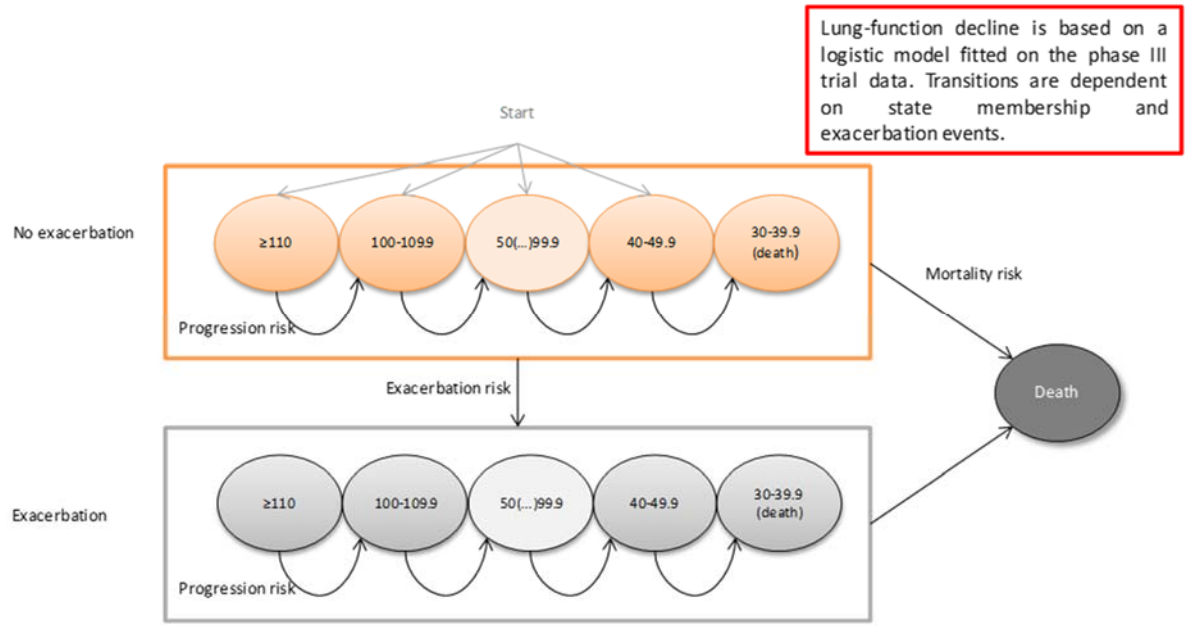
Table 38: Patient distribution at the start of the model

Health state	Distribution (%)
FVC%Pred 110 and above	1.25%
FVC%Pred 100-109.9	1.88%
FVC%Pred 90-99.9	7.34%
FVC%Pred 80-89.9	13.59%
FVC%Pred 70-79.9	20.16%
FVC%Pred 60-69.9	25.00%
FVC%Pred 50-59.9	21.41%
FVC%Pred 40-49.9	9.38%

*Note: all patients entered the model without recent history of exacerbation events

Abbreviations: FVC%Pred, forced vital capacity percentage predicted.

Figure 24: Model structure - loss of lung function



Phase III clinical trial patient level data on lung function decline, defined as a 10-point drop in FVC%Pred were analysed for this model transition for the BSC arm. (55) A logistic regression model was used to capture several predictors of lung function decline. This allowed for the analysis of recurrent events and the incorporation of additional covariates that may have influenced the probability of decline. The final equation was a multivariate mixed effects logistic regression model. However, in order to determine appropriate covariates for this model a series of univariate analyses were undertaken on the candidate predictors outlined below:

- Age (continuous).

- Sex (male or female).
- Race (white, Asian, or other).
- Methotrexate use at baseline (yes or no).
- High-resolution computed tomography (HRCT) results (i.e. UIP-like pattern only, other fibrosis patterns).
- Underlying ILD diagnosis (e.g. autoimmune ILDs, hypersensitivity pneumonitis).
- Group criteria for progressive ILD [PGGR1] (i.e. clinically significant decline in FVC %pred >=10%, marginal decline in FVC %pred (>=5-<10%) combined with worsening of respiratory symptoms or increasing extent of fibrotic changes on chest imaging, worsening of respiratory symptoms and increasing extent of fibrotic changes on chest imaging only).
- FVC%Pred at the start of the time period (continuous).
- Exacerbation during the analysed 3-month period (whether it occurred or not).

A p-value of 0.2 was chosen to determine which variables had a univariate association, with those defined as significant predictors then combined in the final multivariate model. The final model included the following variables: age, HRCT pattern, group criteria for progressive ILD, FVC at start of interval, and exacerbation variable. All other variables were excluded from the multivariate logistic regression.

Progression was defined as the date when ≥10% of absolute decline in FVC%pred compared to baseline occurred for the first time. In the model, this was represented by a binary variable that indicated whether a patient had progressed in a certain cycle. If a patient was marked as progressed in a cycle, they would also be marked as such in subsequent cycles.

Coefficients from the final multivariate model are presented in Table 39 below. The variance - covariance matrix is also presented in Table 40.

Table 39: Coefficients for lung function decline

Term	Estimate	SE	Statistic (t-test)	P-value
(Intercept)	-9.491	1.680	-5.649	0.000
AGE	0.052	0.020	2.626	0.009
HRCTRESUIP-like pattern only	0.832	0.389	2.137	0.033
PGGR1Marginal decline in FVC %pred	-0.877	0.412	-2.126	0.034
PGGR1Worsening of respiratory symptoms	-1.074	0.504	-2.131	0.033
fvc_start_int	0.034	0.011	3.019	0.003
exac_before	2.176	0.847	2.568	0.010

Abbreviations: FVC%pred, forced vital capacity percent predicted; PGGR1, grouped criteria for progressive interstitial lung disease; SE, Standard error.

Table 40: Variance – covariance matrix for lung function decline

	(Intercept)	AGE	HRCTRESUIP-like pattern only	PGGR1Marginal decline in FVC %pred	PGGR1Worsening of respiratory symptoms	fvc_start_int
(Intercept)	2.823	-0.026	-0.081	0.074	0.047	-0.010
AGE	-0.026	0.000	-0.001	0.001	0.001	0.000
HRCTRESUIP-like pattern only	-0.081	-0.001	0.151	-0.021	-0.025	0.001
PGGR1Marginal decline in FVC %pred	0.074	0.001	-0.021	0.170	0.062	-0.002
PGGR1Worsening of respiratory symptoms	0.047	0.001	-0.025	0.062	0.254	-0.001
fvc_start_int	-0.010	0.000	0.001	-0.002	-0.001	0.000

The regression equations (with and without exacerbation) are presented below:

Lung function decline modelling (without exacerbation)

$P = \text{constant} + \beta 1y + \beta 2 + \beta 3 + \beta 4z$

Lung function decline modelling (with exacerbation)

$P = \text{constant} + \beta 1y + \beta 2 + \beta 3 + \beta 4z + \beta 5$

β1	Age covariate
β2	HRCTRESUIP-like pattern only covariate
β3	PGGR1Marginal decline in FVC %pred covariate
β4	fvc_start_int covariate
β5	exac_before covariate
Y	Age at baseline
z	FVC% at interval start

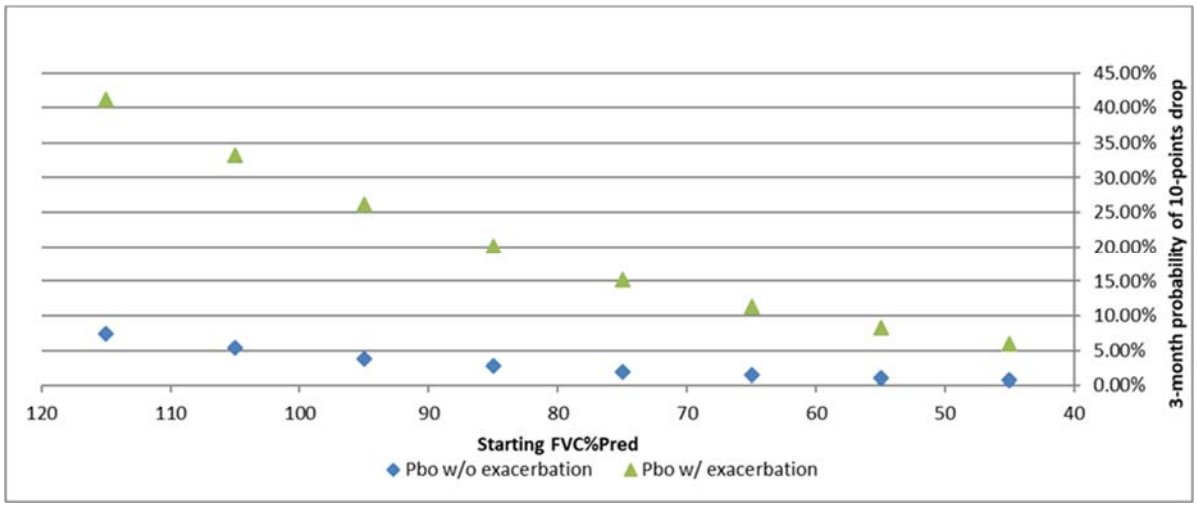
The coefficients in Table 39 were statistically significant. The probabilities of progressing during a one-month interval for each FVC%Pred value at the start of the interval are presented below in Table 41 and graphically in Figure 25. Separate values are presented for patients with no acute exacerbation and after an acute exacerbation. Separate values were generated because, as shown in Table 41, the occurrence of an acute exacerbation event was found to be a statistically significant predictor of lung function. Therefore, once an exacerbation had occurred lung function decline was expected to occur more quickly and a diminishing effect in progression as lung function was lost was observed. Additionally, the absolute risk of progression was considerably higher following an exacerbation.

Table 41: Three-month probabilities of progression, placebo (i.e. BSC)

FVC%Pred at start of interval	No exacerbation at start of interval	Intervals starting after first exacerbation
115	7.35%	41.14%
105	5.34%	33.19%
95	3.85%	26.10%
85	2.77%	20.07%
75	1.99%	15.14%
65	1.42%	11.26%
55	1.01%	8.27%
45	0.72%	6.02%

Abbreviations: FVC%Pred, forced vital capacity percent predicted.

Figure 25: Progression probabilities for placebo (with and without exacerbation)



Abbreviations: FVC%Pred, forced vital capacity percentage predicted; PBO, placebo.

Loss of lung function for nintedanib

The risk of loss of lung function for nintedanib was informed by an odds ratio applied to the baseline placebo risk (described above), assuming a constant relationship over time. The odds ratio for nintedanib vs placebo is presented in Table 42 and was estimated based on a mixed effect logistic regression of data from INBUILD, in which treatment was included as the only predictor. The regression equation was fitted using the "melogit" command in STATA (data analysis and statistical software). The outputs from this equation are presented in Table 42 and Table 43.

The 95% confidence interval for the odds ratio is also presented and indicates that, at the very upper limit of the interval, a value of one occurs. This indicate there is no statistically significant difference in effect between nintedanib and placebo at the 95% level. However, given this occurs at the highest end of the range it was judged appropriate to model a difference in lung function decline between nintedanib and placebo (or BSC) and explore this uncertainty further in the sensitivity analysis.

The estimated transition probabilities for nintedanib are presented in Table 43 and Figure 26.

It was assumed that the nintedanib transition probabilities were applicable as long as a patient remaining on the treatment (i.e. constant transition probabilities applied). However, once a patient had discontinued from nintedanib it was assumed that they would revert to natural disease progression and, therefore, the transition probabilities for placebo (see Table 41) were applied.

Table 42: OR values for loss of lung function

Fixed effects:	Estimate	SE	p-value	Odds ratio	95% CI
Intercept	0.654	0.2405	<0.01		
NDB coefficient	-0.4248	0.226	0.0602	0.654	0.420 – 1.1018

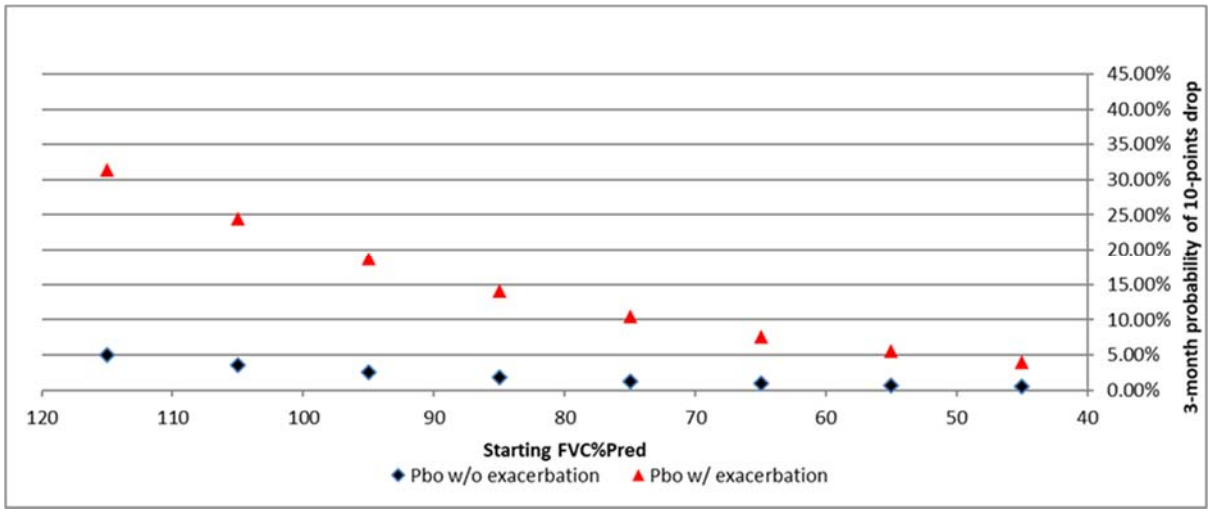
Abbreviations: CI, confidence interval; NDB, nintedanib; SE, standard error.

Table 43: Three-month probabilities of progression, nintedanib

FVC%Pred at start of interval	No exacerbation at start of interval	Intervals starting after first exacerbation
115	4.93%	31.37%
105	3.56%	24.52%
95	2.55%	18.76%
85	1.83%	14.10%
75	1.31%	10.45%
65	0.93%	7.66%
55	0.66%	5.57%
45	0.47%	4.02%

Abbreviations: FVC%Pred, forced vital capacity percent predicted.

Figure 26: Progression probabilities for nintedanib (with and without exacerbation)



Abbreviations: FVC%Pred, forced vital capacity percentage predicted.

Safety and treatment discontinuation

Selection of adverse events in the model

Data informing the frequency of adverse events associated with nintedanib and placebo were obtained from the INBUILD clinical trial report. (37) A set of criteria were developed to select adverse events to be included in the economic analysis based on their severity and incidence. These criteria were:

- An adverse event had to be common i.e. incidence of >10% in either treatment arm.
- An adverse event had to be treatment-related/treatment-emergent.
- Incidence in the treatment arm had to be at least 1.5 times higher than in the control arm.

Based on the above criteria, the adverse events selected for both arms of the model are presented in Table 44.

Table 44: Nintedanib and placebo adverse events

Adverse event	Nintedanib		Placebo		Source
	N (%)	Risk per cycle	N (%)	Risk per cycle	
Patients	332 (100.0)	N/A	331 (100.0)	N/A	INBUILD – data on file (37)
GI events					
Diarrhoea	196 (59.0)	20.05%	59 (17.8)	4.8%	
Nausea	79 (23.8)	6.59%	19 (5.7)	1.47%	
Vomiting	41 (12.3)	3.25%	7 (2.1)	0.53%	
Investigations					
Alanine aminotransferase increased	36 (10.8)	2.84%	8 (2.4)	0.61%	

A cycle-length adjustment was made to obtain a risk per three-month cycle.

Treatment discontinuation

Although the majority of adverse events were mild or moderate severity, the nature of the adverse events is likely to have a greater effect on treatment tolerability and persistence. It is reported that up to DBL2, approximately 34% of had patients discontinued treatment in the nintedanib arm of the clinical trial (Part A + Part B, post-hoc analysis of INBUILD data).

Similarly to the efficacy parameters previously presented, the nintedanib overall discontinuation risk was calculated based on the parametric modelling exploration of phase III clinical trial data. (55) The data were analysed assuming an exponential model with no other parametric distributions considered. The exponential distribution was selected as it implies a constant hazard, thereby indicating the rate of discontinuation was fixed for nintedanib. As with the modelling approach for acute exacerbations, the use of another parametric distribution would have necessitated the application of time-varying discontinuation, which would have made the model structure substantially more complicated. It should be noted that the equivalent approach was adopted in the nintedanib TA submission for IPF and this approach was not critiqued by the ERG during their assessment of the submission (1).

The analyses were performed excluding discontinuations due to death. It was assumed that patients died before discontinuation if the date of discontinuation coincided with the date of death or if it was the very next day. The coefficient of the exponential model for nintedanib is reported in Table 45 below.

It was not necessary to model treatment discontinuation for the BSC arm as no active intervention was included for this comparator.

Table 45: Coefficient for exponential model - overall discontinuation

Variable: constant	Coefficient	SD	95% CI	
Nintedanib	7.270	1.737	7.083	7.457

Abbreviations: CI, confidence interval; SD, standard deviation.

The estimated overall discontinuation risk for nintedanib was calculated to be 5.97% per month (exponential model, constant risk). The model predictions for time to discontinuation, based on this risk, are presented in Figure 27. This figure also includes the available Kaplan-Meier (KM) data from the INBUILD trial.

This indicates that for the first year of the model more patients received the treatment than in the trial but from approximately 15 months onwards the model prediction curve drops below the KM curve.

It was also possible to validate the model predictions for time to discontinuation using data from the Lancaster (2019) (80). As discussed previously, this study provides long-term data on the safety and efficacy of nintedanib in the IPF population and is expected to be an appropriate data source for external validation given similarities between the IPF and PF-ILD populations (as confirmed by the UK clinicians). As this study provides longer-term data on treatment length than is available in the INBUILD study it was judged to be a good source to validate time to discontinuation.

Lancaster and colleagues reported that the median exposure to nintedanib, based on the long-term follow-up data from the nintedanib trials, was 22.5 months with a maximum exposure time of 93.1 months. A shown in Figure 28 (which provides the model predictions but with an adjusted x-axis scale so the shorter-term results can be better visualized), the median survival was approximately 2.3 years (or 27-28 months). Additionally, as shown in Figure 27, a proportion of patients remained on nintedanib after 8 years (or 96 months), which was past the maximum exposure point measured by Lancaster and colleagues. Therefore, the model may underestimate the true rate of discontinuation for nintedanib. For this reason, a scenario analysis was undertaken in which a higher rate of discontinuation was applied to more closely match the data reported by Lancaster and colleagues more details are provided in Section B.3.8.

Figure 27: Time on treatment with nintedanib

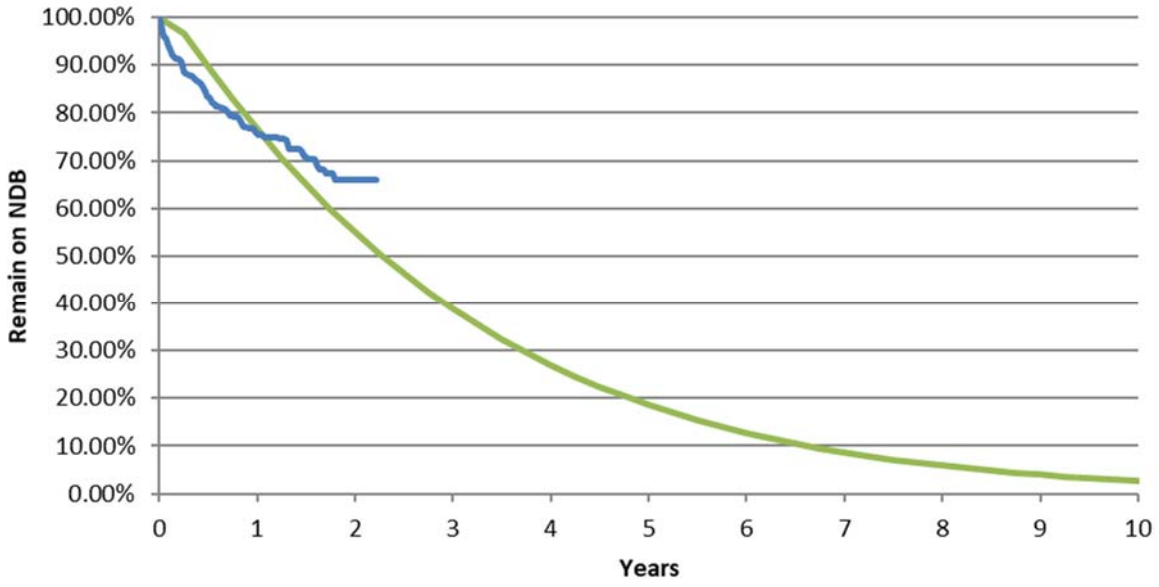
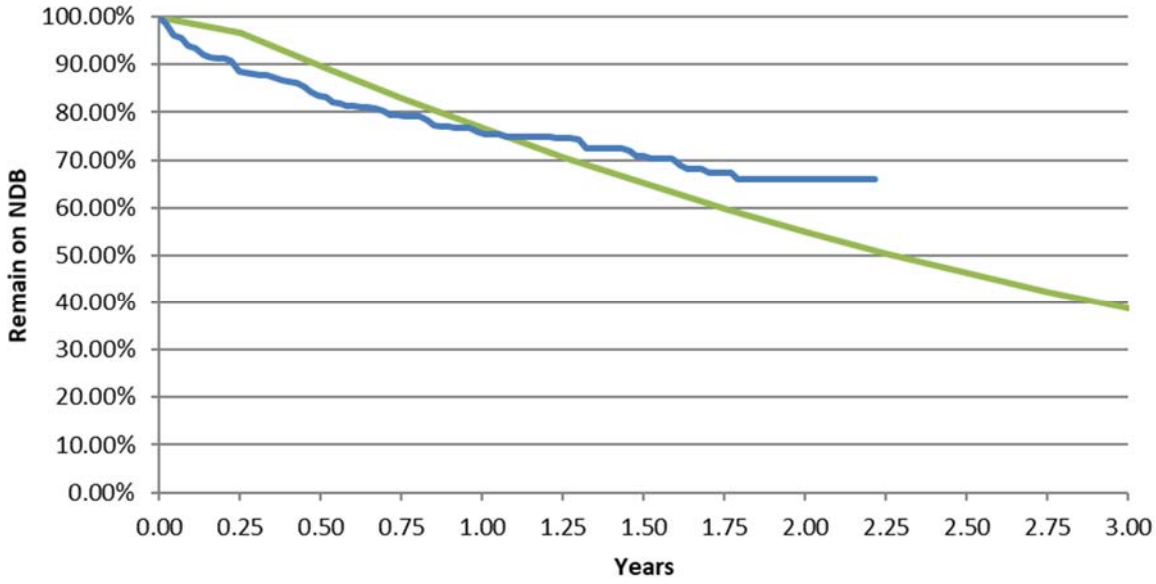


Figure 28: Time on treatment with nintedanib, adjusted x-axis



B.3.4 Measurement and valuation of health effects

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

A systematic literature review was conducted to identify appropriate health state utility values (HSUVs). This search did not identify any relevant data related specifically to PF-ILD. Therefore, the utility data applied in the model were obtained from EQ-5D data collected in the INBUILD trial.

The economic analysis used patient reported EQ-5D data collected in the INBUILD clinical trial to determine HSUV. (55) Baseline utility was represented by values associated with lung function and an acute exacerbation was included as a decrement in the baseline utility. Furthermore, the model also applied a utility decrement (disutility) associated with treatment-related AEs. As the EQ-5D was measured directly within the INBUILD trial, no mapping was required. There was no adjustment of health states utility values and the baseline HRQoL was assumed to be the same as the HRQoL of patients in the health states. Uncertainty was explored in scenario analyses, which are presented in Section B.3.8.

Mapping

As EQ-5D was measured directly from the INBUILD clinical trial, no mapping was required.

Health-related quality-of-life studies

A systematic literature review was conducted in June 2020 to identify data associated with relevant Health State Utility Values (HSUVs) for the *de novo* cost-effectiveness model for nintedanib. Full details of the methods for identifying and selecting studies are provided in Appendix H, including the search strategy and databases searched. All relevant literature and data sources are reported in accordance with PRISMA guidelines.

This search did not identify any relevant data related specifically to PF-ILD. Therefore, the utility data applied in the model were obtained from the INBUILD trial – more details below. Additionally, the impact of applying data from the IPF indication were also examined. This is discussed further below.

Health-related quality-of-life data used in the cost-effectiveness analysis

Utility based on lung function (baseline utility)

The EQ-5D values were compiled from the phase III INBUILD trial by FVC%Pred group. The analysis controlled for exacerbation events (i.e. data before exacerbations were used). Mean utilities were applied across different lung function states to accommodate the memory-less feature of the Markov approach. The change in HRQoL is related to events/change in state rather than time. It was assumed that the utility was 0 (dead) for FVC%Pred values < 40%. Due to a low number of patients in the ≥110 category, the mean utility was assumed equivalent to 100-109.9.

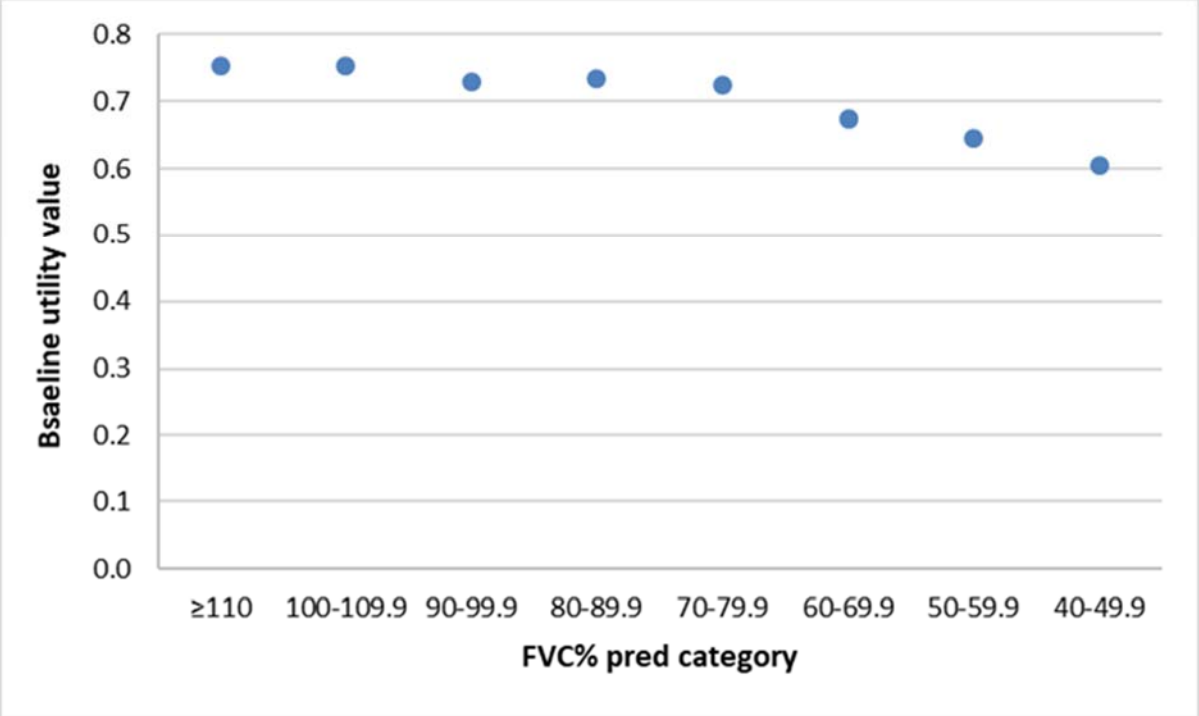
The EQ-5D values for each FVC%Pred category are presented Table 46 and Figure 29.

Table 46: Summary of EQ-5D utility values for cost-effectiveness analysis by FVC%Pred group

FVC%Pred	Mean EQ-5D utility	SD	Number of patients
≥110	0.7521	NA.	NA.
100-109.9	0.7521	0.2570	30
90-99.9	0.7287	0.2278	76
80-89.9	0.7333	0.2051	148
70-79.9	0.7242	0.2113	214
60-69.9	0.6750	0.2349	271
50-59.9	0.6453	0.2240	256
40-49.9	0.6045	0.2457	137

Abbreviations: EQ-5D, European Quality of Life-5 Dimensions; FVC%Pred, forced vital capacity percentage predicted; SD, standard deviation; NA, Not applicable.

Figure 29: Baseline utility values



Abbreviations: FVC%Pred. forced vital capacity percentage predicted

Acute exacerbation-related decrement in utility

When an acute exacerbation occurred, the patient experienced an additional 0.167 (standard error: 0.050) drop in utility. The utility decrement related to acute exacerbation was estimated from a regression equation based on EQ-5D data collected in the INBUILD clinical trial. (55)

Any reduction in patient QoL following an acute exacerbation was assumed to be temporary and, therefore, it was assumed that the disutility would only affect patients for one month. For this reason, the disutility was adjusted to account for the 3-month cycle length in the model (i.e. a value of 0.0556 was applied in the cycle the event occurred within). After one cycle the utility values returned to the values expected if the acute exacerbation had not occurred. Nevertheless, because acute exacerbations permanently affected FVC%pred, and once FVC%pred was decreased it could not improve, the resulting lower FVC%pred values had a lasting indirect impact on utility values. The disutility value estimated from the INBUILD data was assumed to be a conservative estimate because it is likely that the worst patients were missing not at random from the dataset (as they were unable or unwilling to attend the next study visit).

Adverse reactions

AE-related decrement in utility

Data on gastrointestinal (GI) event disutilities from the IPF nintedanib economic model that was submitted to NICE were used as a proxy for PF-ILD based on the assumption that nintedanib has a similar safety profile regardless of the indication (1). Post hoc analysis of INPULSIS safety data showed that the EQ-5D change in patients that experienced a serious GI event is -0.068 (-0.201 to 0.065) (87). The model assumed half of this value (-0.034) as a proxy for GI disutility in patients that experienced a non-serious GI event. This assumption was validated against results from a phase III trial on recurrent non-small cell lung cancer that estimates the disutility for diarrhoea (grade 3/4) at -0.042 (88). The value of a disutility of 0.042 for severe diarrhoea event suggests that our model estimate of 0.034 disutility value for any GI event is reasonable.

For alanine aminotransferase (ALT) increase the model assumed no disutility due to the fact that this event is of a mild to moderate severity and therefore considered asymptomatic. A summary of the disutility values is presented in Table 47.

Table 47: Summary of disutilities due to adverse events

Adverse event	Disutility value	Source/assumption
GI events	-0.034	Assume half of serious GI disutility as proxy
ALT increase	0	Assume no disutility

*Note that nausea, vomiting, and dyspepsia were grouped under "GI events"
Abbreviations: ALT, alanine aminotransferase; AE, adverse event; GI, gastrointestinal.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic literature review was conducted in June 2020 to identify published sources of costs and resource use in PF-ILD. Four publications, reporting data from two studies were identified for inclusion in the systematic review, as described in Appendix I. It was judged that these studies did not provide any data that were applicable to the cost-effectiveness model.

The unit costs in the model were largely taken from a UK NHS setting. More specifically, national values were obtained from NHS Reference Costs and the Unit Costs of Health and Social Care by the Personal Social Services Research Unit (PSSRU). (89, 90). Also, where necessary, costs were inflated to 2018/19 values.

Uncertainty was explored in scenario analyses in Section B.3.8. Full details of the parameter values, range/CIs, probability distributions applied in the sensitivity analyses, and the sources are provided in Section B.3.6.

Intervention and comparators' costs and resource use

Drug acquisition costs

The price per pack applied in the model is the PAS price ([redacted] discount to the list price of £2,151 for both the 100mg and 150mg units = [redacted]). It was assumed in the base case analysis that 79% of patients would receive the 150mg formulation, with the remaining 21% receiving the 100mg formulation. This assumption is based on the current prescription records of nintedanib within IPF. (91) Since the active arm involved oral treatment, it was assumed that there was no administration cost associated with treatment.

No cost was assumed for BSC, as it reflected the placebo (control) arm of the clinical trial.

Health-state unit costs and resource use

Background follow-up costs

The background follow-up costs were compiled using the IPD data from INBUILD (post hoc analysis of INBUILD data). The following healthcare resources and their respective descriptions of components were available in the INBUILD data and were further analysed for the economic model:

- Hospital: average number of hospitalisations, average duration of each hospitalisation (days), percentage (%) hospitalisation associated with intensive care unit (ICU) stay, percentage (%) hospitalisation associated with emergency room (ER) overnight stay, percentage (%) hospitalisation associated with mechanical ventilation, percentage (%) hospitalisation associated with ambulance use.
- ER: average number of ER visits, percentage (%) ER visits associated with ambulance use.
- Visits: visits to GP, specialist, nurse, physiotherapist, occupational therapy, other visits.
- Procedures: oxygen use.

The healthcare resource utilisation (HCRU) data were grouped into 10-point FVC%Pred categories. A 10-point categorisation of FVC%pred was consistent with published literature (46, 92) and allowed the grouping of HCRU inputs in a simple and consistent way. A per-cycle probability (3-month probability) of incurring the resource use was calculated. The number of observations for each FVC%Pred group is presented in Table 48.

Table 48: Number of HCRU observations in each FVC%Pred group

FVC%Pred	Number of observations
≥110	124
100-109.9	274
90-99.9	599

FVC%Pred	Number of observations
80-89.9	1,215
70-79.9	1,958
60-69.9	2,566
50-59.9	2,386
40-49.9	1,497

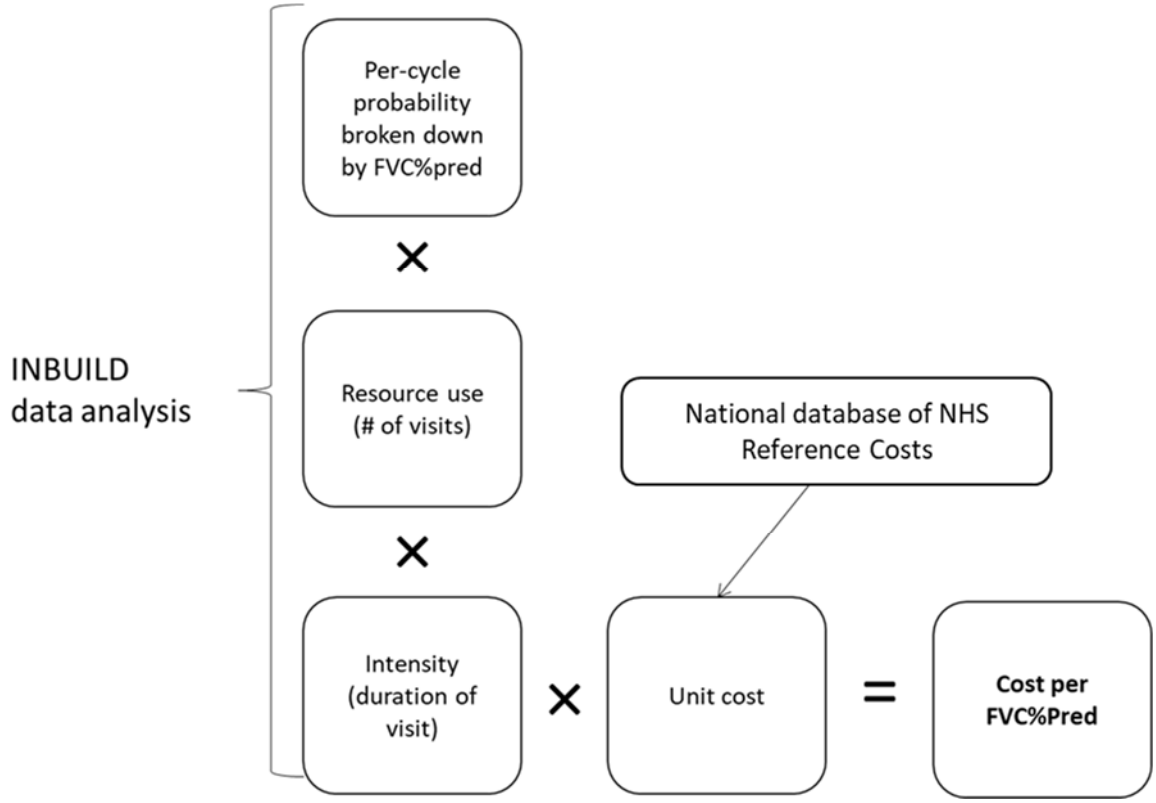
Abbreviations: FVC%pred, forced vital capacity percent predicted; HCRU, healthcare resource utilisation.

Regarding the intensity of use within each HCRU group (i.e. hospital, ER, visits, and procedures) the number of observations was too low to allow a similar analysis by FVC%pred group. Therefore, the intensity of each resource use (e.g. the average number of hospitalisations, the average duration in hospital) was averaged out across all FVC%pred groups.

Synthesis of data

The synthesis of the INBUILD data with unit costs is presented in the diagram below (Figure 30).

Figure 30: Diagram of healthcare resource use analysis



Hospitalisation cost synthesis

The cost inputs for all hospitalisation items (values, assumptions, sources) are presented in Table 49 below.

Table 49: Cost inputs for hospitalisation

Parameter description	Value used	Sources and assumptions
Hospitalisation	£324	National Schedule of Reference Costs - Year 2017-18 - NHS trusts and NHS foundation trusts; Weighted average of DZ27S, DZ27T and DZ27U (Respiratory Failure without Intubation with CC score 11+, 6-10, 0-5 respectively. I National Schedule of Reference Costs Year 2017/18 inflated to 2018/19 price year - excess bed days not reported within 2018/2019 NHS reference costs (93)
ICU stay	£1,073	Weighted average of XC06Z (Adult Critical Care, 1 organ supported) and XC07Z (Adult Critical Care, 0 organs supported), Adult Critical Care Unit National Schedule of Reference Costs Year 2018/19 - NHS trusts and NHS foundation trusts; Critical Care. (89)
Mechanical ventilation	£161	Weighted average of non-invasive ventilation support assessment 19 years and over (DZ37A), Respiratory medicine and Respiratory physiology; procedures in outpatients; National Schedule of Reference Costs Year 2018/19 - NHS trusts and NHS foundation trust. (89)
ER overnight stay	£268	Weighted average across all types (admitted only). Excludes patients that are dead on arrival, dental services and patients with no treatment/investigations. National Schedule of Reference Costs Year 2018/19 - NHS trusts and NHS foundation trusts; Accident and Emergency Services. (89)
Ambulance use	£224	Weighted average of ASH1 (hear and treat or refer), ASS01 (see and treat or refer), ASS02 (see and treat and convey); National Schedule of Reference Costs Year 2018/19 - All NHS trust and NHS foundation trusts - ambulance services. (89)

Abbreviations: A&E, accident and emergency; ICU, intensive care unit; PPP, purchasing power parity.

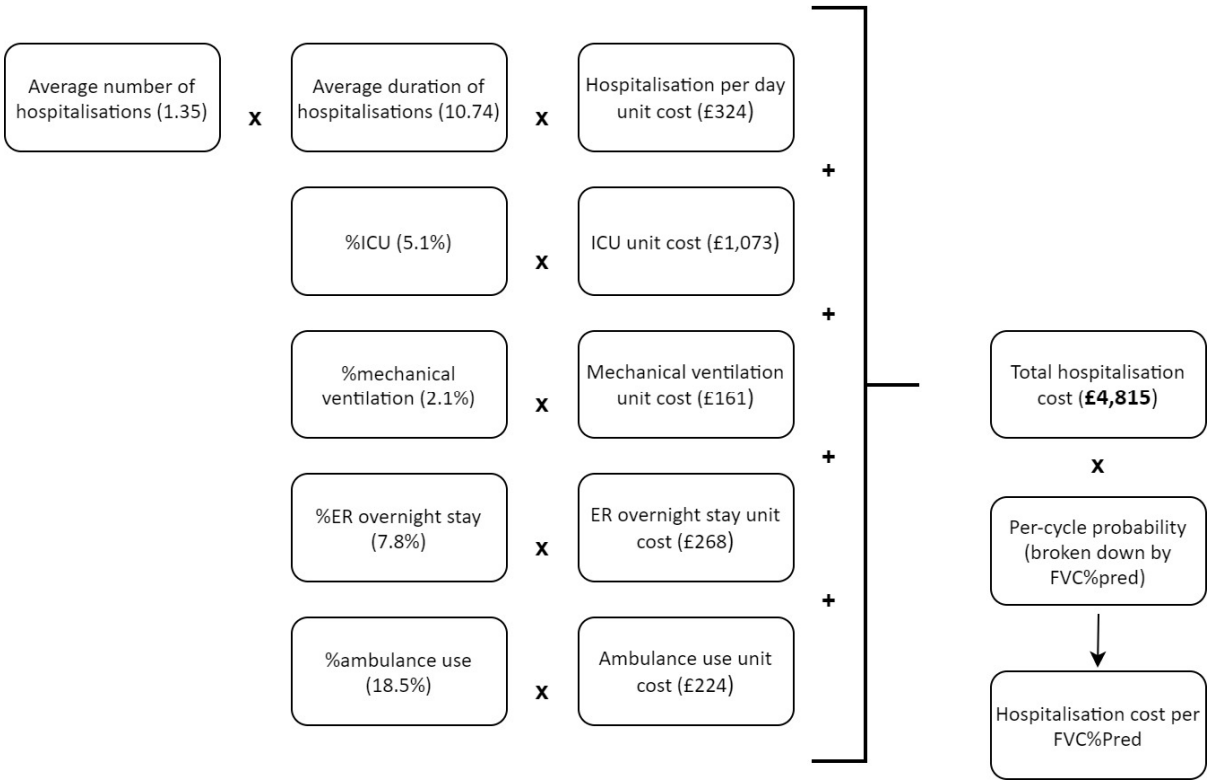
This cost synthesis of the hospitalization resource use was the most complex (Figure 31), as it was composed of:

- Average number of hospitalisations per patient with at least one hospitalisation (1.35, SE 0.22).
- Average duration of hospitalisation (10.74 days, SE 0.62).
- Proportion of hospitalisation associated with an ICU stay (5.1%, SE 1.1%).
- Proportion of hospitalisation associated with mechanical ventilation use (2.1%, SE 0.8%).
- Proportion of hospitalisation associated with an ER overnight stay (7.8%, SE 1.4%).
- Proportion of hospitalisation associated with ambulance use (18.5%, SE 2.0%).

All of the above values were obtained from a post-hoc analysis of INBUILD phase III trial and are per patient values, all-cause (not just PF-ILD-related).

The sum and product of all of the items rendered a total hospitalisation cost of £4,815. This sum was then multiplied by the probabilities of each FVC%pred group (see Figure 32).

Figure 31: Cost synthesis: hospitalisation



Abbreviations: ER, emergency room; FVC%pred, forced vital capacity; ICU, intensive care unit

Figure 32: Hospitalisation cost per FVC%Pred group

FVC% pred group	3-month probability of hospitalisation
>=110	0.12
100-109.9	0.05
90-99.9	0.05
80-89.9	0.05
70-79.9	0.05
60-69.9	0.09
50-59.9	0.09
<40-49.9	0.14

x £4,815 →

3-month total hospitalisation costs	Annual hospitalisation costs
£569	£2,276
£261	£1,045
£263	£1,051
£236	£943
£241	£966
£438	£1,752
£453	£1,812
£651	£2,603

ER cost synthesis

The costs associated to each ER item are reported in Table 50.

Table 50: Cost associated with emergency room visits

Outpatient visit	Cost		Number of visits (per patient)	
	Value	Source	Average value (SE)	Source
ER visit	£182.85	Weighted average across all types. Excludes patients that are dead on arrival, dental services and patients with no treatment/investigations; National Schedule of Reference Costs - Year 2018/19. (89)	1.21 (SE 0.113)	INBUILD trial post hoc analysis (55)
Ambulance use	£224.39	Same as hospitalisation, Table 49. (89)	19.4% (SE 2.724%)	INBUILD trial post hoc analysis (55)

Abbreviations: ER, emergency room; SE, standard error.

The three-month probabilities of incurring an ER cost for each FVC%pred group are presented in Table 51.

Table 51: Three-month probabilities of ER visits

FVC%Pred	3-month probability
≥110	0.095
100-109.9	0.043
90-99.9	0.025
80-89.9	0.042
70-79.9	0.034
60-69.9	0.054
50-59.9	0.060
40-49.9	0.048

Abbreviations: FVC%pred, forced vital capacity percent predicted; ER, emergency room.

Outpatient visits cost synthesis

The unit cost for each outpatient visit is reported in Table 52.

Table 52: Unit cost and average outpatient visits

Outpatient visit	Cost		Number of visits (per patient)	
	Value	Source	Average value (SE)	Source
GP	£39 per visit	PSSRU 2019 (90)	1.497 (SE 0.507)	INBUILD trial post-hoc analysis (55)
Specialist	£109 per contract hour		1.613 (SE 0.344)	
Nurse	£46 per contract hour		0.181 (SE 0.051)	
Physiotherapist	£45 per contact hour		0.068 (SE 0.088)	
Occupational therapy	£45 per contact hour		0.133 (SE 0.105)	
Other visits	Assumed to be the same of a specialist visit.		0.133 (SE 0.105)	

Abbreviations: GP, general practice; PSSRU, personal social services research unit; SE, standard error.

The three-month probabilities of incurring each outpatient visit cost for each FVC%pred group are shown in Table 53.

Table 53: Three-month probabilities of outpatient visits

FVC%Pred	GP	Specialist	Nurse	Physiotherapist	Occupational therapy	Other
≥110	0.118	0.071	0.024	0.012	0.024	0.024
100-109.9	0.097	0.139	0.005	0.005	0.005	0.005
90-99.9	0.161	0.249	0.030	0.005	0.020	0.020
80-89.9	0.180	0.205	0.022	0.015	0.044	0.044
70-79.9	0.311	0.263	0.029	0.030	0.005	0.005
60-69.9	0.186	0.229	0.029	0.002	0.009	0.009
50-59.9	0.166	0.177	0.023	0.004	0.019	0.019
40-49.9	0.152	0.171	0.016	0.001	0.028	0.028

Abbreviations: FVC%pred, forced vital capacity percent predicted; GP, general practitioner.

Oxygen use

Patients with IPF should receive supportive long-term oxygen supplementation in case of resting hypoxemia. The cost of oxygen supplementation was estimated at £0.21 per hour, adjusted from an £1,813 annual cost (NHS Reference Costs 2010/11, value inflated to 2018/19 costs).

The three-month probabilities of incurring oxygen use costs for each FVC%pred group are shown in Table 54.

Table 54: Three-month probabilities of oxygen use

FVC%Pred	Three-month probability
≥110	0.141
100-109.9	0.160
90-99.9	0.166
80-89.9	0.147
70-79.9	0.265
60-69.9	0.329
50-59.9	0.465
40-49.9	0.569

Abbreviations: FVC%pred, forced vital capacity percent predicted.

The average hours of oxygen use per day and days of oxygen use (per patient) were 12.86 (SE: 1.25) and 51.21 (SE: 3.89) respectively (post hoc analysis of INBUILD data). (55)

Total follow-up cost synthesis

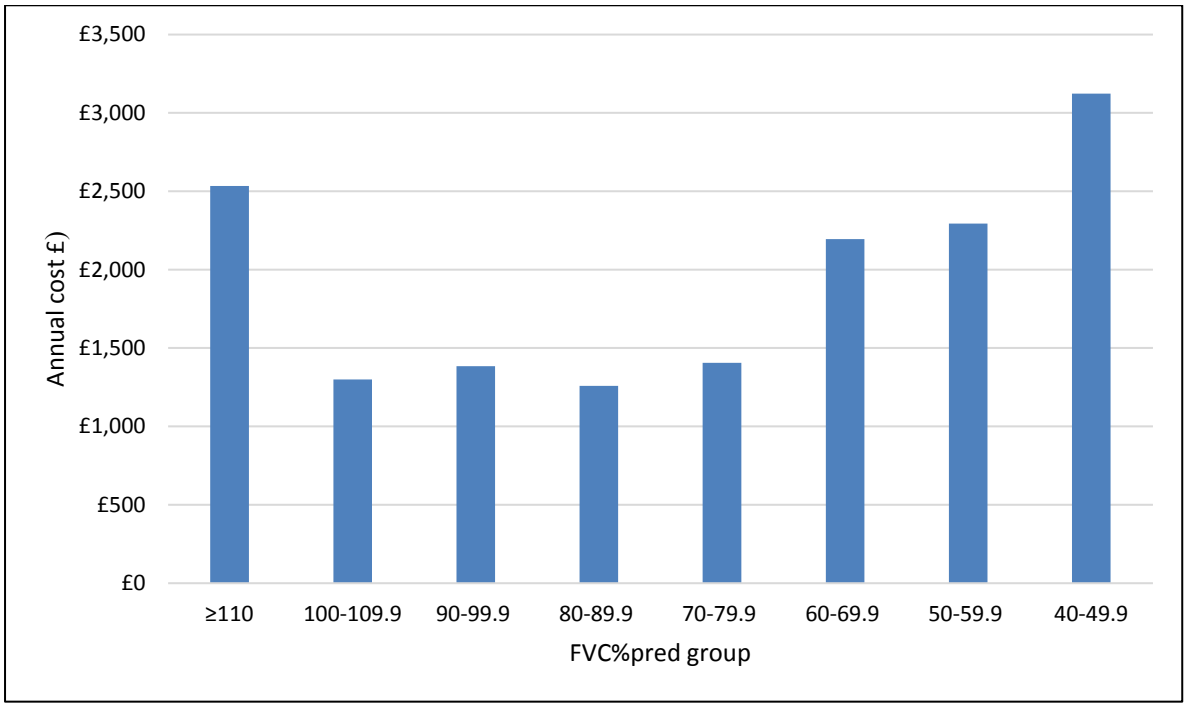
The summation of all follow-up costs (hospitalisation, ER visits, and oxygen use) produces the following total costs per FVC%pred group (Table 55). Figure 33 presents the trend in the costs by FVC%Pred category. As expected, the highest total cost was observed for the lowest FVC%Pred group. Note that the total costs were mainly driven by hospitalisations.

Table 55: Total cost per FVC%pred group

FVC%Pred	Per cycle	Annual
≥110	£633.40	£2,533.61
100-109.9	£324.73	£1,298.92
90-99.9	£345.91	£1,383.62
80-89.9	£314.57	£1,258.30
70-79.9	£351.25	£1,404.99
60-69.9	£548.71	£2,194.86
50-59.9	£573.55	£2,294.18
40-49.9	£780.79	£3,123.14

Abbreviations: FVC%pred, forced vital capacity percent predicted.

Figure 33: Total annual costs for each FVC%pred group



Adverse reactions

The majority of AEs were of mild or moderate nature (see Section B.2.10 Adverse reactions for AE details), were assumed to be resolved without treatment, and were without clinically significant consequences. The model assumed that the proportion of patients experiencing an AE within a three-month cycle would incur the cost of a general practitioner (GP) visit, with a unit cost of £39, defined as a per patient contact visit lasting 9.22 minutes. (90)

Liver function tests

Elevations of hepatic enzymes are a known side effect of nintedanib treatment. The frequencies of patients with adverse events related to increased hepatic enzymes were about four times higher in the nintedanib group (22.6%) than in the placebo group (5.7%). (37).

As a result, liver function tests were included for the nintedanib arm and were assumed to be routinely performed on patients receiving nintedanib. The cost per liver panel blood test was estimated at £2.79 (NHS Reference Costs 2018/19, Direct Access: Pathology Services: DAPS05 Haematology) (89) The model assumed that all patients on active treatment would incur this cost, at a quarterly frequency (every three months). The frequency aligns with the recommended maintenance test frequency by the nintedanib Summary of Product Characteristics, which states that hepatic transaminase and bilirubin levels should be investigated before treatment initiation and during the first month of treatment, and should then be monitored at regular intervals thereafter. (3)

Acute exacerbation costs

The unit cost associated with each acute exacerbation was based on a synthesis of a post-hoc analysis of INPULSIS trial data (92) to calculate three-month probabilities of a patient using an emergency room, visiting a general practitioner, and visiting a specialist following an acute exacerbation. Using patient-level data from the INPULSIS trials, a total exacerbation cost of £4,384 was added to all patients who experienced a new acute exacerbation, for each treatment arm – inflated from £4,134 (2014/2015 prices) to 2018/19 prices.

End of life costs

The nintedanib IPF model that was previously submitted to NICE assumed that patients received palliative care (in addition to background healthcare resources) as they reached the end of their life. This assumption, validated by clinicians, was maintained in the PF-ILD model. Therefore, within the model an end of life cost for the last year of a patient's life was applied. This cost was formed of secondary (acute) hospital care, local authority-funded social care, district nursing, and GP contacts and was estimated at £6,045 per cycle, adjusted for the 3-month cycle length (£3,785 for hospital care, £1,222 for local authority-funded social care, £249 for district nursing care and £125 for GP contacts – inflated to 2018/19 values). (94)

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

The base case model parameters are summarised in Table 56.

Table 56: Summary of variables applied in the economic model

Category	Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
General settings of the model	Age	65.80 years	Fixed	B.3.2
	Cycle length (days)	91.25	Fixed	
	Cycle length (year)	0.25	Fixed	
	Discount rate - effect	3.5%	Fixed	
	Discount rate - cost	3.5%	Fixed	
	WTP	£20,000	Fixed	
Proportion of patients at each starting FVC%Pred	≥110 FVC%Pred group	0.01	Fixed	
	100-109.9 FVC%Pred group	0.02	Fixed	
	90-99.9 FVC%Pred group	0.07	Fixed	
	80-89.9 FVC%Pred group	0.14	Fixed	
	70-79.9 FVC%Pred group	0.20	Fixed	

Category	Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
	60-69.9 FVC%Pred group	0.25	Fixed	
	50-59.9 FVC%Pred group	0.21	Fixed	
	40-49.9 FVC%Pred group	0.09	Fixed	
Efficacy	OS (PBO and NDB)	Time dependent	N/A	B.3.3
	Time to first exacerbation (PBO)	8.55	8.21, 8.88 (CI)	
	Time to first exacerbation (NDB)	9.00	8.59, 9.40 (CI)	
	Loss of lung function: baseline risk (PBO)	(See section B 3.3)	N/A	
	Loss of lung function: OR (NDB vs PBO)	0.65	0.42, 1.02 (CI)	
Risk per cycle (diarrhoea)	PBO arm	4.80%	Fixed	B.3.3
	NDB arm	20.05%	Fixed	
Risk per cycle (nausea)	PBO arm	1.47%	Fixed	
	NDB arm	6.59%	Fixed	
Risk per cycle (vomiting)	PBO arm	0.53%	Fixed	
	NDB arm	3.25%	Fixed	
Risk per cycle (alanine aminotransferase increase)	PBO arm	0.61%	Fixed	
	NDB arm	2.84%	Fixed	
NDB discontinuation	Probability NDB arm	6.16%	5.13%. 7.37% (CI)	B.3.3
Phase III INBUILD trial post-hoc HCRU analysis: Resource use intensity	Frequency of liver function test (per cycle)	1	0.50, 1.50 (CI)	B.3.5
	Number of hospitalisations	1.35	0.92, 1.78 (CI)	
	Average duration of each hospitalisation	10.74	9.52, 11.96 (CI)	
	Proportion in ICU	5.1%	2.9%, 7.3% (CI)	
	Proportion with mechanical ventilation	2.1%	0.7%, 3.6% (CI)	

Category	Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
	Proportion associated with ER overnight	7.8%	5.1%, 10.5% (CI)	
	Proportion associated with ambulance use (hospital)	18.5%	14.6%, 22.4% (CI)	
	Number of GP visits	1.50	0.50, 2.49 (CI)	
	Number of specialist visits	1.61	0.94, 2.29 (CI)	
	Number of nurse visits	0.18	0.08, 0.28 (CI)	
	Number of physiotherapist visits	0.07	0.00, 0.24 (CI)	
	Number of other visits	0.13	0.00, 0.34 (CI)	
	Number of occupational visits	0.13	0.00, 0.34 (CI)	
	Oxygen use (days)	54.21	43.58, 58.83 (CI)	
	Oxygen use (hours)	12.86	10.41, 15.32 (CI)	
	Exacerbations – number of hospitalisations	1.30	0.95, 1.65 (CI)	
	Exacerbations – average duration of each hospitalisation	16.30	7.05, 25.55 (CI)	
Treatment cost	BSC daily cost	£0.00	Fixed	B.3.5
	NBD daily cost	[redacted]	Fixed	
Liver function test cost	Liver function test cost	£2.79	£1.40, £4.19 (CI)	B.3.5
Adverse events cost	Diarrhoea	£39.00	£19.50, £58.50 (CI)	B.3.5
	Nausea	£39.00	£19.50, £58.50 (CI)	
	Vomiting	£39.00	£19.50, £58.50 (CI)	
	Alanine aminotransferase increase	£0.00	£0.00, £0.00 (CI)	
Resource use cost	Hospitalisation	£323.88	Fixed	B.3.5
	ICU stay	£1072.78	Fixed	
	Mechanical ventilation	£160.85	Fixed	

Category	Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
	ER overnight stay	£268.00	Fixed	
	Ambulance use	£224.39	Fixed	
	ER visit	£182.85	Fixed	
	Ambulance use	£224.39	Fixed	
	GP	£39.00	Fixed	
	Specialist	£109.00	Fixed	
	Nurse	£46.00	Fixed	
	Physiotherapist	£45.00	Fixed	
	Occupational therapy	£45.00	Fixed	
	Other visits	£109.00	Fixed	
	Oxygen use (annual cost)	£1,813.44	Fixed	
Baseline health state cost (per cycle)	≥110 FVC%Pred group	£633.40	Fixed	B.3.5
	100-109.9 FVC%Pred group	£324.73	Fixed	
	90-99.9 FVC%Pred group	£345.91	Fixed	
	80-89.9 FVC%Pred group	£314.57	Fixed	
	70-79.9 FVC%Pred group	£351.25	Fixed	
	60-69.9 FVC%Pred group	£548.71	Fixed	
	50-59.9 FVC%Pred group	£573.55	Fixed	
	40-49.9 FVC%Pred group	£780.79	Fixed	
Exacerbation cost	Acute event	£4,368.83	£3,058, £5,679 (CI)	B.3.5
EoL cost	EoL cost	£6,045.15	£4,232, £7,859 (CI)	B.3.5
Baseline utility values	≥110 FVC%Pred group	0.7521	0.68, 0.78 (CI)	B.3.4
	100-109.9 FVC%Pred group	0.7521	0.68, 0.78 (CI)	
	90-99.9 FVC%Pred group	0.7287	0.68, 0.78 (CI)	
	80-89.9 FVC%Pred group	0.7333	0.70, 0.77 (CI)	
	70-79.9 FVC%Pred group	0.7242	0.70, 0.75 (CI)	
	60-69.9 FVC%Pred group	0.6750	0.65, 0.70 (CI)	

Category	Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
	50-59.9 FVC%Pred group	0.6453	0.62, 0.67 (CI)	
	40-49.9 FVC%Pred group	0.6045	0.56, 0.65 (CI)	
Exacerbations disutility	1st month	-0.1670	-0.27, 0.09 (CI)	B.3.4
Treatment-related adverse events disutility	Diarrhoea	-0.0340	-0.02, -0.05 (CI)	B.3.4
	Nausea	-0.0340	-0.02, -0.05 (CI)	
	Vomiting	-0.0340	-0.02, -0.05 (CI)	
	Alanine aminotransferase increase	0.0000	Fixed	

Abbreviations: CI, 95% confidence interval; EoL, end of life; ER, emergency room; FVC% Pred, forced vital capacity percent predicted; GP, general practitioner; ICU, intensive care unit; NDB, nintedanib; OR, odds ratio; OS, overall survival; PBO, placebo; SE, standard error; WTP, willingness to pay.

Assumptions

The assumptions adopted in the analysis are summarised and justified in Table 57.

Table 57: Summary of assumptions in the analysis

Model Input	Assumption	Source/Rationale
Cycle length	The model cycle length was 3-months	The cycle length was selected to be consistent with the clinical trial intervals between observations and was considered a balanced interval for the model outcomes.
BSC model inputs	Efficacy and safety were assumed to be represented by the events observed in control (PBO) arm of the (phase III and phase II) NDB clinical trials.	Since the perspective of the economic evaluation was the incremental cost-effectiveness of NDB vs. BSC, it was assumed that the efficacy and safety of BSC was reflected by the observed outcomes of the PBO arm of the trial.
Survival analysis implementation	Survival analysis extrapolation was assumed to be applied for the full duration of the economic model; that also included the first year of the analysis where clinical trial data were available.	This allowed a more robust representation of uncertainty from the trial results and a formal exploration via a probabilistic sensitivity analysis.
Baseline mortality risk	It was assumed that death could occur at the point that patients reached a level of FVC%Pred of 30-39.9%.	Previous analyses within the IPF population have included an assumption that life is unsustainable once FVC%Pred drops below a certain level. For example, in the UK NICE IPF

Model Input	Assumption	Source/Rationale
		Clinical Guideline (CG163) a threshold of 35% FVC%Pred was applied. Values of 40% have also been applied in previous HTA submissions. (52, 56) Due to similarities between IPF and PF-ILD it was assumed that a similar assumption would be applicable for the PF-ILD population.
Definition of baseline disease progression / loss of lung function	Baseline disease progression was defined as a 10-point drop in FVC%Pred every month (constant risk).	According to many studies the MCID for FVC%Pred ranged between a 2-6% change, or a 10% change. (16, 68) Therefore, it was decided that a 10-point categorization of FVC%Pred was a balanced range to capture granularity of outcomes without overcomplicating the model. Additionally, a 10% change was adopted in the NDB NICE submission for IPF. (52) As described above, IPF assumptions are judged to be applicable to the PF-ILD population.
Progression / loss of lung function	It was assumed that once progressed to a lower FVC%Pred the cohort could not regress back to health states with improved lung function (higher FVC%Pred). NDB patients were assumed to revert to BSC transition probabilities for lung function decline once they discontinued treatment.	Similar assumptions were made in the UK NICE model for PFN and NDB in IPF. (52, 57) As described above, IPF assumptions are judged to be applicable to the PF-ILD population. It was conservatively assumed that any treatment effect would cease as soon as treatment was discontinued.
Exacerbation risk	Exacerbation was assumed to be a constant hazard every month (exponential model).	Several parametric models were considered based on INBUILD trial data. Considering the AIC values and model parsimony, the exponential model was selected.
Effect of exacerbations on mortality and progression	A link between exacerbation and mortality was not included in the model. It was assumed that exacerbation led to a faster loss of lung function in the base-case analysis based on distinct transition probabilities	The effect of exacerbations on mortality was previously explored, but illogical results were obtained. The occurrence of an acute exacerbation was found to be a significant predictor of lung

Model Input	Assumption	Source/Rationale
	with and without an exacerbation.	function during the logistic regression (see Table 39).
Baseline discontinuation risk	Baseline discontinuation was assumed to have a constant hazard every month (exponential model).	Several parametric models were considered based on INBUILD trial data. However, the exponential distribution was selected to simplify the model calculations.
Use of clinical data for discontinuation	The model used clinical trial data for time-to-discontinuation for the NDB (rather than real-world data).	Since NDB is a new treatment for PF-ILD, there is a lack of evidence on treatment tolerability and discontinuation in real life. In the model this was based on rates observed within the investigation trials. This is likely to underestimate "real-world" discontinuation.
Applying OR values to the baseline (PBO) risk – relative treatment effects (NDB)	The relative effect of NDB was assumed to be informed using the OR value estimated from a mixed effect logistic regression model with treatment as a predictor.	The completion of a mixed effect logistic regression model allows for an examination of whether NDB is significantly superior to PBO as a treatment in the context of the model transition probabilities. The regression analysis indicates that NDB approached significance (p=0.0602). Therefore, a treatment effect was modelled in the base case and the uncertainty was explored further in the sensitivity analysis.
	The same relative effects (OR) were applied to the baseline risks, independent of time.	There was a lack of information to explore the analysis of different ORs over time or other time-dependencies.
	Three-month estimates of baseline risk were synthesised in the model with approximately 1-year estimates of relative efficacy from the clinical trials. In effect the analysis assumed that the relative difference observed across the comparators at the end of the trial, was constant and would hold for the intermediate intervals (3 months).	This was consistent with the assumptions made regarding a constant relationship of relative effects over time.
Adverse events	AEs were included if they met each of the following criteria: common (i.e. incidence of >10% in either treatment arm), treatment-related/treatment-emergent, incidence in the	This was to focus on adverse events that had the potential to have a meaningful impact on the overall cost-effectiveness results.

Model Input	Assumption	Source/Rationale
	treatment arm had to be at least 1.5 times higher than in the control arm.	
Liver enzyme elevations	These events were assumed to be asymptomatic for patients. The model assumed that when these events were detected (with appropriate liver function tests), they contributed only to the overall discontinuation from treatment, and that there was no disutility or additional costs associated with them.	Simplifying assumption; in clinical practice patients would discontinue treatment – an outcome analysed separately in the model.
Risk of bleeding	The risk of bleeding was not included in the cost-effectiveness model.	Because all NDB clinical trials excluded patients with high risk of bleeding, the risk for further analysis could not be quantified or assessed.
BSC daily treatment cost	No treatment cost was assumed for the BSC arm.	An analysis on concomitant medications taken within INBUILD showed a small difference between trial arms (PBO and NDB).
Liver function test frequency	The model assumed that all patients on active treatment would incur the cost of liver function test, at a quarterly frequency (every 3 months, i.e. every 3rd cycle).	Frequency schedule was the same with the maintenance test frequency recommended by the PFN SPC [medicines.ie accessed July 2015]
End of life	It was assumed that patients received palliative care (in addition to background health care resources) as they reached the end of their life. The model applied an end of life (EoL) cost for the three months (i.e. one cycle) of patients' life.	Clinical experts advised that palliative care is an important aspect of people's end of life care. Since this is a lifetime model, it does drive the incremental CE results.
Use of clinical trial EQ-5D and HCRU data	The correlation of lung status and patient condition (health state) with HRQL (in the form of EQ-5D) and resource use was based on INBUILD post-hoc analyses. The analysis assumed that the results of the clinical trial in terms of EQ-5D and resource use are generalisable for the UK population.	This was the only available evidence to perform such an analysis for PF-ILD patients.
Baseline EQ-5D value for FVC%Pred ≥110	Assumed the same utility value as for FVC%pred 100 - 110.	The utility value for FVC%Pred ≥110 patients was actually lower (0.7028 vs 0.7521). However, the value was based on a very small sample size (n=10). Additionally, two

Model Input	Assumption	Source/Rationale
		clinicians confirmed that patient HRQoL would not be lower in patients with a FVC%Pred ≥110.
Exacerbation-related disutility values	Exacerbations were assumed to be acute events that affect the health state of the patients. It was assumed that patients experienced an acute phase in the 1st month and a post-acute phase (in the following 2+ months), following an exacerbation.	This assumption was supported by the analysis of INBUILD EQ-5D data (55)[INBUILD post-hoc analysis].

Abbreviations: AE, adverse event; EoL, end of life; NDB, nintedanib; BSC, best supportive care; FVC% Pred, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis; OR, odds ratio.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

The base-case deterministic results of nintedanib vs BSC are presented in Table 58. The total costs for the nintedanib and BSC arms were [redacted] and [redacted] respectively. The total QALYs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with an incremental QALY gain of [redacted] associated with nintedanib. The incremental LYs gained due to nintedanib treatment were [redacted] over the modelled time horizon. Patients receiving treatment with nintedanib experienced an additional 0.0817 exacerbations over the duration of the model.

Table 58: Deterministic results for nintedanib vs BSC

	NDB	BSC	Incremental
Costs			
Treatment costs	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]
Liver panel tests	[redacted]	[redacted]	[redacted]
Patient monitoring and O2 use	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
Exacerbation events	[redacted]	[redacted]	[redacted]

	NDB	BSC	Incremental
Net monetary benefit	[redacted]	[redacted]	[redacted]
Cost-effectiveness	[redacted]	[redacted]	[redacted]
ICER (per QALY)			**<£20,000** [redacted]
ICER (per LY)			**<£20,000** [redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life-year; NDB, nintedanib; QALY, quality-adjusted life year.

Figure 34 presents the analysis of total costs over the entire model duration.

Figure 34: Base-case total costs (nintedanib and BSC)

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

In order to explore uncertainty around the key model variables in the base case, probabilistic sensitivity analysis (PSA) was performed (1,000 iterations). Table 59 below presents the parameters included in the PSA, along with their assumed distributions and standard error or range.

Table 59: Probabilistic sensitivity analysis - parameter inputs

Variable	Variance	Sources/assumption
Transitions		
OS (PBO and NDB)	Multivariate normal	Cholesky decomposition applied – see Table 32 and Table 33
Exacerbations (PBO)	Beta (α=33.80, β=1887.10)	Based on 95% CI (0.024, 0.013)
Exacerbations (NDB)	Beta (α=21.79, β=1916.32)	Based on 95% CI (0.017, 0.007)

Variable	Variance	Sources/assumption
Loss of lung function - PBO	Multivariate Normal	Cholesky decomposition applied – see Table 40
Loss of lung function - NDB	Lognormal (mean OR = 0.654)	LLCI = 0.420, HLCI = 1.108
Discontinuation	Beta (α=108.945, β=1660.737)	Based on 95% CI (7.083, 7.457)
Resource use		
Number of hospitalisations	Lognormal (mean = 1.35, SE = 0.221)	LLCI = 0.92, HLCI = 1.78 (resource use calculations)
Average duration of each hospitalisation	Lognormal (mean = 10.74, SE = 0.621)	LLCI = 9.52, HLCI = 11.96 (resource use calculations)
Proportion in ICU	Beta (α=18.95, β=353.05)	LLCI = 0.03, HLCI = 0.07 (resource use calculations)
Proportion with mechanical ventilation	Beta (α=7.98, β=364.02)	LLCI = 0.01, HLCI = 0.04 (resource use calculations)
Proportion associated with ER overnight	Beta (α=28.92, β=343.08)	LLCI = 0.05, HLCI = 0.10 (resource use calculations)
Proportion associated with ambulance use (hospital)	Beta (α=68.82, β=303.19)	LLCI = 0.15, HLCI = 0.22 (resource use calculations)
Average number of ER visits	Lognormal (mean = 1.21, SE = 0.113)	LLCI = 0.99, HLCI = 1.43 (resource use calculations)
Number of GP visits	Lognormal (mean = 1.50, SE = 0.507)	LLCI = 0.50, HLCI = 2.49 (resource use calculations)
Number of specialist visits	Lognormal (mean = 1.61, SE = 0.344)	LLCI = 0.94, HLCI = 2.29 (resource use calculations)
Number of nurse visits	Lognormal (mean = 0.18, SE = 0.051)	LLCI = 0.08, HLCI = 0.28 (resource use calculations)
Number of physiotherapist visits	Lognormal (mean = 0.07, SE = 0.088)	LLCI = 0.00, HLCI = 0.24 (resource use calculations)
Number of other visits	Lognormal (mean = 0.13, SE = 0.105)	LLCI = 0.00, HLCI = 0.34 (resource use calculations)
Number of occupational visits	Lognormal (mean = 0.13, SE = 0.105)	LLCI = 0.00, HLCI = 0.34 (resource use calculations)
Oxygen use (days)	Lognormal (mean = 51.21, SE = 3.890)	LLCI = 43.58, HLCI = 58.83 (resource use calculations)
Oxygen use (hours)	Lognormal (mean = 12.86, SE 1.253)	LLCI = 10.41, HLCI = 15.32 (resource use calculations)
Exacerbations – number of hospitalisations	Lognormal (mean = 1.3, SE = 0.180)	LLCI = 0.95, HLCI = 1.65 (resource use calculations)
Exacerbations – average duration of each hospitalisation	Lognormal (mean = 16.30, SE = 4.720)	LLCI = 7.05, HLCI = 22.55 (resource use calculations)
Unit costs		
Liver function test frequency	Gamma (α=15.37, β=0.07)	LLCI = every 6 months HLCI = every 2 months
Diarrhoea	Lognormal (mean = £39)	LLCI = £19.50

Variable	Variance	Sources/assumption
Nausea	Lognormal (mean = £39)	HLCI = £58.50
Vomiting	Lognormal (mean = £39)	
Exacerbation: acute event	Lognormal (mean = £4,369, SE = 668.60)	LLCI = £3,058 HLCI = £5,679
EoL cost	Lognormal (mean = £6,045.15, SE = 925.28)	LLCI = £4,232 HLCI = £7,859
Baseline utility values		
≥110 FVC%Pred group	Fixed	Assumption, same as 100-109.9 FVC%Pred group
100-109.9 FVC%Pred group	Beta (α=62.96, β=20.76)	INBUILD baseline utility values
90-99.9 FVC%Pred group	Beta (α=210.26, β=78.28)	
80-89.9 FVC%Pred group	Beta (α=503.66, β=183.15)	
70-79.9 FVC%Pred group	Beta (α=692.39, β=263.64)	
60-69.9 FVC%Pred group	Beta (α=726.80, β=349.96)	
50-59.9 FVC%Pred group	Beta (α=752.61, β=413.62)	
40-49.9 FVC%Pred group	Beta (α=327.29, β=214.18)	
Exacerbation disutility		
Exacerbation disutility	Beta (α=10.35, β=51.62)	INBUILD clinical trial
Adverse event disutility		
Diarrhoea	Beta (α=15.42, β=438.17)	INBUILD clinical trial
Nausea	Beta (α=15.42, β=438.17)	
Vomiting	Beta (α=15.42, β=438.17)	

Abbreviations: AE, adverse event; CI, confidence interval; CT, computed tomography; ER, emergency room; FVC%Pred, forced vital capacity percentage predicted; GP, general practitioner; HLCL, higher level confidence interval; ICU, intensive care unit; LLCL, lower level confidence interval; NDB, nintedanib; OS, overall survival; PBO, placebo; PFN, pirfenidone; SD, standard deviation; SE, standard error.

Table 60 shows that incremental costs for nintedanib vs. BSC are similar between the deterministic and average PSA results. Although the average PSA sample value for incremental QALYs is slightly higher than the deterministic value, Table 61 shows that the check row is very close to one for both the nintedanib and BSC arms. The check row is the ratio of the deterministic result vs. the probabilistic average. It can also be seen that the total QALY samples are 0.0125 lower than the deterministic values for nintedanib and 0.0087 higher than the deterministic values for BSC. This comes to a 0.0211 difference, which explains the difference between the incremental average of samples and the incremental deterministic incremental QALY.

Table 60: PSA results for nintedanib vs. BSC

	Incremental Cost	Incremental QALY	ICER
Deterministic	[redacted]	[redacted]	<£20,000 [redacted]
Average value from PSA	[redacted]	[redacted]	<£20,000 [redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; NDB, nintedanib; BSC, best supportive care; QALY, quality-adjusted life-year.

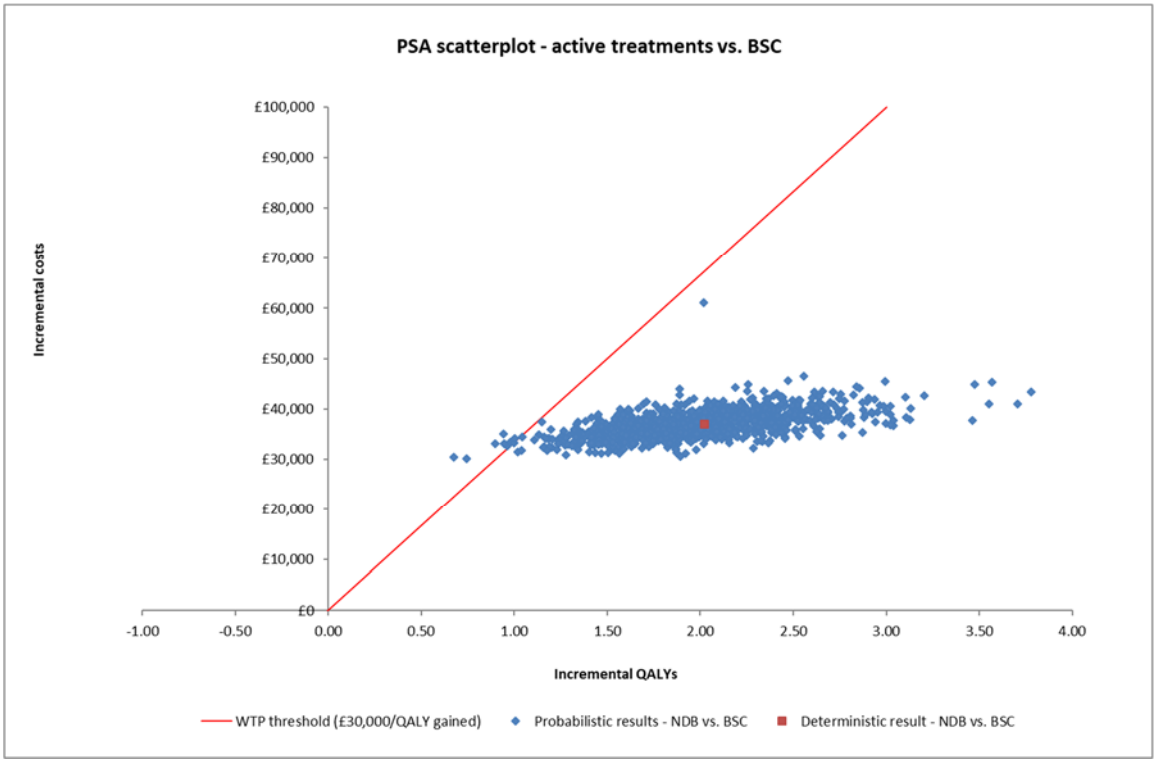
Table 61: QALY results for nintedanib and BSC

	NDB	BSC	Incremental (NDB – BSC)
Deterministic analysis	[redacted]	[redacted]	[redacted]
Average of samples	[redacted]	[redacted]	[redacted]
Variance	[redacted]	[redacted]	[redacted]
Standard error	[redacted]	[redacted]	[redacted]
Lower limit	[redacted]	[redacted]	[redacted]
Upper limit	[redacted]	[redacted]	[redacted]
Check	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; NDB, nintedanib; QALY, quality-adjusted life-year.

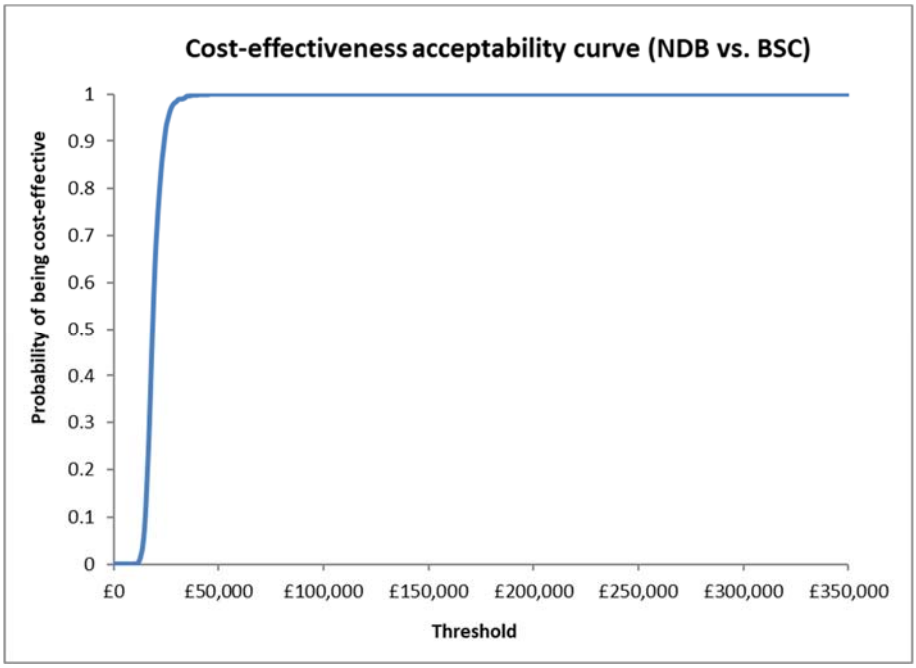
The result of the PSA (1,000 samples) is presented in Figure 35. The scatter-plot indicates that nintedanib is more likely to be cost effective than BSC at a NICE willingness-to-pay threshold of £30,000.

Figure 35: Incremental cost-effectiveness scatter-plot (nintedanib vs. BSC)



The cost-effectiveness acceptability curve (CEAC) is presented in Figure 36. The CEAC shows that there is a 66% and 98% probability that nintedanib will be cost-effective when compared against BSC at the NICE willingness to pay thresholds of and £20,000 and £30,000 respectively.

Figure 36: CEAC (nintedanib vs BSC)



The results from the PSA are comparable with the deterministic results (Table 62).

Table 62: Deterministic results vs. probabilistic results, nintedanib vs. BSC

Intervention/comparator	Total costs	LYs	QALYs	ICER (per QALY)
Deterministic analysis				
Nintedanib	[redacted]	[redacted]	[redacted]	<£20,000
BSC	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic analysis				
Nintedanib	[redacted]	[redacted]	[redacted]	<£20,000
BSC	[redacted]	[redacted]	[redacted]	[redacted]

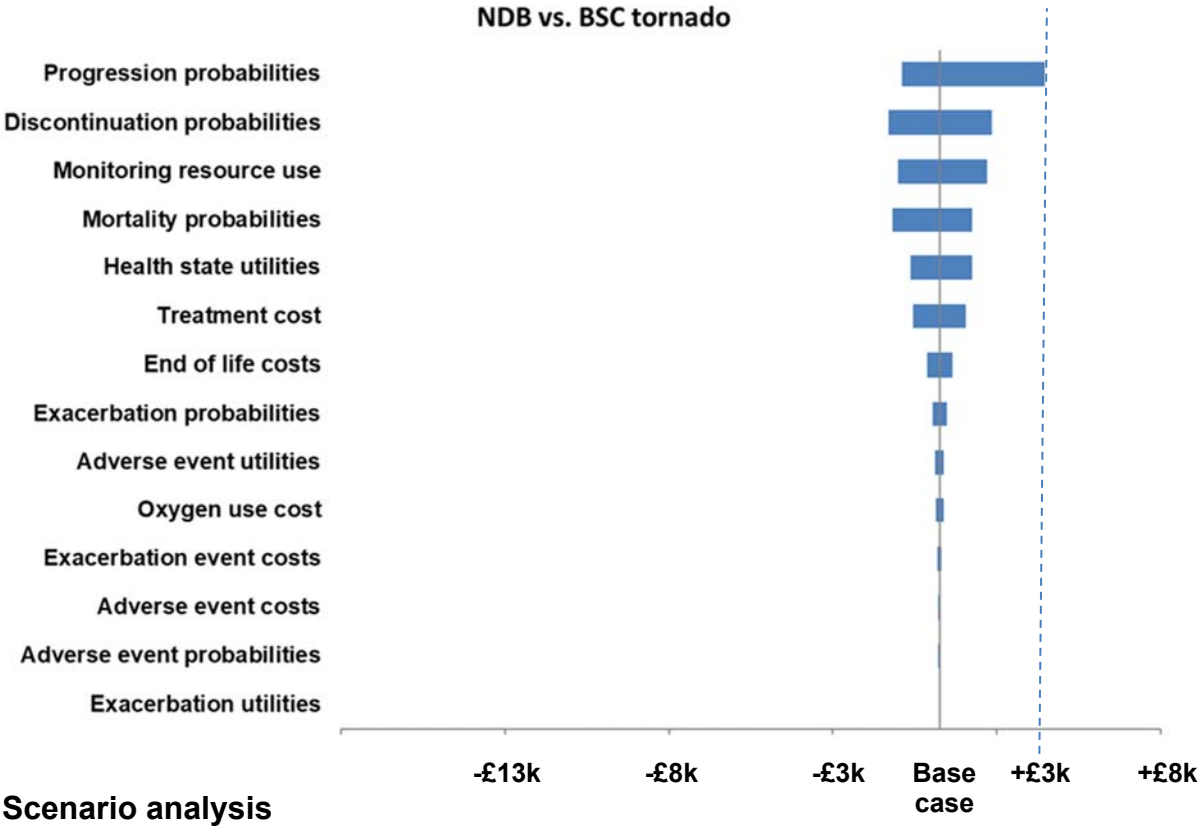
Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; LY, life-year; NDB, nintedanib; PFN, pirfenidone; QALY, quality-adjusted life year.

Deterministic sensitivity analysis

The sensitivity of the model results and drivers of cost-effectiveness were explored within deterministic sensitivity analysis. Tests were performed around the higher and

lower confidence intervals of all model parameters to highlight the parameters that the model results are most sensitive to (Table 59). The results of the deterministic sensitivity analysis are presented in Figure 37. The progression probabilities are the primary driver of cost-effectiveness when all else remain constant at base case settings, and raise the ICER by ~ £3,000 per QALY to approximately [redacted] when varied to the highest confidence interval. The discontinuation and mortality probabilities, resource use associated with patient monitoring and health state utilities also cause some variation in the model results. However, no inputs caused the ICER to raise above the NICE threshold of £30,000 when varied.

Figure 37: Tornado diagram (NDB vs BSC)



Scenario analysis

The assumptions tested to determine the sensitivity of the model results are presented in Table 63 and Table 64.

Overall survival

The distributions used to model overall survival were varied to analyse the variation in cost-effectiveness results when alternative parametric distributions are used to model overall survival, as presented in Table 63.

Table 63: Scenario analysis for OS

Scenario	Parameter varied
1	Gamma – Bayesian distribution (NDB and BSC)
2	Log logistic – Bayesian distribution (NDB and BSC)
3	Weibull – Frequentist distribution (NDB and BSC)
4	Log logistic – Frequentist distribution (NDB and BSC)
5	Gompertz – Frequentist distribution (NDB and BSC)

Abbreviations: BSC, best supportive care; NDB, nintedanib

Utility values

The utility values in the base-case trial were informed from the INBUILD clinical trial (55). In this scenario, the utility inputs were populated using data informed from the IPF INPULSIS trial, as presented in Table 64. The results of the INPULSIS trial indicate higher utility values for all health states. As described previously, IPF and PF-ILD are believed to share similar pathophysiologies so the impact of adopting IPF-specific values was explored.

Table 64: Scenario analysis for utility values

Scenario	FVC% value	Parameter varied	SD
6	≥110	0.8380	0.1782
	100-109.9	0.8380	0.1782
	90-99.9	0.8380	0.1782
	80-89.9	0.8105	0.2051
	70-79.9	0.7800	0.2244
	60-69.9	0.7657	0.2380
	50-59.9	0.7387	0.2317
	40-49.9	0.6634	0.2552

Abbreviations: FVC%Pred: forced vital capacity percentage predicted; SD: standard deviation.

Discontinuation rate

As noted above, Lancaster (2019) report a median time on treatment of 22.5 months, which is lower than the current model predictions (28 to 29 months) (80). Discontinuation was determined by an exponential curve, which was used to predict a discontinuation rate of 5.97% per cycle.

Through a process of trial and error the exponential coefficient was adjusted until an exponential curve was generated that resulted in a median survival of 22.5 months. This was based on a discontinuation rate of 7.67% per cycle and the resulting discontinuation curve is presented in Figure 38.

Additionally, despite the available data from Lancaster 2019, the model base case may actually overestimate the discontinuation rate for nintedanib. This can be seen in Figure 38 as both curves do not provide a good visual match to the end of the KM curve from INBUILD. Therefore, an additional scenario was modelled in which a discontinuation rate was inputted that allowed the long-term predictions to more closely match the tail of the INBUILD KM curve.

A discontinuation rate of 3.97% was chosen by trial and error and the model predictions with this rate, compared with the INBUILD KM data, are presented in Figure 39. It should be noted that when this alternative discontinuation rate is applied the model predictions during the first two years of the model do not provide a good visual match to the INBUILD KM data.

Figure 38: Alternative discontinuation rate to match data from Lancaster 2019 (80) and comparison with INBUILD extrapolations

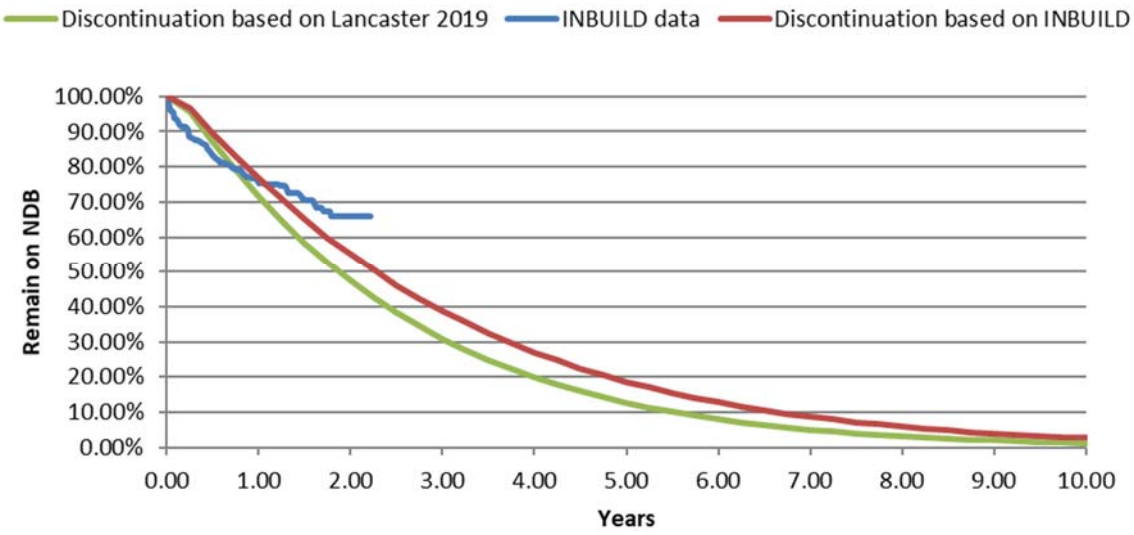
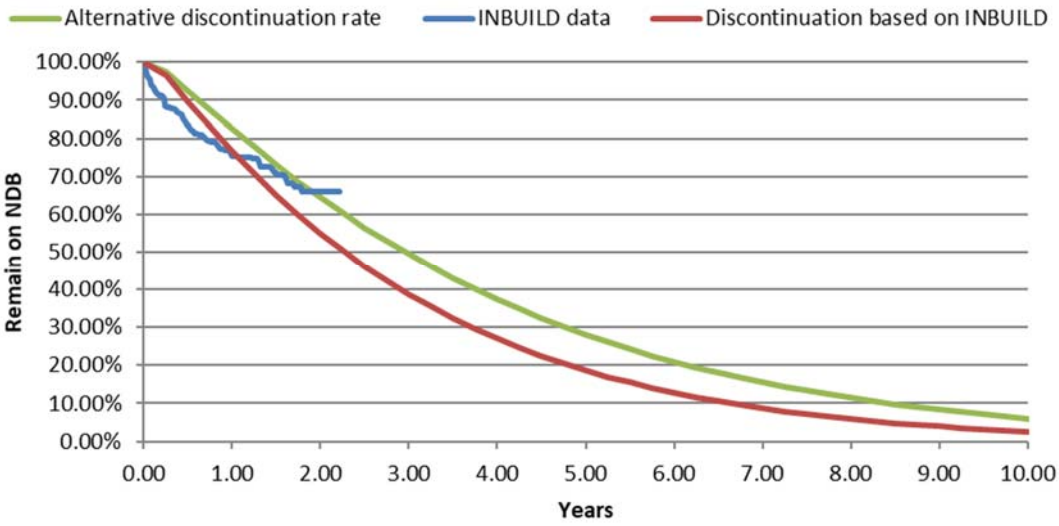


Figure 39: Alternative discontinuation rate to more closely match the tail of the INBUILD Kaplan-Meier curve and comparison with INBUILD extrapolations



Results from scenario analyses

The results of the scenario analyses are presented in Table 65.

Table 65: Scenario analyses: cost-effectiveness results

Scenario	Description	Incremental cost	Incremental QALY	ICER
1	Gamma – Bayesian distribution (NDB and BSC)	[redacted]	[redacted]	<£25,000 [redacted]
2	Log logistic – Bayesian distribution (NDB and BSC)	[redacted]	[redacted]	<£20,000 [redacted]
3	Weibull – Frequentist distribution (NDB and BSC)	[redacted]	[redacted]	<£30,000 [redacted]
4	Log logistic – Frequentist distribution (NDB and BSC)	[redacted]	[redacted]	<£20,000 [redacted]
5	Gompertz – Frequentist distribution (NDB and BSC)	[redacted]	[redacted]	>£30,000 [redacted]
6	Alternative utility values	[redacted]	[redacted]	<£20,000 [redacted]
7	Discontinuation to match Lancaster 2019 study	[redacted]	[redacted]	<£20,000 [redacted]
8	Discontinuation to match INBUILD KM data	[redacted]	[redacted]	<£25,000 [redacted]

Abbreviations: BSC, best supportive care; ICER; KM, Kaplan-Meier, incremental cost-effectiveness ratio; NDB, nintedanib, QALY: quality-adjusted life year.

Nintedanib is associated with greater incremental costs and incremental QALYs than BSC in all of the scenarios considered. Scenarios two, six and seven result in a

reduction in the ICER from the base-case analysis. Nintedanib is not cost-effective compared to BSC at a cost-effectiveness threshold of £30,000 when the Gompertz frequentist curves are used to model OS, as this scenario produced an ICERs >£30,000 ([redacted]). As noted below, this scenario is not clinically plausible.

Summary of sensitivity analyses results

The probabilistic results generated are similar to the base case analysis, with an average ICER of <£20,000 [redacted]). The incremental costs for nintedanib vs BSC are [redacted] higher for the PSA results than the deterministic results. The incremental QALYs for nintedanib vs BSC are [redacted] lower for the PSA results than the deterministic results.

The results of the deterministic sensitivity analysis suggest that the results were most sensitive to a variation in progression probabilities when all else remain constant at base case settings. Variation in progression probabilities to the highest confidence interval raises the ICER by ~£3,000 to approximately [redacted]. The discontinuation and mortality probabilities, resource use associated with patient monitoring and health state utilities also cause some variation in the model results. However, no inputs caused the ICER to raise above the NICE threshold of £30,000 when varied.

The results of the scenario analyses are summarised in Table 65. Overall, the results of the scenario analysis indicate that the results of the base case analysis are robust as the changes implemented as part of these scenarios had a small impact on the overall results, with the exception of scenario five. Nintedanib is not cost-effective compared to BSC when the Gompertz frequentist curves are used to model OS. However, as described previously, the use of the Gompertz distribution was not deemed to be externally valid based on the clinician feedback as they noted the extrapolations with this distribution were overly pessimistic for both treatment arms. Additionally, scenarios two, six and seven resulted in a reduction in the ICER from the base-case analysis.

B.3.9 Subgroup analysis

No sub-group analysis was undertaken as cost-effectiveness analyses, including the base case and sensitivity analyses, indicate that use of nintedanib in the overall

population is likely to be cost-effective. In addition, there is no evidence that clinical outcomes are significantly different across any subgroups specified in the INBUILD trial, with consistent results seen across all pre-specified groups (see Appendix E).

B.3.10 Validation

Validation of cost-effectiveness analysis

The internal validity of the model was examined via a two-step process. Firstly, a cell-by-cell check of all model formulae was undertaken to ensure they were both correct and appropriately applied. Secondly, a model verification checklist was used, which includes a range of tests, including sense checks, for instance, changing certain inputs to zero and checking that the observed effect was as expected (i.e. illogical results were not generated). This internal validation process was undertaken by a health economist who was not directly involved in the conceptualisation and development of the model.

The face validity of the model was also examined during the UK Advisory Board. This was achieved by describing the model structure and inputs to UK clinical experts to ensure the suggested approach appropriately captured costs and outcomes for UK clinical practice. Specific revisions were made to the model upon the advice received.

As aforementioned in Section B.3.3, five clinical experts were approached to validate the assumptions within the model during a teleconference held on the 11th November 2020. The clinicians validated the overall survival extrapolations and agreed that the Weibull Bayesian may be the most appropriate choice for both treatment arms. The overall survival curves were also compared with relevant data identified in the wider literature.

Due to a lack of previous economic models in this indication, it was not possible to examine the external validity of the model by comparing the results.

B.3.11 Interpretation and conclusions of economic evidence

The economic evaluation considered adults with chronic fibrosing ILD with a progressive phenotype, i.e. PF-ILD. This reflects the marketing authorisation for nintedanib which was based on the results of the INBUILD phase III trial. This also

reflects the population included in the final NICE scope. The key drivers of the economic model are: the mortality, progression and discontinuation probabilities, the health state utilities and monitoring resource use.

Strengths and weaknesses of the evaluation

A key strength of the economic evaluation is that it is populated with evidence collected from the INBUILD study, which was an international, prospective, double-blind, placebo-controlled randomised controlled trial evaluating the efficacy and safety of nintedanib for patients with PF-ILD. This enabled the use of robust clinical evidence in conjunction with economic evidence from the same source.

The model structure was designed taking into account feedback following a previous submission of nintedanib to NICE within the IPF population. During this appraisal, the Evidence Review Group judged the model structure to be appropriate and also superior to an approach adopted in a previous submission in IPF for pirferidone. As described previously, IPF and PF-ILD share similar pathophysiologies and, therefore, it was judged that this previous model structure would be applicable to the PF-ILD population.

The main weakness of the economic evaluation is that there is limited information regarding the general trajectory of patient survival, progression and impact of co-morbidities associated with PF-ILD. In particular, immature data regarding overall survival was available from the INBUILD trial, which increased uncertainty around the model results. However, the overall survival curves used in the base case analysis were assessed for external validity by clinicians at an advisory board and compared with relevant data in the wider literature. Additionally, longer-term survival data for nintedanib from the IPF population were included in the survival curve predictions using a Bayesian analysis to improve the robustness of these predictions.

The resource use values to estimate all background costs relating to PF-ILD (e.g. number of hospitalisations, number of GP visits) were taken from the INBUILD trial. The resource use in the trial was at least partially protocol driven and, therefore, may not be fully generalisable to UK clinical practice. However, no other suitable data sources were identified following a systematic literature review. Therefore, it is

expected that the most appropriate data have been adopted for these parameters. Additionally, the results of the sensitivity analysis indicate that these resource use parameters are not a key driver of the overall cost-effectiveness results.

Overall, the results of the economic evaluation indicate that nintedanib is a cost-effective treatment option for patients with chronic fibrosing ILD at the NICE cost-effectiveness threshold of £20,000 to £30,000 per QALY. The base case analysis indicates that nintedanib is associated with increased costs and increased QALYs when compared to BSC and is associated with an ICER of <£20,000 ([redacted]). Nintedanib also leads to an incremental LY gain of [redacted] over the modelled time horizon.

B.4 References

1. National Institute for Health and Care Excellence. Nintedanib for treating idiopathic pulmonary fibrosis [TA379]. Manchester, UK; 2016.

2. Hoffmann-Vold AM, Weigt SS, Saggar R, Palchevskiy V, Volkmann ER, Liang LL, et al. Endotype-phenotyping may predict a treatment response in progressive fibrosing interstitial lung disease. EBioMedicine. 2019;50:379-86.

3. EMA. Ofev: EPAR product information. European Medicines Agency; 2020.

4. Richeldi L, Cottin V, Flaherty KR, Kolb M, Inoue Y, Raghu G, et al. Design of the INPULSIS trials: Two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis. Respiratory Medicine. 2014;108(7):1023-30.

5. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718-27.

6. Thannickal VJ, Toews GB, White ES, Lynch JP, 3rd, Martinez FJ. Mechanisms of pulmonary fibrosis. Annual review of medicine. 2004;55:395-417.

7. Prasse A, Pechkovsky DV, Toews GB, Schäfer M, Eggeling S, Ludwig C, et al. CCL18 as an indicator of pulmonary fibrotic activity in idiopathic interstitial pneumonias and systemic sclerosis. Arthritis & Rheumatism. 2007;56(5):1685–93.

8. Bagnato G, Harari S. Cellular interactions in the pathogenesis of interstitial lung diseases. European Respiratory Review. 2015;24(135):102-14.

9. Wollin L, Distler JHW, Redente EF, Riches DWH, Stowasser S, Schlenker-Herceg R, et al. Potential of Nintedanib in Treatment of Progressive Fibrosing Interstitial Lung Diseases. European Respiratory Journal. 2019:1900161.

10. Flaherty KR, Brown KK, Wells AU, Clerisme-Beaty E, Collard HR, Cottin V, et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ Open Respiratory Research. 2017;4(1):e000212.

11. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733-48.

12. Wong AW, Ryerson CJ, Guler SA. Progression of fibrosing interstitial lung disease. Respir Res. 2020;21(1):32.

13. George PM, Spagnolo P, Kreuter M, Altinisik G, Bonifazi M, Martinez FJ, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med. 2020;8(9):925-34.

14. Brown KK, Martinez FJ, Walsh SLF, Thannickal VJ, Prasse A, Schlenker-Herceg R, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J. 2020.

15. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet journal of rare diseases. 2008;3:8.

16. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824.

17. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. American Journal of Respiratory and Critical Care Medicine. 2002;165(2):277-304.

18. Cottin V, Wollin L, Fischer A, Quaresma M, Stowasser S, Harari S. Fibrosing interstitial lung diseases: knowns and unknowns. Eur Respir Rev. 2019;28(151).

19. Simpson T, Barratt SL, Beirne P, Chaudhuri N, Crawshaw A, Crowley LE, et al. The burden of Progressive Fibrotic Interstitial lung disease across the UK. medRxiv. 2020:2020.11.16.20229591.

20. Kolb M, Vašáková M. The natural history of progressive fibrosing interstitial lung diseases. Respir Res. 2019;20(1):57.

21. European Respiratory Society. European Lung White book. 2018.

22. Chung L, Krishnan E, Chakravarty EF. Hospitalizations and mortality in systemic sclerosis: results from the Nationwide Inpatient Sample. Rheumatology (Oxford). 2007;46(12):1808-13.

23. Fischer A, Kong AM, Swigris JJ, Cole AL, Raimundo K. All-cause Healthcare Costs and Mortality in Patients with Systemic Sclerosis with Lung Involvement. J Rheumatol. 2018;45(2):235-41.

24. Furst DE, Fernandes AW, Iorga SR, Greth W, Bancroft T. Annual medical costs and healthcare resource use in patients with systemic sclerosis in an insured population. J Rheumatol. 2012;39(12):2303-9.

25. Poulos LMC, P.K.; Toelle, B.G.; Reddel, H.K.; Marks, G.B. Lung Disease in Australia. 2014.

26. Raimundo K, Farr A, Cole AL. Rheumatoid arthritis-interstitial lung disease in the United States: prevalence, incidence, and healthcare costs [abstract]. Arthritis Rheumatol 2016;68.

27. Kawalec PP, Malinowski KP. The indirect costs of systemic autoimmune diseases, systemic lupus erythematosus, systemic sclerosis and sarcoidosis: a summary of 2012 real-life data from the Social Insurance Institution in Poland. Expert Rev Pharmacoecon Outcomes Res. 2015;15(4):667-73.

28. Torrisi SE, Pavone M, Vancheri A, Vancheri C. When to start and when to stop antifibrotic therapies. Eur Respir Rev. 2017;26(145).

29. Richeldi L, Varone F, Bergna M, de Andrade J, Falk J, Hallowell R, et al. Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence. European Respiratory Review. 2018;27(150):180074.

30. Wijsenbeek M, Kreuter M, Olson A, Fischer A, Bendstrup E, Wells CD, et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Current Medical Research and Opinion. 2019;35(11):2015-24.

31. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2015;34(1):1-15.

32. Vaidya S, Hibbert CL, Kinter E, Boes S. Identification of Key Cost Generating Events for Idiopathic Pulmonary Fibrosis: A Systematic Review. Lung. 2017;195(1):1-8.

33. Yeung JC, Keshavjee S. Overview of clinical lung transplantation. Cold Spring Harb Perspect Med. 2014;4(1):a015628-a.

34. Todd JL, Christie JD, Palmer SM. Update in lung transplantation 2013. American journal of respiratory and critical care medicine. 2014;190(1):19-24.

35. Gauthier JM, Hachem RR, Kreisel D. Update on Chronic Lung Allograft Dysfunction. Curr Transplant Rep. 2016;3(3):185-91.

36. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med. 2020;383(10):958-68.

37. Boehringer Ingelheim. Clinical Trial Report for the INBUILD trial (study 1199.247). 2019.

38. Wang S-J, O'Neill RT, Hung HMJ. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. Pharmaceutical Statistics. 2007;6(3):227-44.

39. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020;8(5):453-60.

40. Flaherty KR, Wells AU, Cottin V, Devaraj A, Inoue Y, Richeldi L, et al. Effects of nintedanib on progression of ILD in patients with fibrosing ILDs and a progressive phenotype: further analyses of the INBUILD® trial. Poster developed for the European Respiratory Society International Congress, 7–9 September 2020.

41. Wyser C, van Schalkwyk E, Alheit B, Bardin P, Joubert J. Treatment of progressive pulmonary sarcoidosis with cyclosporin A. A randomized controlled trial. American journal of respiratory and critical care medicine [Internet]. 1997; 156(5):[1371-6 pp.]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00145379/full.

42. O'Brien K, Troendle J, Gochuico BR, Markello TC, Salas J, Cardona H, et al. Pirfenidone for the treatment of Hermansky-Pudlak syndrome pulmonary fibrosis. Mol Genet Metab. 2011;103(2):128-34.

43. Gahl WA, Brantly M, Troendle J, Avila NA, Padua A, Montalvo C, et al. Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome. Mol Genet Metab. 2002;76(3):234-42.

44. Guenther A, Prasse A, Kreuter M, Neuser P, Rabe K, Bonella F, et al. Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF). European Respiratory Journal Conference: 29th International Congress of the European Respiratory Society, ERS Spain. 2019;54.

45. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. The Lancet Respiratory Medicine. 2019;27:27.

46. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet (London, England). 2011;377(9779):1760-9.

47. Kafaja S, Clements PJ, Wilhalme H, Tseng C-H, Furst DE, Kim GH, et al. Reliability and minimal clinically important differences of forced vital capacity: Results from the Scleroderma Lung Studies (SLS-I and SLS-II). American journal of respiratory and critical care medicine. 2018;197(5):644-52.

48. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019;380(26):2518-28.

49. Prior TS, Hilberg O, Shaker SB, Davidsen JR, Hoyer N, Birring SS, et al. Validation of the King's Brief Interstitial Lung Disease questionnaire in Idiopathic Pulmonary Fibrosis. BMC Pulmonary Medicine. 2019;19(1):255.

50. Boehringer Ingelheim. Patient-Reported Outcome Validation Report: Relability and Validity for chronic fibrosing Intestitial Lung Diseases (ILDs) with a progressive phenotype (DOF). 2019.

51. British Thoracic Society. BTS ILD Registry Annual Report 2019. 2019.

52. Boehringer Ingelheim. NICE submission for nintedanib (OFEV) for treating idiopathic pulmonary fibrosis (TA379).

53. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019. 2020.

54. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. London: National Institute for Health and Care Excellence.; 2013.

55. Boehringer Ingelheim. INBUILD phase III trial (no. 1199.247) post-hoc analysis. Data on file. 2019.

56. National Institute for Health and Care Excellence. Diagnosis and management of suspected idiopathic pulmonary fibrosis. Clinical Guideline. Methods, evidence and recommendations. Idiopathic pulmonary fibrosis: full guideline draft.; 2013 January.

57. National Institute for Health and Care Excellence. Pirfenidone for treating idiopathic pulmonary fibrosis. NICE technology appraisal guidance [TA282]. Manchester, UK; 2013.

58. Boehringer Ingelheim. Advisory Board Minutes Data On File NIN15-04. 2015.

59. Antoniou KM HD, Rubens MB, Marten K, Desai SR, Siafakas NM, Nicholson AG, et al. Idiopathic pulmonary fibrosis: outcome in relation to smoking status. Am J Respir Crit Care,. 2008;177(2):190-4.

60. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006;61(11):980-5.

61. Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, Nagao T, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest. 2007;131(3):650-6.

62. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, SM K. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174(6):659-64.

63. Lederer DJ, Barr RG, Wilt JS, Bagiella E, D'Ovidio F, Sonett JR, et al. Racial and ethnic disparities in idiopathic pulmonary fibrosis: A UNOS/OPTN database analysis. Am J Transplant. 2006;6(10):2436-42.

64. Lopes AJ CD, Mogami R, Lanzillotti RS, Melo PL, JM. J. Severity classification for idiopathic pulmonary fibrosis by using fuzzy logic. Clinics (Sao Paulo). 2011;66(6):1015-9.

65. Manali ED, Stathopoulos GT, Kollintza A, Kalomenidis I, Emili JM, Sotiropoulou C, et al. The Medical Research Council chronic dyspnea score predicts the survival of patients with idiopathic pulmonary fibrosis. Respir Med. 2008;102(4):586-92.

66. Nathan SD, Shlobin OA, Weir N, Ahmad S, Kaldjob JM, Battle E, et al. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest. 2011;140(1):221-9.

67. Zappala CJ LP, Nicholson AG, Colby TV, Cramer D, Renzoni EA, Hansell DM, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):830-6.

68. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184(4):459-66.

69. Ley B RC, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012;156(10):684-91.

70. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.

71. Jackson CH. flexsurv: a platform for parametric survival modeling in R. Journal of Statistical Software. 2016;70.

72. Richeldi L, et al. Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. Thorax. 2018;73(6):581.

73. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071-82.

74. Crestani B, Huggins JT, Kaye M, al. e. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. The Lancet Respiratory Medicine. 2019;7:60-8.

75. Walsh SL, Sverzellati N, Devaraj A, et al. Connective tissue disease related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants. Thorax. 2014;69:216-22.

76. Akira M, Inoue Y, Arai T, et al. Long-term follow-up high-resolution CT findings in non-specific interstitial pneumonia. Thorax. 2011;66:61-5.

77. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP; 2015.

78. Lunn D, Spiegelhalter D, Thomas A, et al. The BUGS project: Evolution, critique and future directions. Statistics in Medicine. 2009;28:3049-67.

79. Soikkeli F, Hashim M, Ouwens M, et al. Extrapolating Survival Data Using Historical Trial–Based a Priori Distributions. Value in Health. 2019;22:1012-7.

80. Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. BMJ Open Respiratory Research. 2019;6(1):e000397.

81. Vasakova M, Sterclova M, M M, et al. Long-term overall survival and progression-free survival in idiopathic pulmonary fibrosis treated by pirfenidone or nintedanib or their switch. Real world data from the EMPIRE registry. European Respiratory Journal. 2019;54:PA4720.

82. Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. Eur Respir J. 2017;49(2).

83. Antoniou K, Markopoulou K, Tzouvelekis A, Trachalaki A, Vasarmidi E, Organtzis J, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study. ERJ Open Res. 2020;6(1):00172-2019.

84. Wuyts WA, Dahlqvist C, Slabbynck H, Schlesser M, Gusbin N, Compere C, et al. Longitudinal clinical outcomes in a real-world population of patients with idiopathic pulmonary fibrosis: the PROOF registry. Respir Res. 2019;20(1):231.

85. Kaunisto J SE, Hodgson U et al. Demographics and survival of patients with idiopathic pulmonary fibrosis in the FinnishIPF registry. ERJ Open Res. 2019;5:00170-2018.

86. Guenther A, Krauss E, Tello S, Wagner J, Paul B, Kuhn S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respir Res. 2018;19(1):141.

87. EMC. Summary of Product Characteristics Ofev 150mg Electronic Medicines Compendium2020 [Available from: https://www.medicines.org.uk/emc/product/7705/smpc.

88. Homma S, Azuma A, Taniguchi H, Ogura T, Mochiduki Y, Sugiyama Y, et al. Efficacy of inhaled N-acetylcysteine monotherapy in patients with early stage idiopathic pulmonary fibrosis. RESPIROLOGY. 2012;17(3):467-77.

89. NHS Improvement. National schedule of NHS costs 2018/19. 2019.

90. Curtis L, Burns A. Unit Costs of Health and Social Care. 2019.

91. Boehringer Ingelheim. DoF NIN20-09. 2020.

92. Rinciog C, et al. A Cost-Effectiveness Analysis of Nintedanib in Idiopathic Pulmonary Fibrosis in the UK. PHARMACOECONOMICS. 2017;35(4):479-91.

93. NHS Improvement. National schedule of NHS costs 2017/18. 2018.

94. Georghiou T, M B. Exploring the cost of care at the end of life. London, UK; 2014.

95. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

96. Saunders P, Tsipouri V, Keir GJ, Ashby D, Flather MD, Parfrey H, et al. Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. Trials. 2017;18(1):275.

97. Euctr G. A trial of rituximab compared to usual best care in patients with interstitial (inflammatory or scarring conditions) lung disease due to systemic autoimmune (connective tissue) diseases. Http://wwwwhoint/trialsearch/trial2aspx? Trialid=euctr2012-003633-42-gb [Internet]. 2013. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01856333/full.

98. Isrctn. Rituximab versus cyclophosphamide in connective tissue disease-ILD. Http://wwwwhoint/trialsearch/trial2aspx? Trialid=isrctn16474148 [Internet]. 2015. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01879601/full.

99. Nct. Phase II Study of Pirfenidone in Patients With RAILD. Https://clinicaltrialsgov/show/nct02808871 [Internet]. 2016. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01559244/full.

100. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011;184(12):1382-9.

101. Nct. Abatacept for the Treatment of Myositis-associated Interstitial Lung Disease. Https://clinicaltrialsgov/show/nct03215927 [Internet]. 2017. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01495603/full.

102. Nct. Cyclophosphamide Systemic Sclerosis Associated Interstitial Lung Disease. Https://clinicaltrialsgov/show/nct01570764 [Internet]. 2012. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01536601/full.

103. Nct. Evaluation of Efficacy and Safety of Rituximab With Mycophenolate Mofetil in Patients With Interstitial Lung Diseases. Https://clinicaltrialsgov/show/nct02990286 [Internet]. 2016. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01585749/full.

104. SLCTR. Effectiveness of mycophenolate mofetil vs azathioprin on progression of rheumatoid arthritis related interstitial lung disease in patients followed up at the rheumatology clinic, Teaching Hospital Karapitiya – a randomized controlled trial 2019 [Available from: https://slctr.lk/trials/slctr-2018-031.

105. Nct. Pirfenidone in Progressive Interstitial Lung Disease Associated With Clinically Amyopathic Dermatomyositis 2016 [Available from: https://clinicaltrials.gov/show/NCT02821689.

106. Nct. Comparing and Combining Bortezomib and Mycophenolate in SSc Pulmonary Fibrosis 2019 [Available from: https://clinicaltrials.gov/show/NCT02370693.

107. Nct. Efficacy and Safety of Two Glucocorticoid Regimens in the Treatment of Sarcoidosis 2019 [Available from: https://ClinicalTrials.gov/show/NCT03265405.

108. Nct. Cyclosporine A in the Treatment of Interstitial Pneumonitis Associated With Sjogren's Syndrome 2015 [Available from: https://ClinicalTrials.gov/show/NCT02370550.

109. Solomon JJ, Danoff SK, Goldberg HJ, Woodhead F, Kolb M, Chambers DC, et al. The Design and Rationale of the Trial1 Trial: a Randomized Double-Blind Phase 2 Clinical Trial of Pirfenidone in Rheumatoid Arthritis-Associated Interstitial Lung Disease. Advances in therapy. 2019.

110. Euctr GR. A study to find out how nintedanib is taken up in the body and how well it is tolerated in children and adolescents with Interstitial Lung Disease (ILD). http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2018-004530-14-GR. 2019.

111. Aringer M, Pope J, Kelly C, Hoffmann-Vold AM, Belperio J, James A, et al. EFFICACY AND SAFETY OF NINTEDANIB IN PATIENTS WITH AUTOIMMUNE DISEASE-RELATED INTERSTITIAL LUNG DISEASE TREATED WITH DMARDS AND/OR GLUCOCORTICOIDS AT BASELINE. European League Against Rheumatism (EULAR) 2020 E-Congress. 2020.

112. Volkmann E, Castellvi I, Johnson S, Matteson E, Distler J, Seibold J, et al. NINTEDANIB DOSE ADJUSTMENTS AND ADVERSE EVENTS IN PATIENTS WITH PROGRESSIVE AUTOIMMUNE DISEASE-RELATED INTERSTITIAL LUNG DISEASES IN THE INBUILD TRIAL. European League Against Rheumatism (EULAR) 2020 E-Congress. 2020.

113. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. Journal of the Medical Library Association: JMLA. 2016;104(3):240.

114. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Systematic reviews. 2016;5(1):210.

115. CRD. CRD's guidance for undertaking systematic reviews in health care.; 2009.

116. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313(7052):275-83.

117. Papaioannou D, Brazier J, Paisley S. NICE DSU Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature. Available at: http://www.nicedsu.org.uk. Accessed on: April 2017. 2010.

118. Olson AL, Maher TM, Acciai V, Mounir B, Quaresma M, Zouad-Lejour L, et al. Healthcare Resources Utilization and Costs of Patients with Non-IPF Progressive Fibrosing Interstitial Lung Disease Based on Insurance Claims in the USA. Advances in Therapy. 2020;21:21.

119. Wuyts WA, Papiris S, Manali E, Kilpelainen M, Davidsen JR, Miedema J, et al. The Burden of Progressive Fibrosing Interstitial Lung Disease: A DELPHI Approach. Advances in Therapy. 2020;22:22.

120. Olson A, Maher T, Salisbury M, Acciai V, Mounir B, Quaresma M, et al. Health care resources utilisation and costs in patients with non-IPF progressive fibrosing interstitial lung disease. European Respiratory Journal Conference: European Respiratory Society International Congress, ERS. 2018;52(Supplement 62).

121. Wuyts W, Romhild Davidsen J, Kilpelainen M, Durheim MT, Papiris S, Manali E, et al. Prs19 Burden of Disease of Fibrosing Interstitial Lung Diseases in Europe: The Buildup Project. Value in Health. 2019;22 (Supplement 3):S875-S6.

B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

C1.1 SmPC

Ofev 150mg SmPC.pdf

Ofev 100mg SmPC.pdf

C1.2 EPAR

Ofev EPAR_medicines-ove

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to provide evidence on the efficacy of treatments for PF-ILDs other than IPF and to assess whether it was feasible to carry out a network meta-analysis (NMA) of these treatments. Treatments in scope included:

- Nintedanib (the technology being appraised)
- Other treatments used off-label, including pirfenidone, azathioprine, cyclophosphamide, rituximab, mycophenolate mofetil, prednisolone, tocilizumab, abatercept, methotrexate, etanercept, infliximab, adalimumab (comparator technologies)

D.1.1.1 Search strategy

The SLR aimed to identify all randomised controlled trials (RCTs) that have evaluated pharmacological treatments for ILD with a progressive phenotype. The following databases were searched on 13th August 2019:

- Embase
- MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations
- MEDALL
- The Cochrane Library

Following the European Respiratory Society (ERS) Congress (28th September to 2nd October) 2019, searches were updated and the following databases were searched again on 29th October 2019:

- Embase
- MEDALL
- The Cochrane Library

While carrying out the update, MEDLINE In-Process was not accessible. Therefore MEDALL was searched instead since it captures all the records in MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations.

To supplement the electronic searches, a bibliographic review, congress abstract search and clinical trial database search was also carried out. Reference lists of all included articles were scanned to identify any additional studies not already identified. Relevant published SLRs and NMAs identified in the title and abstract screening stage were obtained in full text and their reference lists checked to identify additional studies. The following disease-specific congresses for years not covered by Embase to the present day were also searched:

- American Thoracic Society (ATS) (2019 international conference)
- British Thoracic Society (BTS) (2018 Winter Meeting)
- European League Against Rheumatism (EULAR) - European Congress of Rheumatology (2019 congress)
- European Respiratory Society (ERS) International Congress 2019

Additionally, the following clinical trial databases were searched to identify ongoing and recently completed studies that would meet the inclusion criteria for the present review:

- ClinicalTrials.gov
- The WHO International Clinical Trials Registry Platform

Comprehensive search strategies were developed for each electronic database using terms for disease, treatment and study type. These are shown in Table 66 to Table 73 and were based on the decision problem described in Table 1.

Table 66: MEDLINE search strategy and results, 13th August 2019

ID	Searches	Results
1	Lung Diseases, Interstitial/	8647
2	ILD.tw.	2855
3	Pulmonary Fibrosis/	18168
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	12632
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	18708
6	alveolitis.mp.	5904
7	(diffuse* adj3 parenchymal*).mp.	656
8	Bronchiolitis Obliterans/	2689

ID	Searches	Results
9	(bronchiolitis adj obliterans).mp.	4178
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	7687
11	pneumoconiosis/	6567
12	bagassosis.mp.	63
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	11615
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	16174
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	7
16	((pulmonary$ or lung$) adj3 fibros$).mp.	30143
17	Alveolitis, Extrinsic Allergic/	2839
18	(connective adj3 lung$).mp.	217
19	(allerg$ adj3 pneumonitis).mp.	103
20	Cryptogenic Organizing Pneumonia/	1011
21	cryptogenic organi#ing pneumonia.mp.	1173
22	Idiopathic Interstitial Pneumonias/	350
23	IIP.tw.	897
24	(hypersensitivity adj3 pneumonia$).mp.	163
25	pleuroparenchymal fibroelastosis.mp.	104
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	90312
27	randomized controlled trial/ or randomized controlled trials as topic/	606258
28	(randomi?ed control* or rct).ti.	62331
29	randomization/	99879
30	Single-Blind Method/ or single blind.mp.	31442
31	double blind method/ or double blind.mp.	177818
32	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	114518
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	211507
34	Random Allocation/	99879
35	(allocat* adj3 random*).mp.	125648
36	placebo$.mp.	200939
37	Prospective Studies/	509147
38	(prospective adj (trial or study)).mp.	123734
39	Controlled Clinical Trial/	93169
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	1358352
41	Case Report/	1944432
42	case stud*.hw.	12101
43	case report?.hw.	1944432
44	Letter/	985913
45	Editorial/	444851
46	41 or 42 or 43 or 44 or 45	3180195
47	40 not 46	1315492
48	nintedanib.mp.	510
49	(Vargatef or Ofev).mp.	13
50	pirfenidone.mp.	871
51	(Esbriet or Pirespa or Etuary).mp.	10
52	azathioprine/	14389
53	(azathioprine or Imuran or Azasan).mp.	21266
54	cyclophosphamide/	48774
55	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	65080
56	rituximab/	12861
57	(rituximab or Rituxan or Mabthera).mp.	18322

ID	Searches	Results
58	mycophenolate mofetil/	7635
59	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	11684
60	prednisone/	38570
61	(corticosteroid? or predniso*).mp.	166257
62	prednisolone/	32161
63	tocilizumab.mp.	2112
64	(Acterma or RoActerma or Atlizumab).mp.	17
65	abatacept.mp. or Abatacept/	3234
66	Orencia.mp.	37
67	methotrexate.mp. or Methotrexate/	48726
68	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	10
69	etanercept/	5576
70	(etanercept or enbrel).mp.	7321
71	infliximab/	9644
72	(infliximab or remicade).mp.	12272
73	adalimumab/	4811
74	(adalimumab or humira).mp.	6387
75	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	293275
76	26 and 47 and 75	602
77	limit 76 to english language	548

Table 67: Medline In-Process and non-indexed citations search strategy and results, 13th August 2019

ID	Searches	Results
1	Lung Diseases, Interstitial/	1952
2	ILD.tw.	1694
3	Pulmonary Fibrosis/	1625
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	4624
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	4511
6	alveolitis.mp.	427
7	(diffuse* adj3 parenchymal*).mp.	235
8	Bronchiolitis Obliterans/	345
9	(bronchiolitis adj obliterans).mp.	793
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	491
11	pneumoconiosis/	156
12	bagassosis.mp.	5
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	1566
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	1462
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	7
16	((pulmonary$ or lung$) adj3 fibros$).mp.	7940
17	Alveolitis, Extrinsic Allergic/	179
18	(connective adj3 lung$).mp.	42
19	(allerg$ adj3 pneumonitis).mp.	14
20	Cryptogenic Organizing Pneumonia/	132
21	cryptogenic organi#ing pneumonia.mp.	235
22	Idiopathic Interstitial Pneumonias/	159
23	IIP.tw.	317

ID	Searches	Results
24	(hypersensitivity adj3 pneumonia$).mp.	50
25	pleuroparenchymal fibroelastosis.mp.	119
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	18768
27	randomized controlled trial/ or randomized controlled trials as topic/	106640
28	(randomi?ed control* or rct).ti.	37608
29	randomization/	14925
30	Single-Blind Method/ or single blind.mp.	7865
31	double blind method/ or double blind.mp.	33546
32	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	37018
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	45375
34	Random Allocation/	14925
35	(allocat* adj3 random*).mp.	25663
36	placebo$.mp.	46541
37	Prospective Studies/	109270
38	(prospective adj (trial or study)).mp.	35119
39	Controlled Clinical Trial/	3638
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	312602
41	Case Report/	283800
42	case stud*.hw.	1491
43	case report?.hw.	283800
44	Letter/	184022
45	Editorial/	136378
46	41 or 42 or 43 or 44 or 45	580830
47	40 not 46	305582
48	nintedanib.mp.	607
49	(Vargatef or Ofev).mp.	15
50	pirfenidone.mp.	660
51	(Esbriet or Pirespa or Etuary).mp.	12
52	azathioprine/	978
53	(azathioprine or Imuran or Azasan).mp.	3003
54	cyclophosphamide/	3771
55	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	9411
56	rituximab/	3371
57	(rituximab or Rituxan or Mabthera).mp.	8564
58	mycophenolate mofetil/	1126
59	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	2925
60	prednisone/	2672
61	(corticosteroid? or predniso*).mp.	33152
62	prednisolone/	2260
63	tocilizumab.mp.	1645
64	(Acterma or RoActerma or Atlizumab).mp.	5
65	abatacept.mp. or Abatacept/	941
66	Orencia.mp.	23
67	methotrexate.mp. or Methotrexate/	9259
68	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	9
69	etanercept/	1150
70	(etanercept or enbrel).mp.	2530
71	infliximab/	2157
72	(infliximab or remicade).mp.	4654
73	adalimumab/	1759
74	(adalimumab or humira).mp.	3670

ID	Searches	Results
75	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	62859
76	26 and 47 and 75	225
77	limit 76 to english language	221

Table 68: MEDALL search strategy and results, 29th October 2019

ID	Searches	Results
1	Lung Diseases, Interstitial/	8805
2	ILD.tw.	3666
3	Pulmonary Fibrosis/	18255
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	14593
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	20678
6	alveolitis.mp.	6062
7	(diffuse* adj3 parenchymal*).mp.	780
8	Bronchiolitis Obliterans/	2720
9	(bronchiolitis adj obliterans).mp.	4508
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	7933
11	pneumoconiosis/	6584
12	bagassosis.mp.	68
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	11806
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	16818
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	10
16	((pulmonary$ or lung$) adj3 fibros$).mp.	33539
17	Alveolitis, Extrinsic Allergic/	2855
18	(connective adj3 lung$).mp.	228
19	(allerg$ adj3 pneumonitis).mp.	111
20	Cryptogenic Organizing Pneumonia/	1012
21	cryptogenic organi#ing pneumonia.mp.	1248
22	Idiopathic Interstitial Pneumonias/	353
23	IIP.tw.	1065
24	(hypersensitivity adj3 pneumonia$).mp.	180
25	pleuroparenchymal fibroelastosis.mp.	152
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	98031
27	randomized controlled trial/ or randomized controlled trials as topic/	616236
28	(randomi?ed control* or rct).ti.	79113
29	randomization/	100939
30	Single-Blind Method/ or single blind.mp.	33404
31	double blind method/ or double blind.mp.	191262
32	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	129863
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	229996
34	Random Allocation/	100939
35	(allocat* adj3 random*).mp.	132310
36	placebo$.mp.	223283
37	Prospective Studies/	518360
38	(prospective adj (trial or study)).mp.	140049
39	Controlled Clinical Trial/	93395
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	1446825

ID	Searches	Results
41	Case Report/	2053542
42	case stud*.hw.	12147
43	case report?.hw.	2053542
44	Letter/	1048416
45	Editorial/	506564
46	41 or 42 or 43 or 44 or 45	3411195
47	40 not 46	1402243
48	nintedanib.mp.	779
49	(Vargatef or Ofev).mp.	19
50	pirfenidone.mp.	1128
51	(Esbriet or Pirespa or Etuary).mp.	16
52	azathioprine/	14471
53	(azathioprine or Imuran or Azasan).mp.	22653
54	cyclophosphamide/	49036
55	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	69152
56	rituximab/	13121
57	(rituximab or Rituxan or Mabthera).mp.	21958
58	mycophenolate mofetil/	7717
59	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	12893
60	prednisone/	38757
61	(corticosteroid? or predniso*).mp.	181929
62	prednisolone/	32313
63	tocilizumab.mp.	2784
64	(Acterma or RoActerma or Atlizumab).mp.	19
65	abatacept.mp. or Abatacept/	3565
66	Orencia.mp.	43
67	methotrexate.mp. or Methotrexate/	52801
68	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	14
69	etanercept/	5645
70	(etanercept or enbrel).mp.	8302
71	infliximab/	9819
72	(infliximab or remicade).mp.	14240
73	adalimumab/	4967
74	(adalimumab or humira).mp.	7909
75	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	321845
76	26 and 47 and 75	674
77	limit 76 to english language	620
78	(201908* or 201909* or 201910*).dt,ez,ed.	523129
79	77 and 78	25

Table 69: Embase search strategy and results, 13th August 2019

ID	Searches	Results
1	Lung Diseases, Interstitial/	7974
2	ILD.tw.	8220
3	Pulmonary Fibrosis/	17258
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	24865
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	37532
6	alveolitis.mp.	28790
7	(diffuse* adj3 parenchymal*).mp.	1348

ID	Searches	Results
8	Bronchiolitis Obliterans/	5538
9	(bronchiolitis adj obliterans).mp.	8957
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	10508
11	pneumoconiosis/	9474
12	bagassosis.mp.	148
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	29026
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	22800
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	42
16	((pulmonary$ or lung$) adj3 fibros$).mp.	57571
17	Alveolitis, Extrinsic Allergic/	4595
18	(connective adj3 lung$).mp.	392
19	(allerg$ adj3 pneumonitis).mp.	6369
20	Cryptogenic Organizing Pneumonia/	662
21	cryptogenic organi#ing pneumonia.mp.	839
22	Idiopathic Interstitial Pneumonias/	13113
23	IIP.tw.	1537
24	(hypersensitivity adj3 pneumonia$).mp.	344
25	pleuroparenchymal fibroelastosis.mp.	268
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	176313
27	randomized controlled trial/ or randomized controlled trials as topic/	665637
28	(randomi?ed control* or rct).ti.	98115
29	randomization/	83823
30	Single-Blind Method/ or single blind.mp.	44356
31	double blind method/ or double blind.mp.	246311
32	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	256474
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	298780
34	Random Allocation/	80086
35	(allocat* adj3 random*).mp.	42315
36	placebo$.mp.	449589
37	Prospective Studies/	378916
38	(prospective adj (trial or study)).mp.	611748
39	Controlled Clinical Trial/	464756
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	1917482
41	Case Report/	2488609
42	case stud*.hw.	72499
43	case report?.hw.	2488631
44	Letter/	1026650
45	Editorial/	618248
46	41 or 42 or 43 or 44 or 45	3986515
47	40 not 46	1844929
48	nintedanib.mp.	2531
49	(Vargatef or Ofev).mp.	148
50	pirfenidone.mp.	3165
51	(Esbriet or Pirespa or Etuary).mp.	110
52	azathioprine/	93238
53	(azathioprine or Imuran or Azasan).mp.	95882
54	cyclophosphamide/	214700
55	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	223399
56	rituximab/	73079

ID	Searches	Results
57	(rituximab or Rituxan or Mabthera).mp.	76251
58	mycophenolate mofetil/	14404
59	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	64915
60	prednisone/	173009
61	(corticosteroid? or predniso*).mp.	572875
62	prednisolone/	127020
63	tocilizumab.mp.	10521
64	(Acterma or RoActerma or Atlizumab).mp.	575
65	abatacept.mp. or Abatacept/	8762
66	Orencia.mp.	647
67	methotrexate.mp. or Methotrexate/	181030
68	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	244
69	etanercept/	29863
70	(etanercept or enbrel).mp.	30742
71	infliximab/	47813
72	(infliximab or remicade).mp.	48832
73	adalimumab/	30942
74	(adalimumab or humira).mp.	31623
75	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	905071
76	26 and 47 and 75	3073
77	limit 76 to english language	2972

Table 70: Embase search strategy and results, 29th October 2019

ID	Searches	Results
1	Lung Diseases, Interstitial/	8702
2	ILD.tw.	8683
3	Pulmonary Fibrosis/	17783
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	25774
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	38120
6	alveolitis.mp.	29377
7	(diffuse* adj3 parenchymal*).mp.	1374
8	Bronchiolitis Obliterans/	5614
9	(bronchiolitis adj obliterans).mp.	9103
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	10573
11	pneumoconiosis/	9534
12	bagassosis.mp.	148
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	29187
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	22915
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	44
16	((pulmonary$ or lung$) adj3 fibros$).mp.	58565
17	Alveolitis, Extrinsic Allergic/	4685
18	(connective adj3 lung$).mp.	397
19	(allerg$ adj3 pneumonitis).mp.	6459
20	Cryptogenic Organizing Pneumonia/	722
21	cryptogenic organi#ing pneumonia.mp.	873
22	Idiopathic Interstitial Pneumonias/	13369
23	IIP.tw.	1561

ID	Searches	Results
24	(hypersensitivity adj3 pneumonia$).mp.	353
25	pleuroparenchymal fibroelastosis.mp.	277
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	178880
27	randomized controlled trial/ or randomized controlled trials as topic/	685792
28	(randomi?ed control* or rct).ti.	101398
29	randomization/	85171
30	Single-Blind Method/ or single blind.mp.	45476
31	double blind method/ or double blind.mp.	250525
32	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	263767
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	304193
34	Random Allocation/	81434
35	(allocat* adj3 random*).mp.	43159
36	placebo$.mp.	456389
37	Prospective Studies/	403277
38	(prospective adj (trial or study)).mp.	633123
39	Controlled Clinical Trial/	466255
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	1963873
41	Case Report/	2520414
42	case stud*.hw.	74695
43	case report?.hw.	2520436
44	Letter/	1037531
45	Editorial/	625697
46	41 or 42 or 43 or 44 or 45	4036567
47	40 not 46	1888744
48	nintedanib.mp.	2677
49	(Vargatef or Ofev).mp.	151
50	pirfenidone.mp.	3264
51	(Esbriet or Pirespa or Etuary).mp.	111
52	azathioprine/	94250
53	(azathioprine or Imuran or Azasan).mp.	96915
54	cyclophosphamide/	216866
55	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	225832
56	rituximab/	75031
57	(rituximab or Rituxan or Mabthera).mp.	78401
58	mycophenolate mofetil/	15247
59	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	66115
60	prednisone/	175116
61	(corticosteroid? or predniso*).mp.	580230
62	prednisolone/	128476
63	tocilizumab.mp.	11169
64	(Acterma or RoActerma or Atlizumab).mp.	575
65	abatacept.mp. or Abatacept/	9107
66	Orencia.mp.	653
67	methotrexate.mp. or Methotrexate/	183615
68	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	247
69	etanercept/	30556
70	(etanercept or enbrel).mp.	31443
71	infliximab/	48794
72	(infliximab or remicade).mp.	49838
73	adalimumab/	31937
74	(adalimumab or humira).mp.	32638

ID	Searches	Results
75	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	918005
76	26 and 47 and 75	3162
77	limit 76 to english language	3061
78	(201908* or 201909* or 201910*).dd.	269467
79	77 and 78	51

Table 71: Cochrane search strategy and results, 13th August 2019

ID	Search	Results
#1	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	718
#2	ILD:ti,ab	428
#3	MeSH descriptor: [Pulmonary Fibrosis] explode all trees	420
#4	(interstitial* NEAR/3 (lung* NEAR/3 disease*)):ti,ab	755
#5	(interstitial* NEAR/3 (fibros* or pneumonitis or pneumonia or pneumopathy)):ti,ab	642
#6	alveolitis:ti,ab	125
#7	(diffuse* NEAR/3 parenchymal*):ti,ab	16
#8	MeSH descriptor: [Bronchiolitis Obliterans] explode all trees	62
#9	(bronchiolitis NEXT obliterans):ti,ab	152
#10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis):ti,ab	58
#11	MeSH descriptor: [Pneumoconiosis] explode all trees	95
#12	bagassosis:ti,ab	0
#13	((bird* or farmer* or pigeon* or avian* or budgerigar*) NEXT (lung* or disease*)):ti,ab	8
#14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis):ti,ab	135
#15	((pulmonary* or lung*) NEAR/3 reticulation*):ti,ab	1
#16	((pulmonary* or lung*) NEAR/3 fibros*):ti,ab	1561
#17	MeSH descriptor: [Alveolitis, Extrinsic Allergic] explode all trees	25
#18	(connective NEAR/3 lung*):ti,ab	10
#19	(allerg* NEAR/3 pneumonitis):ti,ab	0
#20	MeSH descriptor: [Cryptogenic Organizing Pneumonia] explode all trees	4
#21	cryptogenic organi*ing pneumonia:ti,ab	11
#22	MeSH descriptor: [Idiopathic Interstitial Pneumonias] explode all trees	222
#23	IIP:ti,ab	132
#24	(hypersensitivity NEAR/3 pneumonia*):ti,ab	4
#25	pleuroparenchymal fibroelastosis:ti,ab	2
#26	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #10 or #11 or #12 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 #24 or #25	3262
#27	MeSH descriptor: [Randomized Controlled Trial] explode all trees	125
#28	(randomi?ed control* or rct):ti	160385
#29	MeSH descriptor: [Random Allocation] explode all trees	20591
#30	MeSH descriptor: [Single-Blind Method] explode all trees	19470
#31	single blind:ti,ab	45211
#32	MeSH descriptor: [Double-Blind Method] explode all trees	132095
#33	double blind:ti,ab	204710
#34	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4):ti,ab	131650
#35	((singl* or doubl* or treb* or tripl*) NEXT (blind* or mask*)):ti,ab	247479
#36	(allocat* NEAR/3 random*):ti,ab	40555
#37	placebo*:ti,ab	272418

ID	Search	Results
#38	MeSH descriptor: [Prospective Studies] explode all trees	87908
#39	(prospective NEXT (trial or study)):ti,ab	27139
#40	MeSH descriptor: [Controlled Clinical Trial] explode all trees	134
#41	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	13900
#42	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 #39 or #40 or #41	607124
#43	MeSH descriptor: [Case Reports] explode all trees	0
#44	case stud*:ti	12392
#45	case report?:ti	733
#46	(letter or editorial):ti	1559
#47	#43 or #44 or #45 or #46	14584
#48	#42 not #47	601332
#49	nintedanib:ti,ab	356
#50	(Vargatef or Ofev):ti,ab	20
#51	pirfenidone:ti,ab	303
#52	(Esbriet or Pirespa or Etuary):ti,ab	15
#53	MeSH descriptor: [Azathioprine] explode all trees	1169
#54	(azathioprine or Imuran or Azasan):ti,ab	2498
#55	MeSH descriptor: [Cyclophosphamide] explode all trees	5079
#56	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan):ti,ab	9452
#57	MeSH descriptor: [Rituximab] explode all trees	970
#58	(rituximab or Rituxan or Mabthera):ti,ab	4108
#59	MeSH descriptor: [Mycophenolic Acid] explode all trees	1236
#60	(Mycophenolate mofetil or Mycophenolic acid or Cellcept):ti,ab	2864
#61	MeSH descriptor: [Prednisone] explode all trees	3679
#62	(corticosteroid? or predniso*):ti,ab	28501
#63	MeSH descriptor: [Prednisolone] explode all trees	4513
#64	tocilizumab:ti,ab	873
#65	(Acterma or RoActerma or Atlizumab):ti,ab	2
#66	MeSH descriptor: [Abatacept] explode all trees	221
#67	(abatacept or orencia):ti,ab	617
#68	MeSH descriptor: [Methotrexate] explode all trees	3770
#69	methotrexate:ti,ab	8965
#70	(Otrexup or Rasurvo or Rheumatrex or Trexall):ti,ab	2
#71	MeSH descriptor: [Etanercept] explode all trees	651
#72	(etanercept or enbrel):ti,ab	1921
#73	MeSH descriptor: [Infliximab] explode all trees	660
#74	(infliximab or remicade):ti,ab	2175
#75	MeSH descriptor: [Adalimumab] explode all trees	579
#76	(adalimumab or humira):ti,ab	2566
#77	#49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76	55790
#78	#26 and #48 and #77	598

Table 72: Cochrane search strategy and results, 29th October 2019

ID	Search	Results
#1	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	733
#2	ILD:ti,ab	454
#3	MeSH descriptor: [Pulmonary Fibrosis] explode all trees	428

ID	Search	Results
#4	(interstitial* NEAR/3 (lung* NEAR/3 disease*)):ti,ab	790
#5	(interstitial* NEAR/3 (fibros* or pneumonitis or pneumonia or pneumopathy)):ti,ab	662
#6	alveolitis:ti,ab	125
#7	(diffuse* NEAR/3 parenchymal*):ti,ab	16
#8	MeSH descriptor: [Bronchiolitis Obliterans] explode all trees	62
#9	(bronchiolitis NEXT obliterans):ti,ab	152
#10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis):ti,ab	60
#11	MeSH descriptor: [Pneumoconiosis] explode all trees	96
#12	bagassosis:ti,ab	0
#13	((bird* or farmer* or pigeon* or avian* or budgerigar*) NEXT (lung* or disease*)):ti,ab	8
#14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis):ti,ab	138
#15	((pulmonary* or lung*) NEAR/3 reticulation*):ti,ab	1
#16	((pulmonary* or lung*) NEAR/3 fibros*):ti,ab	1597
#17	MeSH descriptor: [Alveolitis, Extrinsic Allergic] explode all trees	25
#18	(connective NEAR/3 lung*):ti,ab	10
#19	(allerg* NEAR/3 pneumonitis):ti,ab	0
#20	MeSH descriptor: [Cryptogenic Organizing Pneumonia] explode all trees	4
#21	cryptogenic organi*ing pneumonia:ti,ab	12
#22	MeSH descriptor: [Idiopathic Interstitial Pneumonias] explode all trees	229
#23	IIP:ti,ab	136
#24	(hypersensitivity NEAR/3 pneumonia*):ti,ab	5
#25	pleuroparenchymal fibroelastosis:ti,ab	2
#26	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #10 or #11 or #12 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 #24 or #25	3348
#27	MeSH descriptor: [Randomized Controlled Trial] explode all trees	125
#28	(randomi?ed control* or rct):ti	165752
#29	MeSH descriptor: [Random Allocation] explode all trees	20596
#30	MeSH descriptor: [Single-Blind Method] explode all trees	19673
#31	single blind:ti,ab	46099
#32	MeSH descriptor: [Double-Blind Method] explode all trees	133003
#33	double blind:ti,ab	207747
#34	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4):ti,ab	135699
#35	((singl* or doubl* or treb* or tripl*) NEXT (blind* or mask*)):ti,ab	251684
#36	(allocat* NEAR/3 random*):ti,ab	41317
#37	placebo*:ti,ab	276076
#38	MeSH descriptor: [Prospective Studies] explode all trees	88592
#39	(prospective NEXT (trial or study)):ti,ab	27532
#40	MeSH descriptor: [Controlled Clinical Trial] explode all trees	134
#41	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	13967
#42	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 #39 or #40 or #41	618626
#43	MeSH descriptor: [Case Reports] explode all trees	0
#44	case stud*:ti	12750
#45	case report?:ti	749
#46	(letter or editorial):ti	1605
#47	#43 or #44 or #45 or #46	15004
#48	#42 not #47	612659
#49	nintedanib:ti,ab	378
#50	(Vargatef or Ofev):ti,ab	20

ID	Search	Results
#51	pirfenidone:ti,ab	306
#52	(Esbriet or Pirespa or Etuary):ti,ab	15
#53	MeSH descriptor: [Azathioprine] explode all trees	1171
#54	(azathioprine or Imuran or Azasan):ti,ab	2493
#55	MeSH descriptor: [Cyclophosphamide] explode all trees	5113
#56	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan):ti,ab	9566
#57	MeSH descriptor: [Rituximab] explode all trees	990
#58	(rituximab or Rituxan or Mabthera):ti,ab	4239
#59	MeSH descriptor: [Mycophenolic Acid] explode all trees	1243
#60	(Mycophenolate mofetil or Mycophenolic acid or Cellcept):ti,ab	2894
#61	MeSH descriptor: [Prednisone] explode all trees	3701
#62	(corticosteroid? or predniso*):ti,ab	28747
#63	MeSH descriptor: [Prednisolone] explode all trees	4549
#64	tocilizumab:ti,ab	940
#65	(Acterma or RoActerma or Atlizumab):ti,ab	2
#66	MeSH descriptor: [Abatacept] explode all trees	223
#67	(abatacept or orencia):ti,ab	650
#68	MeSH descriptor: [Methotrexate] explode all trees	3793
#69	methotrexate:ti,ab	9153
#70	(Otrexup or Rasurvo or Rheumatrex or Trexall):ti,ab	2
#71	MeSH descriptor: [Etanercept] explode all trees	659
#72	(etanercept or enbrel):ti,ab	1973
#73	MeSH descriptor: [Infliximab] explode all trees	660
#74	(infliximab or remicade):ti,ab	2215
#75	MeSH descriptor: [Adalimumab] explode all trees	594
#76	(adalimumab or humira):ti,ab	2715
#77	#49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76	56621
#78	#26 and #48 and #77 with Cochrane Library publication date Between Aug 2019 and Oct 2019	21

Table 73: Supplementary and conference abstract search strategies and results

Source	Terms
Clinicaltrials.gov (searched 13th August 2019)	**Condition:** interstitial lung disease OR ILD OR pulmonary fibrosis OR lung fibrosis OR fibrosing lung disease **Intervention:** Nintedanib OR Pirfenidone OR Azathioprine OR Cyclophosphamide OR Rituximab OR Mycophenolate mofetil OR Corticosteroid OR Corticosteroids OR Methotrexate OR Tocilizumab OR Abatacept OR Infliximab OR Etanercept OR Adalimumab Phases 2,3,4 Date of trial start 01/01/2010 to 13/08/2019 Interventional studies (clinical trials) No other limits applied Results: 63 studies found

The WHO International Clinical Trials Registry Platform (searched 13th August 2019)	**Condition:** interstitial lung disease OR ILD OR pulmonary fibros* OR lung fibros* OR fibrosing lung disease* **Intervention:** Nintedanib OR Pirfenidone OR Azathioprine OR Cyclophosphamide OR Rituximab OR Mycophenolate mofetil OR Corticosteroid* OR Methotrexate OR Tocilizumab OR Abatacept OR Infliximab OR Etanercept OR Adalimumab Recruitment status: ALL Phases 2, 3, 4 Date of trial registration 01/01/2010 to 13/08/2019 No other limits applied Results: 342 records for 254 trials found
The American Thoracic Society (ATS) International Conference 2019	**Method (advanced search):** interstitial lung disease OR ILD OR pulmonary fibros* OR lung fibros* OR fibrosing lung disease* (anywhere) + Nintedanib OR Pirfenidone OR Azathioprine OR Cyclophosphamide OR Rituximab OR Mycophenolate mofetil OR Corticosteroid* OR Methotrexate OR Tocilizumab OR Abatacept OR Infliximab OR Etanercept OR Adalimumab (anywhere) Published in: American Thoracic Society International Conference Abstracts Publication date: 2019 to 2019
The British Thoracic Society (BTS) Winter Meeting 2018	**Method:** Advance search with “interstitial lung disease” Search through the relevant title headings: https://thorax.bmj.com/content/73/Suppl_4 Studies None identified
The European League Against Rheumatism (EULAR) - European Congress of Rheumatology (2019 congress)	**Method:** Basic search of PDF book: http://congress.eular.org/myUploadData/files/eular_2019_abstracts_lores.pdf Search terms: interstitial lung disease OR pulmonary fibros OR lung fibros OR fibrosing lung disease (anywhere) Nintedanib OR Pirfenidone

D.1.1.2 Study selection

Results of the electronic searches that were carried out on 13th August 2019 were downloaded into an EndNote library and duplicates were removed. The references were then uploaded to the DistillerSR (Evidence Partners, Ottawa, Canada) systematic review software for screening. Results of the electronic searches for the update carried out on 29th October 2019 were imported into a separate EndNote library and duplicates were removed. References from the two libraries were then combined and additional references from the update were then uploaded to DistillerSR for screening.

Titles and abstracts were assessed against the eligibility criteria shown in Table 74. As PF-ILD is a relatively new disease area, expert clinical opinion was sought to reach a set of criteria that would help determine whether trial patients would be considered as having a progressive-fibrosing phenotype.

One reviewer assessed all titles and abstracts for inclusion and another reviewer independently checked 40% of these. A third reviewer carried out a 20% quality check of the remaining 60% of references that were screened by reviewer 1. Discrepancies between the reviewers were resolved through discussion. Any studies that appeared to meet the inclusion criteria were ordered and assessed for inclusion in full text by two independent reviewers using the criteria shown in Table 1. A third reviewer carried out a 20% quality check of all full texts. Discrepancies between the reviewers were again resolved through discussion.

Table 74: Study eligibility criteria

Study aspect	Inclusion and exclusion criteria
Patient population	Include: • Studies including any proportion of patients with ILD and progressive fibrosing phenotype (defined as): o FVC – any decline in FVC % predicted at baseline o DLCO – any decline in DLCO at baseline o HRCT – worsening of fibrotic features on imaging; images identifying progression of disease o Reference to the progression of lung fibrosis (without any disease specific criteria) are to be included. Exclude: • Patients with IPF
Intervention & Comparator	Include: Any dose of the following therapies: • Nintedanib • Pirfenidone • Azathioprine • Cyclophosphamide • Rituximab • Mycophenolate mofetil • Corticosteroids • Methotrexate • Tocilizumab • Abatacept • Infliximab • Etanercept • Adalimumab Comparators: • Any

Study aspect	Inclusion and exclusion criteria
Outcomes	Include: Main outcomes: • FVC • Progression-free survival/time to progression • Overall survival • Disease-related survival • Acute exacerbation of fibrosis / acute respiratory worsening Additional Outcomes • FEV1 • FEV1/FVC • VC • TLC • DLco • HRCT • Corticosteroid sparing/corticosteroid use • Adverse events • Hospitalisation • Activity measures including, but not restricted to: o 6MWD test • Health related quality of life measures including, but not restricted to: o SGRQ o K-BILD o EQ-5D o SF-36 o HAQ-DI o VAS
Study design	Include: 1. RCTs only Exclude: 2. All other types of study design
Limits	English language only
Timespan	No limits

Abbreviations: 6MWD, 6-minute walk distance; DLCO, diffusing capacity of the lung for carbon monoxide; EQ-5D, EuroQol-5 dimensions questionnaire; FVC, forced vital capacity; HAQ-DI, health assessment questionnaire disability index; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; K-BILD, King's brief interstitial lung disease questionnaire; RCT, randomised controlled trial; SF-36, 36-item short form health survey; SGRQ, St George's respiratory questionnaire; TLC, total lung capacity; VAS, visual analogue scale; VC, Vital Capacity; TLC, total lung capacity.

A data extraction table was designed for the collection of each outcome and methods of reporting outcomes. Details on the study design, population characteristics, interventions, timepoints and outcomes of interest were extracted. Data extraction of included studies was carried out by one reviewer. To ensure consistency and accuracy, another reviewer checked the data extracted.

The methodological quality of included studies was assessed during data extraction using the Cochrane Risk of Bias Tool.(95) Quality assessment of included studies was carried out by one reviewer. To ensure consistency and accuracy, another reviewer checked the quality assessment.

D.1.1.2.1 SLR results

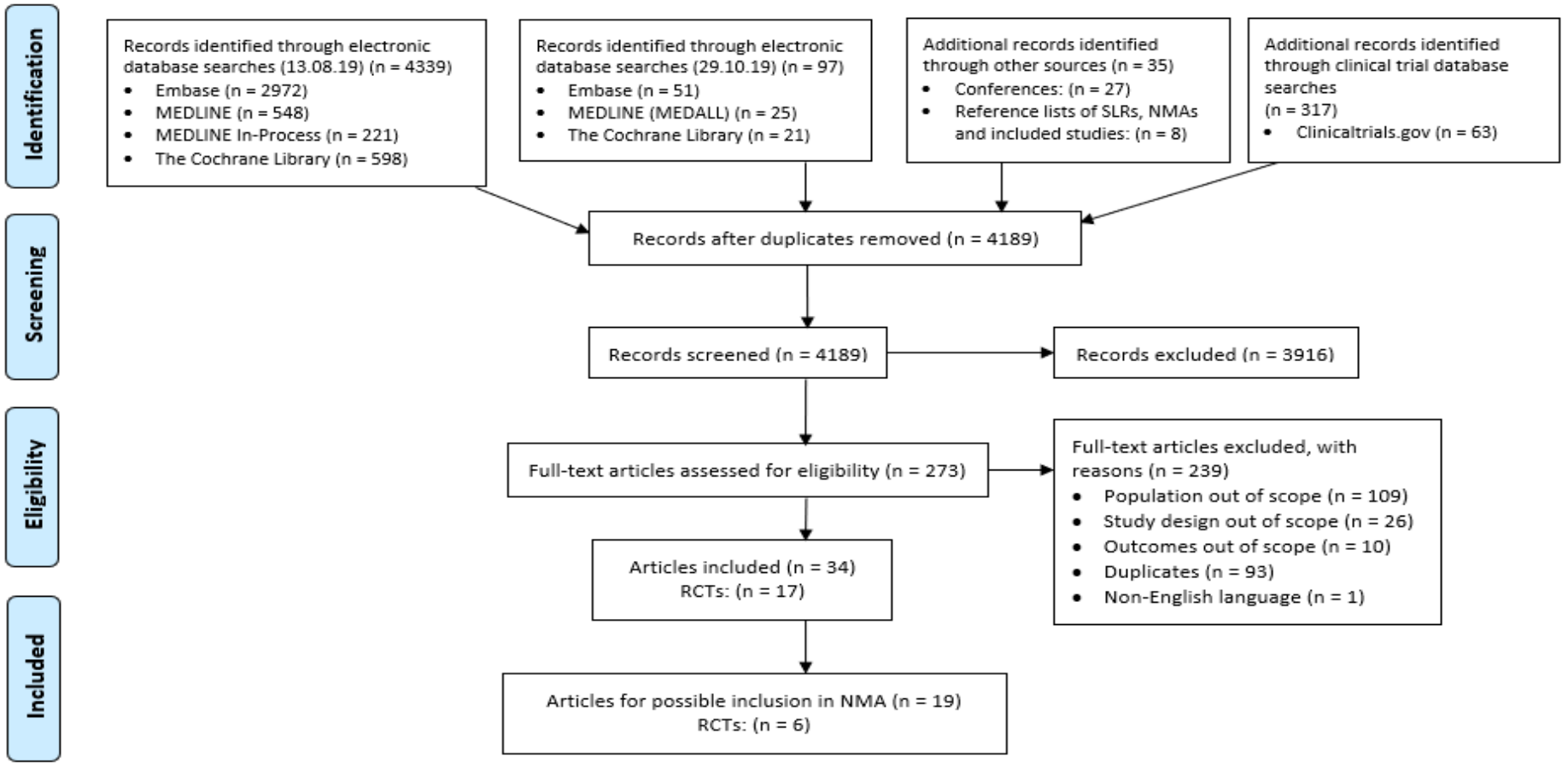
The results of the searches are summarised in the PRISMA diagram in Figure 40. In total 4,339 records were identified from the initial electronic searches carried out in August 2019, and 97 additional records were identified in the search update carried out in October 2019.

Supplementary searches identified 27 additional records from conferences and 317 additional records from clinical trial databases. After the removal of duplicates, a total of 4,189 records remained, and these were assessed for inclusion based on the titles and abstracts. Clinical trial records were assessed for inclusion based on the titles and information provided in the protocol on the date of assessment (13th August 2019).

Two hundred and seventy-three articles were assessed for eligibility at the full-text review stage. A total of 34 publications were finally included in the review, reporting on 17 randomised controlled trials (RCTs). The review also identified 8 SLR and NMA publications. After checking the lists of included studies and bibliographies in the SLR and NMA publications, no further articles were identified for inclusion in this review.

Data extraction was carried out for 6 of the included trials from a total of 19 articles. The remaining 15 articles identifying 11 RCTs were protocols with no published results and therefore there was no data extracted from them. To ensure accuracy in data extraction, one reviewer carried out the data extraction while another reviewer validated the extracted data.

Figure 40: PRISMA flow diagram



Abbreviations: n, number; NMA, network meta-analyses; RCT, randomised clinical trial; SLR, systematic literature review.

D.1.1.2.2 Complete reference lists for included studies and excluded studies

An overview of the included studies with data is given in Table 75. A list of included trials that only had protocols available is given in Table 76. A full list of all references identified for inclusion in the review is given in Table 77.

Articles excluded based on full text are listed in Table 78 to Table 81.

Table 75: Overview of included studies with data

Trial (main reference)	Underlying disease	Intervention and comparator	Baseline FVC_1 (% predicted normal) mean	Definition of progressive fibrosing phenotype
NCT00001596(42)	Hermansky–Pudlak syndrome	Pirfenidone dose was escalated to reach 801 mg t.i.d	72.9 (SD 7.9)	Not defined
		Placebo	73.5 (SD 9.7)	
Gahl 2002 (43)	Hermansky–Pudlak syndrome	Pirfenidone 800 mg t.i.d.	66.5 (SD 13.7)	Defined as either a greater than 5% absolute decline in percent predicted FVC or significant symptomatic worsening not due to cardiac, pulmonary (except worsening of underlying uILD), vascular, or other causes (as determined by the investigator) within the previous 6 months
		Placebo	64.8 (SD 13.6)	
NCT03099187(45)	unclassifiable ILD	Pirfenidone 801 mg t.i.d.	Median (Q1–Q3): 71.0 (59.0–87.3)	Not defined
		Placebo	Median (Q1–Q3): 71.5 (58.0–88.0)	
RELIEF(44)	collagen-vascular disease-ILD; fibrotic non-specific interstitial pneumonia; chronic hypersensitivity pneumonitis; asbestos-related lung fibrosis	Pirfenidone 2403 mg per day	NR	Annual decline in percentage predicted of FVC of more than 5 %
		Placebo	NR	
INBUILD(5)	Hypersensitivity pneumonitis:25.3% Autoimmune ILDs: 24.7% Idiopathic non-specific Interstitial pneumonia: 19.3% Unclassifiable IIP: 19.3%	Nintedanib 150 mg twice daily	68.7 (SD 16.0)	Either: a relative decline in the FVC of at least 10% of the predicted value, a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or, an

Trial (main reference)	Underlying disease	Intervention and comparator	Baseline FVC_1 (% predicted normal) mean	Definition of progressive fibrosing phenotype
	Other ILDs:11.4%	Placebo	69.3 (SD 15.2)	increased extent of fibrosis on HRCT, or worsening of respiratory symptoms and an increased extent of fibrosis within the 24 months before screening, despite standard treatment with an agent other than nintedanib or pirfenidone:
Wyser 1997(41)	Sarcoidosis	Prednisone 20 mg/day for 3 months, followed by 15 mg/day for 3 months and 10 mg/d for up to 18 months combined with cyclosporin A, 5 to 7 mg/kg/d	67.4 (SE 3.2)	Not defined
		Prednisone 20 mg/day for 3 months, followed by 15 mg/day for 3 months and 10 mg/day for up to 18 months	70.4 (SE 4.2)	

Abbreviations: FVC, forced vital capacity; HRCT, high resolution computed tomography; IIP, idiopathic interstitial pneumonia ILD; interstitial lung disease; Q1, median of upper half of data; Q3, median of middle half of data; SD, standard deviation; SE, standard error; t.i.d, three times a day; uILD, unclassifiable interstitial lung disease.

Table 76: Overview of included trials that only had protocols available

Trial (number)	Trial design	Trial duration	Intervention and comparator - dose	Type of ILD	Definition of progressive fibrosing phenotype	Primary outcome(s)
RECITAL trial; NCT01862926(96-98)	multicentre, prospective, randomised, double-blind, double-dummy trial	48 weeks	Rituximab – 1g given at baseline and two weeks Cyclophosphamide – IV 600 mg/m2 body surface area. 6 doses given 4 weekly	severe, progressive Connective Tissue Disease-ILD	"Severe and/or progressive interstitial lung disease"	Absolute rate of change in FVC at week 24
TRIAL 1 trial; NCT02808871(99)	phase 2, randomized, double blind, placebo controlled trial	52 weeks	Pirfenidone – three times daily (2403 mg) for 52 weeks Placebo – three times daily for 52 weeks	Rheumatoid Arthritis - ILD	Change in pre- and post-bronchodilator FVC (measured in liters) between Screening (Visit 1) and Visit 2 must be a <10% relative difference	Incidence of the composite endpoint of ≥ 10% predicted decline FVC of 10% or greater or death
PirFS trial; NCT03260556(100)	phase 4, randomized, double blind, placebo controlled trial	2 years	Pirfenidone – One 267 mg capsule three times a day for two weeks. Two 267 mg capsules three times a day for two weeks Three 267 mg capsules three times a day thereafter Placebo – same dosing schedule as intervention	Sarcoidosis	Study described as "Study comparing pirfenidone versus placebo for patients with advanced fibrotic sarcoidosis"	Time until clinical worsening
ATtackMy-ILD trial; NCT03215927(101)	multi-center randomized, placebo-controlled pilot study	24 weeks	Abatacept – 125 mg SC injection weekly for 24 weeks Placebo – SC injection weekly for 24 weeks	interstitial lung disease associated with the anti-synthetase syndrome	FVC 80-100% with > = 10% decline in FVC in last 12 months as minimal threshold of ILD severity	FVC % change from baseline to week 24 between the treatment arms

Trial (number)	Trial design	Trial duration	Intervention and comparator - dose	Type of ILD	Definition of progressive fibrosing phenotype	Primary outcome(s)
SCLEROCYC trial; NCT01570764(102)	Phase 3, randomized prospective multi-center study	12 months	Cyclophosphamide – prednisone 15 mg/d + monthly pulse cyclophosphamide 700 mg/m ² diminished to 600 mg/m ² in patients over 65 years or having a creatinine clearance lower than 30 ml/min for 12 months Placebo – prednisone 15 mg/d + monthly pulse of placebo of cyclophosphamide. The posology and the methods of administration of the placebo of cyclophosphamide (NaCl) will be the same as those used for cyclophosphamide	Systemic sclerosis	worsening ILD identified on a high-resolution chest CT scan and by worsening of FVC and/or TLC ≥10% and/or worsening of DLCO ≥ 15% as compared to values obtained within the 3 to 18 months preceding inclusion (for DLCO, in the absence of pulmonary arterial hypertension upon echocardiography)	FVC at 12 months
EvER-ILD trial; NCT02990286(103)	Phase 3, randomized controlled trial	6 months	Rituximab with Mycophenolate Mofetil – Rituximab 500mg concentrate for solution for infusion. One course of IV rituximab consisting of a first infusion of 1000 mg (500 ml solution) rituximab (day 1 infusion), and a second infusion	a broad range of patients with Interstitial Lung Diseases	A histological pattern of NSIP	Change in % predicted FVC from baseline to 6 months

Trial (number)	Trial design	Trial duration	Intervention and comparator - dose	Type of ILD	Definition of progressive fibrosing phenotype	Primary outcome(s)
			of 1000 mg (500 ml solution) rituximab two weeks later (day 15 infusion); Mycophenolate Mofetil 500mg film-coated tablets 1 gram twice daily on oral route of MMF (= 2 grams daily) for 6 months. Placebo Comparator - 500 ml of saline (0.9% sodium chloride) for infusion One course of IV placebo of rituximab consisting of a first infusion of 500 ml of saline (0.9% sodium chloride) infusion (day 1 infusion), and a second infusion of 500 ml of saline infusion two weeks later (day 15 infusion); Mycophenolate Mofetil 500mg film-coated tablets 1 gram twice daily on oral route of MMF (= 2 grams daily) for 6 months			
SLCTR/2018/031(104)	Phase 4, un-blinded, randomized controlled trial	12 months	Mycophenolate mofetil – 250mg bd dosage initially and will be titrated up to 2g/daily or maximum	Rheumatoid Arthritis - ILD	Indication of patients with lung fibrosis “Participants will be subject to base line	Absolute change in FVC (mL) and DLCO from baseline

Trial (number)	Trial design	Trial duration	Intervention and comparator - dose	Type of ILD	Definition of progressive fibrosing phenotype	Primary outcome(s)
			tolerating dose over a period of eight weeks. Azathioprine – 50mg daily at the beginning, increasing up to 2mg/kg or maximum tolerating dose over an eight weeks period. Both groups will be given prednisolone 0.5mg/kg up to a maximum dose of 25mg for the initial three months period which will be gradually tailed off over a three month period.		screening tests including pulmonary function test (Forced vital capacity (FVC) and carbon monoxide diffusion capacity (DLCO)) and high resolution computerized tomography chest (HRCT) to identify the radiological pattern and to assess the extent of lung fibrosis"	
NCT02821689(105)	Phase 4, open-label randomised controlled trial	12 months	Pirfenidone – administered in three divided doses (200mg tid), and increased to the manufacturer's instructed target dose (600mg tid) over a 2-week period. Investigators were allowed to adjust the dose according to the participants' tolerance "No Intervention: Blank Eligible participants for clinical trial were	Progressive Interstitial Lung Disease Associated With Clinically Amyopathic Dermatomyositis	worsening of fibrosis on pulmonary HRCT with >10% increase of HRCT score, and/or decrease in %FVC by >10% absolute value	changes of 12-month survival from the onset of ILD

Trial (number)	Trial design	Trial duration	Intervention and comparator - dose	Type of ILD	Definition of progressive fibrosing phenotype	Primary outcome(s)
			randomized in a 2:1 ratio to pirfenidone/blank add-on"			
NCT02370693(106)	Phase 2, randomized controlled trial	24 weeks	Bortezomib plus mycophenolate mofetil – Bortezomib 1.3 mg/m² subcutaneously (or IV push if unable to tolerate subcutaneous injection) once per week for the first two weeks per month and mycophenolate mofetil 1.5 g orally twice daily for 24 weeks Placebo plus mycophenolate mofetil – Placebo (normal saline) 1.3 mg/m² subcutaneously (or IV push if unable to tolerate subcutaneous injection) once per week for the first two weeks per month and mycophenolate mofetil 1.5 g orally twice daily for 24 weeks	Systemic sclerosis	Fall in FVC > 10% over the preceding 12 months or less in the absence of prior therapy or another identified causative process as assessed by the primary scleroderma physician Fall in FVC > 10% over 6 months on at least 12 months of prior therapy	Safety and Tolerability of bortezomib with mycophenolate mofetil assessed by the incidence of serious adverse events
SARCORT trial; NCT03265405(107)	Phase 4, randomized controlled trial	18 months	Low dose prednisolone – An initial dose of 20 mg/day will be administered for 8 weeks, followed by 15 mg/day for	Sarcoidosis	reduced lung function (defined as forced vital capacity or forced expiratory volume in one	Relapse or treatment failure

Trial (number)	Trial design	Trial duration	Intervention and comparator - dose	Type of ILD	Definition of progressive fibrosing phenotype	Primary outcome(s)
			8 weeks, 10 mg/day for 4 weeks, and 5 mg/day for 4 weeks, after which the drug will be discontinued. Medium dose prednisolone – An initial dose of 40 mg/day will be administered for 4 weeks, followed by 30 mg/day for 4 weeks, 20 mg/day for 4 weeks, 15 mg/day for 4 weeks, 10 mg/day for 4 weeks, and 5 mg/day for 4 weeks, after which the drug will be discontinued.		second (FEV1) less than 80% predicted)	
CTRIPS trial; NCT02370550(108)	Phase 4, Prospective, Randomized, Multicenter, Double-Blind Placebo-Controlled Trial	52 weeks	Cyclosporin A(CsA) + glucocorticoid – CsA 2-3 mg/kg/d, BID PO; Prednisone 0.5mg/kg/d QD PO starting at Week 0. After 2-4 weeks, the initial dose is gradually tapered by 2.5 mg each week until a maintenance dosage of 5-7.5 mg/d through week 52 (visit 6). The initial and maintenance doses are determined by the investigators of each centre depending on the patients; Calcium	Interstitial Pneumonitis Associated With Sjogren's Syndrome	Interstitial Pneumonitis - The disease area is Interstitial Pneumonitis which is characterised by progressive fibrosis of the lungs.	The FVC is expressed as percent of expected values corrected baseline level

Trial (number)	Trial design	Trial duration	Intervention and comparator - dose	Type of ILD	Definition of progressive fibrosing phenotype	Primary outcome(s)
			carbonate D 600 mg, QD PO Placebo + glucocorticoid - Placebo tablet 2-3 mg/kg/d, BID PO; Prednisone 0.5mg/kg/d QD PO starting at Week 0. After 2-4 weeks, the initial dose is gradually tapered by 2.5 mg each week until a maintenance dosage of 5-7.5 mg/d through week 52 (visit 6). The initial and maintenance doses are determined by the investigators of each centre depending on the patients; Calcium carbonate D 600 mg, QD PO			

Table 77: List of references included in the SLR

Authors	Reference
Gahl WA, Brantly M, Troendle J, et al.	Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome. Molecular Genetics & Metabolism 2002;76:234-42.
Brantly M, Troendle J, Avila N, et al.	A randomized, placebo-controlled trial of oral pirfenidone for the pulmonary fibrosis of Hermansky-Pudlak Syndrome. American journal of respiratory and critical care medicine. Volume 165, 2002:A728.
O'Brien K, Troendle J, Gochuico BR, et al.	Pirfenidone for the treatment of Hermansky-Pudlak syndrome pulmonary fibrosis. Molecular Genetics & Metabolism 2011;103:128-34.
Clinicaltrials.gov record	Oral Pirfenidone for the Pulmonary Fibrosis of Hermansky-Pudlak Syndrome. Https://clinicaltrials.gov/show/nct00001596, 1999.
Flaherty KR, Brown KK, Wells AU, et al.	Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. BMJ open respiratory research 2017;4:e000212.
European clinical trials record	Efficacy and safety of nintedanib in patients with PF-ILD. Http://www.who.int/trialsearch/trial2.aspx?Trialid=euctr2015-003360-37-es, 2016.
Flaherty KR, Wells AU, Cottin V, et al.	Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. New England Journal of Medicine 2019;381:1718-1727.
Drosos AA, Voulgari PV, Katsaraki A, et al.	Influence of cyclosporin A on radiological progression in early rheumatoid arthritis patients: A 42-month prospective study. Rheumatology International 2000;19:113-118.
Kevin R. Flaherty AUW, Vincent Cottin, Anand Devaraj, Yoshikazu Inoue, Luca Richeldi, Simon Walsh, Susanne Stowasser, Carl Coeck, Rainer-Georg Goeldner, Emmanuelle Clerisme-Beaty, Rozsa Schlenker-Herceg, Kevin K. Brown.	Nintedanib in patients with chronic fibrosing interstitial lung diseases with progressive phenotype: the INBUILD trial. In European Respiratory Society, 2019.
Maher TM, Corte TJ, Fischer A, et al.	Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: design of a double-blind, randomised, placebo-controlled phase II trial. BMJ open respiratory research 2018;5:e000289.
Maher TM, Corte TJ, Fischer A, et al.	Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: Demographic and baseline characteristics. American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS 2018;197.
European clinical trials record	A Study of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing Interstitial Lung Disease. Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2016-002744-17-be, 2018.

Authors	Reference
Maher TM, Corte TJ, Fischer A, et al.	Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. The Lancet Respiratory Medicine 2019;27:27.
M. Maher TJC, Aryeh Fischer, Michael Kreuter, David J. Lederer, Maria Molina-Molina, Judit Axmann, Klaus-Uwe Kirchgaessler, Katerina Samara, Frank Gilberg, Vincent Cottin.	Phase II Trial of Pirfenidone in Patients With Progressive Fibrosing Unclassifiable ILD (uILD). In European Respiratory Society International Congress, 2019.
Behr J, Neuser P, Prasse A, et al.	Exploring efficacy and safety of oral Pirfenidone for progressive, non-IPF lung fibrosis (RELIEF) - a randomized, double-blind, placebo-controlled, parallel group, multi-center, phase II trial. BMC Pulmonary Medicine 2017;17:122.
German Clinical Trials record	Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF) - A randomized, double-blind, placebo-controlled, parallel group,multi-center, phase II trial. Http://www.who.int/trialsearch/trial2.aspx? Trialid=drks00009822, 2016.
European Clinical Trials record	Standard-armed controlled study to assess the impact of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF). Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2014-000861-32-de, 2015.
Guenther A, Prasse A, Kreuter M, et al.	Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF). In European Respiratory Society, 2019.
Wyser C, van Schalkwyk E, Alheit B, et al.	Treatment of progressive pulmonary sarcoidosis with cyclosporin A. A randomized controlled trial. American journal of respiratory and critical care medicine. Volume 156, 1997:1371-1376.
Saunders P, Tsipouri V, Keir GJ, et al.	Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. Trials [Electronic Resource] 2017;18:275.
European Clinical Trials record	A trial of rituximab compared to usual best care in patients with interstitial (inflammatory or scarring conditions) lung disease due to systemic autoimmune (connective tissue) diseases. Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2012-003633-42-gb, 2013.
ISRCTN Clinical Trials record	Rituximab versus cyclophosphamide in connective tissue disease-ILD. Http://www.who.int/trialsearch/trial2.aspx?Trialid=isrctn16474148, 2015.
Clinicaltrials.gov record	Phase II Study of Pirfenidone in Patients With RAILD. Https://clinicaltrials.gov/show/nct02808871, 2016.
Solomon JJ, Danoff SK, Goldberg HJ, et al.	The Design and Rationale of the Trial1 Trial: A Randomized Double-Blind Phase 2 Clinical Trial of Pirfenidone in Rheumatoid Arthritis-Associated Interstitial Lung Disease. Advances in Therapy 2019;36:3279-3287.

Authors	Reference
Clinicaltrials.gov record	Pirfenidone for Progressive Fibrotic Sarcoidosis. Https://clinicaltrials.gov/show/nct03260556, 2017.
Clinicaltrials.gov record	Abatacept for the Treatment of Myositis-associated Interstitial Lung Disease. Https://clinicaltrials.gov/show/nct03215927, 2017.
Clinicaltrials.gov record	Cyclophosphamide Systemic Sclerosis Associated Interstitial Lung Disease. Https://clinicaltrials.gov/show/nct01570764, 2012.
Clinicaltrials.gov record	Evaluation of Efficacy and Safety of Rituximab With Mycophenolate Mofetil in Patients With Interstitial Lung Diseases. Https://clinicaltrials.gov/show/nct02990286, 2016.
Sri Lanka Clinical Trials Registry record	Effectiveness of mycophenolate mofetil vs azathioprin on progression of rheumatoid arthritis related interstitial lung disease in patients followed up at the rheumatology clinic, Teaching Hospital Karapitiya – a randomized controlled trial. Http://www.who.int/trialsearch/trial2.aspx?Trialid=slctr/2018/031, 2018.
Clinicaltrials.gov record	Pirfenidone in Progressive Interstitial Lung Disease Associated With Clinically Amyopathic Dermatomyositis, 2016.
Clinicaltrials.gov record	Comparing and Combining Bortezomib and Mycophenolate in SSc Pulmonary Fibrosis, 2019.
Clinicaltrials.gov record	Efficacy and Safety of Two Glucocorticoid Regimens in the Treatment of Sarcoidosis, 2019.
Clinicaltrials.gov record	Cyclosporine A in the TReatment of Interstitial Pneumonitis Associated With Sjogren's Syndrome. Https://clinicaltrials.gov/show/nct02370550, 2015.
Clinicaltrials.gov record	Cyclosporine A in the TReatment of Interstitial Pneumonitis Associated With Sjogren's Syndrome, 2015.

Table 78: Articles excluded due to population out of scope

Electronic database searches		
Author	**Title**	**Year**
O. Distler, K. B. Highland, M. Gahlemann, A. Azuma, A. Fischer, M. D. Mayes, G. Raghu, W. Sauter, M. Girard, M. Alves, E. Clerisme-Beaty, S. Stowasser, K. Tetzlaff, M. Kuwana, T. M. Maher and S. T. Investigators	Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease	2019
J. G. Goldin, D. A. Lynch, D. C. Strollo, R. D. Suh, D. E. Schraufnagel, P. J. Clements, R. M. Elashoff, D. E. Furst, S. Vasunilashorn, M. F. McNitt-Gray, M. S. Brown, M. D. Roth, D. P. Tashkin and G. Scleroderma Lung Study Research	High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease	2008
A. Pietinalho, P. Tukiainen, T. Haahtela, T. Persson and O. Selroos	Oral prednisolone followed by inhaled budesonide in newly diagnosed pulmonary sarcoidosis: a double-blind, placebo-controlled multicenter study. Finnish Pulmonary Sarcoidosis Study Group	1999
G. A. Yanik, M. M. Horowitz, D. J. Weisdorf, B. R. Logan, V. T. Ho, R. J. Soiffer, S. L. Carter, J. Wu, J. R. Wingard, N. L. Difronzo,	Randomized, double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor: enbrel	2014

J. L. Ferrara, S. Giralt, D. K. Madtes, R. Drexler, E. S. White and K. R. Cooke	(etanercept) for the treatment of idiopathic pneumonia syndrome after allogeneic stem cell transplantation: blood and marrow transplant clinical trials network protocol	
M. A. Johnson, S. Kwan, N. J. Snell, A. J. Nunn, J. H. Darbyshire and M. Turner-Warwick	Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis	1989
O. Distler, K. K. Brown, J. H. W. Distler, S. Assassi, T. M. Maher, V. Cottin, J. Varga, C. Coeck, M. Gahlemann, W. Sauter, H. Schmidt, K. B. Highland and S. t. investigators	Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCISTM)	2017
E. R. Volkmann, D. P. Tashkin, M. D. Roth, P. J. Clements, D. Khanna, D. E. Furst, M. Mayes, J. Charles, C. H. Tseng, R. M. Elashoff and S. Assassi	Changes in plasma CXCL4 levels are associated with improvements in lung function in patients receiving immunosuppressive therapy for systemic sclerosis-related interstitial lung disease	2016
D. P. Tashkin, M. D. Roth, P. J. Clements, D. E. Furst, D. Khanna, E. C. Kleerup, J. Goldin, E. Arriola, E. R. Volkmann, S. Kafaja, R. Silver, V. Steen, C. Strange, R. Wise, F. Wigley, M. Mayes, D. J. Riley, S. Hussain, S. Assassi, V. M. Hsu, B. Patel, K. Phillips, F. Martinez, J. Golden, M. K. Connolly, J. Varga, J. Dematte, M. E. Hinchcliff, A. Fischer, J. Swigris, R. Meehan, A. Theodore, R. Simms, S. Volkov, D. E. Schraufnagel, M. B. Scholand, T. Frech, J. A. Molitor, K. Highland, C. A. Read, M. J. Fritzler, G. H. J. Kim, C. H. Tseng, R. M. Elashoff and I. I. I. Sclerodema Lung Study	Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial	2016
D. Khanna, C. Albera, A. Fischer, N. Khalidi, G. Raghu, L. Chung, D. Chen, E. Schiopu, M. Tagliaferri, J. R. Seibold and E. Gorina	An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial	2016
K. Kamio, A. Azuma, K. Ohta, Y. Sugiyama, T. Nukiwa, S. Kudoh and T. Mizushima	Double-blind controlled trial of lecithinized superoxide dismutase in patients with idiopathic interstitial pneumonia - short term evaluation of safety and tolerability	2014
D. Perez Campos, M. Estevez Del Toro, A. Pena Casanovas, P. P. Gonzalez Rojas, L. Morales Sanchez and A. R. Gutierrez Rojas	Are high doses of prednisone necessary for treatment of interstitial lung disease in systemic sclerosis?	2012
A. C. Theodore, C. H. Tseng, N. Li, R. M. Elashoff and D. P. Tashkin	Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: findings from the Scleroderma Lung Study	2012
D. E. Furst, C. H. Tseng, P. J. Clements, C. Strange, D. P. Tashkin, M. D. Roth, D. Khanna, N. Li, R. Elashoff, D. E. Schraufnagel and S. Scleroderma Lung	Adverse events during the Scleroderma Lung Study	2011

D. S. Domiciano, E. Bonfa, C. T. Borges, R. A. Kairalla, V. L. Capelozzi, E. Parra and R. B. Christmann	A long-term prospective randomized controlled study of non-specific interstitial pneumonia (NSIP) treatment in scleroderma	2011
K. Au, M. D. Mayes, P. Maranian, P. J. Clements, D. Khanna, V. D. Steen, D. Tashkin, M. D. Roth, R. Elashoff and D. E. Furst	Course of dermal ulcers and musculoskeletal involvement in systemic sclerosis patients in the scleroderma lung study	2010
D. Daoussis, S. N. Liossis, A. C. Tsamandas, C. Kalogeropoulou, A. Kazantzi, C. Sirinian, M. Karampetsou, G. Yiannopoulos and A. P. Andonopoulos	Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study	2010
J. Goldin, R. Elashoff, H. J. Kim, X. Yan, D. Lynch, D. Strollo, M. D. Roth, P. Clements, D. E. Furst, D. Khanna, S. Vasunilashorn, G. Li and D. P. Tashkin	Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: findings from the scleroderma lung study	2009
D. P. Tashkin, R. Elashoff, P. J. Clements, M. D. Roth, D. E. Furst, R. M. Silver, J. Goldin, E. Arriola, C. Strange, M. B. Bolster, J. R. Seibold, D. J. Riley, V. M. Hsu, J. Varga, D. Schraufnagel, A. Theodore, R. Simms, R. Wise, F. Wigley, B. White, V. Steen, C. Read, M. Mayes, E. Parsley, K. Mubarak, M. K. Connolly, J. Golden, M. Olman, B. Fessler, N. Rothfield, M. Metersky, D. Khanna, N. Li, G. Li and G. Scleroderma Lung Study Research	Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease	2007
P. J. Clements, M. D. Roth, R. Elashoff, D. P. Tashkin, J. Goldin, R. M. Silver, M. Sterz, J. R. Seibold, D. Schraufnagel, R. W. Simms, M. Bolster, R. A. Wise, V. Steen, M. D. Mayes, K. Connelly, M. Metersky, D. E. Furst and G. Scleroderma Lung Study	Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis	2007
R. K. Hoyles, R. W. Ellis, J. Wellsbury, B. Lees, P. Newlands, N. S. Goh, C. Roberts, S. Desai, A. L. Herrick, N. J. McHugh, N. M. Foley, S. B. Pearson, P. Emery, D. J. Veale, C. P. Denton, A. U. Wells, C. M. Black and R. M. du Bois	A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma	2006
D. P. Tashkin, R. Elashoff, P. J. Clements, J. Goldin, M. D. Roth, D. E. Furst, E. Arriola, R. Silver, C. Strange, M. Bolster, J. R. Seibold, D. J. Riley, V. M. Hsu, J. Varga, D. E. Schraufnagel, A. Theodore, R. Simms, R. Wise, F. Wigley, B. White, V. Steen, C. Read, M. Mayes, E. Parsley, K. Mubarak, M. K. Connolly, J. Golden, M. Olman, B. Fessler, N. Rothfield, M. Metersky and G. Scleroderma Lung Study Research	Cyclophosphamide versus placebo in scleroderma lung disease	2006
D. Khanna, P. J. Clements, D. E. Furst, Y. Chon, R. Elashoff, M. D. Roth, M. G. Sterz, J. Chung, J. D. FitzGerald, J. R. Seibold, J. Varga, A. Theodore, F. M. Wigley, R. M. Silver, V. D. Steen, M. D. Mayes, M. K.	Correlation of the degree of dyspnea with health-related quality of life, functional abilities, and diffusing capacity for carbon monoxide in patients with systemic sclerosis and	2005

Connolly, B. J. Fessler, N. F. Rothfield, K. Mubarak, J. Molitor, D. P. Tashkin and G. Scleroderma Lung Study	active alveolitis: results from the Scleroderma Lung Study	
J. I. Kokkarinen, H. O. Tukiainen and E. O. Terho	Effect of corticosteroid treatment on the recovery of pulmonary function in farmer's lung	1992
A. Gulsvik, F. Kjelsberg, A. Bergmann, S. S. Froland, K. Rootwelt and J. R. Vale	High-dose intravenous methylprednisolone pulse therapy as initial treatment in cryptogenic fibrosing alveolitis. A pilot study	1986
J. G. Goldin, G. H. J. Kim, C.-H. Tseng, E. Volkmann, D. Furst, P. Clements, M. Brown, M. Roth, D. Khanna and D. P. Tashkin	Longitudinal Changes in Quantitative Interstitial Lung Disease on Computed Tomography after Immunosuppression in the Scleroderma Lung Study II	2018
G. Sircar, R. P. Goswami, D. Sircar, A. Ghosh and P. Ghosh	Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial	2018
E. R. Volkmann, D. P. Tashkin, M. Sim, N. Li, E. Goldmuntz, L. Keyes-Elstein, A. Pinckney, D. E. Furst, P. J. Clements, D. Khanna, V. Steen, D. E. Schraufnagel, S. Arami, V. Hsu, M. D. Roth, R. M. Elashoff, K. M. Sullivan, I. Sls and S. I. s. groups	Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts	2019
I. Miniati and M. Matucci Cerinic	Pulmonary fibrosis in systemic sclerosis: is treatment with cyclophosphamide more effective than placebo?	2007
T. Maher, K. Highland, M. Gahlemann, A. Azuma, A. Fischer, M. Mayes, G. Raghu, W. Sauter, M. Girard, M. Alves, E. Clerisme-Beaty, V. Kohlbrenner, M. Kuwana and O. Distler	Gastrointestinal adverse events in patients with systemic sclerosis-associated interstitial lung disease (ssc-ild) treated with nintedanib: Data from the senscis trial	2019
D. Khanna, D. Tashkin, A. Wells, J. Goldin, M. W. Lubell, S. Wax, D. Damian and C. Denton	A phase II randomized controlled trial of abituzumab in systemic sclerosis-associated interstitial lung disease	2018
G. H. Kim, D. P. Tashkin, M. S. Brown, E. Volkmann, P. Lo, D. W. Gjertson, P. Lu, D. Chong and J. Goldin	Using transitional changes on hrct to assess the impact of treatment with cyclophosphamide or mycophenolate on systemic sclerosis-related interstitial lung disease from scleroderma lung study II	2018
G. S. R. S. N. K. Naidu, M. B. Adarsh, S. Sharma, V. Dhir, S. Dhooria, A. Sinha and S. Jain	A randomized controlled trial to compare the efficacy of oral mycophenolate mofetil with placebo in patients with systemic sclerosis-related early interstitial lung disease	2018
C. P. Denton, D. Khanna, J. M. Van Laar, A. Jahreis, S. Cheng, H. Spotswood, J. Siegel and D. E. Furst	Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis: Week 24 data from a phase II/II trial	2015
H. Matsuno, M. Tomomitsu, A. Hagino, S. Shin, J. Lee and Y. W. Song	Phase III, multicentre, double-blind, randomised, parallel-group study to evaluate the similarities between LBEC0101 and etanercept reference product in terms of efficacy and safety in patients with active rheumatoid	2018

	arthritis inadequately responding to methotrexate	
G. Naidu, S. Sharma, V. Dhir, S. Dhooria, A. Sinha, A. Mb and S. Jain	A randomised controlled trial to compare the efficacy of oral mycophenolate mofetil with placebo in patients with systemic sclerosis related early interstitial lung disease	2018
D. P. Tashkin, E. Volkmann, M. Sim, M. Roth, P. Clements, D. E. Furst, R. Elashoff, L. Keyes-Elstein, A. Pinckney, E. Goldlmuntz and K. Sullivan	Predicting mortality in systemic sclerosis-related interstitial lung disease in two independent cohorts	2018
M. Boonstra, J. Meijs, A. L. Dorjee, N. A. Marsan, A. Schouffoer, M. K. Ninaber, K. D. Quint, F. Bonte-Mineur, T. W. J. Huizinga, H. U. Scherer and J. K. De Vries-Bouwstra	Rituximab in early systemic sclerosis	2017
G. Sircar, R. P. Goswami, D. Rath, A. Naskar, H. Sit, S. Haldar, P. Sinhamahapatra, A. Ghosh and P. Ghosh	A randomized controlled, open label trial of cyclophosphamide versus rituximab in diffuse systemic sclerosis	2017
E. R. Volkmann, D. P. Tashkin, M. Sim, D. Khanna, M. Roth, P. J. Clements, D. E. Furst, L. Keyes-Elstein, A. Pinckney, E. Goldmuntz, R. Elashoff and K. Sullivan	The course of the forced vital capacity during treatment for systemic sclerosis-related interstitial lung disease predicts long-term survival in 2 independent cohorts	2017
J. G. Goldin, G. J. Kim, E. Kleerup, R. Elashoff, P. Lu, P. Clements, M. D. Roth and D. P. Tashkin	Association of changes in quantitative CT with outcome measures in the scleroderma lung study II	2017
D. Porter, J. van Melckebeke, J. Dale, C. M. Messow, A. McConnachie, A. Walker, R. Munro, J. McLaren, E. McRorie, J. Packham, C. D. Buckley, J. Harvie, P. Taylor, E. Choy, C. Pitzalis and I. B. McInnes	Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial	2016
G. R. Burmester, A. Rubbert-Roth, A. Cantagrel, S. Hall, P. Leszczynski, D. Feldman, M. J. Rangaraj, G. Roane, C. Ludivico, M. Bao, L. Rowell, C. Davies and E. F. Mysler	Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA)	2016
T. Atsumi, K. Yamamoto, T. Takeuchi, H. Yamanaka, N. Ishiguro, Y. Tanaka, K. Eguchi, A. Watanabe, H. Origasa, S. Yasuda, Y. Yamanishi, Y. Kita, T. Matsubara, M. Iwamoto, T. Shoji, T. Okada, D. Van Der Heijde, N. Miyasaka and T. Koike	The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression	2016
E. R. Volkmann, D. Khanna, C. H. Tseng, R. Elashoff, B. Wang, M. Roth, P. J. Clements, D. E. Furst, A. Theodore and D. P. Tashkin	Improvement in cough and cough-related quality of life in participants undergoing treatment for systemic sclerosis-related interstitial lung disease	2016
J. Goldin, G. School, G. H. Kim, E. Kleerup, G. Kim, P. Clerments, M. Brown, M. Roth and D. Tashkin	Quantitative CT as an Outcome Measure in the Scleroderma Lung Study II	2016
D. Khanna, M. Roth, P. Clements, D. Furst, C. H. Tseng, R. Elashoff, E. Volkmann, S. Kafaja, J. Goldin and D. Tashkin	Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease: Scleroderma lung study II	2016
E. Volkmann, D. Tashkin, P. Clements, M. Roth, D. Furst, D. Khanna, C. H. Tseng, E. Arriola and R. Elashoff	Cyclophosphamide versus mycophenolate for systemic sclerosis-related interstitial lung disease	2015

D. Tashkin, M. Roth, P. Clements, D. Furst, D. Khanna, J. Goldin, E. Kleerup, E. Arriola, C. H. Tseng and R. Elashoff	Efficacy and safety of mycophenolate (MMF) Vs oral cyclophosphamide (CYC) for treatment of Scleroderma-Interstitial Lung Disease (SscILD): Results of scleroderma lung study II	2015
E. R. Volkmann, M. Roth, R. Elashoff, P. J. Clements, D. E. Furst, D. Khanna, J. Goldin and D. Tashkin	Safety and tolerability of cyclophosphamide versus mycophenolate for systemic sclerosis-related interstitial lung disease	2015
P. J. Clements, D. Tashkin, M. Roth, D. Khanna, D. E. Furst, C. H. Tseng, E. R. Volkmann and R. Elashoff	The scleroderma lung study II (SLS II) shows that both oral cyclophosphamide (CYC) and mycophenolate mofitil (MMF) are efficacious in treating progressive interstitial lung disease (ILD) in patients with systemic sclerosis (SSC)	2015
S. Chinnadurai, M. Madeshwaran, M. M. Kavitha, M. Saravanan, J. Euphrasia Latha and S. Rajeswari	Rituximab in mixed connective tissue disease-two year outcome from a tertiary care center in South India	2015
K. Yamamoto, T. Takeuchi, H. Yamanaka, N. Ishiguro, Y. Tanaka, K. Eguchi, A. Watanabe, H. Origasa, T. Shoji, Y. Sakamaki, D. Van Der Heijde, N. Miyasaka and T. Koike	Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial	2014
D. P. Tashkin, M. D. Roth, D. E. Furst, P. Clements, D. Khanna, J. G. Goldin, E. Arriola, J. Kotlerman, C. H. Tseng, G. Kim and R. Elashoff	Double-blind comparison of mycophenolate mofetil and oral cyclophosphamide for treatment of scleroderma-related interstitial lung disease (scleroderma lung study [SLS] II): Rationale, design, methods, baseline characteristics/intercorrelations and patient disposition	2013
D. Khanna, M. Roth, D. Furst, P. Clements, J. Goldin, E. Arriola, J. Kotlerman, C. H. Tseng, G. Kim, R. Elashoff and D. Tashkin	Double-blind comparison of mycophenolate mofetil and oral cyclophosphamide for treatment of scleroderma-related interstitial lung disease (scleroderma lung study [SLS] II): Rationale, design, methods, baseline characteristics and patient disposition	2013
M. H. Schiff, J. M. Kremer, A. Jahreis, E. Vernon, J. D. Isaacs and R. F. van Vollenhoven	Integrated safety in tocilizumab clinical trials	2011
M. D. Roth, C. H. Tseng, P. J. Clements, D. E. Furst, D. P. Tashkin, J. G. Goldin, D. Khanna, E. C. Kleerup, N. Li, D. Elashoff and R. M. Elashoff	Predicting treatment outcomes and responder subsets in scleroderma-related interstitial lung disease	2011
D. Furst, D. Khanna, C. H. Tseng, M. Mayes, M. Roth, J. Seibold, R. Simms, R. Elashoff, V. Hsu, K. Sullivan and D. Tashkin	Patients with systemic sclerosis (SSC) enrolled in the scleroderma lung study (SLS) have a high mortality within 5 years of stopping Cyclophosphamide (CYC)	2010
A. C. Theodore, C. Tseng and D. Tashkin	Correlation of cough with disease activity and treatment with cyclosphosphamide in scleroderma interstitial lung disease	2010

D. E. Furst, D. Khanna, P. J. Clements, K. Sullivan and D. P. Tashkin	Serious complications and mortality among 158 patients with systemic sclerosis (SSc) in the scleroderma lung study (SLS) followed for up to 9 years	2010
P. Seo, Y. I. Min, J. T. Holbrook, G. S. Hoffman, P. A. Merkel, R. Spiera, J. C. Davis, S. R. Ytterberg, E. W. St.Clair, W. J. McCune, U. Specks, N. B. Allen, R. A. Luqmani and J. H. Stone	Damage caused by Wegener's granulomatosis and its treatment: Prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET)	2005
M. C. Genovese, S. Cohen, L. Moreland, D. Lium, S. Robbins, R. Newmark and P. Bekker	Combination Therapy with Etanercept and Anakinra in the Treatment of Patients with Rheumatoid Arthritis Who Have Been Treated Unsuccessfully with Methotrexate	2004
I. A. Dabbous, J. S. Tkachyk and S. J. Stamm	A double-blind study on the effects of corticosteroids in the treatment of bronchiolitis	1966
	Design of the Wegener's Granulomatosis Etanercept Trial (WGET)	2002
M. Rossman, L. Newman, R. Baughman, A. Teirstein, S. Weinberger, W. Miller and B. Sands	A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis	2006
U. Jprn	Double-Blind, parallel-group comparison, investigators initiated phase II clinical trial of IDEC-C2B8 (Rituximab) in patients with Systemic Sclerosis	2017
G. Dy, E. Kim, M. Baumgart, M. Mattes, P. Ma, S. Gadgeel, J. Molina, K. Attwood and A. Adjei	A phase II randomized, placebo-controlled trial evaluating nintedanib versus placebo as prophylaxis against radiation pneumonitis in patients with unresectable non-small cell lung cancer (NSCLC) undergoing chemoradiation therapy (CRT): a National Comprehensive Cancer Network-sponsored study	2016
R. Baughman, M. Drent, M. Kavuru, M. Judson, U. Costabel, B. R. du, C. Albera, M. Brutsche, G. Davis, J. Donohue and et al.	Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement	2006
Nct	Study of Efficacy and Safety of Pirfenidone in Patients With Fibrotic Hypersensitivity Pneumonitis	2016
Nct	Abatacept for the Treatment of Relapsing, Non-Severe, Granulomatosis With Polyangiitis (Wegener's)	2014
J. Stone, P. Merkel, R. Spiera, P. Seo, C. Langford, G. Hoffman, C. Kallenberg, C. E. St, A. Turkiewicz, N. Tchao and et al.	Rituximab versus cyclophosphamide for ANCA-associated vasculitis	2010
E. Miloslavsky, U. Specks, P. Merkel, P. Seo, R. Spiera, C. Langford, G. Hoffman, C. Kallenberg, C. E. St, N. Tchao and et al.	Outcomes of nonsevere relapses in antineutrophil cytoplasmic antibody-associated vasculitis treated with glucocorticoids	2015
Nct	Maintenance of Remission With Rituximab Versus Azathioprine for Newly-diagnosed or Relapsing	2017

	Eosinophilic Granulomatosis With Polyangiitis	
G. Naidu, M. Adarsh, S. Sharma, V. Dhir, S. Dhooria, A. Sinha and S. Jain	A randomized controlled trial to compare the efficacy of oral mycophenolate mofetil with placebo in patients with systemic sclerosis-related early interstitial lung disease	2018
D. Tashkin, M. Roth, P. Clements, D. Furst, D. Khanna, J. Goldin, E. Kleerup, E. Arriola, C.-H. Tseng and R. Elashoff	Efficacy and safety of mycophenolate (MMF) Vs oral cyclophosphamide (CYC) for treatment of Scleroderma-Interstitial Lung Disease (SscILD): results of scleroderma lung study II	2015
E. Miloslavsky, U. Specks, P. Merkel, P. Seo, R. Spiera, C. Langford, G. Hoffman, C. Kallenberg, C. E. St, N. Tchao and et al.	Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody-associated vasculitis	2013
	Safety of etanercept in elderly patients with rheumatoid arthritis: a pooled analysis	2018
R. Baughman, D. Winget and E. Lower	Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial	2000
I. Euctr	A single-center randomized double-blind placebo-controlled trial “Treatment of Systemic Sclerosis with Rituximab: evaluation of the effectiveness of B-cell depletion therapy”	2013
Isrctn	Efficacy of rituximab in patients with systemic sclerosis	2008
H. Kim, M. Brown, R. Elashoff, G. Li, D. Gjertson, D. Lynch, D. Strollo, E. Kleerup, D. Chong, S. Shah and et al.	Quantitative texture-based assessment of one-year changes in fibrotic reticular patterns on HRCT in scleroderma lung disease treated with oral cyclophosphamide	2011
Slctr	Effectiveness of mycophenolate mofetil vs azathioprin on progression of rheumatoid arthritis related interstitial lung disease in patients followed up at the rheumatology clinic, Teaching Hospital Karapitiya – a randomized controlled trial	2018
Nct	Pirfenidone as Treatment of Skin Fibrosis in Systemic Sclerosis	2017
Ctri	A Trial to Compare Nintedanib With Placebo for Patients With Scleroderma Related Lung Fibrosis	2016
N. Euctr	INFLUENCE OF B CELL DEPLETION BY MONOCLONAL ANTI-CD20 ANTIBODIES IN SYSTEMIC SCLERODERMA - RItuximab In Scleroderma (RITIS)	2008
Nct	Clinical Trial to Assess the Efficacy of Rituximab and Azathioprine in the Treatment of Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) in Adult Patients With	2016

	Common Variable Immunodeficiency (CVID)	
A. Theodore, C. Tseng, N. Li, R. Elashoff and D. Tashkin	Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: findings from the Scleroderma Lung Study	2012
Nct	Study to Compare the Efficacy of Mycophenolate Mofetil in Systemic Sclerosis Related Early Interstitial Lung Disease	2016
D. Khanna, V. Nagaraja, C. Tseng, F. Abtin, R. Suh, G. Kim, A. Wells, D. Furst, P. Clements, M. Roth and et al.	Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials	2015
Ctri	to study the efficacy of pirfenidone in systemic sclerosis related interstitial lung disease	2018
I. Euctr	An Open-Label, Randomized, Phase 2 Study of the Safety and Tolerability of Pirfenidone when Administered to Patients with Systemic Sclerosis-Related Interstitial Lung Disease	2013
E. Volkmann, M. Sim, D. Tashkin, D. Khanna, P. Clements, M. Roth, D. Furst, A. Pickney, E. Goldmuntz, L. Keyes-Elstein and et al.	Treatment with cyclophosphamide for systemic sclerosis-related interstitial lung disease does not improve survival after 12 years of follow up	2017
D. Tashkin, P. Clements, M. Roth, D. Furst, N. Li and J. Chung	Two-year outcomes of one-year treatment with oral cyclophosphamide vs placebo for scleroderma-interstitial lung disease (SSc-ILD)	2007
	Etanercept plus standard therapy for Wegener's granulomatosis	2005
R. Seror, C. Pagnoux, M. Ruivard, I. Landru, D. Wahl, S. Rivière, S. Aussant, A. Mahr, P. Cohen, L. Mouthon and et al.	Treatment strategies and outcome of induction-refractory Wegener's granulomatosis or microscopic polyangiitis: analysis of 32 patients with first-line induction-refractory disease in the WEGENT trial	2010
G. Tomasson, M. Boers, M. Walsh, M. LaValley, D. Cuthbertson, S. Carette, J. Davis, G. Hoffman, N. Khalidi, C. Langford and et al.	Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's)	2012
Nct	Stop Exogenous Allergic Alveolitis (EAA) in Childhood	2015
Isrctn	A prospective randomised placebo controlled trial of treatment for fibrosing alveolitis in scleroderma	2002
D. Euctr	Stop allergic alveolitis in childhood	2014
Nct	Nintedanib Compared With Placebo in Treating Against Radiation-Induced Pneumonitis in Patients With Non-small Cell Lung Cancer That Cannot Be Removed by Surgery and Are Undergoing Chemoradiation Therapy	2015

Nct	Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis	2012
Akash, K.	Outcome of interstitial lung disease in patients with scleroderma, a 5 year prospective cohort study	2019
The American Thoracic Society (ATS) International Conference 2019		
C. Ryerson , M.R.J. Kolb , G.P. Cox , S. Shapera , J.J. Swigris , C.D. Fell , M. O'Brien , M. Yang , C. Cabalteja , O. Moran Mendoza	Characteristics of a Real-World Canadian Cohort of Patients with Idiopathic Pulmonary Fibrosis Treated with Pirfenidone	2019
O. Distler , K.B. Highland , M. Gahlemann , A. Azuma , A. Fischer , M. Mayes , G. Raghu , W. Sauter , M. Girard , M. Alves , E. Clerisme-Beaty , M. Kuwana , T.M. Maher , on behalf of the SENSCIS trial investigators	Nintedanib in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD): The SENSCIS Trial	2019
G. George , F. Romero , R.S. Summer	Acceleration of Idiopathic Pulmonary Fibrosis in the Setting of Bortezomib Therapy	2019
The European League Against Rheumatism (EULAR) - European Congress of Rheumatology (2019 congress)		
Oliver Distler1 , Kristin Highland2 , Martina Gahlemann3 , Arata Azuma4 , Aryeh Fischer5 , Maureen Mayes6 , Ganesh Raghu7 , Wiebke Sauter8 , Mannaig Girard9 , Margarida Alves10, Emmanuelle Clerisme-Beaty10, Susanne Stowasser10, Masataka Kuwana11, Toby M Maher12, SENSCIS trial investigators	OP0017: NINTEDANIB REDUCED DECLINE IN FORCED VITAL CAPACITY ACROSS SUBGROUPS OF PATIENTS WITH SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE: DATA FROM THE SENSCIS TRIAL	2019
Kristin Highland*1 , Oliver Distler2 , Martina Gahlemann3 , Arata Azuma4 , Aryeh Fischer5 , Maureen Mayes6 , Ganesh Raghu7 , Wiebke Sauter8 , Mannaig Girard9 , Veronika Kohlbrenner10, Emmanuelle Clerisme-Beaty11, Susanne Stowasser11, Masataka Kuwana12, Toby M Maher13, SENSCIS trial investigators	OP0242: SAFETY PROFILE OF NINTEDANIB IN PATIENTS WITH SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE AND IDIOPATHIC PULMONARY FIBROSIS	2019
Nupoor Acharya1, Debasish Mishra1, Sahajal Dhooria2, Varun Dhir1, Sanjay Jain1, Shefali Khanna Sharma1	OP0243: EFFICACY OF PIRFENIDONE IN SYSTEMIC SCLEROSIS RELATED INTERSTITIAL LUNG DISEASE – A RANDOMISED CONTROLLED TRIAL	2019
Dinesh Khanna1, Celia J. F. Lin2, Jonathan Goldin3, Grace Kim3, Masataka Kuwana4, Yannick Allanore5, Anastas Batalov6, Irena Butrimiene7, Patricia Carreira8, Marco Matucci-Cerinic9, Oliver Distler10, Dušanka Martinović Kaliterna11, Carina Mihai12, Mette Mogensen13, Marzena Olesińska14, Janet Pope15, Gabriela Riemekasten16, Tatiana Sofía Rodriguez-Reyne17, Maria Jose Santos18, Jacob M. van Laar19, Helen Spotswood20, Jeffrey Siegel2, Angelika Jahreis2, Daniel Furst3, Christopher Denton2	OP0245: PRESERVATION OF LUNG FUNCTION OBSERVED IN A PHASE 3 RANDOMIZED CONTROLLED TRIAL OF TOCILIZUMAB FOR THE TREATMENT OF EARLY SSC	2019
Toby Maher1 , Kristin Highland2 , Martina Gahlemann3 , Arata Azuma4 , Aryeh Fischer5 , Maureen Mayes6 , Ganesh Raghu7 , Wiebke Sauter8 , Mannaig Girard9	FRI0301: GASTROINTESTINAL ADVERSE EVENTS IN PATIENTS WITH SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG	2019

, Margarida Alves10, Emmanuelle Clerisme-Beaty10, Veronika Kohlbrenner11, Masataka Kuwana12, Oliver Distler13	DISEASE (SSC-ILD) TREATED WITH NINTEDANIB: DATA FROM THE SENSCIS TRIAL	

Table 79: Articles excluded due to study design out of scope

Electronic database searches		
Author	**Title**	**Year**
J. K. Dawson, D. R. Graham, J. Desmond, H. E. Fewins and M. P. Lynch	Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT scanning and pulmonary function tests	2002
E. R. Volkmann, D. P. Tashkin, N. Li, M. D. Roth, D. Khanna, A. M. Hoffmann-Vold, G. Kim, J. Goldin, P. J. Clements, D. E. Furst and R. M. Elashoff	Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II	2017
E. R. Volkmann, D. P. Tashkin, M. Sim, N. Li, D. Khanna, M. D. Roth, P. J. Clements, A.-M. Hoffmann-Vold, D. E. Furst, G. Kim, J. Goldin and R. M. Elashoff	Cyclophosphamide for Systemic Sclerosis-related Interstitial Lung Disease: A Comparison of Scleroderma Lung Study I and II	2019
A. Sharma, D. Provenzale, A. McKusick and M. M. Kaplan	Interstitial pneumonitis after low-dose methotrexate therapy in primary biliary cirrhosis	1994
E. R. Volkmann, D. P. Tashkin, M. Sim, N. Li, D. Khanna, M. Roth, P. J. Clements, A. M. Hoffmann-Vold, D. E. Furst, G. Kim, J. Goldin and R. Elashoff	Treatment with cyclophosphamide for systemic sclerosis-interstitial lung disease does not lead to a sustained improvement in lung function in two independent cohorts	2017
E. R. Volkmann, D. P. Tashkin, N. Li, M. Roth, D. Khanna, A. M. Hoffmann-Vold, P. J. Clements, D. E. Furst and R. Elashoff	Mycophenolate versus placebo for the treatment of systemic sclerosis-related interstitial lung disease	2016
H. Ohkubo, K. Fukumitsu and A. Niimi	Refractory interstitial lung disease of dermatomyositis: A proposal for a prospective trial for establishing evidence	2015
A. L. Duchange, L. Mouthon, A. Berezne, S. Morell-Dubois, P. Y. Hatron, L. Guillevin, E. Hachulla and D. Launay	Therapeutic strategy combining intravenous cyclophosphamide followed by oral mycophe-nolate mofetil to treat severe or worsening interstitial lung disease associated with systemic sclerosis	2010
H. D. Montenegro, G. M. Fleming and E. H. Chester	Beneficial effect of steroid therapy in diffuse interstitial lung disease monitored by serial gas exchange studies	1976
O. ChiCtr	The open randomized controlled multicenter clinical study of the treatment of connective tissue diseases related interstitial lung disease with cyclophosphamide and mycophenolate mofetil	2012
Tsuji, H.,Nakashima, R.,Hosono, Y.,Imura, Y.,Yagita, M.,Yoshifuji, H.,Hirata, S.,Nojima, T.,Sugiyama, E.,Hatta, K.,Taguchi, Y.,Katayama, M.,Tanizawa, K.,Handa,	A Multicenter Prospective Study of the Efficacy and Safety of Combined Immunosuppressive Therapy with High-Dose Glucocorticoid, Tacrolimus,	2019

T.,Uozumi, R.,Akizuki, S.,Murakami, K.,Hashimoto, M.,Tanaka, M.,Ohmura, K.,Mimori, T.	and Cyclophosphamide in Interstitial Lung Diseases Accompanied by Anti-Melanoma Differentiation-Associated Gene 5-Positive Dermatomyositis	
The American Thoracic Society (ATS) International Conference 2019		
Author	**Title**	**Year**
F.B.R. Mbaye , K. Thiam , M.F. Cissé , Y. Dia Kane , F. Comanbani Koudessi , N.O. Touré	The Place of Respiratory Manifestations During Scleroderma in Dakar: A Multicentric Study	2019
S. Blumhof , R. Crowe , P. Acosta Lara , T. Kulkarni , T. Luckhardt	When the Solution Is the Problem Successful Treatment of Etanercept Induced Granulomatous Interstitial Lung Disease with an Alternate Anti Tumor Necrosis Factor Alpha Inhibitor	2019
N. Klauer , W.W. Wilson , C. Lee , S.M. Montner , M.E. Strek	Occupational Exposures as a Cause of Systemic Sclerosis Related Interstitial Lung Disease	2019
K. Twomey , L. Domaradzki , M.J. Stefanski	The Pneumonia That Won't Resolve in a Patient with Primary Biliary Cholangitis	2019
A. Abdou , A. Kotecha , M. Mandeel , V. Hannosh , G. Krishnamoorthy	RNA Polymerase III Antibody Positive Systemic Sclerosis with Cystic Interstitial Lung Disease and Pulmonary Hypertension	2019
M. Wei , F. Shaikh , N. Kamangar	Amyopathic Dermatomyositis Associated Interstitial Lung Disease with Positive Anti-MDA-5 Antibody but Without Rapid Progression of ILD	2019
S.A. Woods , A.A. Wagh	Myeloperoxidase (MPO)-Positive ANCA-Associated Vasculitis with Initial Presentation of Interstitial Lung Disease in a US Patient	2019
S. Beshay , S. Sahay	COPA Syndrome: A Rare Occurrence of Familial ILD with Rheumatoid Arthritis	2019
D.R. Glick , J.R. Galvin , J. Deepak	A RA-re Case of Obstructive Lung Disease	2019
J.A. Ramzy , J.S. Kim , A. Karanam , R. Townsend , S. Codella , R. Gupta , H. Zhao , G.J. Criner , E.R.A. Narewski	Autoimmune Serologies Predict Response to Treatment in Patients with Connective Tissue Related Interstitial Lung Disease (CTD-ILD)	2019
J.A. Ramzy , R. Townsend , S. Codella , J.S. Kim , A. Karanam , R. Gupta , H. Zhao , G.J. Criner , E.R.A. Narewski	Effect of Cotreatment with Corticosteroids in Connective Tissue Related Lung Disease (CTD-ILD) Patients on Mycophenolate Mofetil (MMF)	2019
S.E. Torrisi , N.C. Kahn , J. Waelscher , N. Sarmand , M. Polke , C.P. Heussel , S. Palmucci , G. Sambataro , C. Vancheri , M. Kreuter	Possible Value of Antifibrotic Drugs in Patients with Progressive Fibrosing Non-IPF Interstitial Lung Diseases	2019
F.F. Rahaghi , M.E. Strek , B.D. Southern , R. Saggar , V. Hsu , M.D. Mayes , R.M. Silver , V. Steen , R.T. Domsic , I.O. Rosas , R.J. Kaner , N.Y. Bhatt , K.R. Flaherty , N. Gupta , F.J. Martinez , L.E. Morrow , N. Patel , O.A. Shlobin , E.J. Bernstein , F.V.	Expert Consensus on the Screening, Treatment, and Management of Patients with Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD), and the Potential Future Role of Anti-fibrotics[asterisk] in a	2019

Castelino , L. Chung , B. Kahaleh , T. Moua , E.R. Volkmann , D. Khanna	Treatment Paradigm for SSc-ILD: A Delphi Consensus Study	
The European League Against Rheumatism (EULAR) - European Congress of Rheumatology (2019 congress)		
Author	**Title**	**Year**
1 Elizabeth Volkmann* , LI Ning1 , Dinesh Khanna2 , Philip Clements1 , Daniel Furst1 , Shervin Assassi3 , Michael Roth1 , Robert Elashoff1 , Donald Tashkin1	AB0695: LONG-TERM OUTCOMES OF AFRICAN AMERICAN PATIENTS WITH SYSTEMIC SCLEROSIS-RELATED INTERSTITIAL LUNG DISEASE	2019
European Respiratory Society (ERS) International Congress 2019		
Author	**Title**	**Year**
Anna Maria Hoffmann Vold, 1 Yannick Allanore, 2 Margarida Alves, 3 Nicole Graf, 4 Paolo Airò, 5 Lidia P Ananyeva, 6 László Czirják, 7 Serena Guiducci, 8 Eric Hachulla, 9 Mengtao Li, 10 Carina Mihai, 11 Gabriela Riemekasten, 12 Petros Sfikakis, 13 Gabriele Valentini, 14 Otylia Kowal Bielecka, 15 Oliver Distler 11	Disease course and outcome of progressive interstitial lung disease in systemic sclerosis: A EUSTAR Database analysis	2019

Table 80: Articles excluded due to outcomes out of scope

Author	Title	Year
D. Khanna, C. H. Tseng, D. E. Furst, P. J. Clements, R. Elashoff, M. Roth, D. Elashoff, D. P. Tashkin and I. for Scleroderma Lung Study	Minimally important differences in the Mahler's Transition Dyspnoea Index in a large randomized controlled trial--results from the Scleroderma Lung Study	2009
D. E. Furst, N. Erikson, L. Clute, R. Koehnke, L. F. Burmeister and J. A. Kohler	Adverse experience with methotrexate during 176 weeks of a longterm prospective trial in patients with rheumatoid arthritis	1990
D. P. Tashkin, E. R. Volkmann, C.-H. Tseng, M. D. Roth, D. Khanna, D. E. Furst, P. J. Clements, A. Theodore, S. Kafaja, G. H. Kim, J. Goldin, E. Ariolla and R. M. Elashoff	Improved Cough and Cough-Specific Quality of Life in Patients Treated for Scleroderma-Related Interstitial Lung Disease: Results of Scleroderma Lung Study II	2017
E. R. Volkmann, D. P. Tashkin, M. Kuwana, N. Li, J. Charles, F. N. Hant, G. S. Bogatkevich, T. Akter, M. Roth, H. J. Grace Kim, J. Goldin, D. Khanna, P. J. Clements, D. E. Furst, R. Elashoff, R. Silver and S. Assassi	Specific pneumoproteins predict progression of interstitial lung disease in systemic sclerosis patients undergoing treatment with immunosuppression	2018
D. P. Tashkin, E. Volkmann, M. D. Roth, N. Li, D. Khanna, D. Furst and R. Elashoff	Mycophenolate versus placebo for the treatment of systemic sclerosis-related interstitial lung disease	2017
D. Tashkin, E. Volkmann, D. Khanna, M. Roth, A. Theodore, B. Wang, C. H. Tseng and R. Elashoff	Frequent cough in scleroderma-related interstitial lung disesae (SSC-ILD): Characterisitcs and response to potentially disease-modifying therapy in a randomized controlled trial (RCT) (scleroderma lung study II)	2016
E. Volkmann, D. Tashkin, A. Fischer, A. M. Hoffmann-Vold, C. H. Tseng, H. LeClair, D.	Predictors of survival in patients with systemic sclerosis-related interstitial	2016

Author	Title	Year
Khanna, P. Clements, M. Roth and R. Elashoff	lung disease enrolled in the scleroderma lung study II	
M. Loza, C. Brodmerkel, B. R. Du, M. Judson, U. Costabel, M. Drent, M. Kavuru, S. Flavin, K. Lo, E. Barnathan and et al.	Inflammatory profile and response to anti-tumor necrosis factor therapy in patients with chronic pulmonary sarcoidosis	2011
E. Volkmann, D. Tashkin, M. Roth, P. Clements, D. Khanna, D. Furst, M. Mayes, J. Charles, C. Tseng, R. Elashoff and et al.	Changes in plasma CXCL4 levels are associated with improvements in lung function in patients receiving immunosuppressive therapy for systemic sclerosis-related interstitial lung disease	2016
Isrctn	A randomised, placebo-controlled, double-blind, factorial trial of prednisolone and/or azathioprine in newly diagnosed cases of cryptogenic fibrosing alveolitis (CFA)	2001

Table 81: Articles excluded due to duplication

Author	Title	Year
E. R. Volkmann, D. P. Tashkin, N. Li, M. D. Roth, D. Khanna, A.-M. Hoffmann-Vold, G. Kim, J. Goldin, P. J. Clements, D. E. Furst and R. M. Elashoff	Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II	2017
O. Distler, K. B. Highland, M. Gahlemann, A. Azuma, A. Fischer, M. D. Mayes, G. Raghu, W. Sauter, M. Girard, M. Alves, E. Clerisme-Beaty, S. Stowasser, K. Tetzlaff, M. Kuwana and T. M. Maher	Nintedanib for systemic sclerosis-associated interstitial lung disease	2019
J. Behr, P. Neuser, A. Prasse, M. Kreuter, K. Rabe, C. Schade-Brittinger, J. Wagner and A. Gunther	Exploring efficacy and safety of oral pirfenidone for progressive, non-IPF lung fibrosis (RELIEF-Study)	2017
J. G. Goldin, G. H. J. Kim, C. H. Tseng, E. Volkmann, D. Furst, P. Clements, M. Brown, M. Roth, D. Khanna and D. P. Tashkin	Longitudinal changes in quantitative interstitial lung disease on computed tomography after immunosuppression in the Scleroderma Lung Study II	2018
T. M. Maher, T. J. Corte, A. Fischer, M. Kreuter, D. J. Lederer, M. Molina-Molina, J. Axmann, K. U. Kirchgaessler and V. Cottin	Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: Design of a double-blind, randomised, placebo-controlled phase II trial	2018
V. Tsipouri, P. Saunders, G. J. Keir, D. Ashby, S. V. Fletcher, M. Gibbons, M. Szigeti, H. Parfrey, E. A. Renzoni and C. P. Denton	Rituximab versus cyclophosphamide for the treatment of connective tissue disease associated interstitial lung disease (RECITAL): A randomised controlled trial	2017
O. Distler, K. B. Kevin, J. H. W. Distler, S. Assassi, T. M. Maher, V. Cottin, J. Varga, C. Coeck, M. Gahlemann, W. Sauter, H. Schmidt and K. B. Highland	Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCISTM)	2017
P. Saunders, V. Tsipouri, G. J. Keir, D. Ashby, M. D. Flather, H. Parfrey, D. Babalis,	Rituximab versus cyclophosphamide for the treatment of connective tissue diseaseassociated interstitial lung	2017

Author	Title	Year
E. A. Renzoni, C. P. Denton, A. U. Wells and T. M. Maher	disease (RECITAL): Study protocol for a randomised controlled trial	
V. Cottin, O. Distler, J. Distler, K. Brown, J. Varga, C. Coeck, H. Schmidt and K. Highland	Design of a randomized, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (senscistm)	2016
D. E. Furst, C. H. Tseng, P. J. Clements, C. Strange, D. P. Tashkin, M. D. Roth, D. Khanna, N. Li, R. Elashoff and D. E. Schraufnagel	Adverse events during the scleroderma lung study	2011
D. S. Domiciano, E. Bonfa, C. T. L. Borges, R. A. Kairalla, V. L. Capelozzi, E. Parra and R. B. Christmann	A long-term prospective randomized controlled study of non-specific interstitial pneumonia (NSIP) treatment in scleroderma	2011
M. D. Roth, C. H. Tseng, P. J. Clements, D. E. Furst, D. P. Tashkin, J. G. Goldin, D. Khanna, E. C. Kleerup, N. Li, D. Elashoff and R. E. Elashoff	Predicting treatment outcomes and responder subsets in scleroderma-related interstitial lung disease	2011
D. Daoussis, S. N. C. Liossis, A. C. Tsamandas, C. Kalogeropoulou, A. Kazantzi, C. Sirinian, M. Karampetsou, G. Yiannopoulos and A. P. Andonopoulos	Experience with rituximab in scleroderma: Results from a 1-year, proof-of-principle study	2010
R. K. Hoyles, R. W. Ellis, J. Wellsbury, B. Lees, P. Newlands, N. S. L. Goh, C. Roberts, S. Desai, A. L. Herrick, N. J. McHugh, N. M. Foley, S. B. Pearson, P. Emery, D. J. Veale, C. P. Denton, A. U. Wells, C. M. Black and R. M. Du Bois	A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma	2006
D. Khanna, P. J. Clements, D. E. Furst, Y. Chon, R. Elashoff, M. D. Roth, M. G. Sterz, J. Chung, J. D. FitzGerald, J. R. Seibold, J. Varga, A. Theodore, F. M. Wigley, R. M. Silver, V. D. Steen, M. D. Mayes, M. K. Connolly, B. J. Fessler, N. F. Rothfield, K. Mubarak, J. Molitor and D. P. Tashkin	Correlation of the degree of dyspnea with health-related quality of life, functional abilities, and diffusing capacity for carbon monoxide in patients with systemic sclerosis and active alveolitis: Results from the scleroderma lung study	2005
W. A. Gahl, M. Brantly, J. Troendle, N. A. Avila, A. Padua, C. Montalvo, H. Cardona, K. Anton Calis and B. Gochuico	Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome	2002
M. A. Johnson, S. Kwan, N. J. C. Snell, A. J. Nunn, J. H. Darbyshire and M. Turner-Warwick	Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis	1989
J. Kokkarinen, H. Tukiainen and E. Terho	Effect of corticosteroid treatment on the recovery of pulmonary function in farmer's lung	1992
D. Furst, N. Erikson, L. Clute, R. Koehnke, L. Burmeister and J. Kohler	Adverse experience with methotrexate during 176 weeks of a longterm prospective trial in patients with rheumatoid arthritis	1990
T. Maher, T. Corte, A. Fischer, M. Kreuter, D. Lederer, M. Molina-Molina, J. Axmann, K.-U. Kirchgaessler and V. Cottin	Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: design of a double-blind, randomised, placebo-controlled phase II trial	2018

Author	Title	Year
D. Tashkin, M. Roth, P. Clements, D. Furst, D. Khanna, E. Kleerup, J. Goldin, E. Arriola, E. Volkmann, S. Kafaja and et al.	Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial	2016
G. Yanik, M. Horowitz, D. Weisdorf, B. Logan, V. Ho, R. Soiffer, S. Carter, J. Wu, J. Wingard, N. Difronzo and et al.	Randomized, double-blind, placebo-controlled trial of soluble tumor necrosis factor receptor: enbrel (etanercept) for the treatment of idiopathic pneumonia syndrome after allogeneic stem cell transplantation: blood and marrow transplant clinical trials network protocol	2014
D. Khanna, M. Roth, D. Furst, P. Clements, J. Goldin, E. Arriola, J. Kotlerman, C.-H. Tseng, G. Kim, R. Elashoff and et al.	Double-blind comparison of mycophenolate mofetil and oral cyclophosphamide for treatment of scleroderma-related interstitial lung disease (scleroderma lung study II): rationale, design, methods, baseline characteristics and patient disposition	2013
D. Tashkin, M. Roth, D. Furst, P. Clements, D. Khanna, J. Goldin, E. Arriola, J. Kotlerman, C.-H. Tseng, G. Kim and et al.	Double-blind comparison of mycophenolate mofetil and oral cyclophosphamide for treatment of scleroderma-related interstitial lung disease (scleroderma lung study II): rationale, design, methods, baseline characteristics/intercorrelations and patient disposition	2013
K. O'Brien, J. Troendle, B. Gochuico, T. Markello, J. Salas, H. Cardona, J. Yao, I. Bernardini, R. Hess and W. Gahl	Pirfenidone for the treatment of Hermansky-Pudlak syndrome pulmonary fibrosis	2011
K. Au, M. Mayes, P. Maranian, P. Clements, D. Khanna, V. Steen, D. Tashkin, M. Roth, R. Elashoff and D. Furst	Course of dermal ulcers and musculoskeletal involvement in systemic sclerosis patients in the scleroderma lung study	2010
D. Furst, C. Tseng, P. Clements, C. Strange, D. Tashkin, M. Roth, D. Khanna, N. Li, R. Elashoff and D. Schraufnagel	Adverse events during the Scleroderma Lung Study	2011
D. Tashkin, R. Elashoff, P. Clements, J. Goldin, M. Roth, D. Furst, E. Arriola, R. Silver, C. Strange, M. Bolster and et al.	Cyclophosphamide versus placebo in scleroderma lung disease	2006
J. Goldin, R. Elashoff, H. Kim, X. Yan, D. Lynch, D. Strollo, M. Roth, P. Clements, D. Furst, D. Khanna and et al.	Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: findings from the scleroderma lung study	2009
T. Maher, T. Corte, A. Fischer, M. Kreuter, D. Lederer, M. Molina-Molina, K. Samara, J. Axmann, K. Kirchgaessler and V. Cottin	Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: demographic and baseline characteristics	2018
D. Khanna, P. Clements, D. Furst, Y. Chon, R. Elashoff, M. Roth, M. Sterz, J. Chung, J. FitzGerald, J. Seibold and et al.	Correlation of the degree of dyspnea with health-related quality of life, functional abilities, and diffusing capacity for carbon monoxide in patients with systemic sclerosis and	2005

Author	Title	Year
	active alveolitis: results from the Scleroderma Lung Study	
D. Furst, D. Khanna, C.-H. Tseng, M. Mayes, M. Roth, J. Seibold, R. Simms, R. Elashoff, V. Hsu, K. Sullivan and et al.	Patients with systemic sclerosis (SSC) enrolled in the scleroderma lung study (SLS) have a high mortality within 5 years of stopping Cyclophosphamide (CYC)	2010
J. Goldin, G. Kim, C.-H. Tseng, E. Volkmann, D. Furst, P. Clements, M. Brown, M. Roth, D. Khanna and D. Tashkin	Longitudinal changes in quantitative interstitial lung disease on computed tomography after immunosuppression in the Scleroderma Lung Study II	2018
O. Distler, K. Highland, M. Gahlemann, A. Azuma, A. Fischer, M. Mayes, G. Raghu, W. Sauter, M. Girard, M. Alves and et al.	Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease	2019
E. Volkmann, D. Tashkin, P. Clements, M. Roth, D. Furst and D. Khanna	Cyclophosphamide versus mycophenolate for systemic sclerosis-related interstitial lung disease	2015
E. Euctr	A Study of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing Interstitial Lung Disease	2017
A. Sharma, D. Provenzale, A. McKusick and M. Kaplan	Interstitial pneumonitis after low-dose methotrexate therapy in primary biliary cirrhosis	1994
C. D. Pérez, D. T. M. Estévez, C. A. Peña, R. P. González, S. L. Morales and R. A. Gutiérrez	Are high doses of prednisone necessary for treatment of interstitial lung disease in systemic sclerosis?	2012
R. Hoyles, R. Ellis, J. Wellsbury, B. Lees, P. Newlands, N. Goh, C. Roberts, S. Desai, A. Herrick, N. McHugh and et al.	A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma	2006
K. Flaherty, K. Brown, A. Wells, E. Clerisme-Beaty, H. Collard, V. Cottin, A. Devaraj, Y. Inoue, M. F. Le, L. Richeldi and et al.	Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease	2017
P. Saunders, V. Tsipouri, G. Keir, D. Ashby, M. Flather, H. Parfrey, D. Babalis, E. Renzoni, C. Denton, A. Wells and et al.	Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial	2017
V. Tsipouri, P. Saunders, G. Keir, D. Ashby, S. Fletcher, M. Gibbons, M. Szigeti, H. Parfrey, E. Renzoni and C. Denton	Rituximab versus cyclophosphamide for the treatment of connective tissue disease associated interstitial lung disease (RECITAL): a randomised controlled trial	2017
P. Saunders, V. Tsipouri, G. Keir, D. Ashby, M. Flather, H. Parfrey, D. Babalis, E. Renzoni, C. Denton, A. Wells and et al.	Rituximab versus cyclophosphamide for the treatment of connective tissue diseaseassociated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial	2017
J. Behr, P. Neuser, A. Prasse, M. Kreuter, K. Rabe, C. Schade-Brittinger, J. Wagner and A. Günther	Exploring efficacy and safety of oral Pirfenidone for progressive, non-IPF lung fibrosis (RELIEF) - a randomized, double-blind, placebo-controlled,	2017

Author	Title	Year
	parallel group, multi-center, phase II trial	
D. Tashkin, E. Volkmann, D. Khanna, M. Roth, A. Theodore, B. Wang, C.-H. Tseng and R. Elashoff	Frequent cough in scleroderma-related interstitial lung disesae (SSC-ILD): characterisitcs and response to potentially disease-modifying therapy in a randomized controlled trial (RCT) (scleroderma lung study II)	2016
S. Chinnadurai, M. Madeshwaran, M. Kavitha, M. Saravanan, L. J. Euphrasia and S. Rajeswari	Rituximab in mixed connective tissue disease-two year outcome from a tertiary care center in South India	2015
D. Tashkin, M. Roth, D. Furst, P. Clements, D. Khanna and J. Goldin	Double-Blind comparison of mycophenolate mofetil and oral cyclophosphamide for treatment of scleroderma-related interstitial lung disease (Scleroderma Lung Study II): rationale, design, methods, baseline characteristics/intercorrelations and patient	2013
W. Gahl, M. Brantly, J. Troendle, N. Avila, A. Padua, C. Montalvo, H. Cardona, K. Calis and B. Gochuico	Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome	2002
O. Distler, K. Brown, J. Distler, S. Assassi, T. Maher, V. Cottin, J. Varga, C. Coeck, M. Gahlemann, W. Sauter and et al.	Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS™)	2017
O. Distler, K. B. Kevin, J. Distler, S. Assassi, T. Maher, V. Cottin, J. Varga, C. Coeck, M. Gahlemann, W. Sauter and et al.	Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCISTM)	2017
J. Goldin, G. Kim, E. Kleerup, R. Elashoff, P. Lu, P. Clements, M. Roth and D. Tashkin	Association of changes in quantitative CT with outcome measures in the scleroderma lung study II	2017
P. Clements, M. Roth, R. Elashoff, D. Tashkin, J. Goldin, R. Silver, M. Sterz, J. Seibold, D. Schraufnagel, R. Simms and et al.	Scleroderma lung study (SLS): differences in the presentation and course of patients with limited versus diffuse systemic sclerosis	2007
D. Domiciano, E. Bonfá, C. Borges, R. Kairalla, V. Capelozzi, E. Parra and R. Christmann	A long-term prospective randomized controlled study of non-specific interstitial pneumonia (NSIP) treatment in scleroderma	2011
D. Khanna, C. Albera, A. Fischer, N. Khalidi, G. Raghu, L. Chung, D. Chen, E. Schiopu, M. Tagliaferri, J. Seibold and et al.	An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial	2016
P. Seo, Y. Min, J. Holbrook, G. Hoffman, P. Merkel, R. Spiera, J. Davis, S. Ytterberg, C. E. St, W. McCune and et al.	Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET)	2005
J. Goldin, D. Lynch, D. Strollo, R. Suh, D. Schraufnagel, P. Clements, R. Elashoff, D. Furst, S. Vasunilashorn, M. McNitt-Gray and et al.	High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease	2008

Author	Title	Year
G. Kim, D. Tashkin, M. Brown, E. Volkmann, P. Lo, D. Gjertson, P. Lu, D. Chong and J. Goldin	Using transitional changes on hrct to assess the impact of treatment with cyclophosphamide or mycophenolate on systemic sclerosis-related interstitial lung disease from scleroderma lung study II	2018
D. Tashkin, E. Volkmann, M. Roth, N. Li, D. Khanna, D. Furst and R. Elashoff	Mycophenolate versus placebo for the treatment of systemic sclerosis-related interstitial lung disease	2017
E. Volkmann, D. Tashkin, N. Li, M. Roth, D. Khanna, A.-M. Hoffmann-Vold, P. Clements, D. Furst and R. Elashoff	Mycophenolate versus placebo for the treatment of systemic sclerosis-related interstitial lung disease	2016
P. Euctr	A trial to compare nintedanib with placebo for patients with scleroderma related lung fibrosis	2016
M. Brantly, J. Troendle, N. Avila, A. Padua, C. Montalvo, H. Cardone, H. Clis, B. Gochuico and W. Gahl	A randomized, placebo-conrolled trial of oral pirfenidone for the pulmonary fibrosis of hermansky-pudlak syndrome	2002
M. Roth, C. Tseng, P. Clements, D. Furst, D. Tashkin, J. Goldin, D. Khanna, E. Kleerup, N. Li, D. Elashoff and et al.	Predicting treatment outcomes and responder subsets in scleroderma-related interstitial lung disease	2011
D. Khanna, C. Tseng, D. Furst, P. Clements, R. Elashoff, M. Roth, D. Elashoff and D. Tashkin	Minimally important differences in the Mahler's Transition Dyspnoea Index in a large randomized controlled trial--results from the Scleroderma Lung Study	2009
D. Tashkin, R. Elashoff, P. Clements, M. Roth, D. Furst, R. Silver, J. Goldin, E. Arriola, C. Strange, M. Bolster and et al.	Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease	2007
E. Volkmann, D. Tashkin, N. Li, M. Roth, D. Khanna, A.-M. Hoffmann-Vold, G. Kim, J. Goldin, P. Clements, D. Furst and et al.	Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis–Related Interstitial Lung Disease: an Analysis of Scleroderma Lung Studies I and II	2017
E. Volkmann, D. Tashkin, M. Sim, N. Li, E. Goldmuntz, L. Keyes-Elstein, A. Pinckney, D. Furst, P. Clements, D. Khanna and et al.	Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts	2018
D. Khanna, M. Roth, P. Clements, D. Furst, C.-H. Tseng, R. Elashoff, E. Volkmann, S. Kafaja, J. Goldin and D. Tashkin	Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease: scleroderma lung study II	2016
D. Tashkin, E. Volkmann, M. Sim, M. Roth, P. Clements, D. Furst, R. Elashoff, L. Keyes-Elstein, A. Pinckney, E. Goldlmuntz and et al.	Predicting mortality in systemic sclerosis-related interstitial lung disease in two independent cohorts	2018
E. Volkmann, D. Tashkin, M. Sim, N. Li, D. Khanna, M. Roth, P. Clements, A. Hoffmann-Vold, D. Furst, G. Kim and et al.	Treatment with cyclophosphamide for systemic sclerosis-interstitial lung disease does not lead to a sustained improvement in lung function in two independent cohorts	2018
E. Volkmann, D. Tashkin, M. Sim, D. Khanna, M. Roth, P. Clements, D. Furst, L. Keyes-Elstein, A. Pinckney, E. Goldmuntz and et al.	The course of the forced vital capacity during treatment for systemic sclerosis-related interstitial lung disease predicts long-term survival in 2 independent cohorts	2018

Author	Title	Year
E. Volkmann, D. Khanna, C.-H. Tseng, R. Elashoff, B. Wang, M. Roth, P. Clements, D. Furst, A. Theodore and D. Tashkin	Improvement in cough and cough-related quality of life in participants undergoing treatment for systemic sclerosis-related interstitial lung disease	2016
E. Volkmann, D. Tashkin, A. Fischer, A.-M. Hoffmann-Vold, C.-H. Tseng, H. LeClair, D. Khanna, P. Clements, M. Roth and R. Elashoff	Predictors of survival in patients with systemic sclerosis-related interstitial lung disease enrolled in the scleroderma lung study II	2016
E. Volkmann, D. Tashkin, M. Sim, N. Li, D. Khanna, M. Roth, P. Clements, A.-M. Hoffmann-Vold, D. Furst, G. Kim and et al.	Treatment with cyclophosphamide for systemic sclerosis-interstitial lung disease does not lead to a sustained improvement in lung function in two independent cohorts	2017
G. Sircar, R. Goswami, D. Sircar, A. Ghosh and P. Ghosh	Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial	2018
E. Volkmann, D. Tashkin, M. Sim, D. Khanna, M. Roth, P. Clements, D. Furst, L. Keyes-Elstein, A. Pinckney, E. Goldmuntz and et al.	The course of the forced vital capacity during treatment for systemic sclerosis-related interstitial lung disease predicts long-term survival in 2 independent cohorts	2017
M. Johnson, S. Kwan, N. Snell, A. Nunn, J. Darbyshire and M. Turner-Warwick	Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis	1989
A. Gulsvik, F. Kjelsberg, A. Bergmann, S. Frøland, K. Rootwelt and J. Vale	High-dose intravenous methylprednisolone pulse therapy as initial treatment in cryptogenic fibrosing alveolitis. A pilot study	1986

D.1.1.2.3 SLR update (May 2020)

An update to the SLR was conducted in May 2020. The search strings are presented in Table 82, Table 83, Table 84,

Table 85, Table 86, Table 87.

Table 82: Ovid Medline search strategy and results (searched 26 May 2020)

	Searches	Results
1	Lung Diseases, Interstitial/	9287
2	ILD.tw.	4029
3	Pulmonary Fibrosis/	18518
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	15514
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	21344
6	alveolitis.mp.	6145
7	(diffuse* adj3 parenchymal*).mp.	802
8	Bronchiolitis Obliterans/	2775
9	(bronchiolitis adj obliterans).mp.	4595
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	8005
11	Pneumoconiosis/	6622
12	bagassosis.mp.	69
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	12063
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	17016
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	13
16	((pulmonary$ or lung$) adj3 fibros$).mp.	34781
17	Alveolitis, Extrinsic Allergic/	2904
18	(connective adj3 lung$).mp.	234
19	(allerg$ adj3 pneumonitis).mp.	112
20	Cryptogenic Organizing Pneumonia/	1029
21	cryptogenic organi#ing pneumonia.mp.	1282
22	Idiopathic Interstitial Pneumonias/	379
23	IIP.tw.	1096
24	(hypersensitivity adj3 pneumonia$).mp.	189
25	pleuroparenchymal fibroelastosis.mp.	167
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	100944
27	randomized controlled trial/ or randomized controlled trials as topic/	633566
28	(randomi?ed control* or rct).ti.	85560
29	Random Allocation/	102805
30	Single-Blind Method/ or single blind.mp.	34562
31	double blind method/ or double blind.mp.	195794
32	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	135109
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	236222
34	(allocat* adj3 random*).mp.	135592
35	placebo$.mp.	228977
36	Prospective Studies/	538388

	Searches	Results
37	(prospective adj (trial or study)).mp.	144471
38	Controlled Clinical Trial/	93684
39	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	1494175
40	Case Reports/	2098702
41	case stud*.hw.	12313
42	case report?.hw.	2098702
43	Letter/	1078684
44	Editorial/	529259
45	40 or 41 or 42 or 43 or 44	3505495
46	39 not 45	1447727
47	nintedanib.mp.	886
48	(Vargatef or Ofev).mp.	24
49	pirfenidone.mp.	1216
50	(Esbriet or Pirespa or Etuary).mp.	17
51	Azathioprine/	14601
52	(azathioprine or Imuran or Azasan).mp.	22950
53	Cyclophosphamide/	49616
54	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	70307
55	Rituximab/	14443
56	(rituximab or Rituxan or Mabthera).mp.	23503
57	Mycophenolic Acid/	7895
58	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	13258
59	Prednisone/	39187
60	(corticosteroid? or predniso*).mp.	186261
61	Prednisolone/	32686
62	tocilizumab.mp.	3146
63	(Actemra or RoActemra or Atlizumab).mp.	73
64	abatacept.mp. or Abatacept/	3688
65	Orencia.mp.	46
66	methotrexate.mp. or Methotrexate/	53929
67	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	17
68	Etanercept/	5804
69	(etanercept or enbrel).mp.	8574
70	Infliximab/	10158
71	(infliximab or remicade).mp.	14807
72	Adalimumab/	5278
73	(adalimumab or humira).mp.	8402
74	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73	330050
75	26 and 46 and 74	704
76	limit 75 to english language	649

	Searches	Results
77	limit 76 to ed="20190813-20200526"	37

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to May 22, 2020

Table 83: Ovid Embase corrected search strategy and results (searched 26 May 2020)

	Searches	Results
1	Lung Diseases, Interstitial/	10281
2	ILD.tw.	9428
3	Pulmonary Fibrosis/	15229
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	27154
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	37004
6	alveolitis.mp.	29528
7	(diffuse* adj3 parenchymal*).mp.	1373
8	Bronchiolitis Obliterans/	5685
9	(bronchiolitis adj obliterans).mp.	9269
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	6426
11	pneumoconiosis/	5428
12	bagassosis.mp.	51
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	22297
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	15159
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	28
16	((pulmonary$ or lung$) adj3 fibros$).mp.	55809
17	Alveolitis, Extrinsic Allergic/	4737
18	(connective adj3 lung$).mp.	375
19	(allerg$ adj3 pneumonitis).mp.	6586
20	Cryptogenic Organizing Pneumonia/	782
21	cryptogenic organi#ing pneumonia.mp.	926
22	Idiopathic Interstitial Pneumonias/	12002
23	IIP.tw.	1578
24	(hypersensitivity adj3 pneumonia$).mp.	372
25	pleuroparenchymal fibroelastosis.mp.	311
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	159497
27	randomized controlled trial/ or randomized controlled trials as topic/	714971
28	(randomi?ed control* or rct).ti.	108001
29	randomization/	86720
30	Single-Blind Method/ or single blind.mp.	47096
31	double blind method/ or double blind.mp.	249742
32	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	273982
33	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	305219
34	Random Allocation/	82884

	Searches	Results
35	(allocat* adj3 random*).mp.	44503
36	placebo$.mp.	452764
37	Prospective Studies/	493221
38	(prospective adj (trial or study)).mp.	668381
39	Controlled Clinical Trial/	463761
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	2018371
41	Case Report/	2476609
42	case stud*.hw.	69069
43	case report?.hw.	2476632
44	Letter/	1052261
45	Editorial/	638137
46	41 or 42 or 43 or 44 or 45	4012080
47	40 not 46	1940226
48	nintedanib.mp.	3070
49	(Vargatef or Ofev).mp.	164
50	pirfenidone.mp.	3522
51	(Esbriet or Pirespa or Etuary).mp.	115
52	azathioprine/	91842
53	(azathioprine or Imuran or Azasan).mp.	94552
54	cyclophosphamide/	212802
55	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	222305
56	rituximab/	78080
57	(rituximab or Rituxan or Mabthera).mp.	81936
58	mycophenolate mofetil/	16782
59	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	67954
60	prednisone/	167911
61	(corticosteroid? or predniso*).mp.	546353
62	prednisolone/	123052
63	tocilizumab.mp.	11793
64	(Acterma or RoActerma or Atlizumab).mp.	569
65	abatacept.mp. or Abatacept/	9268
66	Orencia.mp.	661
67	methotrexate.mp. or Methotrexate/	180361
68	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	249
69	etanercept/	31032
70	(etanercept or enbrel).mp.	31960
71	infliximab/	49956
72	(infliximab or remicade).mp.	51065
73	adalimumab/	32928
74	(adalimumab or humira).mp.	33670

	Searches	Results
75	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	879724
76	26 and 47 and 75	3266
77	limit 76 to english language	3165
78	interstitial lung disease/	21072
79	ILD.tw.	9428
80	lung fibrosis/	33634
81	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	27154
82	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	37004
83	alveolitis.mp.	29528
84	(diffuse* adj3 parenchymal*).mp.	1373
85	bronchiolitis obliterans/	5685
86	(bronchiolitis adj obliterans).mp.	9269
87	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	6426
88	pneumoconiosis/	5428
89	bagassosis.mp.	51
90	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	22297
91	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	15159
92	((pulmonary$ or lung$) adj3 reticulation$).mp.	28
93	((pulmonary$ or lung$) adj3 fibros$).mp.	55809
94	allergic pneumonitis/	6535
95	(connective adj3 lung$).mp.	375
96	(allerg$ adj3 pneumonitis).mp.	6586
97	bronchiolitis obliterans organizing pneumonia/	1815
98	cryptogenic organi#ing pneumonia.mp.	926
99	interstitial pneumonia/	15491
100	IIP.tw.	1578
101	(hypersensitivity adj3 pneumonia$).mp.	372
102	pleuroparenchymal fibroelastosis.mp.	311
103	78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102	159496
104	randomized controlled trial/	603101
105	"randomized controlled trial (topic)"/	179269
106	(randomi?ed control* or rct).ti.	108001
107	randomization/	86720
108	Single-Blind Method/ or single blind.mp.	47096
109	double blind method/ or double blind.mp.	249742
110	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	273982
111	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	305219
112	(allocat* adj3 random*).mp.	44503

	Searches	Results
113	placebo$.mp.	452764
114	prospective study/	600130
115	(prospective adj (trial or study)).mp.	668381
116	controlled clinical trial/	463761
117	104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116	2056879
118	case report/	2476609
119	case stud*.hw.	69069
120	case report?.hw.	2476632
121	letter/	1052261
122	editorial/	638137
123	118 or 119 or 120 or 121 or 122	4012080
124	117 not 123	1973940
125	nintedanib.mp.	3070
126	(Vargatef or Ofev).mp.	164
127	pirfenidone.mp.	3522
128	(Esbriet or Pirespa or Etuary).mp.	115
129	azathioprine/	91842
130	(azathioprine or Imuran or Azasan).mp.	94552
131	cyclophosphamide/	212802
132	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	222305
133	rituximab/	78080
134	(rituximab or Rituxan or Mabthera).mp.	81936
135	mycophenolate mofetil/	16782
136	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	67954
137	prednisone/	167911
138	(corticosteroid? or predniso*).mp.	546353
139	prednisolone/	123052
140	tocilizumab.mp.	11793
141	(Actemra or RoActemra or Atlizumab).mp.	1171
142	abatacept.mp. or Abatacept/	9268
143	Orencia.mp.	661
144	methotrexate.mp. or Methotrexate/	180361
145	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	249
146	etanercept/	31032
147	(etanercept or enbrel).mp.	31960
148	infliximab/	49956
149	(infliximab or remicade).mp.	51065
150	adalimumab/	32928
151	(adalimumab or humira).mp.	33670

	Searches	Results
152	125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151	879728
153	103 and 124 and 152	3351
154	limit 153 to english language	3245
155	154 not 77	80

Ovid Embase 1974 to 2020

Table 84: Ovid Embase corrected search strategy and results with date limit (searched 26 May 2020)

	Searches	Results
1	interstitial lung disease/	21072
2	ILD.tw.	9428
3	lung fibrosis/	33634
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	27154
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	37004
6	alveolitis.mp.	29528
7	(diffuse* adj3 parenchymal*).mp.	1373
8	bronchiolitis obliterans/	5685
9	(bronchiolitis adj obliterans).mp.	9269
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	6426
11	pneumoconiosis/	5428
12	bagassosis.mp.	51
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	22297
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	15159
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	28
16	((pulmonary$ or lung$) adj3 fibros$).mp.	55809
17	allergic pneumonitis/	6535
18	(connective adj3 lung$).mp.	375
19	(allerg$ adj3 pneumonitis).mp.	6586
20	bronchiolitis obliterans organizing pneumonia/	1815
21	cryptogenic organi#ing pneumonia.mp.	926
22	interstitial pneumonia/	15491
23	IIP.tw.	1578
24	(hypersensitivity adj3 pneumonia$).mp.	372
25	pleuroparenchymal fibroelastosis.mp.	311
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	159496
27	randomized controlled trial/	603101
28	"randomized controlled trial (topic)"/	179269
29	(randomi?ed control* or rct).ti.	108001

	Searches	Results
30	randomization/	86720
31	Single-Blind Method/ or single blind.mp.	47096
32	double blind method/ or double blind.mp.	249742
33	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).mp.	273982
34	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).mp.	305219
35	(allocat* adj3 random*).mp.	44503
36	placebo$.mp.	452764
37	prospective study/	600130
38	(prospective adj (trial or study)).mp.	668381
39	controlled clinical trial/	463761
40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	2056879
41	case report/	2476609
42	case stud*.hw.	69069
43	case report?.hw.	2476632
44	letter/	1052261
45	editorial/	638137
46	41 or 42 or 43 or 44 or 45	4012080
47	40 not 46	1973940
48	nintedanib.mp.	3070
49	(Vargatef or Ofev).mp.	164
50	pirfenidone.mp.	3522
51	(Esbriet or Pirespa or Etuary).mp.	115
52	azathioprine/	91842
53	(azathioprine or Imuran or Azasan).mp.	94552
54	cyclophosphamide/	212802
55	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan).mp.	222305
56	rituximab/	78080
57	(rituximab or Rituxan or Mabthera).mp.	81936
58	mycophenolate mofetil/	16782
59	(Mycophenolate mofetil or Mycophenolic acid or Cellcept).mp.	67954
60	prednisone/	167911
61	(corticosteroid? or predniso*).mp.	546353
62	prednisolone/	123052
63	tocilizumab.mp.	11793
64	(Actemra or RoActemra or Atlizumab).mp.	1171
65	abatacept.mp. or Abatacept/	9268
66	Orencia.mp.	661
67	methotrexate.mp. or Methotrexate/	180361
68	(Otrexup or Rasurvo or Rheumatrex or Trexall).mp.	249
69	etanercept/	31032
70	(etanercept or enbrel).mp.	31960

	Searches	Results
71	infliximab/	49956
72	(infliximab or remicade).mp.	51065
73	adalimumab/	32928
74	(adalimumab or humira).mp.	33670
75	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74	879728
76	26 and 47 and 75	3351
77	limit 76 to english language	3245
78	limit 77 to dc="20190813-20200526"	216

Ovid Embase 1974 to 2020

Table 85: Cochrane library corrected search strategy and results (searched 26 May 2020)

	Search	Results
#1	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	786
#2	ILD:ti,ab	458
#3	MeSH descriptor: [Pulmonary Fibrosis] explode all trees	504
#4	(interstitial* NEAR/3 (lung* NEAR/3 disease*)):ti,ab	798
#5	(interstitial* NEAR/3 (fibros* or pneumonitis or pneumonia or pneumopathy)):ti,ab	629
#6	alveolitis:ti,ab	130
#7	(diffuse* NEAR/3 parenchymal*):ti,ab	16
#8	MeSH descriptor: [Bronchiolitis Obliterans] explode all trees	66
#9	(bronchiolitis NEXT obliterans):ti,ab	152
#10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis):ti,ab	62
#11	MeSH descriptor: [Pneumoconiosis] explode all trees	97
#12	bagassosis:ti,ab	0
#13	((bird* or farmer* or pigeon* or avian* or budgerigar*) NEXT (lung* or disease*)):ti,ab	8
#14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis):ti,ab	121
#15	((pulmonary* or lung*) NEAR/3 reticulation*):ti,ab	0
#16	((pulmonary* or lung*) NEAR/3 fibros*):ti,ab	1681
#17	MeSH descriptor: [Alveolitis, Extrinsic Allergic] explode all trees	25
#18	(connective NEAR/3 lung*):ti,ab	7
#19	(allerg* NEAR/3 pneumonitis):ti,ab	0
#20	MeSH descriptor: [Cryptogenic Organizing Pneumonia] explode all trees	4
#21	cryptogenic organi*ing pneumonia:ti,ab	9
#22	MeSH descriptor: [Idiopathic Interstitial Pneumonias] explode all trees	220
#23	IIP:ti,ab	141
#24	(hypersensitivity NEAR/3 pneumonia*):ti,ab	4
#25	pleuroparenchymal fibroelastosis:ti,ab	1
#26	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 #10 or #11 or #12 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 #24 or #25	3420
#27	MeSH descriptor: [Randomized Controlled Trial] explode all trees	119
#28	(randomi?ed control* or rct):ti	171663
#29	MeSH descriptor: [Random Allocation] explode all trees	20595
#30	MeSH descriptor: [Single-Blind Method] explode all trees	20296
#31	single blind:ti,ab	48494
#32	MeSH descriptor: [Double-Blind Method] explode all trees	135561
#33	double blind:ti,ab	216252
#34	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4):ti,ab	142588
#35	((singl* or doubl* or treb* or tripl*) NEXT (blind* or mask*)):ti,ab	263155
#36	(allocat* NEAR/3 random*):ti,ab	43505

	Search	Results
#37	placebo*:ti,ab	291020
#38	MeSH descriptor: [Prospective Studies] explode all trees	89710
#39	(prospective NEXT (trial or study)):ti,ab	27070
#40	MeSH descriptor: [Controlled Clinical Trial] explode all trees	128
#41	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	14175
#42	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 #39 or #40 or #41	644883
#43	MeSH descriptor: [Case Reports] explode all trees	0
#44	case stud*:ti	12088
#45	case report?:ti	630
#46	(letter or editorial):ti	1713
#47	#43 or #44 or #45 or #46	14332
#48	#42 not #47	638698
#49	nintedanib:ti,ab	420
#50	(Vargatef or Ofev):ti,ab	24
#51	pirfenidone:ti,ab	317
#52	(Esbriet or Pirespa or Etuary):ti,ab	14
#53	MeSH descriptor: [Azathioprine] explode all trees	1214
#54	(azathioprine or Imuran or Azasan):ti,ab	2476
#55	MeSH descriptor: [Cyclophosphamide] explode all trees	5411
#56	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan):ti,ab	9845
#57	MeSH descriptor: [Rituximab] explode all trees	1216
#58	(rituximab or Rituxan or Mabthera):ti,ab	4337
#59	MeSH descriptor: [Mycophenolic Acid] explode all trees	1346
#60	(Mycophenolate mofetil or Mycophenolic acid or Cellcept):ti,ab	2933
#61	MeSH descriptor: [Prednisone] explode all trees	3921
#62	(corticosteroid? or predniso*):ti,ab	29670
#63	MeSH descriptor: [Prednisolone] explode all trees	4818
#64	tocilizumab:ti,ab	972
#65	(Acterma or RoActerma or Atlizumab):ti,ab	3
#66	MeSH descriptor: [Abatacept] explode all trees	271
#67	(abatacept or orencia):ti,ab	645
#68	MeSH descriptor: [Methotrexate] explode all trees	4100
#69	methotrexate:ti,ab	9433
#70	(Otrexup or Rasurvo or Rheumatrex or Trexall):ti,ab	2
#71	MeSH descriptor: [Etanercept] explode all trees	747
#72	(etanercept or enbrel):ti,ab	1992
#73	MeSH descriptor: [Infliximab] explode all trees	712
#74	(infliximab or remicade):ti,ab	2075
#75	MeSH descriptor: [Adalimumab] explode all trees	724
#76	(adalimumab or humira):ti,ab	2772

	Search	Results
#77	#49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76	58382
#78	#26 and #48 and #77	677
#79	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	786
#80	ILD:ti,ab	458
#81	MeSH descriptor: [Pulmonary Fibrosis] explode all trees	504
#82	(interstitial* NEAR/3 (lung* NEAR/3 disease*)):ti,ab	798
#83	(interstitial* NEAR/3 (fibros* or pneumonitis or pneumonia or pneumopathy)):ti,ab	629
#84	alveolitis:ti,ab	130
#85	(diffuse* NEAR/3 parenchymal*):ti,ab	16
#86	MeSH descriptor: [Bronchiolitis Obliterans] explode all trees	66
#87	(bronchiolitis NEXT obliterans):ti,ab	152
#88	(pneumoconiosis or pneumokoniosis or pneumonoconiosis):ti,ab	62
#89	MeSH descriptor: [Pneumoconiosis] explode all trees	97
#90	bagassosis:ti,ab	0
#91	((bird* or farmer* or pigeon* or avian* or budgerigar*) NEXT (lung* or disease*)):ti,ab	8
#92	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis):ti,ab	121
#93	((pulmonary* or lung*) NEAR/3 reticulation*):ti,ab	0
#94	((pulmonary* or lung*) NEAR/3 fibros*):ti,ab	1681
#95	MeSH descriptor: [Alveolitis, Extrinsic Allergic] explode all trees	25
#96	(connective NEAR/3 lung*):ti,ab	7
#97	(allerg* NEAR/3 pneumonitis):ti,ab	0
#98	MeSH descriptor: [Cryptogenic Organizing Pneumonia] explode all trees	4
#99	cryptogenic organi*ing pneumonia:ti,ab	9
#100	MeSH descriptor: [Idiopathic Interstitial Pneumonias] explode all trees	220
#101	IIP:ti,ab	141
#102	(hypersensitivity NEAR/3 pneumonia*):ti,ab	4
#103	pleuroparenchymal fibroelastosis:ti,ab	1
#104	#79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103	3726
#105	MeSH descriptor: [Randomized Controlled Trial] explode all trees	119
#106	(randomi?ed control* or rct):ti	171663
#107	MeSH descriptor: [Random Allocation] explode all trees	20595
#108	MeSH descriptor: [Single-Blind Method] explode all trees	20296
#109	single blind:ti,ab	48494
#110	MeSH descriptor: [Double-Blind Method] explode all trees	135561
#111	double blind:ti,ab	216252
#112	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4):ti,ab	142588

	Search	Results
#113	((singl* or doubl* or treb* or tripl*) NEXT (blind* or mask*)):ti,ab	263155
#114	(allocat* NEAR/3 random*):ti,ab	43505
#115	placebo*:ti,ab	291020
#116	MeSH descriptor: [Prospective Studies] explode all trees	89710
#117	(prospective NEXT (trial or study)):ti,ab	27070
#118	MeSH descriptor: [Controlled Clinical Trial] explode all trees	128
#119	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	14175
#120	#105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119	699262
#121	MeSH descriptor: [Case Reports] explode all trees	0
#122	case stud*:ti	12088
#123	case report?:ti	630
#124	(letter or editorial):ti	1713
#125	#121 or #122 or #123 or #124	14332
#126	#120 not #125	692314
#127	nintedanib:ti,ab	420
#128	(Vargatef or Ofev):ti,ab	24
#129	pirfenidone:ti,ab	317
#130	(Esbriet or Pirespa or Etuary):ti,ab	14
#131	MeSH descriptor: [Azathioprine] explode all trees	1214
#132	(azathioprine or Imuran or Azasan):ti,ab	2476
#133	MeSH descriptor: [Cyclophosphamide] explode all trees	5411
#134	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan):ti,ab	9845
#135	MeSH descriptor: [Rituximab] explode all trees	1216
#136	(rituximab or Rituxan or Mabthera):ti,ab	4337
#137	MeSH descriptor: [Mycophenolic Acid] explode all trees	1346
#138	(Mycophenolate mofetil or Mycophenolic acid or Cellcept):ti,ab	2933
#139	MeSH descriptor: [Prednisone] explode all trees	3921
#140	(corticosteroid? or predniso*):ti,ab	29670
#141	MeSH descriptor: [Prednisolone] explode all trees	4818
#142	tocilizumab:ti,ab	972
#143	(Actemra or RoActemra or Atlizumab):ti,ab	113
#144	MeSH descriptor: [Abatacept] explode all trees	271
#145	(abatacept or orencia):ti,ab	645
#146	MeSH descriptor: [Methotrexate] explode all trees	4100
#147	methotrexate:ti,ab	9433
#148	(Otrexup or Rasurvo or Rheumatrex or Trexall):ti,ab	2
#149	MeSH descriptor: [Etanercept] explode all trees	747
#150	(etanercept or enbrel):ti,ab	1992
#151	MeSH descriptor: [Infliximab] explode all trees	712
#152	(infliximab or remicade):ti,ab	2075

	Search	Results
#153	MeSH descriptor: [Adalimumab] explode all trees	724
#154	(adalimumab or humira):ti,ab	2772
#155	#127 or #128 or #129 or #130 or #131 or #132 or #133 or #134 or #135 or #136 or #137 or #138 or #139 or #140 or #141 or #142 or #143 or #144 or #145 or #146 or #147 or #148 or #149 or #150 or #151 or #152 or #153 or #154	58383
#156	#104 and #126 and #155	738
#157	#156 not #78	61

Table 86: Cochrane library corrected search strategy and results with date limit (searched 26 May 2020)

ID	Search	Results
#1	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	786
#2	ILD:ti,ab	458
#3	MeSH descriptor: [Pulmonary Fibrosis] explode all trees	504
#4	(interstitial* NEAR/3 (lung* NEAR/3 disease*)):ti,ab	798
#5	(interstitial* NEAR/3 (fibros* or pneumonitis or pneumonia or pneumopathy)):ti,ab	629
#6	alveolitis:ti,ab	130
#7	(diffuse* NEAR/3 parenchymal*):ti,ab	16
#8	MeSH descriptor: [Bronchiolitis Obliterans] explode all trees	66
#9	(bronchiolitis NEXT obliterans):ti,ab	152
#10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis):ti,ab	62
#11	MeSH descriptor: [Pneumoconiosis] explode all trees	97
#12	bagassosis:ti,ab	0
#13	((bird* or farmer* or pigeon* or avian* or budgerigar*) NEXT (lung* or disease*)):ti,ab	8
#14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis):ti,ab	121
#15	((pulmonary* or lung*) NEAR/3 reticulation*):ti,ab	0
#16	((pulmonary* or lung*) NEAR/3 fibros*):ti,ab	1681
#17	MeSH descriptor: [Alveolitis, Extrinsic Allergic] explode all trees	25
#18	(connective NEAR/3 lung*):ti,ab	7
#19	(allerg* NEAR/3 pneumonitis):ti,ab	0
#20	MeSH descriptor: [Cryptogenic Organizing Pneumonia] explode all trees	4
#21	cryptogenic organi*ing pneumonia:ti,ab	9
#22	MeSH descriptor: [Idiopathic Interstitial Pneumonias] explode all trees	220
#23	IIP:ti,ab	141
#24	(hypersensitivity NEAR/3 pneumonia*):ti,ab	4
#25	pleuroparenchymal fibroelastosis:ti,ab	1
#26	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25	3726
#27	MeSH descriptor: [Randomized Controlled Trial] explode all trees	119
#28	(randomi?ed control* or rct):ti	171663
#29	MeSH descriptor: [Random Allocation] explode all trees	20595

ID	Search	Results
#30	MeSH descriptor: [Single-Blind Method] explode all trees	20296
#31	single blind:ti,ab	48494
#32	MeSH descriptor: [Double-Blind Method] explode all trees	135561
#33	double blind:ti,ab	216252
#34	(phase II or phase 2 or phase III or phase 3 or phase IV or phase 4):ti,ab	142588
#35	((singl* or doubl* or treb* or tripl*) NEXT (blind* or mask*)):ti,ab	263155
#36	(allocat* NEAR/3 random*):ti,ab	43505
#37	placebo*:ti,ab	291020
#38	MeSH descriptor: [Prospective Studies] explode all trees	89710
#39	(prospective NEXT (trial or study)):ti,ab	27070
#40	MeSH descriptor: [Controlled Clinical Trial] explode all trees	128
#41	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees	14175
#42	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41	699262
#43	MeSH descriptor: [Case Reports] explode all trees	0
#44	case stud*:ti	12088
#45	case report?:ti	630
#46	(letter or editorial):ti	1713
#47	#43 or #44 or #45 or #46	14332
#48	#42 not #47	692314
#49	nintedanib:ti,ab	420
#50	(Vargatef or Ofev):ti,ab	24
#51	pirfenidone:ti,ab	317
#52	(Esbriet or Pirespa or Etuary):ti,ab	14
#53	MeSH descriptor: [Azathioprine] explode all trees	1214
#54	(azathioprine or Imuran or Azasan):ti,ab	2476
#55	MeSH descriptor: [Cyclophosphamide] explode all trees	5411
#56	(Cyclophosphamide or cytophosphane or Cytoxan or Endoxan):ti,ab	9845
#57	MeSH descriptor: [Rituximab] explode all trees	1216
#58	(rituximab or Rituxan or Mabthera):ti,ab	4337
#59	MeSH descriptor: [Mycophenolic Acid] explode all trees	1346
#60	(Mycophenolate mofetil or Mycophenolic acid or Cellcept):ti,ab	2933
#61	MeSH descriptor: [Prednisone] explode all trees	3921
#62	(corticosteroid? or predniso*):ti,ab	29670
#63	MeSH descriptor: [Prednisolone] explode all trees	4818
#64	tocilizumab:ti,ab	972
#65	(Actemra or RoActemra or Atlizumab):ti,ab	113
#66	MeSH descriptor: [Abatacept] explode all trees	271
#67	(abatacept or orencia):ti,ab	645
#68	MeSH descriptor: [Methotrexate] explode all trees	4100
#69	methotrexate:ti,ab	9433

ID	Search	Results
#70	(Otrexup or Rasurvo or Rheumatrex or Trexall):ti,ab	2
#71	MeSH descriptor: [Etanercept] explode all trees	747
#72	(etanercept or enbrel):ti,ab	1992
#73	MeSH descriptor: [Infliximab] explode all trees	712
#74	(infliximab or remicade):ti,ab	2075
#75	MeSH descriptor: [Adalimumab] explode all trees	724
#76	(adalimumab or humira):ti,ab	2772
#77	#49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76	58383
#78	#26 and #48 and #77 with Cochrane Library publication date Between Aug 2019 and May 2020	102

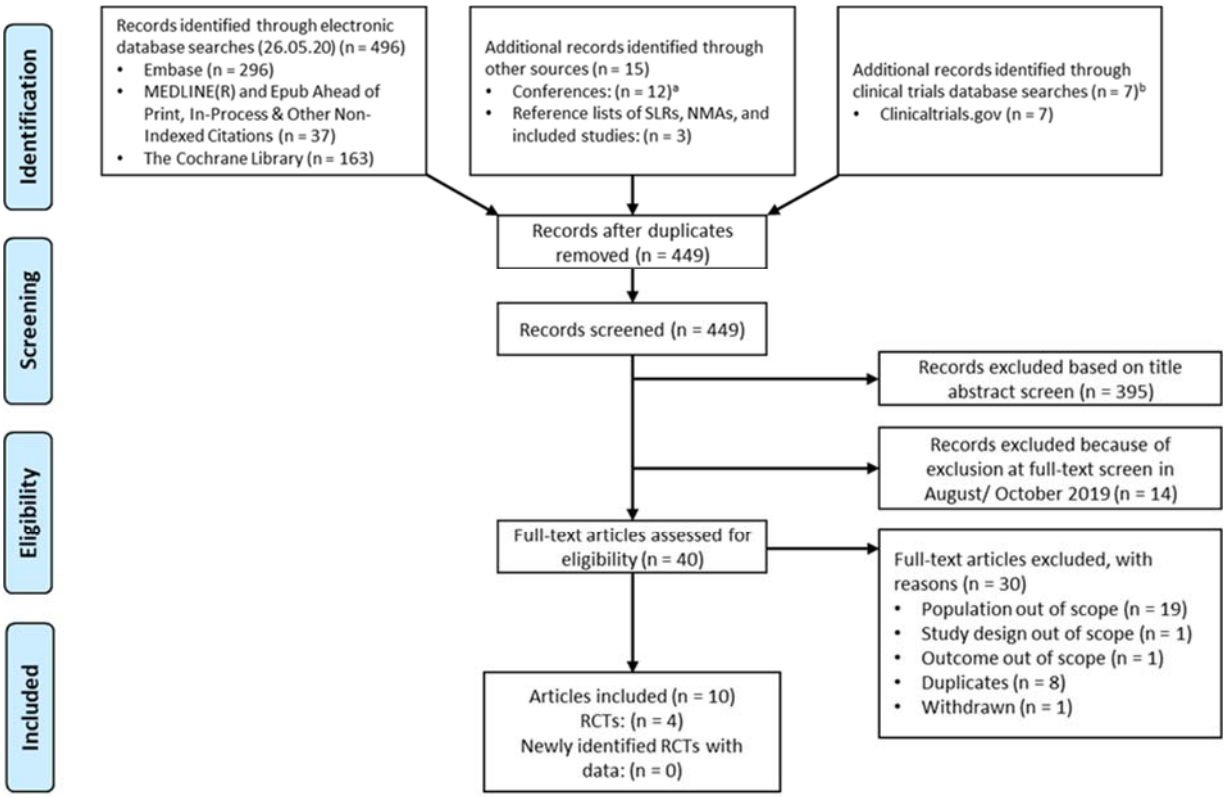
Table 87: Supplementary and conference abstract search strategies and results (May 2020 update)

Database	Searches and results
Clinicaltrials.gov	Searched (26/05/2020) Condition: interstitial lung disease OR ILD OR pulmonary fibrosis OR lung fibrosis OR fibrosing lung disease Intervention: Nintedanib OR Pirfenidone OR Azathioprine OR Cyclophosphamide OR Rituximab OR Mycophenolate mofetil OR Corticosteroid OR Corticosteroids OR Methotrexate OR Tocilizumab OR Abatacept OR Infliximab OR Etanercept OR Adalimumab Phases 2, 3, 4 Date of trial start 13/08/2019 to 26/05/2020 Interventional studies (clinical trials) Results: 7 studies found.
The WHO International Clinical Trials Registry Platform	Hand-searching of WHO ICTRP for this SLR update on the 26 May 2020 was not able to be conducted due to the website being unavailable.
The British Thoracic Society (BTS) Winter Meeting 2019	Search: interstitial lung disease Abstracts: https://thorax.bmj.com/content/74/Suppl_2 No relevant studies identified.
The European League Against Rheumatism (EULAR) - European Congress of Rheumatology (2020 E-congress)	Search of abstract archive: http://scientific.sparx-ip.net/archiveeular/index.cfm Search terms: interstitial lung disease OR pulmonary fibros OR lung fibros OR fibrosing lung disease, nintedanib OR pirfenidone 12 studies identified.

The results are summarised in the PRISMA flow diagram in Figure 41. In total, 10 records were identified for inclusion from his update, however no additional trials with reported data were identified.

The 10 publications identified for inclusion and their descriptions are presented in Table 88. Excluded studies with the reasons are presented in Table 82.

Figure 41: PRISMA diagram for the SLR update (May 2020)



[a]Conferences searched for update include the British Thoracic Society winter 2019 meeting and the EULAR European Congress of Rheumatology 2020 congress. [b]WHO International Clinical Trials Registry Platform (ICTRP) was unable to be searched due to the website being unavailable. RCTs, randomised controlled trial.

Table 88: Descriptions of the publications identified in the SLR update (May 2020)

Reference	Description
Guenther et al. 2019(44)	• Identified in Aug/ Oct 2019 searches.
Flaherty et al. 2019(5)	• Identified in Aug/ Oct 2019 searches.
NCT02808871(99)	• Identified in Aug/ Oct 2019 searches. • Protocol only of TRAIL 1 trial presented in Appendix 5 of the original report.
Maher et al. 2019(45)	• Identified in Aug/ Oct 2019 searches.
Solomon et al. 2019(109)	• Published protocol/ rationale for the TRAIL 1 trial (NCT02808871).
Euctr 2019(110)	• Clinical trial protocol only. • Trial design: Phase 3, double blind, randomised, placebo-controlled trial. • Duration: 24 weeks.

Reference	Description
	• Intervention/ comparator: nintedanib vs placebo. • Type of ILD and definition of fibrosing phenotype: fibrosing ILD, evidence of fibrosing ILD on HRCT within 12 months of visit 1. • Primary outcomes: Area under the Plasma Concentration-Time Curve at Steady State ($AUC_{T,ss}$) based on sampling at steady state, number of patients with TEAEs at week 24.
Aringer et al. 2020(111) [a]	• INBUILD trial: efficacy and safety results in patients with autoimmune disease related ILD by baseline use of DMARDs/glucocorticoids
Matteson et al. 2020(112) [a]	• INBUILD trial: progression in patients with autoimmune disease related ILDs.
Volkmann et al. 2020(112) [a]	• INBUILD trial: dose adjustments and adverse events in patients with autoimmune disease related ILD.
Wells et al. 2020(39)	• INBUILD trial: results displayed by ILD diagnosis.

[a]EULAR conference abstract, full-text not available.
Abbreviations: DMARDs, disease-modifying antirheumatic drugs; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; TEAEs, treatment-emergent adverse events.

Table 89: References excluded at full text with reasons (May 2020 update)

Author (year[a])	Title
Population out of scope	
Kuwana, M. and Ogura, T. and Makino, S. and Homma, S. and Kondoh, Y. and Saito, A. and Ugai, H. and Gahlemann, M. and Takehara, K. and Azuma, A. (2020)	Nintedanib in patients with systemic sclerosis-associated interstitial lung disease: A Japanese population analysis of the SENSCIS trial
Nct (2020)	Efficacy and Safety of Nintedanib in the Treatment of Pulmonary Fibrosis in Patients With Moderate to Severe COVID -19
Nct (2020)	Effects of Tofacitinib vs Methotrexate on Rheumatoid Arthritis Interstitial Lung Disease
Nct (2017)	Scleroderma Lung Study III (SLS III): Combining the Anti-fibrotic Effects of Pirfenidone (PFD) With Mycophenolate (MMF) for Treating Scleroderma-related Interstitial Lung Disease.
Nct (2018)	Cyclophosphamide and Azathioprine vs Tacrolimus in Antisynthetase Syndrome-related Interstitial Lung Disease : Multicentric Randomized Phase III Trial.
Nct (2019)	Pirfenidone in the Treatment of Hermansky Pudlak Syndrome (HPS) - Related Interstitial Lung Disease (ILD)
Nct (2019)	Randomized Open-label Study of the Impact of Prolonged Systemic Corticosteroid Therapy on the Course and Relapse Risk of Checkpoint Inhibitor Interstitial Lung Disease (Pneumonitis) Related to the Treatment of Solid Tumors With Anti-programmed-death Type 1 Receptor or Ligand Antibodies.
Nct (2019)	A Phase III, Randomized, Double-blind, Placebo Controlled, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of Pirfenidone in Subjects With

Author (year[a])	Title
Population out of scope	
	Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD).
Nct (2019)	A Phase III, Randomized, Double-blind, Placebo Controlled, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of Pirfenidone in Subjects With Dermatomyositis Interstitial Lung Disease (Dm-ILD).
Acharya, N. and Sharma, S. K. and Mishra, D. and Dhooria, S. and Dhir, V. and Jain, S. (2020)	Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease-a randomised controlled trial
Mateos-Toledo, H. and Mejia-Avila, M. and Rodriguez-Barreto, O. and Mejia-Hurtado, J. G. and Rojas-Serrano, J. and Estrada, A. and Castillo-Pedroza, J. and Castillo-Castillo, K. and Gaxiola, M. and Buendia-Roldan, I. and Selman, M. (2019)	An Open-label Study With Pirfenidone on Chronic Hypersensitivity Pneumonitis
Naidu, G. and Sharma, S. K. and Adarsh, M. B. and Dhir, V. and Sinha, A. and Dhooria, S. and Jain, S. (2020)	Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial
Volkmann, E. R. and Tashkin, D. P. and Kuwana, M. and Li, N. and Roth, M. D. and Charles, J. and Hant, F. N. and Bogatkevich, G. S. and Akter, T. and Kim, G. and Goldin, J. and Khanna, D. and Clements, P. J. and Furst, D. E. and Elashoff, R. M. and Silver, R. M. and Assassi, S. (2019)	Progression of Interstitial Lung Disease in Systemic Sclerosis: The Importance of Pneumoproteins Krebs von den Lungen 6 and CCL18
Distler, O. and Highl and , K. B. and Gahlemann, M. and Azuma, A. and Fischer, A. and Mayes, M. D. and Raghu, G. and Sauter, W. and Girard, M. and Alves, M. and Clerisme-Beaty, E. and Stowasser, S. and Tetzlaff, K. and Kuwana, M. and Maher, T. M. (ATS 2019)	Nintedanib reduces lung function decline in patients with systemic sclerosis-associated interstitial lung disease: Results of the SENSCIS trial
Denton, C. P. and Lin, C. J. F. and Goldin, J. and Kim, G. and Kuwana, M. and Allanore, Y. and Batalov, A. and Butrimiene, I. and Carreira, P. and Matucci-Cerinic, M. and Distler, O. and Kaliterna, D. M. and Mihai, C. M. and Mogensen, M. and Olesinska, M. and Pope, J. E. and Riemekasten, G. and Rodriguez-Reyne, T. S. and Santos, M. J. and Van Laar, J. and Spotswood, H. and Siegel, J. and Jahreis, A. and Furst, D. E. and Khanna, D. (ERS 2019)	Lung function preservation in a phase 3 trial of tocilizumab (TCZ) in systemic sclerosis (SSc)
Highland, K. B. and Azuma, A. and Fischer, A. and Kuwana, M. and Maher, T. M. and Mayes, M. D. and Raghu, G. and Girard, M. and Alves, M. and Gahlemann, M. and Distler, O. (ERS 2019)	Changes in FVC in the SENSCIS trial of nintedanib in patients with systemic sclerosis-associated ILD (SSc-ILD)

Author (year[a])	Title
Population out of scope	
Highland , K. B. and Kuwana, M. and Azuma, A. and Fischer, A. and Maher, T. M. and Mayes, M. D. and Raghu, G. and Girard, M. and Kohlbrenner, V. and Clerisme-Beaty, E. and Alves, M. and Distler, O. (ERS 2019)	Dose adjustments in the SENSCIS trial of nintedanib in patients with systemic sclerosis-associated ILD (SSc-ILD)
Maher, T. and Distler, O. and Azuma, A. and Fischer, A. and Highland , K. B. and Kuwana, M. and Mayes, M. D. and Wachtlin, D. and Alves, M. and Gahlemann, M. and et al. (ERS 2019)	Effects of nintedanib in patients with systemic sclerosisassociated ILD (SSc-ILD) and differing FVC at baseline: the SENSCIS trial
Raghu, G. and Distler, O. and Azuma, A. and Fischer, A. and Highland , K. B. and Kuwana, M. and Mayes, M. D. and Wachtlin, D. and Stowasser, S. and Alves, M. and et al. (ERS 2019)	Effects of nintedanib in patients with systemic sclerosis-associated ILD (SSc-ILD) and differing extents of lung fibrosis: the SENSCIS trial
Y. Allanore, V. Steen, M. Kuwana, C. Denton, M. Matucci-Cerinic, E. Volkmann, D. Khanna, D. Wachtlin, M. Gahlemann, M. Quaresma, M. Alves, O. Distler, on behalf of the SENSCIS Trial Investigators (EULAR 2020)	EFFECTS OF NINTEDANIB IN PATIENTS WITH SYSTEMIC SCLEROSIS-ASSOCIATED ILD (SSC-ILD) AND DIFFERING EXTENTS OF SKIN FIBROSIS: FURTHER ANALYSES OF THE SENSCIS TRIAL
V. K. Bournia, D. Mitsikostas, O. Distler, P. Sfikakis (EULAR 2020)	THE NOCEBO PHENOMENON PARTLY ACCOUNTS FOR DIARRHOEA AMONG PARTICIPANTS IN THE RANDOMIZED PLACEBO-CONTROLLED TRIAL OF NINTEDANIB FOR INTERSTITIAL LUNG DISEASE ASSOCIATED WITH SYSTEMIC SCLEROSIS (SENSCIS)
O. Distler, K. Highland, A. M. Hoffmann-Vold, O. Kowal-Bielecka, U. Walker, F. Del Galdo, M. Vonk, L. Hummers, E. Erhardt, M. Quaresma, M. Alves, V. Smith (EULAR 2020)	CORRELATION BETWEEN PROGRESSION OF SKIN FIBROSIS AND PROGRESSION OF INTERSTITIAL LUNG DISEASE (ILD) IN PATIENTS WITH SSC-ILD: DATA FROM THE SENSCIS TRIAL
A. Lescoat, S. Jouneau, B. Crestani, G. Riemekasten, Y. Kondoh, V. Smith, N. Patel, J. Huggins, C. Stock, M. Gahlemann, M. Alves, C. Denton (EULAR 2020)	IS THE RATE OF LUNG FUNCTION DECLINE THE SAME IN PATIENTS WITH SYSTEMIC SCLEROSIS-ASSOCIATED ILD (SSC-ILD) WHO EXPERIENCE WEIGHT LOSS? DATA FROM THE SENSCIS TRIAL
G. Riemekasten, P. Carreira, L. A. Saketkoo, M. Aringer, L. Chung, J. Pope, C. Miede, S. Stowasser, M. Gahlemann, M. Alves, D. Khanna (EULAR 2020)	EFFECTS OF NINTEDANIB IN PATIENTS WITH SYSTEMIC SCLEROSIS-ASSOCIATED ILD (SSC-ILD) AND NORMAL VERSUS ELEVATED C-REACTIVE PROTEIN (CRP) AT BASELINE: ANALYSES FROM THE SENSCIS TRIAL
E. Volkmann, S. Vettori, J. Varga, A. Herrick, M. Cutolo, A. Cordeiro, V. F. Azevedo, S. Johnson, C. Stock, M. Gahlemann, L. Moros, M. Alves, M. Mayes (EULAR 2020)	IS THERE A DIFFERENCE BETWEEN THE SEXES IN THE RATE OF PROGRESSION OF SYSTEMIC SCLEROSIS-ASSOCIATED ILD (SSC-ILD)? DATA FROM THE SENSCIS TRIAL
Study design out of scope	
Li, J. and Chen, X. and Qu, Y. (2019)	Effects of cyclophosphamide combined with prednisone on TNF-alpha expression in treatment of patients with interstitial lung disease

Author (year[a])	Title
Population out of scope	
C. Fernández-Díaz, S. Castañeda, R. Melero, J. Loricera, F. Ortiz-Sanjuán, A. Juan-Mas, C. Carrasco-Cubero, S. Rodriguéz-Muguruza, S. Rodrigez-Garcia, R. Castellanos-Moreira, R. Almodovar, C. Aguilera Cros, I. Villa-Blanco, S. Ordoñez, S. Romero-Yuste, C. Ojeda-Garcia, M. Moreno, G. Bonilla, I. Hernández-Rodriguez, M. Lopez Corbeto, J. L. Andréu Sánchez, T. Pérez Sandoval, A. López Robles, P. Carreira, N. Mena-Vázquez, C. Peralta-Ginés, A. Urruticoechea-Arana, L. M. Arboleya Rodríguez, J. Narváez, D. Palma Sanchez, O. Maiz-Alonso, J. Fernández- Leroy, I. Cabezas-Rodriguez, I. Castellví, A. Ruibal-Escribano, J. De Dios-Jiménez Aberásturi, P. Vela-Casasempere, C. González-Montagut Gómez , J. M. Blanco, N. Alvarez-Rivas, N. Del-Val, M. Rodíguez-Gómez, E. Salgado-Pérez, C. Fernández-López, E. C. Cervantes Pérez, A. Devicente-Delmas, B. Garcia-Magallon, C. Hidalgo, S. Fernández, E. García-Fernández, R. López-Sánchez, S. Castro, P. Morales-Garrido, A. García-Valle, R. Expósito, L. Exposito-Perez, L. Pérez Albaladejo, Á. García-Aparicio, M. A. González-Gay, R. Blanco (EULAR 2020)	ABATACEPT IN INTERSTITIAL LUNG DISEASE ASSOCIATED WITH RHEUMATOID ARTHRITIS. NATIONAL MULTICENTER STUDY OF 263 PATIENTS
A. M. Hoffmann-Vold, H. Fretheim, B. Maurer, M. Durheim, Ø. Midtvedt, M. O. Becker, R. Dobrota, Ø. Molberg, S. Jordan, O. Distler (EULAR 2020)	INTERSTITIAL LUNG DISEASE IN SYSTEMIC SCLEROSIS: DECLINE IN FORCED VITAL CAPACITY DOES NOT PREDICT FURTHER PROGRESSION IN THE FOLLOWING PERIOD
F. Salaffi, M. Tardella, M. Carotti, M. DI Carlo, A. Giovagnoni (EULAR 2020)	ABATACEPT IN RHEUMATOID ARTHRITIS ASSOCIATED-INTERSTITIAL LUNG DISEASE: SHORT TERM OUTCOME AND PROGNOSTIC FACTORS
Outcome out of scope	
Humphries, S. M. and Notary, A. M. and Centeno, J. and Lynch, D. A. (ATS 2019)	Use of quantitative CT to determine disease extent and identify UIP pattern in rheumatoid arthritis ILD
Duplicate articles	
Nct (2000)	Scleroderma Lung Disease
Nct (2009)	Comparison of Therapeutic Regimens for Scleroderma Interstitial Lung Disease (The Scleroderma Lung Study II)
Nct (2013)	Safety and Tolerability of Pirfenidone in Participants With Systemic Sclerosisâˆ'Related Interstitial Lung Disease (SSc-ILD) (LOTUSS)
Nct (2015)	A Trial to Compare Nintedanib With Placebo for Patients With Scleroderma Related Lung Fibrosis
Flaherty, K. R. and Wells, A. U. and Clerisme-Beaty, E. and Cottin, V. and Devaraj, A. and Inoue, Y. and Richeldi, L.	Characteristics of patients with progressive fibrosing interstitial lung diseases (ILDS) in the inbuild trial of nintedanib

Author (year[a])	Title
Population out of scope	
and Walsh, S. and Goeldner, R. and Schlenker-Herceg, R. and Brown, K. K. (ATS 2019)	
Solomon, J. (ATS 2019)	The design and rationale of the trail trial: A randomized double-blind phase II clinical trial of pirfenidone in rheumatoid arthritis-associated interstitial lung disease
Tashkin, D. P. and Volkmann, E. R. and Li, N. and Roth, M. D. and Kim, G. and Goldin, J. and Elashoff, R. M. and Assassi, S. (ATS 2019)	Circulating Krebs von den Lungen and CC chemokine lligand 2 predict progression of interstitial lung disease in systemic sclerosis patients undergoing immunosuppressive therapy
Flaherty, K. R. and Wells, A. U. and Cottin, V. and Devaraj, A. and Inoue, Y. and Richeldi, L. and Walsh, S. and Stowasser, S. and Coeck, C. and Goeldner, R. G. and Clerisme-Beaty, E. and Schlenker-Herceg, R. and Brown, K. K. (ERS 2019)	Nintedanib in patients with chronic fibrosing interstitial lung diseases with progressive phenotype: the INBUILD trial
Withdrawn	
Inoue, Y. and Wells, A. U. and Song, J. W. and Xu, Z. and Kitamura, H. and Suda, T. and Okamoto, M. and Schlenker-Herceg, R. and Kolb, M. and Brown, K. K. and Quaresma, M (ASPR 2019)	The inbuild trial of nintedanib in patients with progressive fibrosing interstitial lung diseases: Subgroup of Asian patients

[a]Conference abstracts are specified by conference abbreviation. ASPR, Asian Pacific Society of Respirology; ATS, American Thoracic Society; ERS, European Respiratory Society; EULAR, The European League Against Rheumatism- European Congress of Rheumatology.

D.1.1.3 Summary of trials used for indirect or mixed treatment comparison

As noted above, it was not possible to conduct indirect or mixed treatment comparisons due to a lack of robust published data for comparators. This section of Appendix D has therefore not been completed.

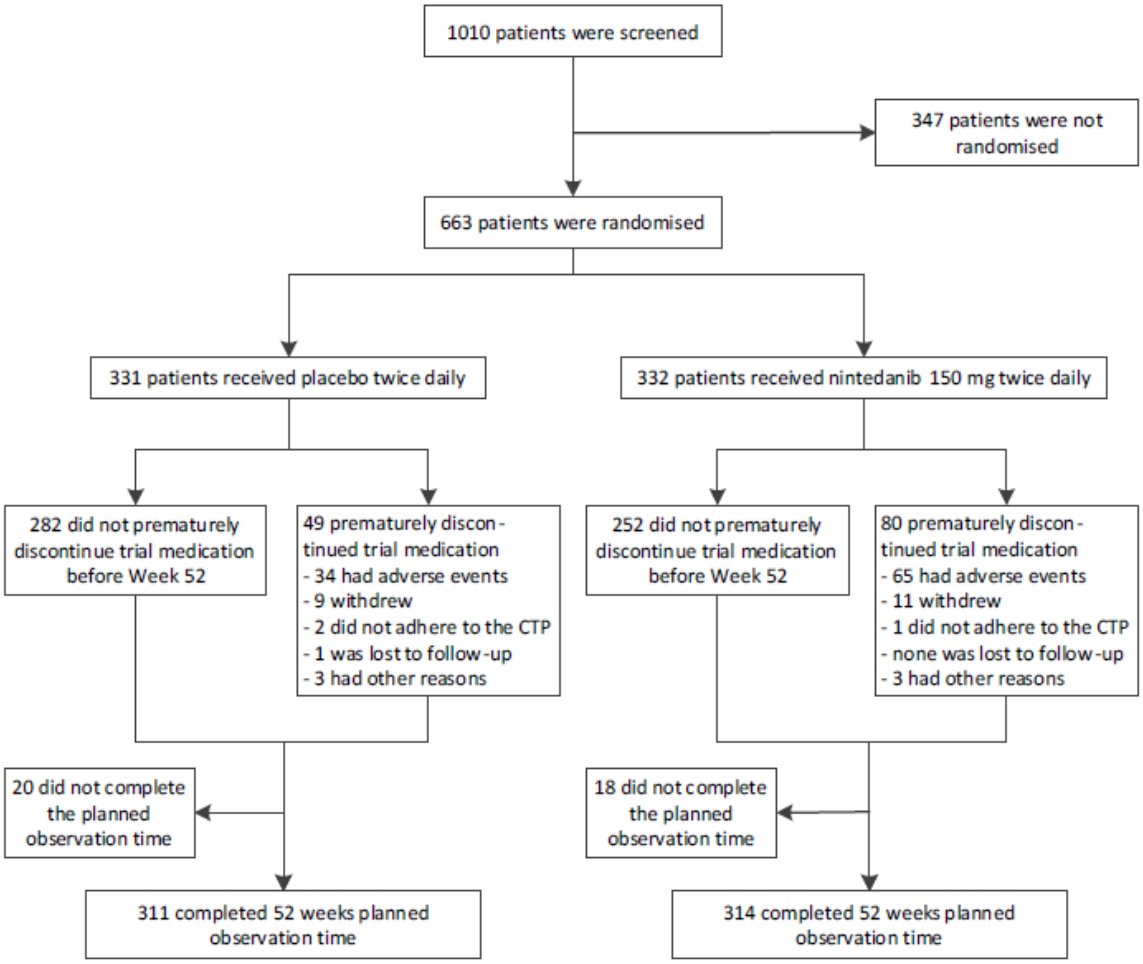
D1.2 Participant flow in the relevant randomised control trials

Overall population

A total of 663 patients were randomised, all of whom were treated with nintedanib (332 patients) or placebo (331 patients) (Figure 42). Over 52 weeks, 24.1% of patients in the nintedanib group and 14.8% of patients in the placebo group prematurely discontinued treatment. Reasons (by decreasing overall frequency) were AEs, withdrawal by the patient, other reasons, protocol deviations and loss to follow up. Overall, 94.3% of patients completed the 52 weeks planned observation time. Reasons for not completing the planned observation time (by decreasing overall

frequency) were death, withdrawal by the patient and loss to follow-up. Vital status information at 52 weeks was collected for patients who did not complete the 52 weeks observation time. Of these 38 patients, 5 (13.2%, 0.8% in TS) were reported to be alive and 31 (81.6%, 4.7% in TS) had died by week 52.

Figure 42: Overview of disposition of patients at 52 weeks (overall population)



Abbreviations: CTP, clinical trial protocol

After completing 52 weeks of treatment (Part A), patients continued on blinded randomised treatment (Part B). Patient disposition at the end of the trial (Part A + B) for the overall population is shown in Figure 43. Of the 663 treated patients, 34.3% of patients in the nintedanib group and 30.2% of patients in the placebo group prematurely discontinued treatment. Reasons (by decreasing frequency) were AEs, withdrawal by the patient, other reasons, protocol deviations and loss to follow-up. More patients in the nintedanib group than in the placebo group discontinued trial

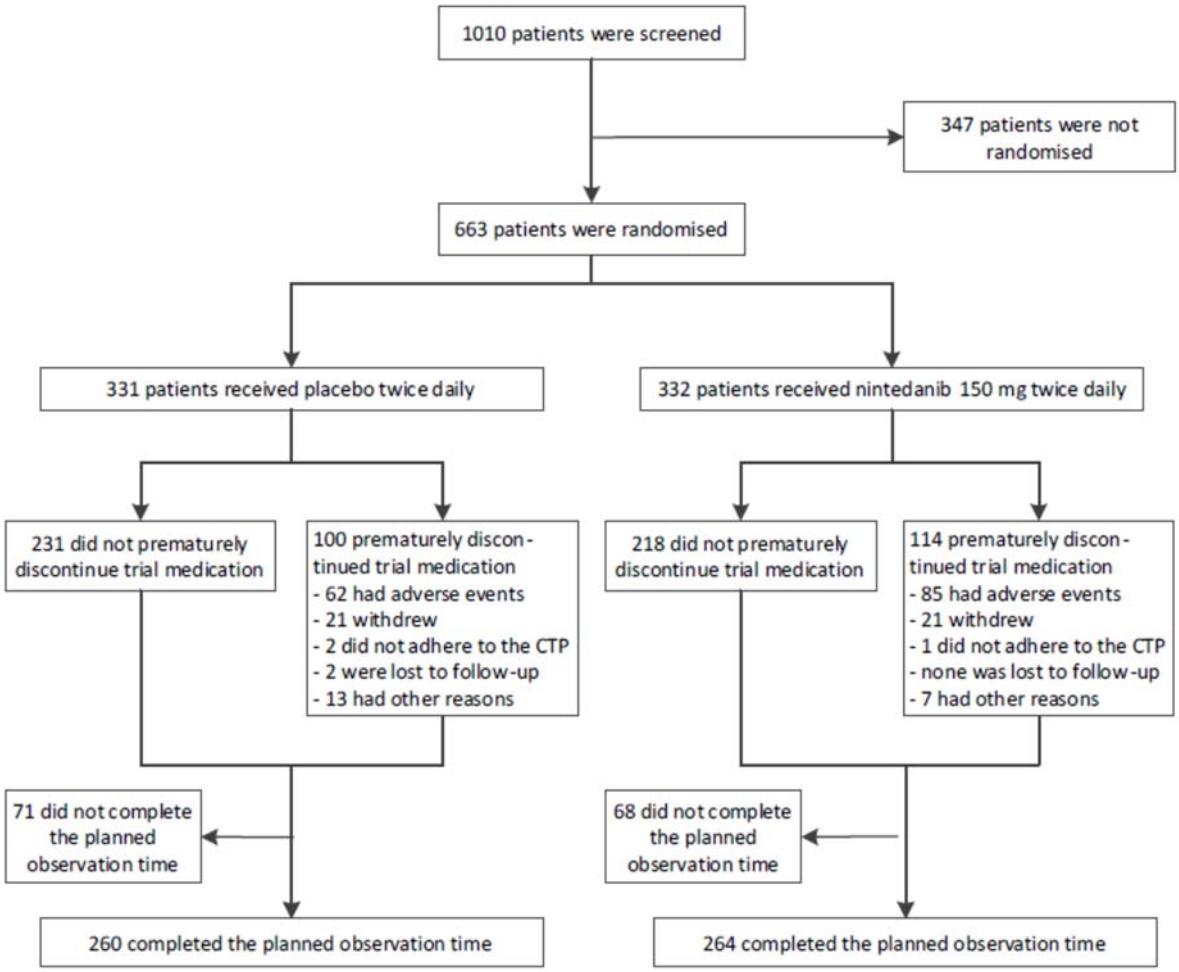
treatment prematurely due to AEs (nintedanib: 25.6%, placebo: 18.7%). The proportions of patients who discontinued treatment due to other reasons were comparable between the treatment groups.

Overall, 79.5% of patients in the nintedanib group and 78.5% of patients in the placebo group completed the planned observation time. Reasons for early trial discontinuation (by decreasing overall frequency) were death, withdrawal by the patient, other reasons and loss to follow-up. Of these 139 patients, 54 patients (38.8%, 8.1% in TS) were reported to be alive and 81 patients (58.3%, 12.2% in TS) had died by the time of database lock 2. The proportions and reasons for discontinuation from the trial were generally comparable between the treatment groups.

Subgroup evaluations for disposition over the whole trial (Part A + B) in the overall population, including by gender, age group, race, baseline FVC % predicted, underlying clinical ILD diagnosis (grouped), baseline body weight and the use of certain drugs at baseline, are available in the Clinical Trial Report. Disposition data were generally comparable across subgroups.

Eligible patients were offered the option of participating in an open-label extension trial; 436 patients were enrolled.

Figure 43: Overview of disposition of patients over the whole trial (Part A + B) up to DBL2 (overall population)



Abbreviations: CTP, clinical trial protocol; DBL, database lock

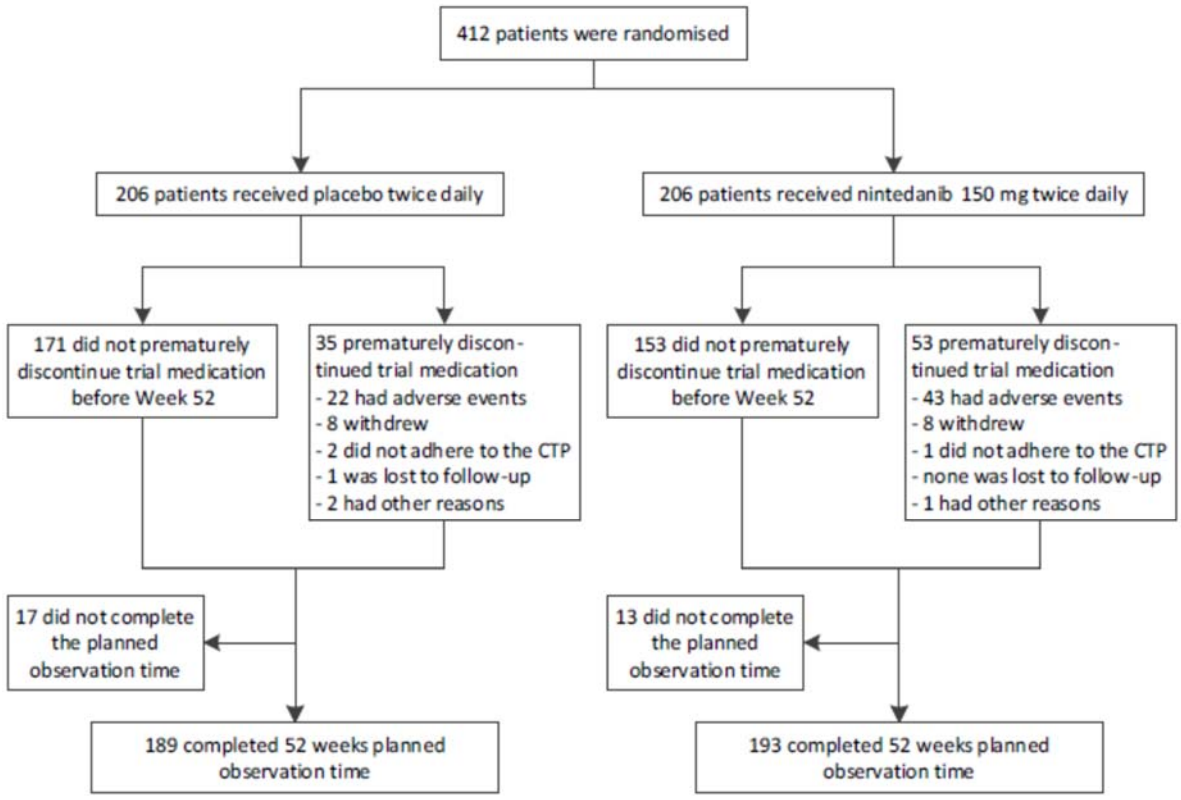
Patients with UIP-like fibrotic pattern on HRCT

Patient disposition at 52 weeks for patients with UIP-like fibrotic pattern on HRCT is shown in Figure 44. All 412 randomised patients were treated with nintedanib (206 patients) or placebo (206 patients). Over 52 weeks, 25.7% of patients in the nintedanib group and 17.0% of patients in the placebo group prematurely discontinued treatment. Reasons (by decreasing overall frequency) were AEs, withdrawal by the patient, protocol deviation, other and loss to follow-up.

Overall, 92.7% of patients completed the 52 weeks planned observation time. Reasons for not completing the planned observation time (by decreasing overall

frequency) were death, withdrawal by the patient and loss to follow-up. Vital status information at 52 weeks was collected for the patients who did not complete the 52 weeks observation time. Of these 30 patients, 3 (10.0%, 0.7% in TS) were reported to be alive and 25 (83.3%, 6.1% in TS) had died by week 52.

Figure 44: Overview of patient disposition at 52 weeks (UIP-like fibrotic pattern)



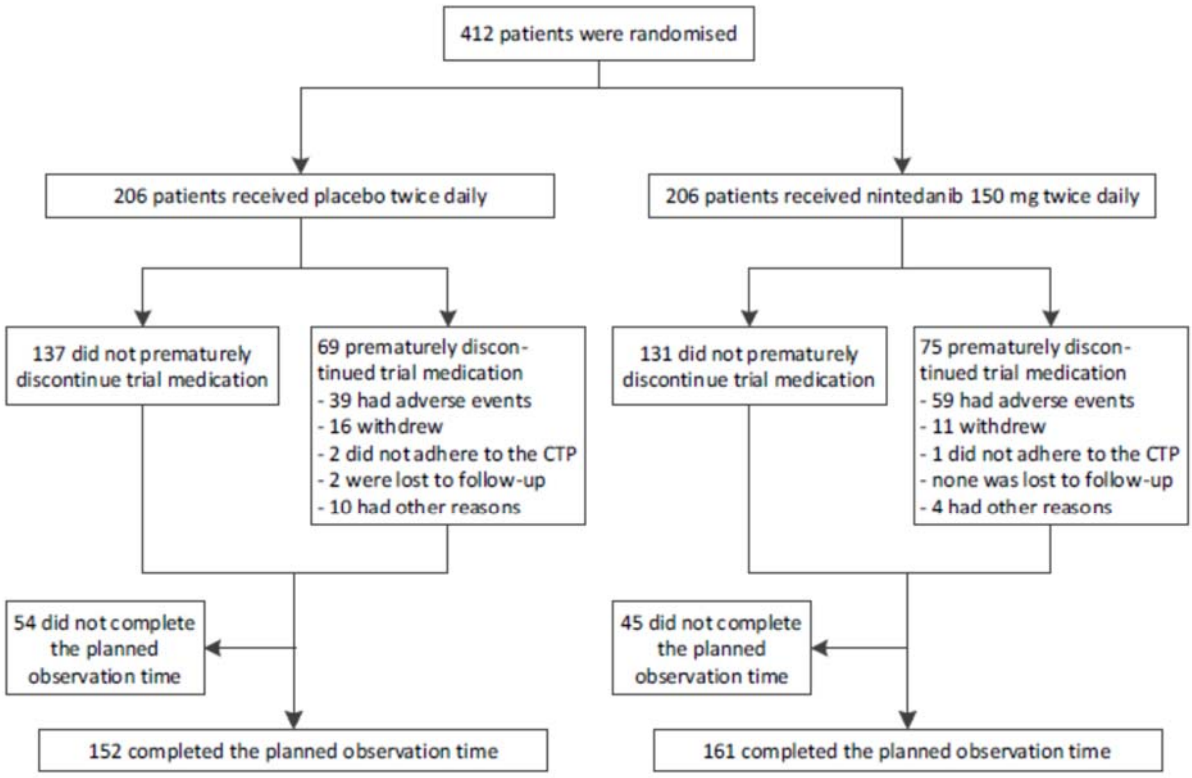
Abbreviations: CTP, clinical trial protocol.

Patient disposition at the end of the trial (Part A + B) for patients with UIP-like fibrotic pattern on HRCT is shown in Figure 45. Of the 412 treated patients, 36.4% in the nintedanib group and 33.5% in the placebo group prematurely discontinued treatment. Reasons (by decreasing overall frequency) were AEs, withdrawal by the patient, other reasons, protocol deviations and loss to follow-up. As in the overall population, more patients in the nintedanib group than in the placebo group prematurely discontinued treatment due to AEs.

Overall, 78.2% of patients in the nintedanib group and 73.8% of patients in the placebo group completed the planned observation time. Reasons for early trial discontinuation (by decreasing frequency) were death, withdrawal by the patient, other reasons and

loss to follow-up. Vital status information at database lock 2 was collected for patients who discontinued the trial early. Of these 99 patients, 35 (35.4%, 8.5% in TS) were reported to be alive and 61 (61.6%, 14.8% in TS) had died by the time of database lock 2. The proportions and reasons for discontinuation from the trial were comparable between the treatment groups.

Figure 45: Overview of disposition of patients over the whole trial (Part A + B) up to DBL2 (UIP-like fibrotic pattern)



Abbreviations: CTP, clinical trial protocol; DBL, database lock

Subgroup evaluations over the whole trial up to database lock 2 for patients with UIP-like fibrotic pattern on HRCT are available in the Clinical Trial Report. Subgroups were generally comparable with regard to disposition data.

D1.3 Quality assessment for each trial

Critical appraisal of the INBUILD trial is presented in Table 90. Overall, we consider this trial to be of high quality, with a low risk of bias.

In addition, the design of the INBUILD trial is likely to be reflective of clinical practice in England and Wales in terms of trial endpoints, study population and comparators.

The trial also included patients from 5 UK sites. As a result we expect the results of the INBUILD trial to be relevant to clinical practice in England. Please see Section B.2.13 (page 49) for a greater discussion on the trial's external validity.

Table 90: Quality assessment results for parallel group RCTs

Trial number (acronym)	Study 1199.247 (INBUILD)	
	Reviewer's judgement	**Justification**
Was the randomisation carried out appropriately?	Yes	Randomisation was performed using an IRT system.
Was the concealment of treatment allocation adequate?	Yes	Randomisation was performed by IRT, and trial packaging and labelling were identical. Colour, size and shape of nintedanib and placebo capsules were indistinguishable within dose strength, but were different between dose strengths.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Participants in all populations had similar baseline characteristics and treatment arms were well balanced.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained blinded with regard to the randomised treatment assignments until after DBL1.
Were there any unexpected imbalances in drop-outs between groups?	No	Although there were some differences, these were consistent with the known safety profile of nintedanib in IPF and other indications.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All pre-specified outcomes have been reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Efficacy and safety analyses were performed based on the treated set, which included all randomised patients who received ≥1 dose of trial medication; however since all patients who were randomised received treatment with nintedanib or placebo this included all randomised patients. To reduce the amount of missing data, patients who discontinued trial drugs for any reason prior to completing the 52 week treatment period were asked to attend all visits and undergo all examinations as previously planned. In additional, for all patients who prematurely discontinued trial medication and were unable to complete the scheduled visits, every attempt was made to collect information on vital status at week 52, at the time of data cut-off for the primary analysis and at the end of the trial. The statistical model used for the primary analysis allowed for missing data, assuming they were missing at random.
Did the authors of the study publication declare any conflicts of interest?	Yes	All authors have clearly declared any conflicts of interest, and these are not considered to have biased the reporting or results of the study.

Abbreviations: DBL1, database lock 1; IRT, Interactive Response Technology

Appendix E: Subgroup analysis

The following subgroups were investigated for the overall population: gender, age group, race, baseline FVC % predicted and underlying clinical ILD diagnosis (grouped). For the co-primary population of patients with UIP-like fibrotic pattern on HRCT, the subgroups were defined by gender, age group and race.

Overall population

None of the demographics or clinical characteristics above had a substantial influence on the treatment effect of nintedanib vs. placebo in the overall population (Figure 46). All point estimates were in favour of nintedanib vs. placebo, and all CIs of subgroup results included the point estimate for the overall population. Subgroup analyses were not adjusted for multiplicity and were limited by small sample sizes in some cases.

An additional analysis investigated the impact of the underlying ILD diagnoses by employing the method of excluding ILD diagnosis groups one by one, thus exploring the influence of the excluded ILD diagnosis group on the overall treatment effect. The point estimates and CIs were very similar in these analyses, showing that the treatment effect was not driven by one of the ILD diagnosis groups (Figure 47).

Patients with UIP-like fibrotic pattern

None of the demographic characteristics (gender, age and race) substantially influenced the treatment effect of nintedanib vs. placebo in patients with UIP-like fibrotic patterns on HRCT (Figure 48). All point estimates for the adjusted treatment difference in rate of decline in FVC over 52 weeks were in favour of nintedanib compared with placebo, and all CIs of subgroup results included the point estimate of the population of patients with UIP-like fibrotic patterns. Subgroup analyses were not adjusted for multiplicity and were limited by small sample sizes in some cases.

Figure 46: Forest plot for the primary endpoint analysis in subgroups (overall population)

	N analysed Placebo	N analysed Nintedanib	Estimate [95% CI]	Treatment-by-subgroup-by-time interaction p-value
Gender				0.0553
Male	177	179	145.20 [88.47; 201.93]	
Female	154	153	64.21 [3.87; 124.55]	
Age group				0.5123
<65 years	121	139	86.87 [21.53; 152.21]	
>=65 years	210	193	115.13 [61.41; 168.84]	
Race				0.7736
White	246	242	110.59 [61.97; 159.20]	
Asian	80	84	92.98 [9.30; 176.67]	
Black or African American	5	5	222.48 [-143.09; 588.05]	
Baseline FVC % predicted				0.3695
<=70%	193	196	91.68 [37.36; 145.99]	
>70%	138	136	129.98 [66.22; 193.73]	
Underlying ILD Diagnosis in Groups				0.4139
Hypersensitivity pneumonitis	89	84	73.12 [-8.57; 154.81]	
Idiopathic nonspecific interstitial pneumonia	61	64	141.61 [46.04; 237.17]	
Unclassifiable idiopathic interstitial pneumonia	50	64	68.33 [-31.43; 168.10]	
Autoimmune ILDs	88	82	104.02 [21.11; 186.92]	
Other ILDs	43	38	197.13 [77.57; 316.70]	
ALL	331	332	106.96 [65.42; 148.50]	

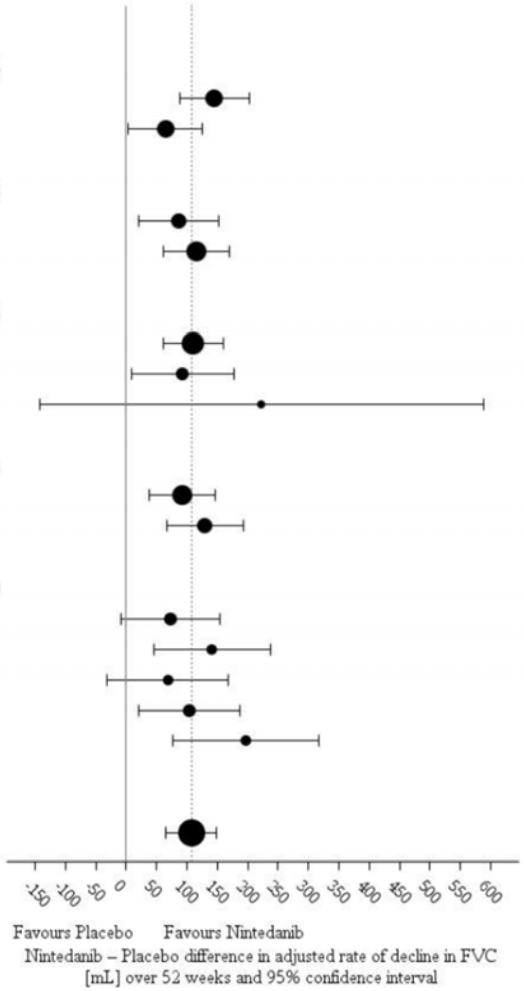
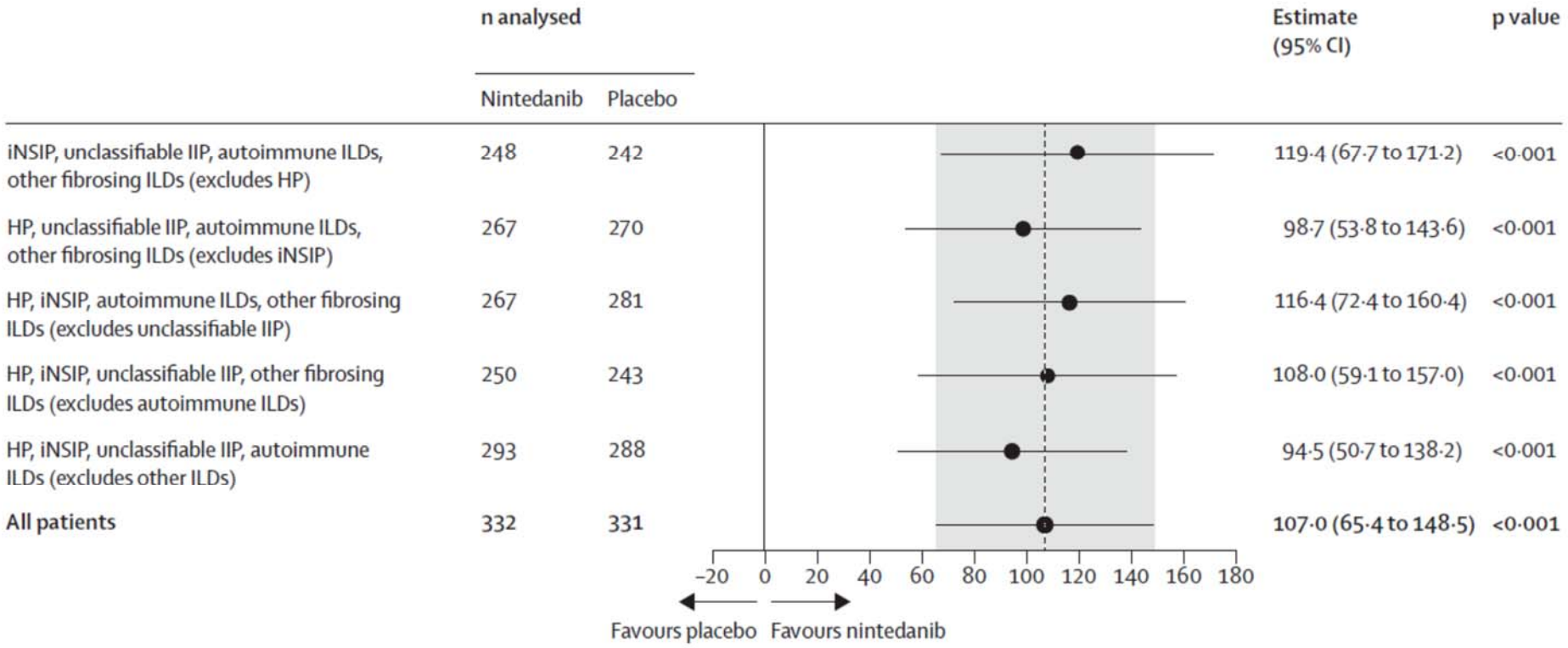


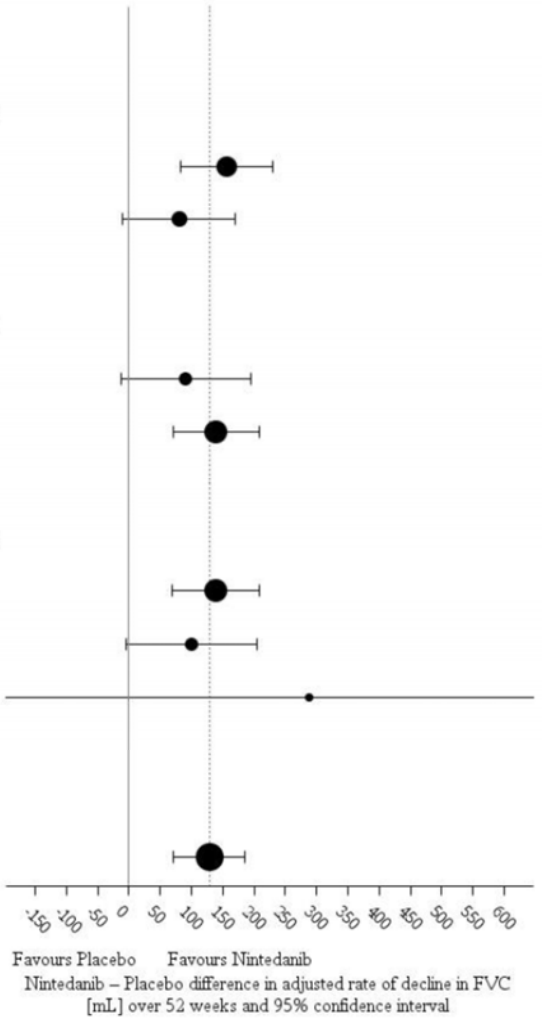
Figure 47: Annual rate of decline in FVC (mL/year) with one of the five groups by ILD diagnosis excluded at a time (overall population)



Abbreviations: FVC, forced vital capacity; HP, hypersensitivity pneumonitis; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; iNSIP, idiopathic non-specific interstitial pneumonia

Figure 48: Forest plot for the primary endpoint analysis in subgroups (patients with UIP-like fibrotic pattern)

	N analysed Placebo	N analysed Nintedanib	Estimate [95% CI]	Treatment-by-subgroup-by-time interaction p-value
Gender				0.1962
Male	127	120	156.82 [82.92; 230.71]	
Female	79	86	80.26 [-9.56; 170.08]	
Age group				0.4419
<65 years	57	67	90.81 [-12.42; 194.03]	
>=65 years	149	139	139.46 [70.44; 208.48]	
Race				0.7401
White	143	142	138.69 [69.31; 208.07]	
Asian	62	60	99.85 [-4.57; 204.28]	
Black or African American	1	4	288.74 [-373.37; 950.86]	
ALL	206	206	128.20 [70.81; 185.59]	



Main secondary endpoints in patients with UIP-like fibrotic patterns

The results of the main secondary endpoints in the UIP-like population are presented in Table 91. Overall, these were consistent with, and supported the effect seen in the overall trial population.

Table 91: Main secondary endpoint results in the population with UIP-like fibrotic patterns

Endpoint	Nintedanib (N = 332)	Placebo (N = 331)	Difference (95% CI)
Main secondary endpoints			
Absolute change from baseline in total score on K-BILD questionnaire at 52 weeks¶	0.75±0.80	−0.78±0.79	1.53 (−0.68 to 3.74)§
Acute exacerbation of ILD or death at 52 weeks (no. with event/total no. [%])	17/206 (8.3)	25/206 (12.1)	0.67 (0.36 to 1.24)§‖
Acute ILD exacerbation or death over the whole trial period up to DBL2 (no. with event/total no. [%])	31/206 (15.0)	47/206 (22.8)	0.62 (0.39 to 0.97)‖
Death at 52 weeks (no. with event/total no. [%])	11/206 (5.3)	16/206 (7.8)	0.68 (0.32 to 1.47)§‖
Death over the whole trial period up to DBL2 (no. with event/total no. [%])	25/206 (12.1)	36/206 (17.5)	0.66 (0.40 to 1.10)‖

Abbreviations: DBL2, database lock 2; FVC, forced vital capacity; ILD, interstitial lung disease; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; UIP, usual interstitial pneumonia. Source: (5)
* Changes from baseline are adjusted means ±SE based on the statistical models. The two primary populations for analysis were the overall population and patients with a UIP-like fibrotic pattern.
§ The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.
¶ For the analysis of the scores on the K-BILD questionnaire, 332 patients were included in the nintedanib group and 330 in the placebo group in the overall population; among the patients with a UIP-like fibrotic pattern, included were 206 patients and 205 patients, respectively.
‖ The difference was assessed as a hazard ratio.

Appendix F: Adverse reactions

There are no studies reporting additional AEs to those reported in section 2.2.

Appendix G: Published cost-effectiveness studies

A systematic literature review (SLR) was conducted to identify published cost-effectiveness studies, health-related quality-of-life studies, and costs and healthcare resource use. The methodology for this SLR is described in this appendix, including search strategy, study selection, data extraction, and quality assessment. The overall PRISMA diagram for all three aspects of the SLR is also presented in this appendix along with results for the cost-effectiveness study part of the SLR. **Appendix H** and **Appendix I** present identified studies from the health-related quality-of-life and cost/HCRU parts of the SLR.

G.1.1 Search strategy

The following databases were searched:

- Ovid Embase.
- Ovid Medline.
- Cochrane Library.
- EconLit.
- NHS Economic Evaluation Database.
- NIHR Centre for Reviews and Dissemination.
- Tufts Medical Center Cost Effectiveness Analysis registry.
- SCHARR health utilities database.
- HERC utilities database.

The electronic searches were supplemented by hand searching to identify other published or unpublished material (grey literature). The described approach is a combination of Cochrane guidelines and the Canadian Agency for Drugs and Technology in Health practical search tool.

The reference lists of key papers and systematic reviews identified through the electronic searches were checked manually by an analyst to identify any peer-reviewed evidence that may have been missed in the electronic search.

Conference databases were searched manually if abstracts were not identified through electronic literature searches. The following congresses have been considered:

- American Thoracic Society (ATS)
- British Thoracic Society (BTS)
- European League Against Rheumatism (EULAR) - European Congress of Rheumatology
- European Respiratory Society (ERS)
- International Society of Pharmacoeconomics and Outcomes Research (ISPOR)

Searches for meeting abstracts were restricted to 2018 onwards, because those abstracts of relevance from previous years should have fully published data in peer-reviewed journals. Published studies from earlier years should be captured in the electronic database literature search.

Additionally, the following clinical trial databases have been searched to identify ongoing and recently completed studies that meet the inclusion criteria for the present review:

- Clinicaltrials.gov
- The WHO International Clinical Trials Registry Platform

Comprehensive search strategies were developed for each electronic database combining terms to identify the disease of interest, costs/HCRU, economic evaluations, and utilities (Table 92, Table 93, Table 94, Table 95, Table 96). The search strategy was devised using Ovid Medline and translated and applied to the other electronic databases. All searches were performed 9 June 2020.

Table 92: Search string and results for Ovid Medline (9 June 2020)

	Search	Hits
1	Lung Diseases, Interstitial/	9314
2	ILD.tw.	4084
3	Pulmonary Fibrosis/	18545
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	15621
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	21435
6	alveolitis.mp.	6147

	Search	Hits
7	(diffuse* adj3 parenchymal*).mp.	808
8	Bronchiolitis Obliterans/	2777
9	(bronchiolitis adj obliterans).mp.	4623
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	8012
11	Pneumoconiosis/	6624
12	bagassosis.mp.	69
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	12087
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	17029
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	13
16	((pulmonary$ or lung$) adj3 fibros$).mp.	34941
17	Alveolitis, Extrinsic Allergic/	2906
18	(connective adj3 lung$).mp.	234
19	(allerg$ adj3 pneumonitis).mp.	112
20	Cryptogenic Organizing Pneumonia/	1029
21	cryptogenic organi#ing pneumonia.mp.	1287
22	Idiopathic Interstitial Pneumonias/	385
23	IIP.tw.	1099
24	(hypersensitivity adj3 pneumonia$).mp.	191
25	pleuroparenchymal fibroelastosis.mp.	170
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	101298
27	Economics/	27188
28	exp "Costs and Cost Analysis"/	235719
29	Economics, Dental/	1911
30	exp Economics, Hospital/	24461
31	Economics, Medical/	9073
32	Economics, Nursing/	3999
33	Economics, Pharmaceutical/	2936
34	exp "Fees and Charges"/	30249
35	exp Budgets/	13680
36	(budget$ or financ$).tw.	130765
37	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).kf,ti.	227459
38	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	288391
39	exp Health Care Costs/	64868
40	exp Drug Costs/	16003
41	exp Hospitalization/	237709
42	exp "Cost of Illness"/	27005

	Search	Hits
43	Health Expenditures/	20124
44	exp Drug Utilization/	25158
45	exp "Utilization Review"/	13419
46	exp Cost-Benefit Analysis/	80695
47	(cost? adj2 (illness or disease or sickness or health care or healthcare or treatment or direct or indirect or medical or resource)).tw.	68688
48	(burden? adj2 (illness or disease? or condition? or economic*)).tw.	37013
49	(utili?ation adj2 (health or medical or resource)).tw.	25260
50	(out-of-pocket adj2 (payment? or expenditure? or cost? or spending or expense?)).tw.	4723
51	(expenditure? adj3 (health or direct or indirect)).tw.	8713
52	(expenditure? not energy).tw.	29655
53	(health care cost$ or hospitali?ation or health care utili?ation or bed day$ or cost of illness).tw.	157116
54	(value adj2 (money or monetary)).tw.	2359
55	(cost* adj2 (effective* or utilit* or benefit* or analy* or outcome or outcomes)).tw.	168983
56	(expenditure or value for money or budget).tw.	64784
57	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56	1052447
58	((energy or oxygen) adj cost).tw.	4095
59	(metabolic adj cost).tw.	1409
60	((energy or oxygen) adj expenditure).tw.	24932
61	58 or 59 or 60	29456
62	57 not 61	1025081
63	quality-adjusted life years/	12139
64	(qaly$ or qald$ or qale$ or qtime$).tw.	10574
65	(quality adjusted or adjusted life year$ or quality adjusted life year$).tw.	16656
66	(disability adjusted life or daly$).tw.	3983
67	((index and wellbeing) or (quality and wellbeing) or qwb or qwbsa).tw.	4355
68	(multiattribute$ or multi attribute$).tw.	870
69	(utilit$ adj2 (value$ or cost$ or health or analys$ or index or indices)).tw.	10570
70	disutilit$.tw.	463
71	(hsuv or hsuvs).tw.	67
72	(health$1 year$1 equivalent$1 or hye$).tw.	1021
73	(illness state$ or health state$ or health status$).tw.	63234
74	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).tw.	10907
75	(hui or hui1 or hui2 or hui3 or hui-1 or hui-2 or hui-3).tw.	1511
76	health utilit$.tw.	2069
77	quality of wellbeing$.tw.	24
78	(quality of well being or index of wellbeing or index of well being or qwb).tw.	557
79	(short form$ or short-form$ or shortform$).tw.	33226

	Search	Hits
80	(sf36$ or sf-36$ or sf 36 or sf6 or sf 6 or sf-6 or sf6d or sf 6d or sf-6d or sf8 or sf-8 or sf 8 or sf12 or sf-12 or sf 12 or sf16 or sf-16 or sf 16 or sf20 or sf-20 or sf 20 or sf thirtysix or sf thirty six).tw.	29467
81	(15d or 15-d or 15 dimension).tw.	5226
82	(standard gamble$ or sg).tw.	10663
83	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).tw.	1886
84	(visual analog$ scale$ or EQ-VAS).tw.	55057
85	discrete choice experiment$.tw.	1605
86	63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85	208977
87	62 or 86	1192418
88	26 and 87	1898
89	Case Reports/	2101889
90	case stud*.hw.	12330
91	case report?.hw.	2101889
92	Letter/	1082698
93	Editorial/	531609
94	89 or 90 or 91 or 92 or 93	3514773
95	88 not 94	1734
96	limit 95 to english language	1512

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to June 08, 2020

Table 93: Search string and results for Ovid Embase (9 June 2020)

	Search	Hits
1	interstitial lung disease/	21165
2	ILD.tw.	9497
3	lung fibrosis/	33753
4	(interstitial$ adj3 (lung$ adj3 disease$)).mp.	27300
5	(interstitial$ adj3 (fibros$ or pneumonitis or pneumonia or pneumopathy)).mp.	37227
6	alveolitis.mp.	29687
7	(diffuse* adj3 parenchymal*).mp.	1377
8	bronchiolitis obliterans/	5735
9	(bronchiolitis adj obliterans).mp.	9333
10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis).mp.	6436
11	pneumoconiosis/	5439
12	bagassosis.mp.	51
13	((bird$ or farmer$ or pigeon$ or avian$ or budgerigar$) adj (lung$ or disease$)).mp.	22517
14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis).mp.	15179
15	((pulmonary$ or lung$) adj3 reticulation$).mp.	28
16	((pulmonary$ or lung$) adj3 fibros$).mp.	56063

	Search	Hits
17	allergic pneumonitis/	6556
18	(connective adj3 lung$).mp.	377
19	(allerg$ adj3 pneumonitis).mp.	6607
20	bronchiolitis obliterans organizing pneumonia/	1823
21	cryptogenic organi#ing pneumonia.mp.	928
22	interstitial pneumonia/	15568
23	IIP.tw.	1580
24	(hypersensitivity adj3 pneumonia$).mp.	375
25	pleuroparenchymal fibroelastosis.mp.	312
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	160364
27	economics/	237566
28	exp pharmacoeconomics/	201592
29	exp health economics/	841713
30	exp economic evaluation/	304997
31	exp "cost"/	347443
32	exp fee/	39929
33	budget/	28989
34	(budget$ or financ$).ab,kw,ti.	177563
35	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).kw,ti.	280448
36	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	404769
37	exp "health care cost"/	289836
38	exp "drug cost"/	77093
39	exp hospitalization/	368361
40	exp "cost of illness"/	19124
41	drug utilization/	20051
42	exp "utilization review"/	64332
43	exp "cost benefit analysis"/	84227
44	(cost? adj2 (illness or disease or sickness or health care or healthcare or treatment or direct or indirect or medical or resource)).tw.	108587
45	(burden? adj2 (illness or disease? or condition? or economic*)).tw.	58310
46	(utili?ation adj2 (health or medical or resource)).tw.	38930
47	(out-of-pocket adj2 (payment? or expenditure? or cost? or spending or expense?)).tw.	6627
48	(expenditure? adj3 (health or direct or indirect)).tw.	11274
49	(expenditure? not energy).tw.	40114
50	(health care cost$ or hospitali?ation or health care utili?ation or bed day$ or cost of illness).tw.	260445
51	(value adj2 (money or monetary)).tw.	3252

	Search	Hits
52	(cost* adj2 (effective* or utilit* or benefit* or analy* or outcome or outcomes)).tw.	234748
53	(expenditure or value for money or budget).tw.	85854
54	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53	1833425
55	((energy or oxygen) adj cost).tw.	4306
56	(metabolic adj cost).tw.	1499
57	((energy or oxygen) adj expenditure).tw.	31614
58	55 or 56 or 57	36318
59	54 not 58	1798796
60	exp quality adjusted life year/	26477
61	(qaly$ or qald$ or qale$ or qtime$).tw.	20049
62	(quality adjusted or adjusted life year$ or quality adjusted life year$).tw.	24493
63	(disability adjusted life or daly$).tw.	5094
64	((index and wellbeing) or (quality and wellbeing) or qwb or qwbsa).tw.	8122
65	(multiattribute$ or multi attribute$).tw.	1113
66	(utilit$ adj2 (value$ or cost$ or health or analys$ or index or indices)).tw.	17575
67	disutilit$.tw.	918
68	(hsuv or hsuvs).tw.	120
69	(health$1 year$1 equivalent$1 or hye$).tw.	1535
70	(illness state$ or health state$ or health status$).tw.	83861
71	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).tw.	20338
72	(hui or hui1 or hui2 or hui3 or hui-1 or hui-2 or hui-3).tw.	2281
73	health utilit$.tw.	3415
74	quality of wellbeing$.tw.	42
75	(quality of well being or index of wellbeing or index of well being or qwb).tw.	673
76	(short form$ or short-form$ or shortform$).tw.	45298
77	(sf36$ or sf-36$ or sf 36 or sf6 or sf 6 or sf-6 or sf6d or sf 6d or sf-6d or sf8 or sf-8 or sf 8 or sf12 or sf-12 or sf 12 or sf16 or sf-16 or sf 16 or sf20 or sf-20 or sf 20 or sf thirtysix or sf thirty six).tw.	49248
78	(15d or 15-d or 15 dimension).tw.	6598
79	(standard gamble$ or sg).tw.	16138
80	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).tw.	2757
81	(visual analog$ scale$ or EQ-VAS).tw.	78789
82	discrete choice experiment$.tw.	2421
83	60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82	304642
84	59 or 83	2033042
85	26 and 84	6659
86	case report/	2484949
87	case stud*.hw.	69843
88	case report?.hw.	2484972

	Search	Hits
89	letter/	1057433
90	editorial/	640863
91	86 or 87 or 88 or 89 or 90	4028297
92	85 not 91	5742
93	limit 92 to english language	5335

Embase 1974 to 2020 June 08

Table 94: Search string and results for Cochrane library (9 June 2020)

	Search	Hits
#1	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	789
#2	ILD:ti,ab	468
#3	MeSH descriptor: [Pulmonary Fibrosis] explode all trees	509
#4	(interstitial* NEAR/3 (lung* NEAR/3 disease*)):ti,ab	807
#5	(interstitial* NEAR/3 (fibros* or pneumonitis or pneumonia or pneumopathy)):ti,ab	632
#6	alveolitis:ti,ab	130
#7	(diffuse* NEAR/3 parenchymal*):ti,ab	16
#8	MeSH descriptor: [Bronchiolitis Obliterans] explode all trees	67
#9	(bronchiolitis NEXT obliterans):ti,ab	157
#10	(pneumoconiosis or pneumokoniosis or pneumonoconiosis):ti,ab	62
#11	MeSH descriptor: [Pneumoconiosis] explode all trees	97
#12	bagassosis:ti,ab	0
#13	((bird* or farmer* or pigeon* or avian* or budgerigar*) NEXT (lung* or disease*)):ti,ab	8
#14	(asbestosis or byssinosis or siderosis or silicosis or berylliosis or anthracosilicosis or silicotuberculosis):ti,ab	121
#15	((pulmonary* or lung*) NEAR/3 reticulation*):ti,ab	0
#16	((pulmonary* or lung*) NEAR/3 fibros*):ti,ab	1694
#17	MeSH descriptor: [Alveolitis, Extrinsic Allergic] explode all trees	25
#18	(connective NEAR/3 lung*):ti,ab	7
#19	(allerg* NEAR/3 pneumonitis):ti,ab	0
#20	MeSH descriptor: [Cryptogenic Organizing Pneumonia] explode all trees	4
#21	cryptogenic organi*ing pneumonia:ti,ab	9
#22	MeSH descriptor: [Idiopathic Interstitial Pneumonias] explode all trees	221
#23	IIP:ti,ab	143
#24	(hypersensitivity NEAR/3 pneumonia*):ti,ab	4
#25	pleuroparenchymal fibroelastosis:ti,ab	1
#26	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25	3758
#27	MeSH descriptor: [Economics] explode all trees	12184
#28	MeSH descriptor: [Costs and Cost Analysis] explode all trees	10275
#29	MeSH descriptor: [Fees and Charges] explode all trees	245
#30	MeSH descriptor: [Budgets] explode all trees	27

	Search	Hits
#31	budget* or financ*:ti,ab,kw	8110
#32	economic* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR pharmaco-economic* OR expenditure OR expenditures OR expense OR expenses OR financial OR finance OR finances OR financed:ti,ab,kw	95888
#33	MeSH descriptor: [Health Care Costs] explode all trees	3370
#34	MeSH descriptor: [Drug Costs] explode all trees	754
#35	MeSH descriptor: [Hospitalization] explode all trees	13624
#36	MeSH descriptor: [Cost of Illness] explode all trees	803
#37	MeSH descriptor: [Drug Utilization] explode all trees	511
#38	MeSH descriptor: [Utilization Review] explode all trees	225
#39	cost? near/2 (illness OR disease OR sickness OR health care OR healthcare OR treatment OR direct OR indirect OR medical OR resource):ti,ab,kw	18105
#40	burden? near/2 (illness OR disease? OR condition? OR economic?):ti,ab,kw	3156
#41	utili?ation near/2 (health OR medical OR resource):ti,ab,kw	5776
#42	out-of-pocket near/2 (payment? Or expenditure? Or cost? or spending or expense?):ti,ab,kw	314
#43	expenditure? near/3 (health or direct or indirect):ti,ab,kw	805
#44	Expenditure? NOT energy	2046
#45	health care cost? OR hospitali?ation OR health care utili?ation OR bed day? OR cost of illness:ti,ab,kw	72354
#46	value near/2 (money OR monetary):ti,ab,kw	295
#47	cost* near/2 (effective* OR utilit* OR benefit* OR analy* OR outcome or outcomes):ti,ab,kw	33322
#48	expenditure OR value for money OR budget:ti,ab,kw	7252
#49	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48	141718
#50	(energy OR oxygen) near/1 cost:ti,ab,kw	440
#51	metabolic near/1 cost:ti,ab,kw	122
#52	(energy OR oxygen) near/1 expenditure:ti,ab,kw	4361
#53	#50 or #51 or #52	4787
#54	#49 not #53	136931
#55	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	1213
#56	qaly* OR qald* OR qale* OR qtime*:ti,ab,kw	3601
#57	quality adjusted OR adjusted life year* OR quality adjusted life year*:ti,ab,kw	15041
#58	disability adjusted life of daly*:ti,ab,kw	118
#59	index AND wellbeing OR quality AND wellbeing OR qwb OR qwbsa:ti,ab,kw	8779
#60	multiattribute* OR multi attribute*:ti,ab,kw	454
#61	utilit* near/2 value* OR cost OR health OR analy* OR index OR indices:ti,ab,kw	700830
#62	disutilit*:ti,ab,kw	74
#63	hsuv OR hsuvs:ti,ab,kw	8
#64	health*1 year*1 equivalent*1 OR hye*:ti,ab,kw	43
#65	illness state* OR health state* OR health status*:ti,ab,kw	103590

	Search	Hits
#66	euro qual* OR euro qual5d OR euro qol5d OR eq-5d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d:ti,ab,kw	9728
#67	hui OR hui1 OR hui2 OR hui3 OR hui-1 OR hui-2 OR hui-3:ti,ab,kw	1867
#68	health utilit*:ti,ab,kw	5784
#69	quality of wellbeing* OR quality of well being OR index of wellbeing OR index of well being OR qwb:ti,ab,kw	18329
#70	short form* OR short-form* OR shortform*:ti,ab,kw	28029
#71	sf36* OR sf-36* OR sf 36 OR sf6 OR sf 6 OR sf-6 OR sf6d OR sf 6d OR sf-6d OR sf8 OR sf-8 OR sf 8 OR sf12 OR sf-12 OR sf 12 OR sf16 OR sf-16 OR sf 16 OR sf20 OR sf-20 OR sf 20 OR sf thirtysix OR sf thirty six:ti,ab,kw	21040
#72	15d OR 15 dimension:ti,ab,kw	1105
#73	standard gamble* OR sg:ti,ab,kw	1673
#74	time trade off*1 OR time tradeoff*1 OR tto OR timetradeoff*1:ti,ab,kw	152
#75	visual analog* scale* OR EQ-VAS:ti,ab,kw	48469
#76	discrete choice experiment*:ti,ab,kw	242
#77	#55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76	738337
#78	#54 or #77	764341
#79	#26 and #78	1977
#80	MeSH descriptor: [Case Reports] explode all trees	0
#81	case stud*:ti	12301
#82	case report?:ti	640
#83	(letter or editorial):ti	1746
#84	#80 or #81 or #82 or #83	14587
#85	#79 not #84	1952

Table 95: Search string and results for Econlit (9 June 2020)

	Search	Hits
1	interstitial lung disease.af.	0
2	pulmonary fibros*.af.	0
3	lung fibros*.af.	0
4	fibrosing lung disease*.af.	0
5	1 or 2 or 3 or 4	0

Econlit 1886 to June 04, 2020

Table 96: Supplementary and conference abstract search strategies and results

Source	Terms
NIHR Centre for Reviews and Dissemination (CRD; including NHS EED, DARE, and HTA)	Search term: interstitial lung disease OR pulmonary fibrosis OR lung fibrosis OR fibrosing lung disease (any field) Four relevant results found.
Tufts Medical Center Cost Effectiveness Analysis registry	Search term: interstitial lung disease OR pulmonary fibrosis OR lung fibrosis OR fibrosing lung disease No relevant results found.
SCHARR health utilities database	Search term: interstitial lung disease OR pulmonary fibros OR lung fibros OR fibrosing lung disease (any field)

Source	Terms
	No results found.
HERC utilities database	Search term: interstitial lung disease OR pulmonary fibrosis OR lung fibrosis OR fibrosing lung disease No relevant results found.
Clinicaltrials.gov	Condition: interstitial lung disease OR ILD OR pulmonary fibrosis OR lung fibrosis OR fibrosing lung disease Phases 2, 3, 4 One potentially relevant trial identified.
WHO International Clinical Trials Registry Platform (ITCRP)	Website unavailable. WHO ITCRP is searched as part of the Cochrane library database.
Conference abstracts	
American Thoracic Society (ATS)	Abstracts identified via electronic database searches.
British Thoracic Society (BTS)	Abstracts identified via database search.
European League Against Rheumatism (EULAR) - European Congress of Rheumatology (2020 E-Congress)	Abstract archive: http://scientific.sparx-ip.net/archiveeular/index.cfm Search terms used: interstitial lung disease, pulmonary fibrosis, lung fibrosis, fibrosing lung disease, nintedanib, pirfenidone No relevant results found.
European Respiratory Society (ERS)	Abstracts identified via electronic database searches.
International Society of Pharmacoeconomics and Outcomes Research (ISPOR)	Abstracts identified via electronic database searches.
Reference lists	
Two additional relevant studies were identified via reference list hand-searching.	

G.1.2 Study selection

Abstracts from the electronic searches were downloaded and de-duplicated in Endnote. (113) The references were then uploaded to Rayyan(114) for screening. Titles and abstracts were screened against the eligibility criteria displayed in Table 97.

Two blinded, independent reviewers assessed all titles and abstracts for inclusion and exclusion. All discrepancies between the reviewers were resolved through discussion. A full paper review was performed by two independent reviewers on all included studies using the criteria in Table 97. Where full manuscripts were not available, abstracts were considered for inclusion.

Table 97: Study eligibility criteria for costs and healthcare resource use, economic evaluations, and utilities systematic review

Element	Focus	Further information	
Patients	Patients with ILD and progressive fibrosing phenotype.	Include: Studies including any proportion of patients with ILD and progressive fibrosing phenotype defined as: • FVC – any decline in FVC % predicted at baseline • DLCO – any decline in DLCO at baseline • HRCT – worsening of fibrotic features on imaging; images identifying progression of disease • Reference to the progression of lung fibrosis (without any disease specific criteria) are to be included. Exclude: Patients with IPF	
Intervention/ comparator	No limits to be applied in searching. No limits applied during screening for costs, HCRU, or utilities.	Economic evaluation studies will be limited to the following specific treatments during screening:	
		• Nintedanib • Pirfenidone • Azathioprine • Cyclophosphamide • Rituximab • Mycophenolate mofetil • Prednisone	• Prednisolone • Tocilizumab • Abatacept • Methotrexate • Etanercept • Infliximab • Adalimumab
Outcomes	• Direct and indirect costs. • Direct and indirect resource use.	• Cost-utility analysis.	• Utility values. • Mapping algorithms.
Studies	Any.	Exclude: • Case reports and case studies. • Editorials. • Retracted studies/ data.	
Timeframe	No limit.		
Geography	No geographic limits.	Studies not conducted in Ireland and England will be considered only where no data specific to Ireland and England are identified.	
Language	English language abstracts.		
Databases to search	• Ovid Embase. • Ovid Medline. • EconLit. • Cochrane Library. • NHS EED.	• NIHR Centre for Reviews and Dissemination. • Tufts Medical Center Cost Effectiveness Analysis registry. • SCHARR health utilities database. • HERC utilities database.	
Other	• Trials registries: clinicaltrials.gov, WHO ICTRP. • Conference meeting abstracts (limited to last 2 years): ATS, BTS, ERS, EULAR European Congress of Rheumatology, ISPOR. • Reference list/ citation checking; key author searching.		

ATS, American Thoracic Society; BTS, British Thoracic Society; DLCO, diffusing capacity of the lung for carbon monoxide; ERS, European Respiratory Society; EULAR, European League Against Rheumatism; FVC, forced vital capacity; HCRU, healthcare resource use; HERC, Health Economics Research Centre; HRCT, high-resolution computed tomography; ICTRP, International Clinical Trials Registry Platform; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ISPOR, International Society of Pharmacoeconomics and Outcomes Research; NHS EED, National Health Service Economic Evaluation Database; NIHR, National Institute for Health Research; SCHARR, School of Health and Related Research; WHO, World Health Organisation.

G.1.3 Data extraction

Data from relevant publications was extracted into data extraction tables in MS Word. One reviewer extracted the study data into a standardised template and a second reviewer validated the extracted data. Full bibliographic details were extracted to enable the reader to access the source document.

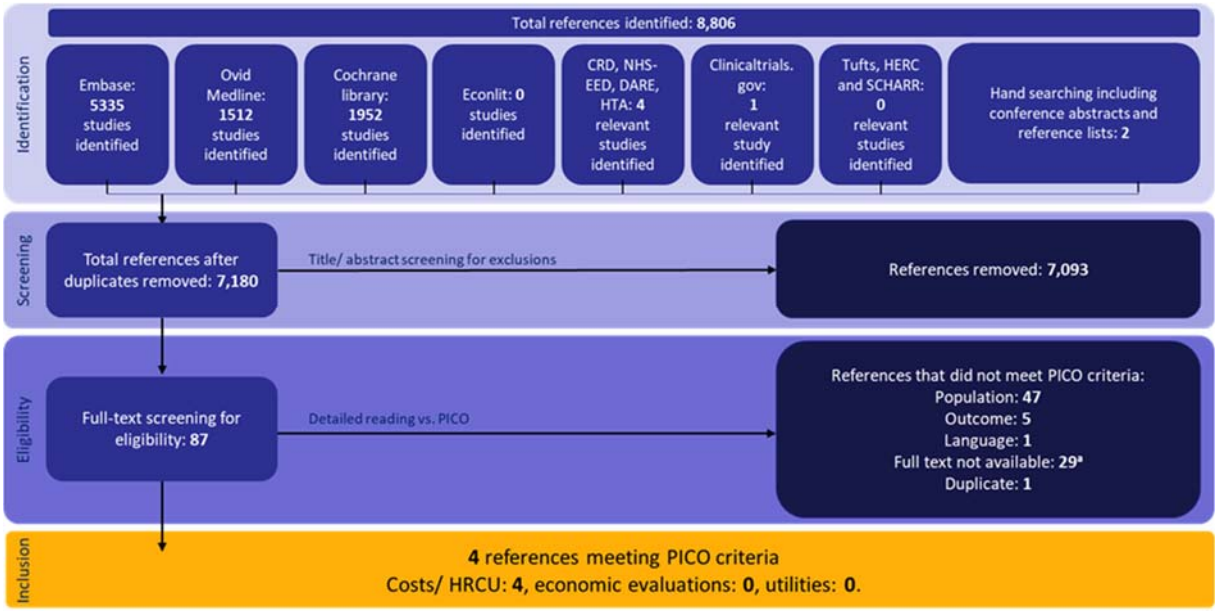
G.1.4 Quality assessment

All included studies have been quality assessed. In the absence of specific quality assessment tools for costs and resource use studies, quality assessment was undertaken with reference to the recommendations for assessing economic evaluations in the CRD's guidance for undertaking reviews in health care. (115) The Drummond checklist would have been used to assess the quality of the cost-utility studies(116) and the NICE Decision Support Unit Recommendations to quality assess studies reporting utilities(117).

G.1.5 Results

The results of the SLR are summarised in the PRISMA flow diagram in Figure 49. A total of 8,806 studies were identified. After deduplication, 7,180 were screened for inclusion by title/ abstract. After excluding 7,093 references, 87 references were subject to detailed full text screening, 83 of which were excluded (reasons for exclusion detailed in Table 98). For 29 of these references, full text was not available, 26 of which were conference abstracts. No cost-effectiveness studies were identified. The included studies are described in **Appendix I**.

Figure 49: PRISMA flow diagram of identified studies



[a]26 of which were conference abstracts. CRD, Centre for Reviews and Dissemination; HERC, Health Economics Research Centre (University of Oxford); NHS EED, UK National Health Service Economic Evaluation Database; PICO, patients, interventions, comparators, and outcomes; SCHARR, School of Health and Related Research (University of Sheffield).

Table 98: References excluded at full text with reasons

Reference
Population
Akl Y, Elhendway A, Elnady MA, Moussa H, Abdelsalam E, Abuelhassan UE. Medical thoracoscopic lung biopsy in undiagnosed non-UIP-DPLD: Diagnostic yield, complication rate, and cost-effectiveness, a single-experience study in Egypt. Egyptian Journal of Chest Diseases and Tuberculosis. 2020;69(1):178-82.
Al Moamary MS. Impact of a pulmonary rehabilitation programme on respiratory parameters and health care utilization in patients with chronic lung diseases other than COPD. Eastern Mediterranean Health Journal. 2012;18(2):120-6.
Algamdi M, Sadatsafavi M, Fisher JH, Morisset J, Johannson KA, Fell CD, et al. Costs of Workplace Productivity Loss in Patients With Fibrotic Interstitial Lung Disease. Chest. 2019;156(5):887-95.
Algamdi M, Sadatsafavi M, Fisher JH, Morisset J, Johannson KA, Fell CD, et al. Costs of Workplace Productivity Loss in Patients with Connective Tissue Disease Associated Interstitial Lung Disease. Annals of the American Thoracic Society. 2020;21:21.
Aryan Z, Modaresi M. Paediatric orphan lung diseases in Asia. The Lancet Respiratory Medicine. 2016;4(3):174-5.
Bagheri R, Haghi SZ, Attaran D, Hashem Asnaashari AM, Basiri R, Rajabnejad A. Efficacy of minimally invasive surgery in diagnosis of interstitial lung disease. Asian Cardiovascular & Thoracic Annals. 2015;23(7):851-4.
Barclay WR. Asbestos. An industrial asset with a health cost. Journal of the American Medical Association. 1984;252(1):96.
Bilaceroglu S. Role of Palliative Care in Improving the Quality of Life in Elderly with Advanced Lung Disease. Current Geriatrics Reports. 2016;5(2):103-9.
Blackhall V, Asif M, Renieri A, Civitelli S, Kirk A, Jilaihawi A, et al. The role of surgical lung biopsy in the management of interstitial lung disease: experience from a single institution in the UK. Interactive Cardiovascular & Thoracic Surgery. 2013;17(2):253-7.

Reference
Bloem AEM, Mostard RLM, Stoot N, Vercoulen JH, Peters JB, Janssen DJA, et al. Severe Fatigue is Highly Prevalent in Patients with IPF or Sarcoidosis. Journal of Clinical Medicine. 2020;9(4):20.
Boland J, Martin J, Wells AU, Ross JR. Palliative care for people with non-malignant lung disease: summary of current evidence and future direction. Palliative Medicine. 2013;27(9):811-6.
Bresnitz EA. Epidemiology of advanced lung disease in the United States. Clinics in Chest Medicine. 1997;18(3):421-33.
Chung F, Barnes N, Allen M, Angus R, Corris P, Knox A, et al. Assessing the burden of respiratory disease in the UK. Respiratory Medicine. 2002;96(12):963-75.
Dang GT, Barros N, Higgins SA, Langley RL, Lipton D. Descriptive review of asbestosis and silicosis hospitalization trends in North Carolina, 2002-2011. North Carolina Medical Journal. 2013;74(5):368-75.
De Giacomi F, Baqir M, Cox CW, Moua T, Matteson EL, Ryu JH. Spontaneous Pneumomediastinum in Connective Tissue Diseases. J Clin Rheumatol. 2019 Sep;25(6):239-245.
Dolidon S, Dupuis J, Molano Valencia LC, Salaun M, Thiberville L, Muir JF, et al. Characteristics and outcome of patients set up on high-flow oxygen therapy at home. Therapeutic Advances in Respiratory Disease. 2019;13:1753466619879794.
Ekren PK, Mogulkoc N, Toreyin ZN, Egrilmez S, Veral A, Akalin T, et al. Conjunctival biopsy as a first choice to confirm a diagnosis of sarcoidosis. Sarcoidosis Vasculitis and Diffuse Lung Diseases. 2016;33(3):196-200.
Esme H, Sezer M, Solak O, Sahin O. Importance of open lung biopsy in patients suspected interstitial lung disease. European Journal of General Medicine. 2007;4(1):16-8.
Fibla J, Brunelli A, Halgren LA, Allen MS, Wigle DA, Nichols FC, et al. Microbiology specimens obtained at the time of surgical lung biopsy for interstitial lung disease: Clinical yield and cost analysis. Interactive Cardiovascular and Thoracic Surgery. 2010;11(SUPPL. 1):S24-S5.
Frank AL, Kreuter M, Schwarzkopf L. Economic burden of incident interstitial lung disease (ILD) and the impact of comorbidity on costs of care. Respiratory Medicine. 2019;152:25-31.
Geidenberger CA, Nestel G, Socie EM. Cost-effectiveness of hospital discharge records for reaching selected endpoints in the surveillance of silicosis. American Journal of Industrial Medicine. 1998;34(5):484-92.
Geidenberger CA, Nestel G, Socie EM. Erratum: Cost effectiveness of hospital discharge records for reaching selected endpoints in the surveillance of silicosis (American Journal of Industrial Medicine (1998) 34 (484-492)). American Journal of Industrial Medicine. 1999;35(1):99.
Han B, Liu H, Zhai G, Wang Q, Liang J, Zhang M, et al. Estimated economic costs of coal workers' pneumoconiosis among coal workers redeployed from the Fuxin mining group in China. Journal of Public Health Policy. 2018;39(1):57-67.
Hernandez-Gonzalez F, Lucena CM, Ramirez J, Sanchez M, Jimenez MJ, Xaubet A, et al. Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost-effectiveness analysis. Archivos de Bronconeumologia. 2015;51(6):261-7.
Johannson KA, Pendharkar SR, Mathison K, Fell CD, Guenette JA, Kalluri M, et al. Supplemental oxygen in interstitial lung disease: An art in need of science. Annals of the American Thoracic Society. 2017;14(9):1373-7.
Jprn U. Efficacy of support program by multiple professionals for patients with interstitial pneumonia on patients' disease understanding, self-effectiveness, quality of life, and adherence. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=JPRN-UMIN000029887. 2017.
Kundrick A, Kirby J, Ba D, Leslie D, Olsen N, Foulke G. Positron emission tomography costs less to patients than conventional screening for malignancy in dermatomyositis. Seminars in Arthritis & Rheumatism. 2019;49(1):140-4.
Kurth L, Casey M, Schleiff P, Halldin C, Mazurek J, Blackley D. Medicare Claims Paid by the Federal Black Lung Benefits Program: US Medicare Beneficiaries, 1999 to 2016. Journal of Occupational and Environmental Medicine. 2019;61(12):E510-E5.

Reference
Li X, Cao X, Guo M, Xie M, Liu X. Trends and risk factors of mortality and disability adjusted life years for chronic respiratory diseases from 1990 to 2017: systematic analysis for the Global Burden of Disease Study 2017. Bmj. 2020;368:m234.
Lieberman S, Gleason JB, Ilyas MIM, Martinez F, Mehta JP, Savage EB. Assessing the safety and clinical impact of thoracoscopic lung biopsy in patients with interstitial lung disease. Journal of Clinical and Diagnostic Research. 2017;11(3):OC57-OC9.
Molin LJ, Steinberg JB, Lanza LA. VATS increases costs in patients undergoing lung biopsy for interstitial lung disease. Annals of Thoracic Surgery. 1994;58(6):1595-8.
Montero Fernandez MA. Transbronchial Cryobiopsy in Interstitial Lung Disease: Advantageous Costs to Benefits Ratio. Archivos de Bronconeumologia. 2015;51(6):257-8.
Nct. PFOX: pulmonary Fibrosis Ambulatory Oxygen Trial. https://clinicaltrialsgov/show/NCT03737409. 2018.
Nl. Cryo- vs surgical Lung biopsy for diagnosing interstitial lung disease: a randomized controlled trial. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=NL7634. 2019.
Oyunbileg S, Wang JD, Sumberzul N, Chang YY, Erdenchimeg E. Health impact of pneumoconiosis in Mongolia: estimation of losses in life expectancy and quality adjusted life expectancy. American Journal of Industrial Medicine. 2011;54(4):285-92.
Pompeo E, Rogliani P, Atinkaya C, Guerrera F, Ruffini E, Iniguez-Garcia MA, et al. Nonintubated surgical biopsy of undetermined interstitial lung disease: A multicentre outcome analysis. Interactive Cardiovascular and Thoracic Surgery. 2019;28(5):744-50.
Pompeo E, Rogliani P, Cristino B, Schillaci O, Novelli G, Saltini C. Awake thoracoscopic biopsy of interstitial lung disease. Annals of Thoracic Surgery. 2013;95(2):445-52.
Povitz M, Li L, Hosein K, Shariff S, Mura M. Implementing an interstitial lung disease clinic improves survival without increasing health care resource utilization. Pulmonary Pharmacology & Therapeutics. 2019;56:94-9.
Preventza O, Hui HZ, Hramiec J. Fast track video-assisted thoracic surgery. American Surgeon. 2002;68(3):309-11.
Raimundo K, Solomon JJ, Olson AL, Kong AM, Cole AL, Fischer A, Swigris JJ. Rheumatoid Arthritis-Interstitial Lung Disease in the United States: Prevalence, Incidence, and Healthcare Costs and Mortality. J Rheumatol. 2019 Apr;46(4):360-369.
Rena O, Casadio C, Leo F, Giobbe R, Cianci R, Baldi S, et al. Videothoracoscopic lung biopsy in the diagnosis of interstitial lung disease. European Journal of Cardio-Thoracic Surgery. 1999;16(6):624-7.
Russo L, Wiechmann RJ, Magovern JA, Szydlowski GW, Mack MJ, Naunheim KS, et al. Early chest tube removal after video-assisted thoracoscopic wedge resection of the lung. Annals of Thoracic Surgery. 1998;66(5):1751-4.
Saunders P, Tsipouri V, Keir GJ, Ashby D, Flather MD, Parfrey H, et al. Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. Trials. 2017;18(1):275.
Schiavon F, Savastano S. Cost-benefit evaluation of HRCT. Monaldi Archives for Chest Disease. 1995;50(3):211-7.
Sharp C, McCabe M, Adamali H, Medford AR. Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease-a systematic review and cost analysis. Qjm. 2017;110(4):207-14.
Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, Wilson EC, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. Thorax. 2013;68(2):155-62.
Sinclair C, Auret KA, Evans SF, Jane F, Dormer S, Wilkinson A, et al. Impact of a Nurse-Led Advance Care Planning Intervention on Satisfaction, Health-Related Quality of Life, and Health Care Utilization Among Patients With Severe Respiratory Disease: A Randomized Patient-Preference Trial. Journal of Pain and Symptom Management. 2020;59(4):848-55.

Reference
Szentes BL, Kreuter M, Bahmer T, Birring SS, Claussen M, Waelscher J, et al. Quality of life assessment in interstitial lung diseases:a comparison of the disease-specific K-BILD with the generic EQ-5D-5L. Respiratory Research. 2018;19(1):101.
Wapenaar M, Patel AS, Birring SS, Domburg RTV, Bakker EW, Vindigni V, et al. Translation and validation of the King's Brief Interstitial Lung Disease (K-BILD) questionnaire in French, Italian, Swedish, and Dutch. Chronic Respiratory Disease. 2017;14(2):140-50.
Outcome
Holtze C, Flaherty K, Kreuter M, Luppi F, Moua T, Vancheri C, et al. Healthcare utilisation and costs in the diagnosis and treatment of progressive-fibrosing interstitial lung diseases. European Respiratory Review. 2018;27(150):31.
Kreuter M, Herth FJ, Wacker M, Leidl R, Hellmann A, Pfeifer M, et al. Exploring Clinical and Epidemiological Characteristics of Interstitial Lung Diseases: Rationale, Aims, and Design of a Nationwide Prospective Registry--The EXCITING-ILD Registry. BioMed Research International. 2015;2015:123876.
Ryerson CJ, Tan B, Fell CD, Manganas H, Shapera S, Mittoo S, et al. The Canadian Registry for Pulmonary Fibrosis: Design and Rationale of a National Pulmonary Fibrosis Registry. Canadian Respiratory Journal. 2016;2016:3562923.
Swigris JJ, Brown KK, Abdulqawi R, Buch K, Dilling DF, Koschel D, et al. Patients' perceptions and patient-reported outcomes in progressive-fibrosing interstitial lung diseases. European Respiratory Review. 2018;27(150):31.
Wijsenbeek M, Kreuter M, Olson A, Fischer A, Bendstrup E, Wells CD, Denton CP, Mounir B, Zouad-Lejour L, Quaresma M, Cottin V. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Curr Med Res Opin. 2019 Nov;35(11):2015-2024
Language
Aydogdu K, Findik G, Kaya S, Agackiran Y, Yazici U, Demirag F, et al. Comparison of thoracotomy and videothorocoscopy for taking lung biopsies in the diagnosis of interstitial lung diseases. Turk Toraks Dergisi. 2013;14(2):59-63.
Full text not available
Algamdi M, Sadatsafavi M, Fisher JH, Morisset J, Johannson KAM, Fell CD, et al. Workplace productivity in patients with fibrotic interstitial lung disease. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2018;197(MeetingAbstracts).
Algamdi M, Sadatsafavi M, Fisher JH, Morisset J, Johannson KAM, Fell CD, et al. Workplace productivity in patients with connective tissue disease associated interstitial lung disease. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2018;197(MeetingAbstracts).
Arif A, Patel R, Owusu C, Paul R. Healthcare utilization among medicare beneficiaries with coal worker's pneumoconiosis in the US. American Journal of Respiratory and Critical Care Medicine Conference. 2019;199(9).
Ayed AK, Raghunathan R. Thoracoscopy versus open lung biopsy in the diagnosis of interstitial lung disease: a randomised controlled trial. Journal of the royal college of surgeons of edinburgh. 2000;45(3):159-63.
Chaaban S, Bissell B, Sturgill JL, Chaaban N, Kothari B, Morris PE. Early versus late enteral nutrition for interstitial lung disease patients requiring mechanical ventilation. American journal of respiratory and critical care medicine. 2019;199(9).
Dolidon S, Johan D, Salaun M, Thiberville L, Muir JF, Cuvelier A, et al. Post acute high flow oxygen therapy: Our centre experience. American Journal of Respiratory and Critical Care Medicine Conference. 2019;199(9).
Guerra SIS, Conceicao M, Cunha A, Correia J, Vale J, Antonio C, et al. Acute exacerbation admissions of fibrosing interstitial lung diseases - 3 years study. European Respiratory Journal

Reference
Conference: 29th International Congress of the European Respiratory Society, ERS Spain. 2019;54(Supplement 63).
Guler S, Kwan J, Wilcox P, Ryerson C. Frailty is an independent predictor of number and length of hospitalizationsin patients with fibrotic ILD. European Respiratory Journal Conference: European Respiratory Society International Congress, ERS. 2018;52(Supplement 62).
Guler SA, Kwan JM, Leung JM, Khalil N, Wilcox PG, Ryerson CJ. Functional ageing in fibrotic interstitial lung disease: the impact of frailty on adverse health outcomes. European Respiratory Journal. 2020;55(1).
Kreuter M, Herth FJF, Witt S, Kabitz H, Hagmeyer L, Hammerl P, et al. Diagnosis and management of patients with interstitial lung disease (ILD) in clinical practice in germany: Exciting-ILD registry. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2018;197(MeetingAbstracts)
Kreuter M, Kabitz HJ, Hagmeyer L, Hammerl P, Esselmann A, Wiederhold C, et al. Treatment and survival diversities in different forms of ILD in Germany - EXCITING registry. European Respiratory Journal Conference: 29th International Congress of the European Respiratory Society, ERS Spain. 2019;54(Supplement 63).
Kreuter M, Witt S, Polke M, Waelscher J, Schwarzkopf L. Financial burden of interstitial lung disease-a claims data based study. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2018;197(MeetingAbstracts).
Kurth L, Casey M, Blackley D, Halldin CN, Schleiff PL, Mazurek J. Medical benefits paid by the federal black lung benefits program: U.S. medicare beneficiaries, 1999-2016. American Journal of Respiratory and Critical Care Medicine Conference. 2019;199(9).
Langton C, D'Costa J, Dougherty B, Lance D, Meng R, Rose A. Transbronchial lung cryobiopsy (TBLC) in the diagnosis of interstitial lung disease: Diagnostic yield, complication rate and cost-effectiveness. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2018;197(MeetingAbstracts).
Lum Y, Abdul-Rashid A, Bethireddy S, Lightburn T, Wang R, Gudur S, et al. Late breaking abstract-the effectiveness of respiratory hot clinic service in two north west centers, UK. European Respiratory Journal Conference: European Respiratory Society International Congress, ERS. 2018;52(Supplement 62).
Maqhuzu P, Kreuter M, Schwarzkopf L. Pro25 Cost of Healthcare Resource Utilization in Interstitial Lung Diseases in Germany in 2017. Value in Health. 2019;22 (Supplement 3):S845.
Maqhuzu P, Schwarzkopf L, Kreuter M. Healthcare resource utilization and direct costs of interstitial lung disease management in Germany. European Respiratory Journal Conference: 29th International Congress of the European Respiratory Society, ERS Spain. 2019;54(Supplement 63).
Maqhuzu P, Schwarzkopf L, Kreuter M. First insights into the cost of treatment of interstitial lung diseases in germany of the exciting ild register analysis. Pneumologie Conference. 2019;60.
Natalini JG, Porteous M, Lederer DJ, Wille KM, Weinacker AB, Orens JB, et al. Hospital length of stay following lung transplantation for connective tissue disease-associated interstitial lung disease and idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine Conference. 2019;199(9).
Olson A, Maher T, Salisbury M, Acciai V, Mounir B, Quaresma M, et al. Health care resources utilisation and costs in patients with non-IPF progressive fibrosing interstitial lung disease. European Respiratory Journal Conference: European Respiratory Society International Congress, ERS. 2018;52(Supplement 62).
Schwarzkopf L, Witt S, Walscher J, Kreuter M. Longitudinal cost of care in individuals with different subtypes of interstitial lung diseases. European Respiratory Journal Conference: 29th International Congress of the European Respiratory Society, ERS Spain. 2019;54(Supplement 63).

Reference
Szentes B, Kreuter M, Bahmer T, Claussen M, Walscher J, Schwarzkopf L. Does qualtity of life differ in ILD entities-a comparison using EQ-5D-5L and K-BILD. Pneumologie Conference. 2018;59.
Tsai A, Hur S, Assayag D, Johannson KA, Morisset J, Fell CD, et al. Minimally important difference (MID) for the European quality of life-5 dimensions (EQ-5D) in fibrotic interstitial lung disease. American Journal of Respiratory and Critical Care Medicine Conference. 2019;199(9).
Whitty J, Rankin J, Sestini P, Mori L, Tsipouri V, Visca D, et al. Cost-Effectiveness of Ambulatory Oxygen in Improving Quality of Life in Fibrotic Lung Disease: A Tale of Two Outcomes. Value in Health. 2018;21 (Supplement 3):S413-S4.
Witt S, Szentes B, Walscher J, Polke M, Kreuter M, Schwarzkopf L. Financial burden of ILD-a claims data based study. Pneumologie Conference. 2018;59.
Witt S, Waelscher J, Schwarzkopf L, Kreuter M. Hospitalisation pattern in Interstitial Lung Diseases: A claims data study. European Respiratory Journal Conference: European Respiratory Society International Congress, ERS. 2018;52(Supplement 62).
Witt S, Chabashvili M, Buchvald F, Bush A, Cunningham S, Kiper N, et al. Healthcare utilisation and costs of care in childhood Interstitial lung disease in Europe - A cross-sectional analysis of the European registry chILD-EU. Atemwegs- und Lungenkrankheiten. 2019;45 (2):76.
Duplicate
Euctr GB. A trial of rituximab compared to usual best care in patients with interstitial (inflammatory or scarring conditions) lung disease due to systemic autoimmune (connective tissue) diseases. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2012-003633-42-GB. 2013.

Appendix H: Health-related quality-of-life studies

An SLR was performed in June 2020, as described in **Appendix G**. No health-related quality-of-life studies were identified.

Appendix I: Cost and healthcare resource identification, measurement and valuation

An SLR was performed in June 2020, as described in **Appendix G**. Four references met the inclusion criteria for the systematic review, all presenting cost and resource use data (Figure 49).

The four publications report on two studies, summarised in Table 99. Costs and HCRU data are reported from each study as a peer-reviewed journal article (118, 119) and a conference poster (120, 121). Data from these studies did not provide cost estimates for use in the cost-effectiveness model. The studies by Olson and colleagues were completed within a US setting and, therefore, the costings presented are not expected to be generalisable to UK clinical practice. The studies by Wuyts and collegues did report resource use data relating to background costs, which are included in the model (e.g. patient monitoring, hospital inpatient episodes). However, to be applicable for the model structure, the data needs to be stratified by FVC%, in order to match the model health states, and such stratification was not undertaken.

Table 99: Overview of the identified cost studies

	Olson et al. (2020)(118) Olson et al. (2018)(120)	**Wuyts et al. (2020)(119) Wuyts et al. (2019)(121)**
Sponsor/ funder	Boehringer Ingelheim Pharma GmbH	Supported by Boehringer Ingelheim
Journal/ conference	• Advances in Therapy, Olson et al. (2020)(118) • Data presented at the ERS 2018 (European Respiratory Journal), Olson et al. (2018)(120)	• Advances in Therapy, Wuyts et al. (2020)(119) • Data presented at ISPOR Europe 2019 (Value of Health), Wuyts et al. (2019)(121)
Study title	Healthcare Resources Utilization and Costs of Patients with Non-IPF Progressive Fibrosing Interstitial Lung Disease Based on Insurance Claims in the USA	The Burden of Progressive Fibrosing Interstitial Lung Disease: A DELPHI Approach
Study aim	To facilitate understanding about healthcare resources utilization and costs associated with PF-ILD in the USA	To evaluate the consensus among healthcare providers on the concept and management of non-IPF progressive fibrosing ILD and to estimate the burden of disease progression in non-IPF fibrosing ILD in mid-sized European countries
Study design	Medical insurance claims database and Electronic Health Record data	Clinician survey (Delphi questionnaire) to evaluate

	Olson et al. (2020)(118) Olson et al. (2018)(120)	Wuyts et al. (2020)(119) Wuyts et al. (2019)(121)
	analysis comparing all claims and ILD-specific claims in patients with ILD and PF-ILD	consensus on the definition and management of non-IPF fibrosing ILD (including non-/slow-progressive fibrosing ILD and PF-ILD) and estimate HCRU and cost
Country	US	Belgium, Denmark, Greece, the Netherlands, Portugal, Finland, Norway, Sweden
Date of study	2014–2016	2019
Subject information	N=373 patients with PF-ILD	N=40 clinicians (N=32 pulmonologists, N=8 rheumatologists) reported on 1,674 patients with PF-ILD attending hospitals/ clinics
PF-ILD definition	Patients were considered to have ILD if they had at least two claims with an ILD diagnosis (based on ILD ICD-9/10 codes) and at least one pulmonologist visit between 2014 and 2016. Patients with PF-ILD were defined as the subset of patients with non-IPF ILD with: • At least four pulmonologist visits in 2016 (indicative of severe disease); or • At least three more pulmonologist visits in 2016 than in 2014 (indicative of worsening disease).	The definition of progression in fibrosing ILD used in this analysis is the one of the INBUILD trial(5) Patients considered ‘‘progressive’’ when they presented one of the three following criteria despite treatment for ILD: • Clinically significant decline of lung function (≥10% relative decline in FVC over the last 24 months); or • A combination of worsening lung function (≥5–<10% relative decline in FVC over the last 24 months) plus worsening respiratory symptoms or evidence of increasing fibrosis on chest imaging; or • A combination of worsening respiratory symptoms and evidence of increasing fibrosis on chest imaging.
Applicability to clinical practice in England	Analyses reported were based on US-based medical insurance claims and Electronic Health Record data.	Specialist opinion on treatment and HRCU from Belgium, Denmark, Greece, Netherlands, Portugal, Finland, Norway, and Sweden. Unit costs were given by local health economists, extracted from national or regional cost databases, and published literature from the respective countries.
Costs presented	Costs associated with claims from physician offices, emergency rooms, hospitals, and other healthcare places of service	• Number of visits/ tests at diagnosis and follow-up • Percentage of patients and mean dose used during maintenance treatment • Annual costs of diagnosis, follow-up, and end-of-life care

ERS, European Respiratory Society; FVC, forced vital capacity; HCRU, healthcare resource use; ICD, International Classification of Diseases; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ISPOR, International Society of Pharmacoeconomics and Outcomes Research; PF-ILD, progressive fibrosing interstitial lung disease; US, United States of America.

Following guidance from the Centre for Reviews and Dissemination, we considered: appropriateness of study design to the research objective, risk of bias, quality of reporting, generalisability(115). Quality assessment for the included studies is presented in Table 100.

Table 100: Quality assessment of the two identified cost and HCRU studies

	Olson et al. (2020)(118) **Olson et al. (2018)(120)**	**Wuyts et al. (2020)(119)** **Wuyts et al. (2019)(121)**
Appropriateness of study design to the research objective	Good. Uses US-medical insurance claims data to facilitate understanding about healthcare resources utilization and costs associated with PF-ILD in the USA.	Good. Uses clinician opinion/ survey (Delphi questionnaire) input to estimate the burden of disease of progression in non-IPF fibrosing ILD in mid-sized European countries.
Risk of bias	None	None
Quality of reporting	Good	Good
Generalisability	US data presented in number of billable claims and costs associated with medical insurance claims. The US healthcare systems consists of mainly private insurance and therefore, the study results are unlikely to be generalisable to clinical practice in England.	Data is presented from Belgium, Denmark, Greece, the Netherlands, Portugal, Finland, Norway, and Sweden. Resource use data may be generalisable if patients are treated similarly in different countries. Costs vary between study countries and are likely to further differ in England. Therefore, cost data are not generalisable.
Additional Comments	Pulmonologist visit frequency was used as a proxy to identify patients with a progressive phenotype; therefore, costs might not reflect a pure PF-ILD population.	Patient population split into PF-ILD and non-/slow- progressive fibrosing ILD, but criteria for non-/slow- progressive ILD is not defined. Diagnosis, acute exacerbation, and end-of -life costs are not split between these two groups, there, annual cost may not reflect a pure PF-ILD population. Results are based on opinions of clinicians so may not accurately reflect real-world costs.

HCRU, healthcare resource use; ILD, interstitial lung disease; PF-ILD, progressive fibrosing interstitial lung disease; US, United States of America.

Appendix J: Clinical outcomes and disaggregated results from the model

J.1.1 Clinical outcomes from the model

J.1.1.2 Validation of overall survival at the end of two years: model projections vs. clinical trial

Figure 50 and Figure 51 compare the fit of the parametric models to the Kaplan-Meier curves from the INBUILD clinical trial for both the placebo and nintedanib arms. This allows for a visual inspection of each distribution and corroborates the findings from the AIC scores (i.e. that all presented distributions appear to offer a robust fit to the available data).

Figure 50: OS model fit vs Kaplan-Meier for placebo

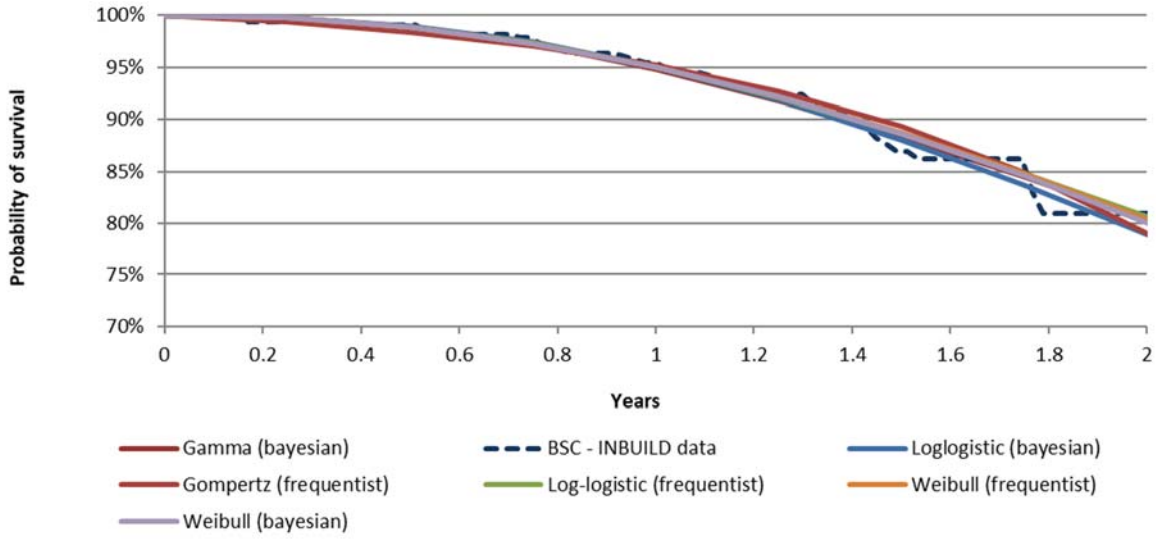
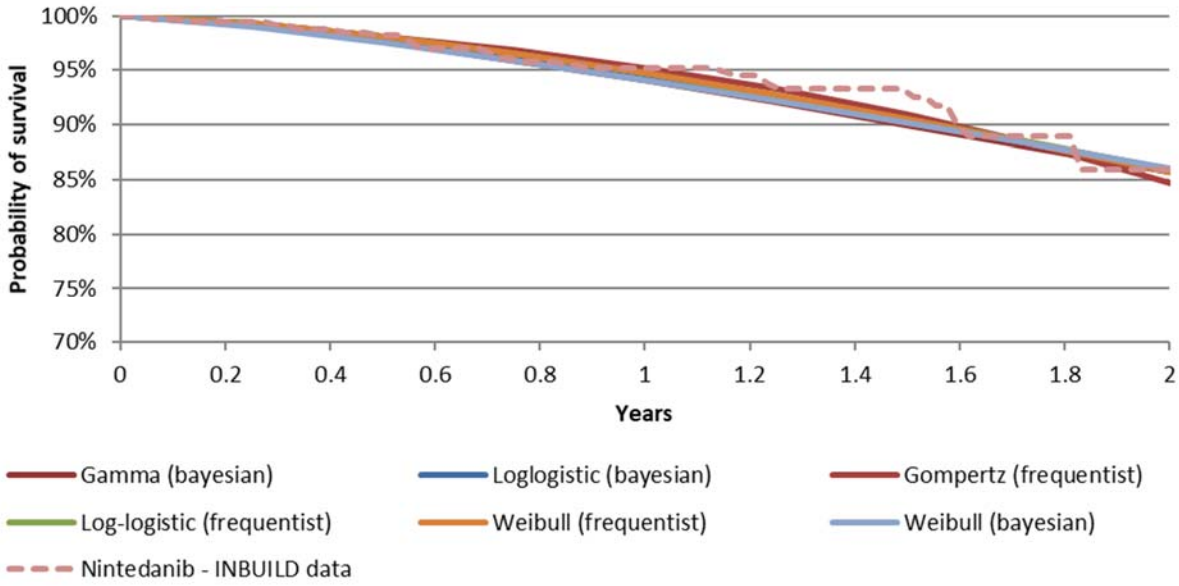


Figure 51: OS model fit vs Kaplan-Meier for nintedanib



A comparison of the proportion of patients alive at the end of the two years associated with each parametric model and the Kaplan-Meier curves from the INBUILD clinical trial for both the placebo and nintedanib arms are presented in Table 101.

Table 101: Proportion of patients alive at the end of two years

		Patients alive in the placebo arm	Patients alive in the nintedanib arm
INBUILD Clinical trial		0.810	0.860
Frequentist	Weibull	0.803	0.857
	Log-logistic	0.806	0.859
	Gompertz	0.791	0.847
Bayesian	Weibull	0.801	0.861
	Gamma	0.803	0.857
	Log-logistic	0.789	0.858

J.1.1.3 Validation of exacerbation at the end of two years: model projections vs. clinical trial

Figure 52 compares the exponential parametric models for both types of exacerbations to the Kaplan-Meier curves from the clinical trial (study period: two years) for time to exacerbation.

Figure 52: Exacerbation model fit vs. clinical trial Kaplan-Meier

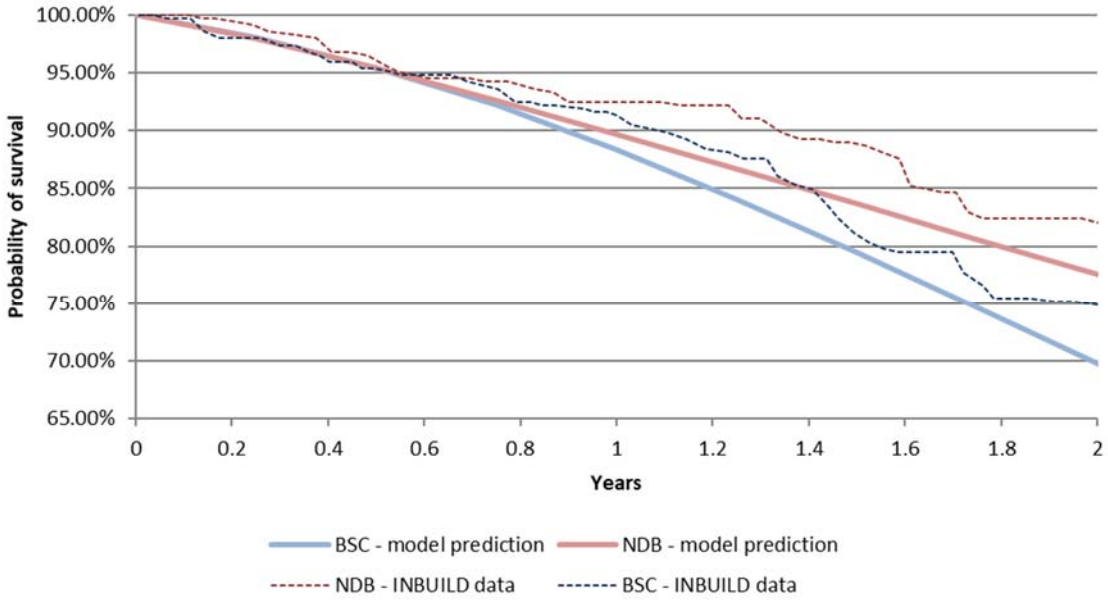


Table 102 presents the proportion of patients that are alive and have had an exacerbation at the end of the second year.

Table 102: Proportion of patients alive with exacerbations at the end of the second year

	Placebo arm	Nintedanib arm
INBUILD Clinical trial	0.061	0.039
Model projection	0.105	0.081

J.1.1.4 Proportion of the cohort in different states over time

The proportion of the time each cohort spends alive (with and without exacerbations) and dead are presented in Figure 53 and Figure 54 for nintedanib and BSC respectively.

Figure 53: Proportion in each state in nintedanib arm

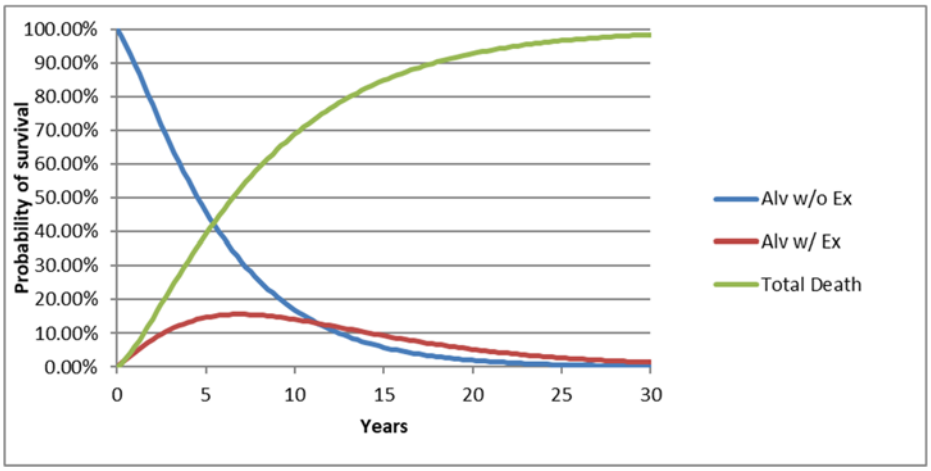
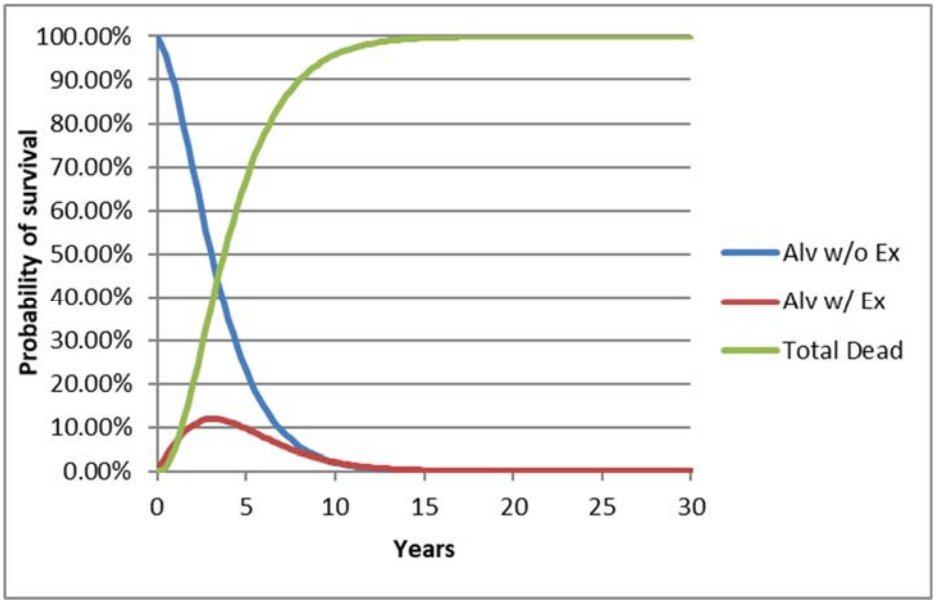


Figure 54: Proportion in each state in BSC arm



J.1.1.5 Description of how QALYs are accrued in the model

The Markov model has a number of health states determined by FVC%Pred and exacerbation status. These states are outlined in section B.3.2 of Company Submission Document B.

The cycle length in the model is three months and patients can transition between states at each cycle. This component of the QALY is calculated per cycle based on the distribution of the cohort across the health states and the utility associated with being in the health state.

Utility reductions (disutility) due to adverse events are applied in the model based on the estimated proportion of patients suffering from adverse events in each treatment arm (section B.3.3 of Company Submission Document B).

The model uses a lifetime time horizon in order to fully incorporate the health outcomes of PF-ILD.

J.1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

The disaggregated results of the base case cost-effectiveness analysis are shown in Table 103 and Abbreviations: BSC, best supportive care; FVC%Pred, forced vital capacity percentage predicted.
Table 104.

Table 103: Summary of QALY gain by health state

FVC%Pred	QALY intervention (Nintedanib)	QALY comparator (BSC)	Increment (Nintedanib – BSC)	Absolute increment	% absolute increment
≥110	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100-109.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90-99.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80-89.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70-79.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-69.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: BSC, best supportive care; FVC%Pred, forced vital capacity percentage predicted.

Table 104: Summary of predicted resource use by category of cost

Category		Costs intervention (Nintedanib)	Costs comparator (BSC)	Increment	Absolute increment	% absolute increment
Treatment costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient monitoring costs: FVC%Pred	≥110	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	100-109.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	90-99.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	80-89.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	70-79.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	60-69.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50-59.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	40-49.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver panel costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	Total absolute increment	[redacted]

Abbreviations: BSC, best supportive care; FVC%Pred, forced vital capacity percentage predicted.

Appendix K: Checklist of confidential information

Appendix D - confidential informa

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Clarification questions

February 2021

File name	Version	Contains confidential information	Date
ID1599 Nintedanib ERG clarification questions_company response	V1	**Yes**	19th February 2021

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searching

A1. Please explain the rationale for limiting the Embase and Medline searches reported in Appendix D and Appendix G to English language only. Please describe what steps were taken to mitigate for potential language bias.

While it is possible that some trials may have been published in languages other than English, it is considered that most high-quality trials are likely to have been published in English language journals. Furthermore, it has been demonstrated that English language restriction does not result in major differences in outcomes of meta-analyses and does not introduce systematic bias into systematic review-based meta-analyses (1). Systematic reviews including English language restrictions can therefore be considered an appropriately robust methodology.

The searches reported in Appendix G were limited to English language because the aims of the review were to identify economic evaluations, costs, resource use, and utilities of relevance to the UK. It is possible that some studies published in languages other than English may have reported utilities. However, we consider it unlikely that the language restriction will have excluded any major publications with relevance to the UK.

A2. Please confirm the database hosts used to search the databases specified in the searches reported in Appendix D and for the Cochrane Library and Econlit searches reported in Appendix G.

The databases used for the searches in Appendix D are listed below.

August & October 2019:

- Ovid MEDLINE® 1946 to date of search
- Ovid Embase 1974 to date of search
- Cochranelibrary.com

May 2020:

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to May 22, 2020
- Ovid Embase 1974 to 2020
- Cochranelibrary.com (Cochrane Database of Systematic Reviews [CDSR] and Cochrane Central Register of Controlled Trials [CENTRAL]).

For the searches reported in Appendix G, EconLit was searched via Ovid with coverage from 1886 to present (i.e., May 2020) and Cochrane Library was searched via Cochranelibrary.com (Cochrane Database of Systematic Reviews [CDSR] and Cochrane Central Register of Controlled Trials [CENTRAL]).

A3. Please clarify which resources within the Cochrane Library were searched for the searches reported in Appendix D and Appendix G.

The August and October 2019 searches searched the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Cochrane Clinical Answers.

The May 2020 searches in Appendix D and the searches reported in Appendix G searched Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL).

A3. Tables 83-86 Appendix D state the strategy is 'corrected' please clarify what was corrected?

During searches conducted in May 2020, the following alterations were made:

1. Spelling mistakes were corrected in the drug name Actemra and RoActemra, previously spelled Acterma and RoActerma in 2019 searches.
2. Some MeSH subject headings had been included in the August 2019 Embase search and these were translated to Emtree.

Correcting the spelling of Actemra/RoActemra in the Ovid Medline search did not affect the number of records identified.

The updated searches in Ovid Embase and Cochrane Library were performed without date limits and combined with the original search terms using the NOT function to identify any records which may have been missed during the original searches (Table 83 of company submission for Embase and Table 85 for Cochrane). Studies identified from these searches were screened as part of the May 2020 systematic review. The corrected searches were then conducted in Medline, Embase, and Cochrane Library using a date limit from August 2019 to 26 May 2020 to identify studies published since the original searches (Tables 82, 84, 86 of the company submission).

The PRISMA diagram in Figure 41 of the company submission shows the total number of records identified from each database prior to deduplication:

- Embase, total records = 296: 80 (Table 82) and 216 (Table 84)
- Medline, total records = 37: 37 (Table 82)
- Cochrane Library, total records = 163: 61 (Table 85) and 102 (Table 86)

Clinical effectiveness

A4. PRIORITY QUESTION:

A. Please explain how well the control arm in the INBUILD trial reflects the comparator described in the NICE scope.

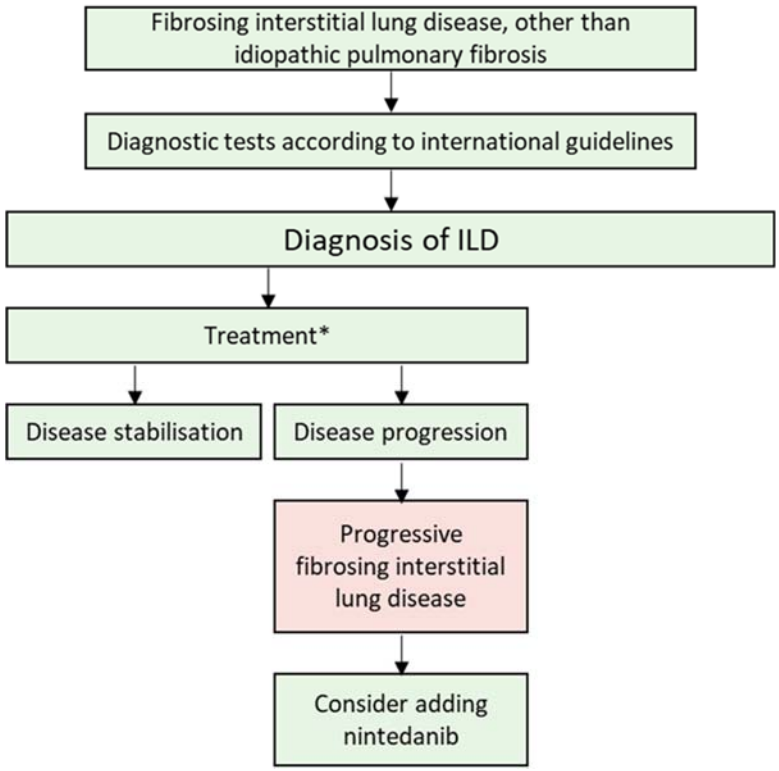
B. Please provide the number of patients in the INBUILD trial (by study arm) that received immunosuppressants (such as azathioprine, cyclophosphamide, or mycophenolate), corticosteroids, infliximab or rituximab. Please provide numbers separately for the period up to database lock (DBL) 1 and the period up to DBL 2.

The comparator as stated in the final NICE scope was established clinical management without nintedanib.

The clinical management of PF-ILD in the UK is illustrated in Figure 1 (adapted from a recent publication by UK clinical experts).(2) When diagnosis of ILD is confirmed,

patients receive conventional treatment (such as corticosteroids or immunomodulatory agents) based on the specific type of ILD. If the disease continues to progress despite use of these conventional treatments, a diagnosis of PF-ILD is then confirmed through pulmonary function tests as well as radiological and clinical assessments. It is at this stage, once PF-ILD has been confirmed, that nintedanib should be considered as a treatment

Figure 1: Treatment pathway adapted from George et al(2)



*Conventional treatments based on the specific interstitial lung disease, including, but not limited to corticosteroids, mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, rituximab. Adapted from: (2).
Abbreviations: ILD, interstitial lung disease

A consensus of clinical experts who manage patients with a confirmed diagnosis of PF-ILD in tertiary specialist centres in England advised that, while immunomodulatory treatments may still be used to treat the inflammatory component of the disease, there are no randomised controlled trials to suggest that these unlicensed treatments have a positive impact on the chronic fibrotic progression of PF-ILD.

As stated in our submission, there are currently no other treatments licensed for chronic fibrosing ILD with a progressive phenotype, and therefore there were no

appropriate active comparators for the INBUILD trial. However, initiation of concomitant corticosteroids and immunosuppressants (azathioprine, cyclosporine, mycophenolate mofetil, tactrolimus, rituximab, cyclophosphamide) was allowed for the worsening of disease after the first six months of the trial treatment in patients with clinically significant deterioration of ILD or connective tissues disease.

The number and proportion of patients who received concomitant therapies and restricted therapies over the whole trial up to DBL2 are reported in Table 1 and Table 2 respectively. A list of all baseline and on-treatment concomitant medications over the whole trial is available in the embedded file below.

Concomitant medications over wh

- Overall, 73.0% of patients received corticosteroids for systemic use (74.9% in the placebo group and 71.1% in the nintedanib group)
- In total, 19.6% of patients received immunosuppressants (23.6% in the placebo group and 15.7% in the nintedanib group)
- There was limited use of rituximab (0.8% overall, 0.6% in the placebo group and 0.9% in the nintedanib group)
- Infliximab use was reported at baseline in two patients in the placebo arm (0.6%) and no patients in the nintedanib arm.

The list of concomitant and restricted therapies were shared with two clinical experts working in tertiary centres in the UK. Both experts agreed that these were broadly in line with what they would expect to see in clinical practice in the UK (see clinical validation documents below).

Clinical validation_A West.d

Clinical validation_S Barrett.docx

We have also conducted research with a larger group of pulmonologists and rheumatologists in the UK into the current treatments they prescribe for PF-ILD. The list of background medications used in INBUILD aligns well with current treatment practices reported by these clinicians.

PF-ILD current treatment from UK T

Overall, we believe this use of background medication means that the control arm aligns closely with clinical practice in the UK, and therefore the comparator stated in the final scope (established clinical management without nintedanib).

Table 1: All on-treatment restricted concomitant therapies over the whole trial up to DBL2 (ATC3 categories with incidence at category-level of >20% in at least 1 treatment group) – treated set, overall population(3)

ATC3 category	Placebo		Nintedanib		Total	
	N	%	N	%	N	%
Number of patients	331	100.0	332	100.0	663	100.0
Number of patients with ≥1 therapy	329	99.4	330	99.4	659	99.4
Adrenergics for systemic use	80	24.2	58	17.5	138	20.8
Adrenergics, inhalants	115	34.7	89	26.8	204	30.8
Agents for treatment of haemorrhoids and anal fissures for topical use	150	45.3	155	46.7	305	46.0
All other therapeutic products	113	34.1	104	31.3	217	32.7
Angiotensin II receptor blockers (ARBS), plain	63	19.0	78	23.5	141	21.3
Anti-acne preparations for topical use	122	36.9	103	31.0	225	33.9
Antibiotics for topical use	71	21.5	69	20.8	140	21.1
Antihistamines for systemic use	87	26.3	72	21.7	159	24.0
Anti-infectives	144	43.5	130	39.2	274	41.3
Anti-infectives and antiseptics, excl. combinations with corticosteroids	72	21.8	60	18.1	132	19.9
Anti-inflammatory agents	248	74.9	243	73.2	491	74.1
Anti-inflammatory and anti-rheumatic products, non-steroids	143	43.2	146	44.0	289	43.6
Anti-propulsives	40	12.1	155	46.7	195	29.4
Antithrombotic agents	128	38.7	120	36.1	248	37.4
Anxiolytics	92	27.8	66	19.9	158	23.8
Beta blocking agents	66	19.9	71	21.4	137	20.7
Beta-lactam antibacterials, penicillins	89	26.9	89	26.8	178	26.8
Blood glucose lowering drugs, excl. insulins	63	19.0	69	20.8	132	19.9
Calcium	79	23.9	78	23.5	157	23.7
Corticosteroids	110	33.2	108	32.5	218	32.9
Corticosteroids for systemic use, plain	248	74.9	236	71.1	484	73.0
Corticosteroids, plain	191	57.7	175	52.7	366	55.2

ATC3 category	Placebo		Nintedanib		Total	
	N	%	N	%	N	%
Cough suppressants, excl. combinations with expectorants	85	25.7	81	24.4	166	25.0
Decongestants and other nasal preparations for topical use	201	60.7	192	57.8	393	59.3
Drugs for constipation	86	26.0	69	20.8	155	23.4
Drugs for peptic ulcer and gastrooesophageal reflux disease (GORD)	216	65.3	251	75.6	467	70.4
Expectorants, excl. combinations with cough suppressants	113	34.1	110	33.1	223	33.6
IV solution additives	74	22.4	60	18.1	134	20.2
IV solutions	77	23.3	59	17.8	136	20.5
Immunosuppressants	78	23.6	52	15.7	130	19.6
Intestinal anti-inflammatory agents	212	64.0	206	62.0	418	63.0
Lipid modifying agents, plain	127	38.4	133	40.1	260	39.2
Macrolides, lincosamides and streptogramins	70	21.1	84	25.3	154	23.2
Opioids	105	31.7	91	27.4	196	29.6
Other analgesics and antipyretics	203	61.3	182	54.8	385	58.1
Other beta-lactam antibacterials	68	20.5	78	23.5	146	22.0
Other cardiac preparations	61	18.4	79	23.8	140	21.1
Other dermatological preparations	134	40.5	108	32.5	242	36.5
Other drugs for obstructive airway diseases, inhalants	126	38.1	102	30.7	228	34.4
Other gynecologicals	97	29.3	94	28.3	191	28.8
Other ophthalmologicals	143	43.2	121	36.4	264	39.8
Other respiratory system products	71	21.5	75	22.6	146	22.0
Quinolone antibacterials	88	26.6	69	20.8	157	23.7
Selective calcium channel blockers with mainly vascular effects	51	15.4	71	21.4	122	18.4
Stomatological preparations	217	65.6	219	66.0	436	65.8
Throat preparations	116	35.0	114	34.3	230	34.7
Topical products for joint and muscular pain	177	53.5	174	52.4	351	52.9
Vitamin A and D, incl. combinations of the two	102	30.8	81	24.4	183	27.6

Abbreviations: ATC, Anatomical Therapeutic Chemical code; DBL, database lock; IV, intravenous

Table 2: All on-treatment restricted concomitant therapies over the whole trial up to DBL2 by CDG and preferred name – treated set, overall population(3)

ATC3 category	Placebo		Nintedanib		Total	
	N	%	N	%	N	%
Number of patients	331	100.0	332	100.0	663	100.0
Number of patients with ≥1 restricted therapy	329	99.4	330	99.4	659	99.4
Biologic DMARDs	2	0.6	3	0.9	5	0.8
Rituximab	2	0.6	3	0.9	5	0.8
Corticosteroids[1]	90	27.2	55	16.6	145	21.9
Prednisone	36	10.9	30	9.0	66	10.0
Prednisolone	27	8.2	13	3.9	40	6.0
Methylprednisolone sodium succinate	27	8.2	9	2.7	36	5.4
Methylprenisolone	13	3.9	10	3.0	23	3.5
Hydrocortisone	5	1.5	2	0.6	7	1.1
Steroids	2	0.6	3	0.9	5	0.8
Dexamethasone sodium phosphate	2	0.6	1	0.3	3	0.5
Dexamethasone	1	0.3	1	0.3	2	0.3
Meprednisone	1	0.3	1	0.3	2	0.3
Betamethasone sodium phiosphate	0	0	1	0.3	1	0.2
Carisoprodol;dexamethasone; hydroxocobalamin; piroxicam; pyridoxine hydrochloride	1	0.3	0	0	1	0.2
Deflazacort	0	0	1	0.3	1	0.2
Methylprednisolone; succinate sodium	1	0.3	0	0	1	0.2
Prednisolone sodium phosphate	0	0	1	0.3	1	0.2
Immunomodulatory medications for ILD	35	10.6	15	4.5	50	7.5
Mycophenolate mofetil	12	3.6	5	1.5	17	2.6
Azathioprine	9	2.7	1	0.3	10	1.5
Tacrolimus	7	2.1	3	0.9	10	1.5
Cyclophosphamide	4	1.2	3	0.9	7	1.1
Ciclosporin	5	1.5	0	0	5	0.8
Rituximab	2	0.6	3	0.9	5	0.8
Non-biologic DMARDs	33	10.0	12	3.6	45	6.8
Mycophenolate mofetil	12	3.6	5	1.5	17	2.6
Azathioprine	9	2.7	1	0.3	10	1.5
Tacrolimus	7	2.1	3	0.9	10	1.5
Cyclophosphamide	4	1.2	3	0.9	7	1.1
Ciclosporin	5	1.5	0	0	5	0.8

A patient may be counted in more than one category. A medication can appear under several CDG categories. CDG categories do not reflect the actual indication for which the patients took the medication. Medications are displayed whatever the dose and route, except for the CDG 'corticosteroids'.

[1] Medications are only included in the CDG 'corticosteroids' in case of high doses, and if delivered by oral, intravenous, intravenous bolus, intravenous drip or intramuscular route of administration.

A5. PRIORITY QUESTION: Please provide a Figure such as Figure 6 for the 'Annual rate of decline in FVC (mL/ year) over the whole trial period up to DBL2' including a line for the whole population and one for patients with UIP-like fibrotic pattern.

The annual rate of decline in FVC (mL) over the whole trial period to DBL2 is shown in Figure 2 and Figure 3 (overall population and UIP-like population, respectively).

The analysis of annual rate of decline in FVC (mL/year) including data over the whole trial should be interpreted with caution. Because of the trial design with a variable duration of Part B, many patients had missing FVC assessment values after week 52. In general, it can be assumed that missing data were present for patients who had a rapidly progressive form of the disease and were likely to drop out early, for patients in the placebo group who did not derive any benefit from the study medication and progressed, or for patients who had little observation time in Part B because of the timing of DBL1. The primary analysis model was based on the missing at random assumption, which may not have been fulfilled in Part B of the trial.

The main outcomes of the analysis of the annual rate of decline in FVC (mL/year) over the trial are:

- The treatment of nintedanib vs. placebo observed in the primary analysis over 52 weeks was maintained over the whole trial
- Treatment with nintedanib reduced the annual rate of decline in FVC (mL/year) over the whole trial in both co-primary populations and in the complementary population of patients with other HRCT fibrotic patterns.

Figure 2: Mean of observed absolute change from baseline in FVC (mL) over the whole trial – treated set, overall population

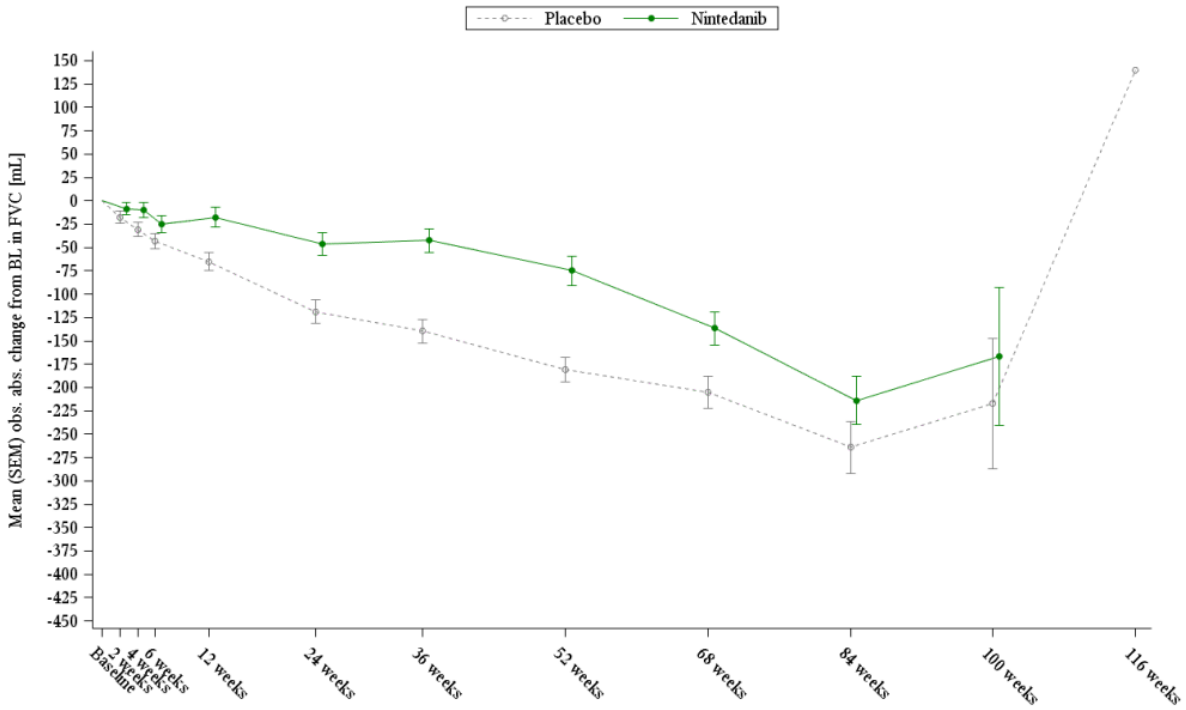
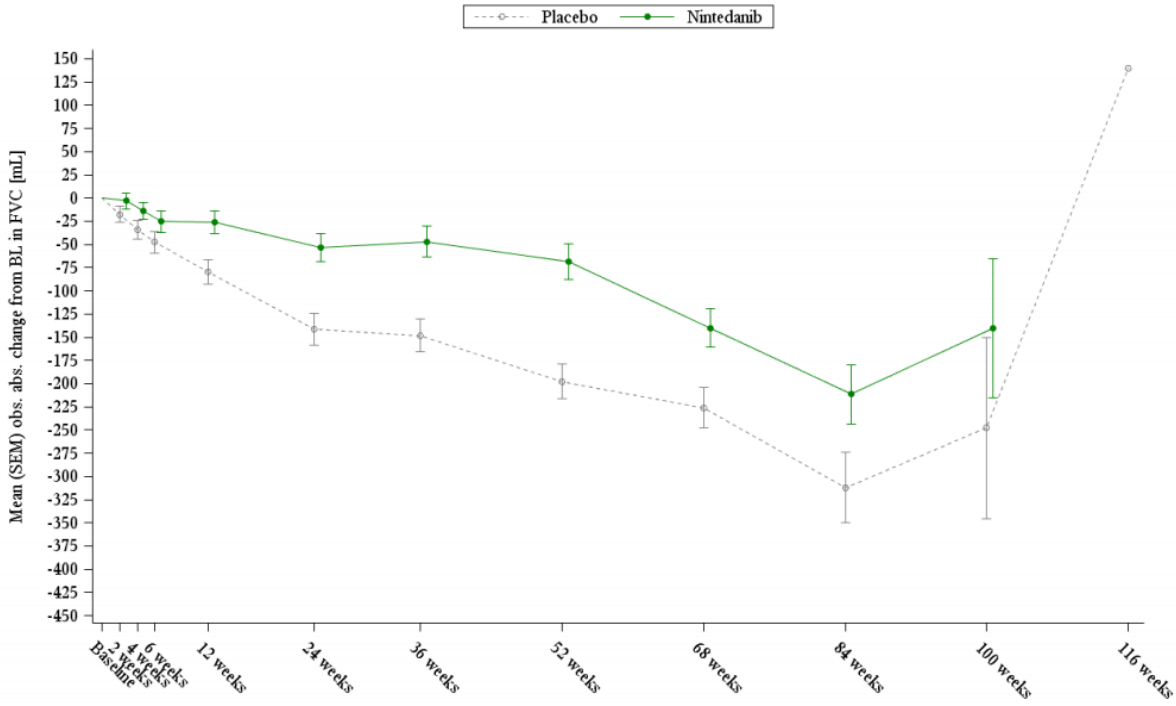


Figure 3: Mean of observed absolute change from baseline in FVC (mL) over the whole trial – treated set, patients with HRCT with UIP-like fibrotic pattern only



A6. Please provide a full Clinical Study Report for the INBUILD trial. The current version (references 37 and 55 in the reference pack – both look the same document) has only 456 pages and does not include any Tables, Figures or Appendices (chapters 15 and 16).

The full Clinical Study Report will be uploaded separately to NICE Docs alongside this document.

Section B: Clarification on cost-effectiveness data

Model structure

B1. PRIORITY QUESTION: Drops in %FVC predicted and the occurrence of exacerbations are considered as independent and mutually exclusive in the model.

a. **Please explain whether this assumption is clinically plausible, and whether it was validated by clinical opinion.**

b. **If this assumption is potentially implausible, please explain the implications for considering an alternative model structure, requirements for and availability of alternative data inputs, and the cost-effectiveness results.**

Within the model, lung function decline was dependent on state membership (i.e. different transition probabilities were applied based on health state) and exacerbation (i.e. the probability of decline increased after an exacerbation). Therefore, the two parameters were not modelled completely independently. However, the occurrence of exacerbations was independent of FVC % predicted decline. This overall approach matched the methods applied during the NICE TA submission of nintedanib for IPF [TA379] and this modelling approach was not critiqued by the ERG or committee during that appraisal. Given the similar clinical characteristics of PF-ILD and IPF, it is expected that the same approach within PF-ILD should also be considered valid.

The assumption that decline in FVC % predicted and the occurrence of exacerbations are independent and mutually exclusive may be a simplification of

reality, but clinical experts that we consulted with found it difficult to quantify this relationship or suggest any sources that could be used to support this (see documents provided in response to question A4, page 7). They also stated that there may be confounding factors, such as steroid use, that would make estimation of how exacerbations and drops in FVC % predicted are linked difficult.

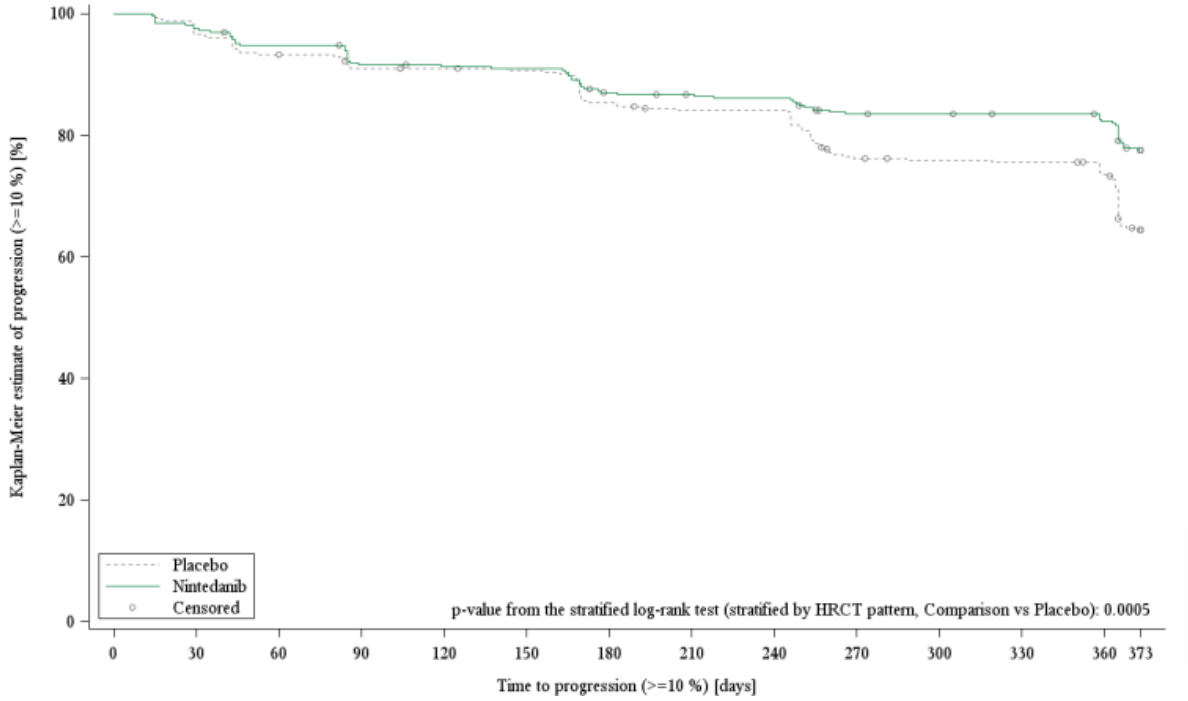
Overall, we believe that this assumption is not implausible. Exacerbations were an uncommon event in the INBUILD trial (7.8% for nintedanib vs. 9.7% for placebo) and the outputs from the sensitivity analysis in the current model indicate that exacerbations are not a key driver of the model results. Therefore, even if the model structure was to be amended we do not expect the cost-effectiveness results to change in a meaningful way.

B2. PRIORITY QUESTION: Is it clinically plausible that patients could experience a decline in FVC%Pred greater than 10% FVC%Pred interval within a 3-month cycle and therefore skip a health state? Was this observed in the trial? Please comment on the implications for the model structure.

Clinical experts working at two specialist ILD centres in the UK confirmed that the vast majority of patients would not experience a greater than 10% decline in their FVC % predicted within three months (see documents provided in response to question A4, page 7). Both expected that less than 5% of patients would experience such a decline over three months. Therefore, the model structure is likely to be reflective of the lung function decline for the majority of patients in the UK.

Figure 4 shows the Kaplan-Meier plot of time to absolute decline in FVC % predicted ≥10% over 52 weeks. This shows that the proportion of patients losing ≥10% of their predicted FVC is low over 52 weeks, and that only a very small proportion of patients lose ≥10% of their predicted FVC within a three month interval.

Figure 4: Kaplan-Meier plot of time to absolute decline in FVC % predicted ≥10% over 52 weeks – treated set, overall population



B3. As stated on p. 59 of the CS, a model cycle length of 3 months was "chosen to match the nintedanib pack usage size".

a. **Please explain how the choice of a 3-month cycle length matches the use of a pack size of 60 capsules.**

b. **Please provide details on how pharmacy dispensing of nintedanib is assumed to occur.**

c. **Please explain whether costs due to potential wastage, for example due to treatment discontinuation, can be expected, and, if so, please provide the option in the model to include these costs.**

d. **Please explain if any other considerations, for example in relation to clinical aspects of the disease and data availability, were relevant in justifying the choice of model cycle length.**

The 3-month cycle length does not match the pack size for nintedanib, but equates to three packs of 60 capsules. This was stated in error within the Company Submission.

The majority of prescriptions for nintedanib for the treatment of IPF are dispensed via Homecare (an average of 85% over the last 6 months in England, see embedded Excel document below). Of these units, 75% are one month's supply, 12.6% are for two months' supply and 12.5% are for three months' supply. If nintedanib is dispensed in hospital (the remaining 15% of prescriptions), previous experience with nintedanib in IPF suggests that pharmacies will split the packs.

Since most dispensing is via Homecare, and most of these prescriptions are for one month's supply, there should be minimal wastage even if patients discontinue treatment after one month.

Overall, the cycle length of 3 months was chosen to be consistent with the clinical trial intervals between observations, and as it was considered to be a balanced interval for model outcomes. It was also chosen to align with the methods applied during the NICE TA submission of nintedanib for IPF [TA379], as this cycle length was deemed to be appropriate by the ERG during that appraisal. Given the similar clinical characteristics of PF-ILD and IPF it is expected that the same approach within PF-ILD should also be considered valid.

[redacted]

Treatment effectiveness

B4. PRIORITY QUESTION: Please provide the results of tests for proportional hazards for all survival analyses in the model

The results of the tests for proportional hazards for the PF-ILD data (INBUILD) are available in the below document. The Bayesian survival analysis uses the same PF-ILD dataset as the standard frequentist analysis, so this document applies for both analyses.

Proportional hazards for survival

We could potentially assess the proportional hazards assumptions for the matched IPF data; however, the results may not be meaningful for the following reasons:

- It would not be possible to assess whether the proportional hazards assumption holds over the duration of the analysis as only the nintedanib arm has long-term data.

- Data were pooled from multiple trials and IPF patients were weighted in the matching algorithm to create a patient dataset whose baseline characteristics most closely matched the corresponding PF-ILD patient characteristics. Whether proportionality holds is therefore dependent on the results of the matching algorithm (or which algorithm was used) and is not reflective of the actual proportionality within the IPF trials.

For the above reasons, we do not believe it is meaningful to provide the results of this test for the matched IPF data.

B5. PRIORITY QUESTION: Please provide Figures for the nintedanib and placebo arms, which include all extrapolation curves from Table 25 and allow the use of any of these extrapolations within the model. Please do the same for all extrapolations in Table 28 for the Bayesian analysis.

A frequentist analysis was conducted on the PF-ILD data alone that considered all of these distributions, including exponential, log-normal and Gompertz, in line with NICE requirements.(4) The Bayesian survival analysis was conducted to make use of long-term data that could not be used in a standard frequentist analysis. For the original submission, the Bayesian survival curve coefficients were only generated for the Weibull, log-logistic and gamma distributions. This is because these were the three best fitting models of the matched IPF data (see Table 3 below). The remaining exponential, log-normal, generalised gamma and Gompertz survival coefficients were not generated in the Bayesian analysis as these were the poorer fitting models.

As the Bayesian Gompertz, exponential and log-normal distributions were poorer fitting models of the matched IPF data, it is unlikely that there would be justification for using these results in the economic model compared to the best fit Bayesian models or the frequentist analyses. The exponential model in particular is a very

poor fit for the matched IPF placebo data, producing an AIC that is over 11 points higher than the second poorest fitting model (Table 1).

Table 3: Bayesian analysis goodness of fit

Distribution	Nintedanib		Placebo	
	AIC	BIC	AIC	BIC
Weibull	1468.961	1476.535	567.0736	574.6227
Exponential	1471.934	1475.721	580.1805	583.9613
Generalised gamma	1470.677	1482.037	569.1665	580.4714
Log-logistic	1469.346	1476.920	567.0456	574.5948
Log-normal	1470.437	1478.010	568.6821	576.2312
Gompertz	1470.285	1477.859	568.4749	576.0240
Gamma	1468.814	1476.388	567.2287	574.7778

Similarly, six parametric distributions were considered for the frequentist analysis; the exponential, log-normal and generalised gamma distributions were found to be a poor statistical fit, and were not pursed further.

Boehringer Ingelheim conducted a further clinical validation exercise with UK experts to review assumptions within the model on the basis that they had a vast range of previous publications and were involved in clinical trials and guidelines/guidance development. Five clinical experts were consulted to validate the assumptions within the model.

The clinicians were presented with the overall survival extrapolations presented in the below two figures and were able to provide more commentary on the curves for BSC given the limited knowledge on the long-term impact of nintedanib in the PF-ILD population. The clinicians agreed that for both curves the frequentist Gompertz curve was likely to underestimate survival, as they would expect a proportion of patients to live beyond 5 years. Therefore, this analysis can be considered to be clinically implausible and not relevant for decision-making.

Figure 5: OS models fit versus INBUILD clinical trial KM – placebo arm

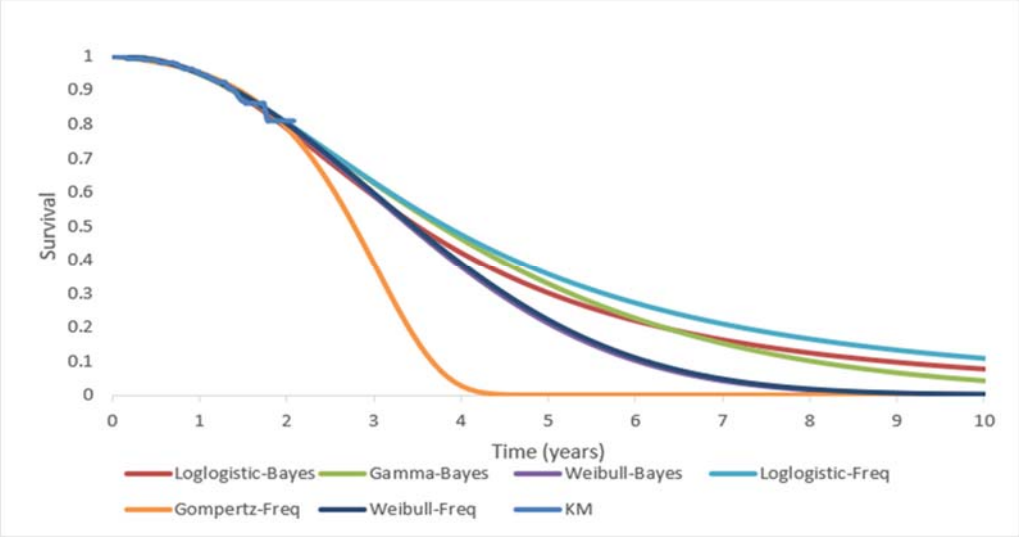
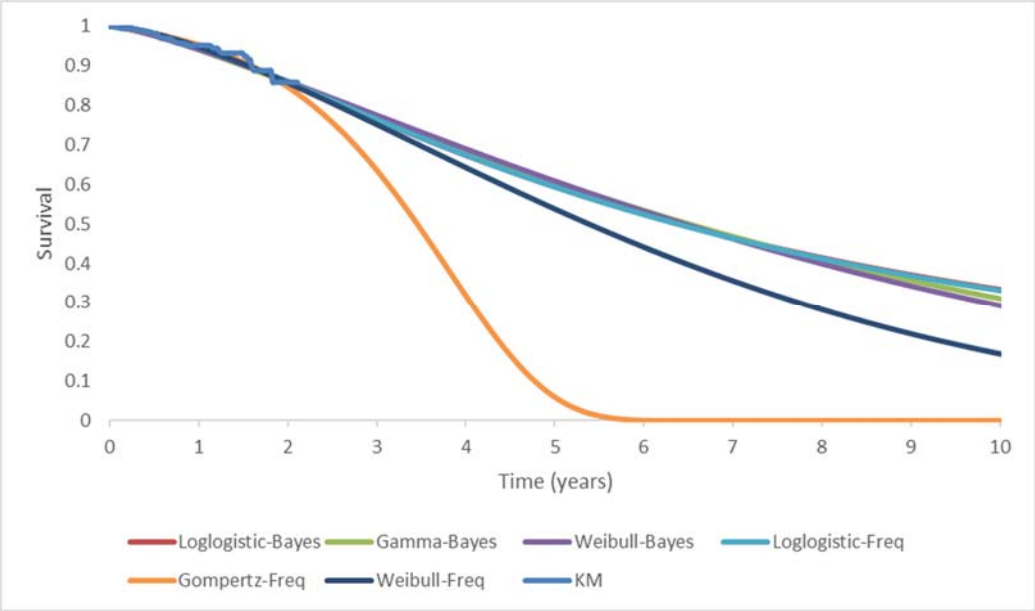


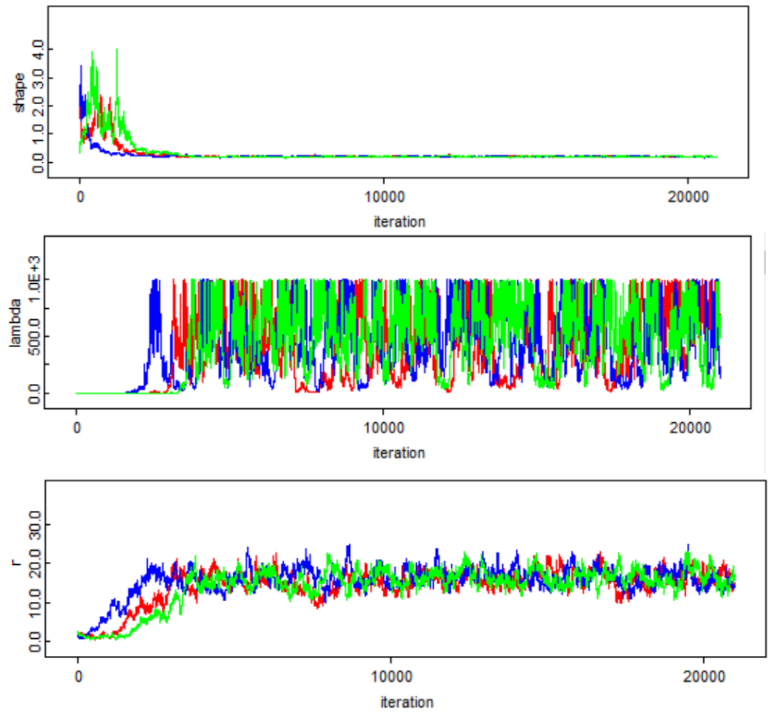
Figure 6: OS models fit versus clinical trial KM – nintedanib arm



Additional analyses have now been conducted to generate the Bayesian survival curve coefficients for the exponential, log-normal and Gompertz distributions. It was unfortunately not possible to produce Bayesian survival curve coefficients for the generalised gamma distribution. A variety of different prior distributions for the three parameters were assessed, including uniform, gamma and truncated normal distributions. When uniform vague priors were used, the model ran very slowly and did not reach convergence for the lambda prior (see Figure 7; this example was produced using vague priors and the PF-ILD nintedanib dataset). For the other prior

distributions examined, it was not feasible to run the analysis in the time available as the code ran too slowly (taking between 4-382 seconds per 1,000 iterations) and often caused OpenBUGS to freeze. It was possible to run the generalised gamma model if very precise priors were used; however, this was not reflective of the actual priors generated by the matched IPF data. Therefore, it was not possible to generate Bayesian survival curve coefficients for the generalised gamma distribution.

Figure 7. History plots generated by OpenBUGS for generalised gamma distribution



The requested additional survival curves, with the exception of the Bayesian generalised gamma for the reasons mentioned above, have been added into the model. The extrapolated curves from all distributions are presented in Figure 8 and Figure 9 for nintedanib and placebo respectively.

Figure 8: Extrapolated survival curves for all distributions (nintedanib)

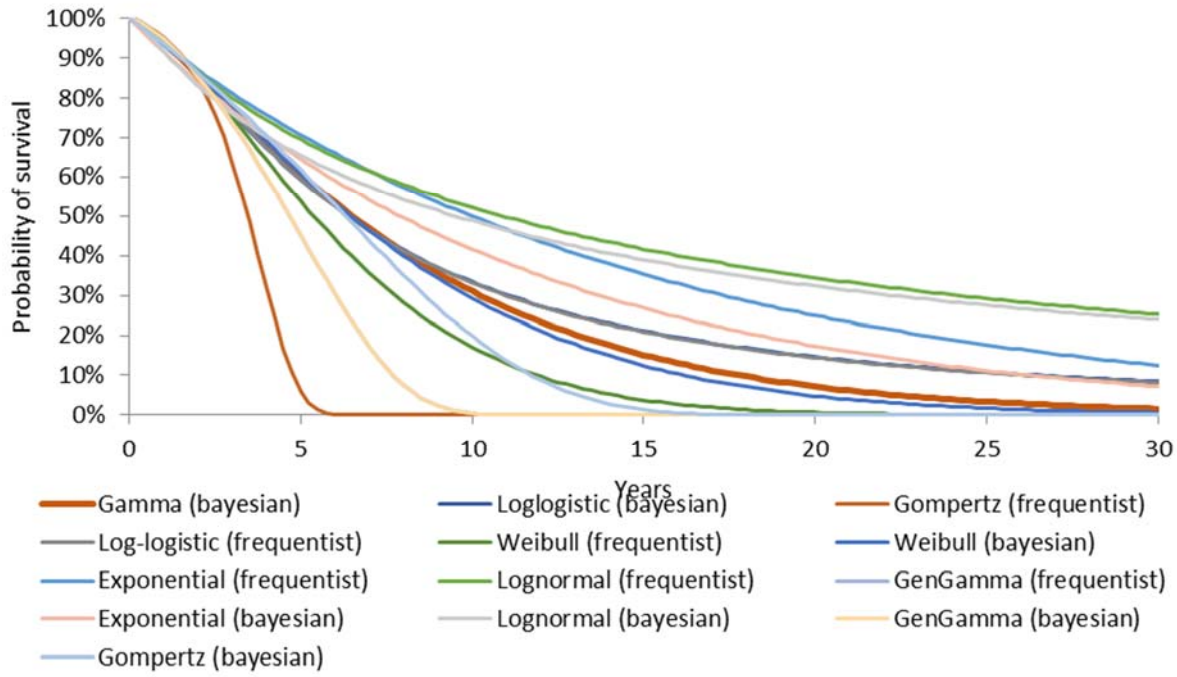
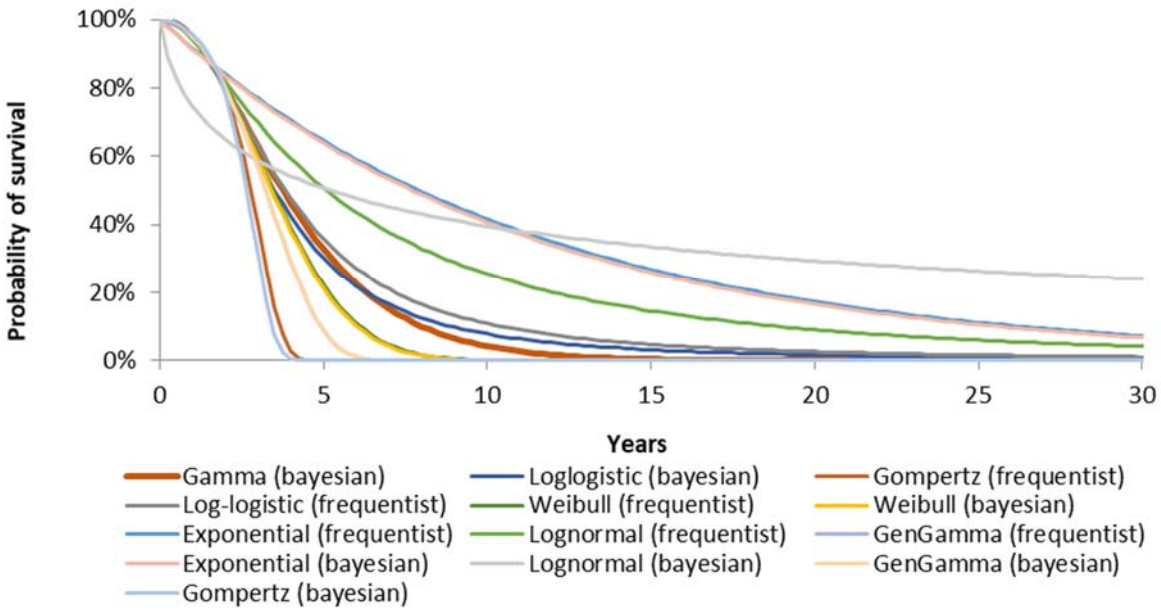


Figure 9: Extrapolated survival curves for all distributions (placebo)



B6. PRIORITY QUESTION: Please provide a Figure comparing the KM data from INBUILD, TOMORROW, INPULSIS I, INPULSIS II and INPULSIS-ON.

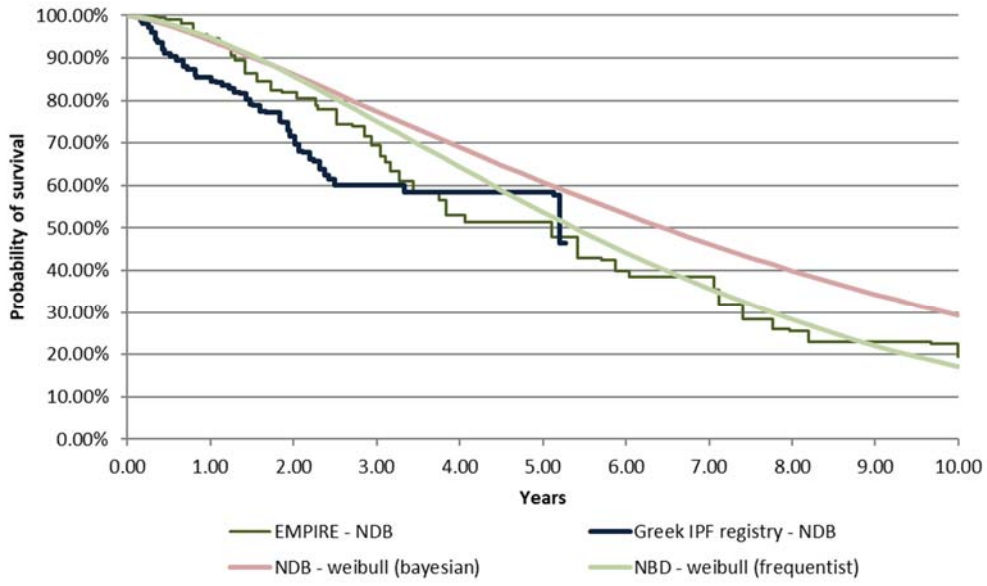
Figure 10 shows a combined figure of the Kaplan-Meier survival data from INBUILD, TOMORROW and a pooled analysis of six IPF trials (TOMORROW and its open-label extension, INPUSLSIS I and II and their open-label extensions, INPULSIS-ON and a phase IIIb trial with a placebo-controlled period of ≥6 months followed by open-label nintedanib).(5-7) This figure shows that the data from INBUILD show a good visual match with the data from nintedanib's IPF trials.

[redacted]

B7. PRIORITY QUESTION: Please add the model prediction based on the frequentist Weibull curve to Figure 20 and justify the choice of the Bayesian Weibull over the frequentist Weibull.

A comparison of data on long-term survival with nintedanib in the IPF population versus both the frequentist and Bayesian Weibull curves is presented in Figure 11.

Figure 11: Comparison of data on long-term survival with nintedanib in the IPF population (EMPIRE study and Greek IPF registry) versus the model predictions



Five clinical experts were presented with the overall survival extrapolations presented in Figure 16 and Figure 17 of the company submission document. As described in the company submission, the clinicians could not confirm which specific distribution was likely to be valid for nintedanib patients, but it was agreed that either of the Weibull curves could be plausible for BSC. Given the advice of the clinicians, it was judged that either of the Weibull curves (either frequentist or Bayesian) should be adopted in the base case for both nintedanib and BSC. However, it was judged that the Bayesian analysis should provide more robust estimates of long-term survival, given the inclusion of longer-term IPF data within that analysis to support to use of immature PF-ILD data. Therefore, the Bayesian Weibull curves were adopted for both nintedanib and BSC in the base case.

The UK clinicians were also asked to comment on the appropriateness of longer-term data regarding the efficacy of nintedanib in the IPF population to validate the model predictions. Overall, based on the feedback from the UK clinicians, and a visual comparison of the BSC curve in the model to data from alternative studies it was judged that the Weibull Bayesian distribution generated the most valid long-term extrapolations for the BSC arm (not shown). The Weibull Bayesian curve also produced one of the lower AIC and BIC scores thereby indicating a good statistical fit to the data. Therefore, the Weibull Bayesian distribution was selected for both

treatment arms (i.e. including the nintedanib arm). The choice of distribution was examined further in the scenario analyses. Further information on the methods used to estimate such curves, and the data sources used for validation can be found in Section B.3.3 of the company submission.

B8. PRIORITY QUESTION: Please provide data on the number and proportion of patients who experienced a recurrent exacerbation in INBUILD. Please provide the option in the model for patients to experience recurrent exacerbation based on plausible estimates from the trial or literature.

The total number of exacerbation episodes recorded during the INBUILD study are presented below. They indicate that 1.5% and 1.2% of placebo and nintedanib patients experienced a recurrent exacerbation during the 52-week follow-up period of the study. This equates to 9/663 patients (1.36%) with a recurrent exacerbation overall.

Table 4: Exacerbations reported in the INBUILD trial up to 52 weeks

No. of exacerbation episodes	Placebo		Nintedanib	
0	297	89.7%	311	93.7%
1	29	8.8%	17	5.1%
2	3	0.9%	1	0.3%
3	2	0.6%	3	0.9%
>=4	0	0.0%	0	0.0%

The functionality has also been added to the model to enable recurrent episodes to be captured. This functionality can be found on the 'Efficacy' sheet in which the tickbox labelled as "Include recurrent exacerbation risk" can be used to select the option. When ticked, this includes recurrent exacerbations in the model. This is based on 3-month probabilities of a recurrent exacerbation, which are shown to the right of the tickbox. These have been included in the model based on the rates of 1.5% and 1.2% quoted above for placebo and nintedanib respectively (converted to 3-month probabilities).

The inclusion of recurrent exacerbations in the base case of the latest model causes the ICER to change by <£100 thereby indicating that this is not a driver of the cost-effectiveness results.

B9. PRIORITY QUESTION: Please clarify whether the disposition of the cohort at the start of the model presented in Table 38 is based on baseline data from INBUILD? If it is not, please clarify why and include this as an option in the model.

The disposition of the patient cohort at the start of the model (Table 38) is based on baseline data from the INBUILD trial.

B10. PRIORITY QUESTION: Please justify why the risk of loss of lung function for nintedanib was informed by an odds ratio, rather than using the same approach of estimation used for the placebo arm. Please estimate the three-month probabilities for progression in nintedanib arm using the same approach as applied for the BSC arm and allow the option to use these in the model.

The risk of loss of lung function for nintedanib was informed by an odds ratio, as this was the approach taken for the assessment of nintedanib in IPF.

We have now replicated the multivariate logistic regression analysis for lung function decline that is described in the company submission but with treatment included as an additional covariate. The outputs from this regression equation are presented in Table 5 below, with the new covariate included second in the table.

Table 5: Outputs of the regression equation for lung function decline

Term	Estimate	SE	Statistic (t-test)	P-value
(Intercept)	-6.929	1.031	-6.723	0.000
Nintedanib treatment	-0.422	0.231	-1.829	0.067
AGE	0.029	0.013	2.258	0.024
HRCTRESUIP-like pattern only	0.135	0.248	0.546	0.585
PGGR1Marginal decline in FVC %pred	-0.648	0.277	-2.342	0.019
PGGR1Worsening of respiratory symptoms	-0.699	0.339	-2.061	0.039
fvc_start_int	0.027	0.007	3.793	0.000
exac_before	1.230	0.712	1.728	0.084

Abbreviations: FVC%pred, forced vital capacity percent predicted; PGGR1, grouped criteria for progressive interstitial lung disease; SE, Standard error.

In the model, a drop-down box has been added to the “Efficacy” sheet to allow a choice between using the odds ratio, or direct regression outputs presented above,

in order to inform the loss of lung function for nintedanib. The three-month probabilities for progression in the nintedanib and placebo arm, using the new regression outputs, are presented in Table 6 and Table 7 and respectively.

Table 6: Three-month probabilities of progression, nintedanib (based on new regression output)

FVC%Pred at start of interval	No exacerbation at start of interval	Intervals starting after first exacerbation
115	5.57%	16.81%
105	4.29%	13.31%
95	3.30%	10.45%
85	2.53%	8.15%
75	1.93%	6.31%
65	1.47%	4.87%
55	1.12%	3.75%
45	0.86%	2.87%

Table 7: Three-month probabilities of progression, placebo (based on new regression output)

FVC%Pred at start of interval	No exacerbation at start of interval	Intervals starting after first exacerbation
115	8.26%	23.56%
105	6.41%	18.98%
95	4.94%	15.11%
85	3.80%	11.92%
75	2.92%	9.32%
65	2.23%	7.25%
55	1.71%	5.61%
45	1.30%	4.32%

In the base case of the latest version of the model, the use of transition probabilities from the new regression equation (i.e. with treatment as a covariate) causes the ICER to change by <£100 in the base case.

B11. PRIORITY QUESTION: Given that the extrapolated time on treatment with the assumed exponential curve appears to underestimate discontinuation from nintedanib, please further justify why other extrapolations were not considered and provide alternative plausible extrapolations, or constant or time dependent discontinuation rates for possible use in the model which better represent the INBUILD KM data.

Other extrapolations for discontinuation risk were not considered, as this would have required a more complicated and less transparent model structure. As noted in our submission, it is possible that the base case may underestimate the rate of discontinuation for nintedanib over the course of the INBUILD trial. We therefore conducted a sensitivity analysis where the discontinuation rate was varied to the upper and lower confidence intervals reported in INBUILD (7.083 – 7.457).(8) This resulted in only small differences to the results, increasing or decreasing the ICER by ~£1,500 per QALY (Figure 37 in the Company Submission). We also conducted a scenario analysis varying the exponential coefficient until a curve was generated that was more consistent with that reported by Lancaster et al.(7) This scenario was based on a discontinuation rate of 7.67% per cycle, compared with 5.97% used in the base case, resulting in an ICER of [redacted] per QALY.

It should be noted that while the base case may underestimate the discontinuation rate over the duration of the INBUILD trial, the curve used in the base case does not provide a good visual match for the end of the INBUILD Kaplan-Meier curve. This is also true for the scenario analysis based on Lancaster et al (Figure 12 below, or Figure 38 in the Company Submission). As a result, the base case may actually overestimate the discontinuation rate for nintedanib over the long term. Therefore an additional scenario was modelled in which a discontinuation rate was inputted that allowed the long-term predictions to more closely match the tail of the INBULD Kaplan-Meier curve (Figure 13 below, or Figure 39 in the Company Submission). This rate (3.97%) resulted in an ICER of [redacted] per QALY.

Figure 12: Alternative discontinuation rate to match data from Lancaster et al and comparison with INBUILD extrapolations

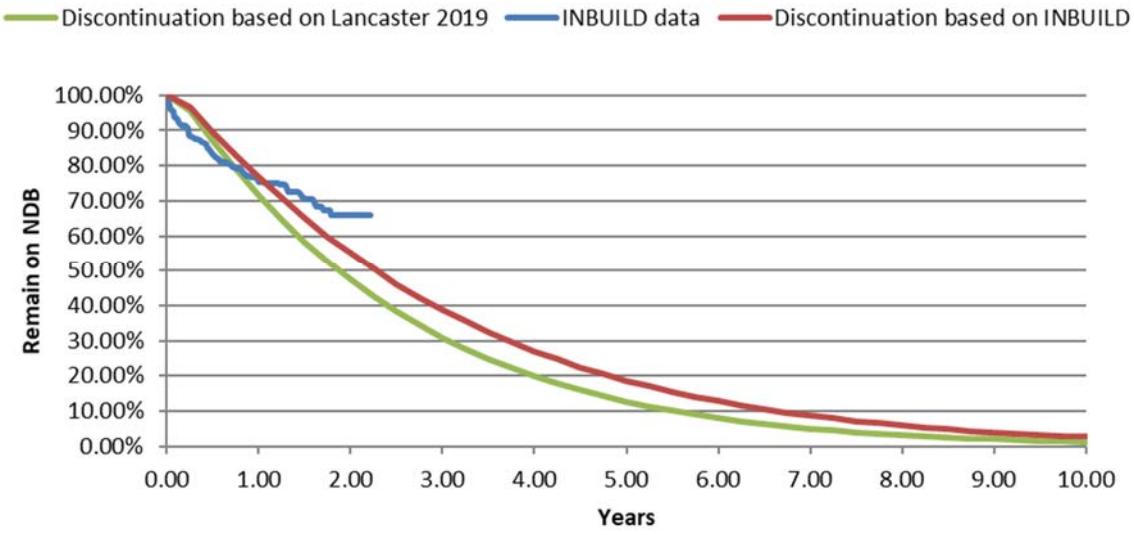
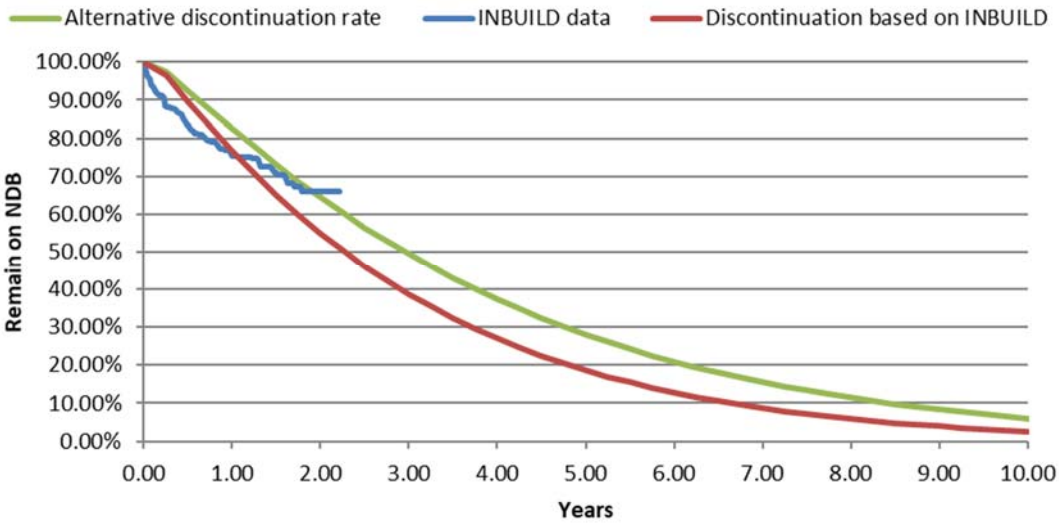


Figure 13: Alternative discontinuation rate to more closely match the tail of the INBUILD Kaplan-Meier curve and comparison with INBUILD extrapolations



Following the clarification meeting, we investigated the possibility of updating the model to allow for two different rates for discontinuation, as well as a time-dependent exacerbation rate, however these were both found to require substantial changes to the structure of the model that were unfortunately not feasible in the time allowed. As a pragmatic solution, and to test the uncertainty around the assumptions on discontinuation, we conducted further scenario analyses to vary the exacerbation rate between 1% and 10%. These changed the ICER to [redacted] and [redacted] per

QALY, respectively. Analyses of real-world data from IPF patients in the UK show similar discontinuation rates to clinical trials.(9-11) Therefore we believe that the discontinuation rates tested represent a more extreme situation than can be expected in real-life. In addition, increasing the discontinuation rate of nintedanib results in a lower ICER than is reported in the base case.

Therefore, we believe that the way discontinuation rate has been modelled in our submission is not a significant cause of uncertainty and that it should not affect decision-making.

B12. PRIORITY QUESTION: Please explain the reasoning and evidence behind the inclusion of the options in the model to assume that patients discontinue nintedanib at a certain FVC%Pred or due to a relative change in FVC%Pred.

The economic model submitted to NICE was not designed solely for the purposes of the appraisal but had multiple purposes. Therefore, this functionality was included to inform internal decision-making and was not intended for use in the NICE appraisal. It was included in error for the version of the model originally submitted to NICE and, therefore, the functionality has been removed in the latest version.

B13. PRIORITY QUESTION: Table 38 shows the distribution of patients at the beginning of the model. This shows that very few participants in the trial have an FVC%Pred>99.9. In TA379, the ERG expressed concerns that "the population used in the economic model may not represent the clinical population treated in the UK because they have included patients with FVC% predicted more than 80% which represents IPF that is milder than would typically be seen in current UK practice".

a. **Please explain whether the population used in the economic model can be considered to represent the population who will be diagnosed with PF-IPD, seen and treated with nintedanib in UK clinical practice.**

b. **Please provide the option in the model to perform an analysis that only includes patients with an FVC% predicted that is lower than 80%.**

Clinical experts working at specialist ILD centres in the UK validated the population used in the economic model in an Advisory Board in November 2020 (see page 84

of the Company Submission). In addition, two clinical experts specifically validated the inclusion of patients with an FVC % predicted >80%, stating that these patients are referred to specialist centres as they may have other factors that mean they need treatment, and that patients often present with symptoms of cough and breathlessness with an FVC % predicted above 80%. They also emphasised that treatment should be considered based on the trajectory of disease, rather than a baseline FVC % predicted value. These responses can be found in the documents provided in answer to question A4 (page 7).

Although the model does not present an automatic option to perform an analysis of patients with FVC% predicted <80%, it is possible to conduct this analysis with the current model by removing the patients with an FVC% predicted >80% in the control tab (i.e. replacing the values in cells K8-K11 with zero). After performing this analysis, the results show a slight increase in the ICER value ([redacted] vs [redacted]) showing that nintedanib remains under the WTP threshold and proves to be cost-effective in the whole population including patients with FVC % predicted >80%.

In a previous TA of nintedanib for the treatment of IPF (TA379), the “ERG suggested that the population in the company's model may not represent those treated in clinical practice in England because it included people with percent predicted FVC of more than 80% (accounting for approximately 45% of people in the model).” In the current submitted model, this patient population (FVC>80%) represents a much lower percentage (24.06%).

B14. PRIORITY QUESTION: Please provide evidence supporting the assumed constant hazard of exacerbation, independent of FVC%Pred. This assumption was previously criticised by the clinical adviser to the ERG in TA379 of nintedanib for IPF. Please provide a Figure including all extrapolations of time to first acute exacerbation shown in Table 36 compared to the INBUILD KM data and allow for their use in the model.

The extrapolations for all six distributions are presented in Figure 14 and Figure 15 for placebo and nintedanib respectively. These figures suggest that the distributions are likely to underestimate the probability of exacerbation. This has occurred because the curves presented in Figure 14 and Figure 15 were completed a number of months ago. Since being completed an updated data cut has become available

from the INBUILD study and it is this data that are presented in the Kaplan-Meier curves shown in these figures. However, within the model the total number of exacerbations is based on both the exacerbation rate that has been implemented, plus the total number of patients alive in each cycle (i.e. the outcome becomes alive with exacerbation). As presented in Figure 23 of the CS, and also shown below in response to question C5, when deaths are also accounted for the model predictions for exacerbations are much more closely aligned with the Kaplan-Meier data from the INBUILD study (based on the latest data cut).

There are a couple of other points of interest. Firstly, whilst the curves shown in Figure 14 and Figure 15 suggests that the fitted distributions may underestimate the rate of exacerbations as recorded in INBUILD, the effect is very similar in both treatment arms. Additionally, and perhaps most importantly, as noted in our responses to questions B1b and B8, while exacerbations have a very important impact on patients, they are not a key driver of the cost-effectiveness results. Therefore, overall it is expected that the extrapolations for time to first acute exacerbation do not have a meaningful impact on the cost-effectiveness results.

Figure 14: Time to first acute exacerbation with all six distributions, placebo.

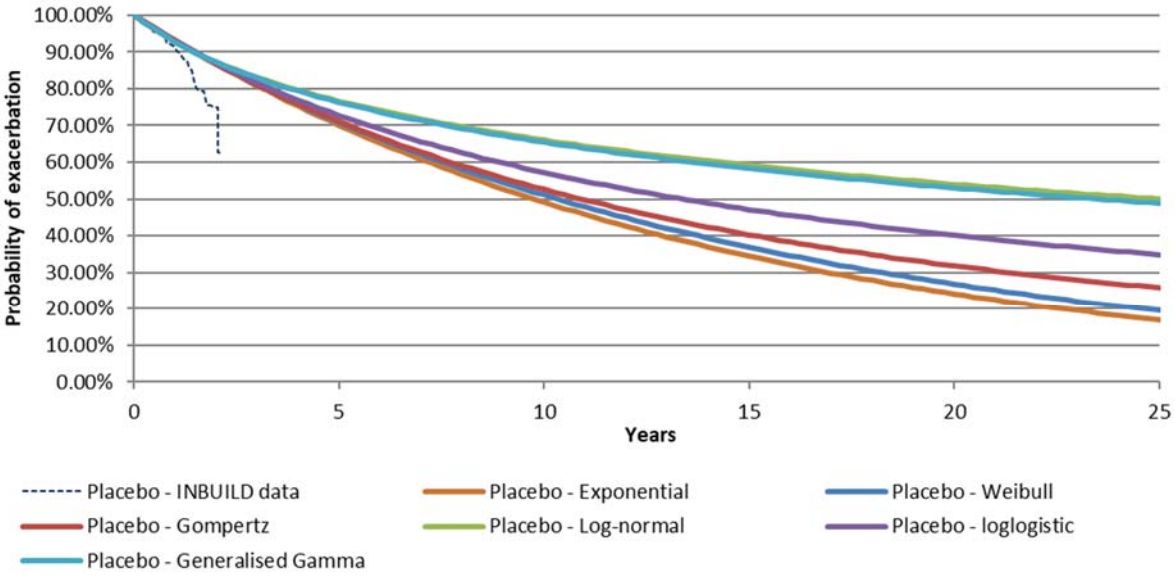
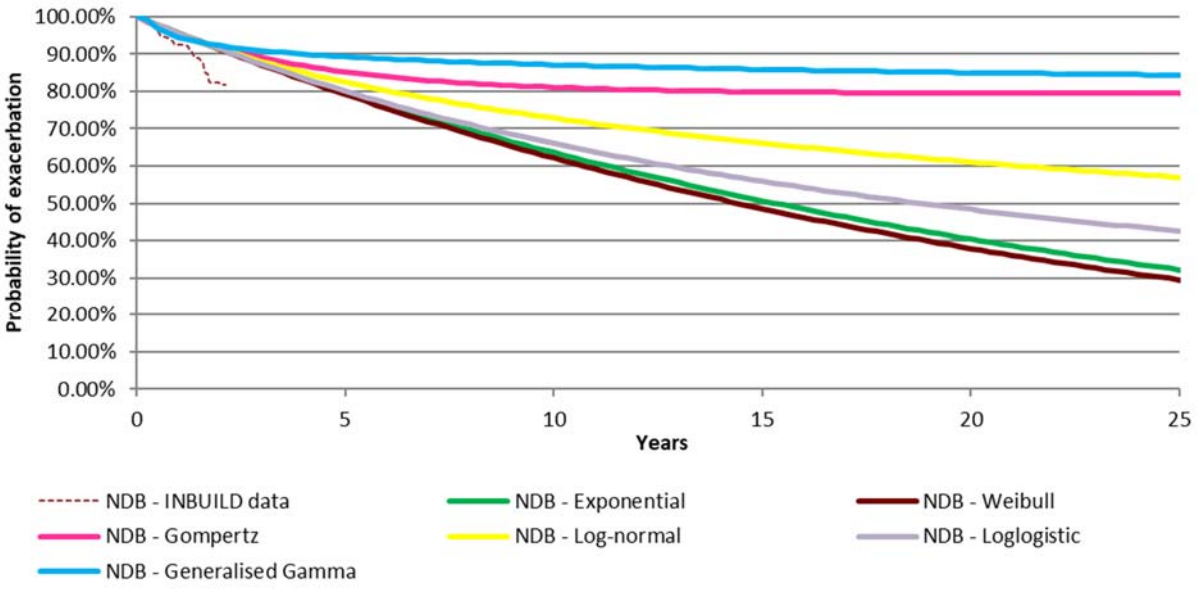


Figure 15: Time to first acute exacerbation with all six distributions, nintedanib.



As stated above, six different extrapolations were considered for time to first acute exacerbation, and the exponential curve was selected because it had the lowest AIC score for the placebo arm and the second lowest for the nintedanib arm. In addition, a constant hazard of exacerbation allowed for a simpler and more transparent model than a time-varying probability.

As discussed in our clarification meeting, adapting the model to allow for a time-varying risk of exacerbation would require significant changes that were unfortunately not possible to conduct in the time allowed. An alternative option of allowing two different rates to be applied across the modelled time horizon was also investigated, but this was also found to require substantial changes to the model structure, resulting in a less transparent model. As a pragmatic solution, and to test the level of uncertainty resulting from the assumption of a constant risk of exacerbation, we have run a scenario analysis where the rate of exacerbation with nintedanib was varied from 1.12% to 20% per cycle. This resulted in only a small increase to the ICER of £3,000 per QALY. The upper value adopted in the scenario analysis in particular represents an extreme and unlikely value compared with the exacerbation rate reported over 52 weeks in the INBUILD trial (6.9%), as well as that reported in the INPULSIS trials for IPF (5.9%).(3, 12) We therefore believe that

exacerbations are not a driver of the cost-effectiveness results, and that the related uncertainty is very limited and unlikely to have a significant impact on the ICER.

B15. PRIORITY QUESTION: Please explain the clinical plausibility of the results that the risk of experiencing a further reduction in %FVC predicted declines in relation to a lower starting %FVC predicted (i.e. as shown in Figures 25 and 26 of the CS).

This concept was discussed with two clinical experts working in specialist ILD centres in the UK (see response to question A4, page 7). Both experts stated that it is difficult to estimate how patients' FVC will decline based on a starting FVC % predicted, because there are other confounding factors affecting the decline. The starting FVC % predicted value also does not give an indication of how quickly the patient has progressed in the past. Therefore, the information shown in Figures 25 and 26 of the Company Submission may be clinically plausible.

The probabilities depicted in Figures 25 and 26 were derived from a regression analysis which predicted reduction in FVC % predicted using baseline FVC and other covariates as explanatory variables (see below embedded file). This model predicted a lower reduction in FVC % predicted with lower baseline FVC values.

Endpoint analyses_FVC progr

In summary:

- In INBUILD, FVC % predicted was evaluated at multiple time points. The objective of the model was to predict the probability of progression (absolute reduction in FVC % predicted ≥10%) in three month time periods, 0-3 months, 3-6 months, 6-9 months and 9-12 months. Based on the trial's schedule, these periods included the assessments reported in Table 8. Whether a patient progressed was assessed relative to a previous assessment, meaning that it was not always assessed relative to baseline.

- We tried to include all the relevant predictors in the models. All candidate predictors were first tested on their own to assess whether they were

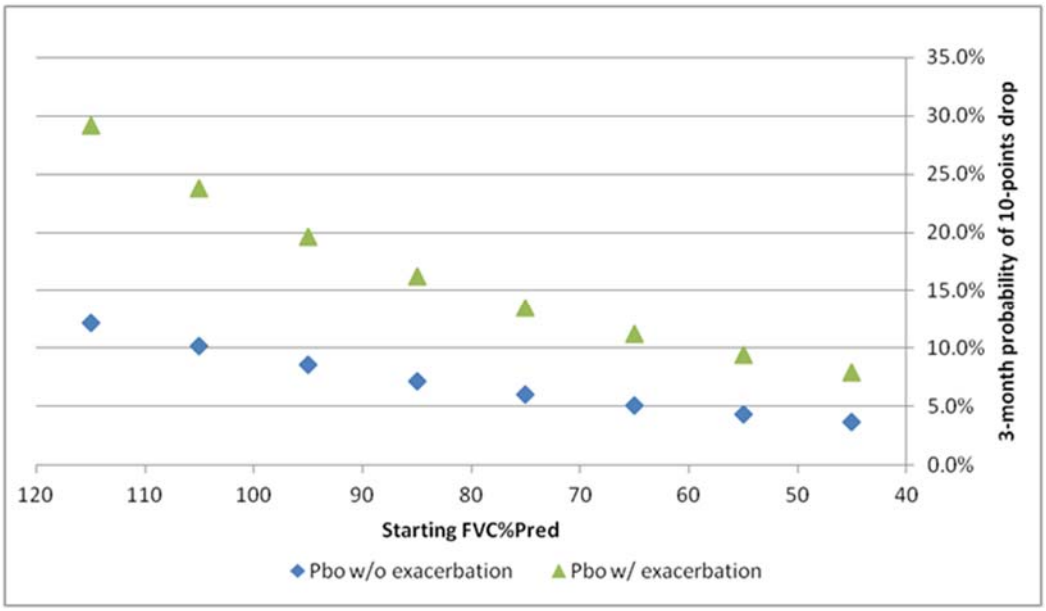
associated with the outcome. A p-value of 0.2 was used to decide which variables had a univariate association. Significant predictors were combined in a multivariate model, which was then manually trimmed to exclude predictors that became non-significant at a p-value of 0.2 or higher. The cut-off of p≥0.2 was selected to avoid missing important predictors.

- The model suggests that a smaller value of FVC at the start of the interval is associated with reduced probability of progression. Looking at the trial data, except for the 6-9 month time period, a higher proportion of progressions were observed with higher starting FVC values, although it should be noted that these results are guided by a small number of events. A similar relationship between starting FVC values and probability of progression was also observed in IPF (Figure 16, originally Figure 47 in the Company Submission for nintedanib in IPF). These observations are consistent with the predictions in the model

Table 8: Trial assessment periods used to model probability of FVC progression

Time-point reported in weeks	Group	Loss of lung function assessed relative to
2	0-3 months	Baseline
4		
6		
12		
24	3-6 months	12 weeks
36	6-9 months	24 weeks
52	9-12 months	36 weeks

Figure 16: Progression probabilities from the NICE assessment of nintedanib in IPF



B16. PRIORITY QUESTION: As stated on p. 63 of the CS, "patients were allowed to use a range of background medication that closely resembled BSC in this disease".

a. **Please provide details on the use of background medication in the nintedanib and BSC arms, and whether this is representative of clinical practice in the UK.**

b. **Please justify why the costs for the use of concomitant medication are not included in the model.**

c. **Please provide the option to include the costs of concomitant medication use in the model.**

The use of background medication in the INBUILD trial up to database lock 2 is provided in Table 1 (page 8), with restricted therapies shown in Table 2 (page 10). An overview of the background medications used in INBUILD was shared with two clinical experts working in ILD specialist centres in the UK (see documents provided in response to question A4, page 7). Both experts confirmed that the background medication use was reasonable and representative of clinical practice in the UK.

The cost of concomitant medications was not included in the original model as medication use was generally comparable between arms. In addition, the majority of

therapies used are low-cost, generic medicines. Inclusion of these costs in the model would therefore be unlikely to bias results in favour of nintedanib.

Following the clarification meeting and based on discussion with the ERG, we looked again at the concomitant and background medications used in the trial to identify any classes with greater use in the nintedanib arm (≥10%) that included high cost drugs. The Clinical Trial Report states that use of baseline and concomitant on-treatment therapies was generally comparable between the treatment groups based on ATC3 and preferred name. However, antipropulsives and drugs for peptic ulcer and gastro-oesophageal reflux disease were more frequently used in the nintedanib than in the placebo group (difference between the treatment groups ≥10%). With regard to drugs for gastro-oesophageal reflux disease, the use was already more common in the nintedanib group at baseline (nintedanib: 58.4%, placebo: 50.2%), while the use of antipropulsives commenced nearly exclusively on treatment (baseline use: nintedanib: 1.2%, placebo: 0.9%; Table 15.1.4.3.2.1.1: 1)."

The drugs included in the two classes with greater use in the nintedanib arm are listed in Table 9, along with their indicative NHS prices. This table shows that the cost of these drugs is very low and therefore very unlikely to have a meaningful impact on the cost-effectiveness result.

Since no drug classes met the criteria of being more commonly used in the nintedanib arm as well as including high-cost drugs, no further costs for concomitant medication were added to the model.

Table 9: List and prices of drugs included in the classes that were more common for nintedanib than placebo (≥10%)

Class	Active ingredient	Size	NHS indicative price(13)
Antipropulsives	Loperamide hydrochloride and loperamide	10	£1.11
		30	£2.99
Drugs for peptic ulcer and gastro-oesophageal reflux disease	Omeprazole	30	£13.92
	Pantoprazole	28	£2.26
	Lansoprazole	28	£3.22
	Esomeprazole magnesium	28	£2.83
	Pantoprazole sodium sesquihydrate	28	£2.26

Class	Active ingredient	Size	NHS indicative price(13)
	Famotidine	28	£38.99
	Rebamipide	28	Not available
	Esomeprazole	10	£2.83
	Rabeprazole sodium	28	£1.46
	Ranitidine and ranitidine hydrochloride	28	£2.79
	Dexlansoprazole	12	Not available
	Teprenone	12	Not available

B17. Please provide the OpenBUGS code that was used for the Bayesian analysis of OS, including prior distributions, starting values, number of iterations used for burn-in, thinning factor settings, and the results of the assessment of convergence.

The OpenBUGS code is available in the document below.

BayesianAnalysis_OpenBugs_Info_Code

B18. As stated on p. 83 of the CS, visual inspection of the OS curves in Figures 18 and 19 "corroborates the findings from the AIC scores (i.e. that all presented distributions appear to offer a robust fit to the available data)". Given that the presented curves in Figures 18 and 19 appear to align very closely, please provide details on how visual inspection corroborates findings that indicate that all distributions offer a robust fit.

Figure 18 and Figure 19 in the Company Submission present the overall survival curves for each of the distributions fitted for both placebo and nintedanib and also provide a comparison to the Kaplan-Meier data from the INBUILD study, over a 2-year period. These figures show that each distribution provides a prediction for overall survival that is very similar to the Kaplan-Meier data from the INBUILD study. As the fitted distributions do not deviate from the available Kaplan-Meier plots this indicates that, during the initial 2-year period of the overall survival curves for both

placebo and nintedanib, the model predictions closely match the available data, regardless of the distribution that is chosen.

HRQoL

B19. PRIORITY QUESTION: Table 46 in the company submission shows the EQ-5D utility values by FVC%Pred group used in the model. Please comment on the plausibility of the reversal of the decline in utility with decline in FVC%pred for category 80-89 FVC%pred and make an adjustment so that the relationship between utility and FVC%pred continues to decline in the model.

The reversal in decline in utility for the 80-89 FVC%pred category is unexpected but is what was recorded during the INBUILD trial. It is likely this has occurred due to anomalies in the data. It is already possible to input utilities in the model such that they decline as FVC%pred also declines. This can be achieved by inputting alternative values into cells D8:D14 on the 'Utilities' sheet of the model. If a utility value of 0.7265 is inputted for the 80-89 FVC%pred health state, which equates to a linear decline in utility from the 90-99 and 70-79 health states, the ICER changes by <£100 per QALY, thereby indicating this is not an important driver of model results.

B20. PRIORITY QUESTION: Please provide the following details for the estimation of the decrement in utility due to acute exacerbation:

- **How was this decrement estimated? CS reference 55 is referenced for details of the regression equation, but these details could not be found. Please provide them.**
- **On how many exacerbations was this analysis based?**
- **Is there evidence that exacerbations have the same impact on utility in patients with high or low pre-exacerbation FVC%pred?**
- **On what evidence was the assumed duration acute exacerbation disutility of 1 month based on?**

A linear mixed-effects model with a random intercept was fit to assess utility as a function of baseline utility, baseline characteristics (age, sex, race, HRCT pattern) and time-dependent predictors (FVC% pred, progression status and acute ILD

exacerbation). Covariates were selected via backwards stepwise regression with a p-value cut-off of 0.05. Treatment was not included as a covariate because it was not significant in initial testing, suggesting that there is no evidence of a difference between INBUILD patients on nintedanib and placebo in terms of utility. The results of the mixed-effects regression model to model utility over time are shown in Table 10. The utility decrement due to acute exacerbation was estimated to be 0.167, with a p-value of 0.001.

Table 10. UK utility model parameter estimates

Effect	Group	Term	Estimate	SE	Statistic	DF	P-value
Fixed	NA	(Intercept)	0.226	0.045	5.061	618.635	0.000
Fixed	NA	baseline_utility	0.612	0.025	24.381	606.699	0.000
Fixed	NA	fvc	0.002	0.000	6.658	792.484	0.000
Fixed	NA	AGE	-0.002	0.001	-3.086	595.732	0.002
Fixed	NA	HRCTRESUIP-like pattern only	0.027	0.012	2.201	593.350	0.028
Fixed	**NA**	**as.factor(acute_ild_exacerbation)**	**-0.167**	**0.050**	**-3.345**	**2192.934**	**0.001**
Fixed	NA	as.factor(progression)	-0.075	0.011	-6.773	2090.326	0.000
Random	USUBJID	sd_Intercept	0.121	NA	NA	NA	NA
Random	Residual	sd_Observation	0.133	NA	NA	NA	NA

Abbreviations: BL: baseline; DF: degrees of freedom; FVC: forced vital capacity; HRCTRES: high resolution computed tomography pattern; ILD: interstitial lung disease; NA: not applicable; SE: standard error; UIP: usual interstitial pneumonia.

In total, 69 acute exacerbation events were recorded across both treatment arms in the 52-week follow-up period of the INBUILD study.

Due to the relatively low number of exacerbation events that occurred during the INBUILD study it was not possible to undertake a robust assessment of whether FVC % predicted score had an impact on the disutility associated with the event.

The assumed disutility of one month for acute exacerbations is based on the definition proposed by Kolb et al(14), which is in turn based on the definition of acute exacerbation in IPF adopted by the International Working Group for IPF.

B21. PRIORITY QUESTION: Which EQ-5D value set was used to estimate utilities from the EQ-5D-5L data collected in the trial? Please ensure that the UK cross-walk value set was used to ensure that the choice of value set is aligned with NICE's position statement on the use of EQ-5D-5L value set for England. This can be done using either the published syntax or the cross-walk index value calculator, both available on the Euroqol website.

The EQ-5D cross-walk value set for the UK was used, derived using the index value calculator available on the Euroqol website.

B22. Please adjust utilities based on age (i.e., utilities decline due to ageing) within the model.

We have updated the model so that age-adjusted utilities are included. This causes the base case ICER to increase by around £4,000 per QALY (to [redacted]).

Costs

B23. PRIORITY QUESTION: In TA379 more types of procedures were considered for the estimation of background follow-up costs than in the current submission (e.g. TA379 includes chest HRCT, chest X-ray and oxygen requirement, bronchoalveolar, CT pulmonary angiogram, right heart catheterization procedure, and a general diagnostic procedure (for example bronchoscopy). Please provide justification for why these procedures are not relevant for the current submission or provide the option in the model to include these procedures.

As described in the CS, resource use values applied in the model were based on data from the INBUILD study. Of the resources noted in this question, oxygen use was explicitly captured and this is described in Section B.3.5 of the CS. The remaining resources that are listed in the question were not included in the analysis as they were only incurred in a very small number of patients, if at all. Therefore, they would not be expected to have an impact on the model results. Additionally, the resources that were applied in the model were presented to UK clinicians at the

advisory board described in the CS. They did not recommend that any additional resources should be included in the model for people with PF-ILD.

B24. PRIORITY QUESTION: In response to clarification questions by the ERG in TA379, a cost estimate of £2830 for mechanical ventilation was provided that was preferred by the ERG in that appraisal. Please use this cost estimate for the current submission, inflated to 2018 / 2019 costs, instead of the cost estimate of £161 that is currently used.

The cost estimate of £2,830 used in TA379 was obtained from the 2012/2013 NHS Reference Costs (Non-Invasive Ventilation Support Assessment, 19 years and over, Non-Elective Long Stay, DZ37A).

To ensure accuracy, it was considered more appropriate to identify the equivalent cost from the 2018/19 NHS Reference Costs rather than to inflate the value that was used in TA379. Therefore, the unit cost of mechanical ventilation was updated to £1,735 which is reported in the 2018/19 NHS Reference Costs (Non-Invasive Ventilation Support Assessment, 19 years and over, Non-Elective Long Stay, DZ37A). This cost of £1,735 has now been added into the model to estimate the cost of mechanical ventilation, with a very small impact on the ICER (<£200 per QALY).

B25. PRIORITY QUESTION: As stated on p. 114 of the CS, all included AEs were assumed to be resolved without treatment. In contrast, TA379 included several AEs (e.g. serious cardiac events, serious GI events, skin disorders, and GI perforation) for which the associated costs of treatment were substantial. Please provide justification for the assumptions regarding costs of the treatment of AEs, also considering the approach that was used in TA379.

The rationale for inclusion of adverse events in the model for TA379 for the IPF indication was as follows:

“Safety in the model was analysed by selecting events (individual or grouped in classes) that satisfied all of the following criteria in at least one of the clinical studies considered:

- AEs with a significant impact on costs and QALYs: assumed to be those that were severe or serious
- AEs with an incidence greater or equal to 5%
- AEs with an incidence of 1.5 times greater between the two arms

In addition, the following AEs of particular focus to clinicians were implemented in the model regardless of whether they met above criteria or not:

- For nintedanib: gastrointestinal perforation
- For pirfenidone: photosensitivity and rash”

No severe or serious adverse events occurred in greater than 5% of patients receiving nintedanib in the INBUILD trial vs. the comparator arm. Therefore, for the current submission for PF-ILD the following criteria were applied:

- An adverse event had to be common i.e. incidence of >10% in either treatment arm.
- An adverse event had to be treatment-related/treatment-emergent.
- Incidence in the treatment arm had to be at least 1.5 times higher than in the control arm.

In the current model for the PF-ILD indication there is no requirement for the adverse event to be serious or severe as was previously required in TA379 (except for gastrointestinal perforation, photosensitivity and rash). Therefore, applying the higher threshold of 10% in either treatment arm was considered appropriate, given the lower severity, to ensure that the most costly events on average per treatment arm were included.

None of the adverse events listed from TA379, but not included in the current PF-ILD model, occurred in greater than 5% of patients in either treatment arm of the INBUILD study. Only one patient each in the nintedanib arm and in the placebo arm were reported with non-serious AEs of anal abscess, representing the only gastrointestinal perforation adverse events. Excluding these events is considered reasonable as they occurred with a frequency of <5% and rates were not 1.5 times higher in the nintedanib arm. Photosensitivity and rash were included in TA379 as

adverse events of special interest for pirfenidone and therefore were not considered relevant in this appraisal.

Adverse events occurring in greater than 5% of patients over 52 weeks are presented in the following table.

Table 11: AEs reported for more than 5% of patients in either treatment group on the preferred term level over 52 weeks

MedDRA system organ class Preferred term	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	331	100.0	332	100.0
Patients with any AE	296	89.4	317	95.5
Gastrointestinal disorders	149	45.0	268	80.7
Diarrhoea	79	23.9	222	66.9
Nausea	31	9.4	96	28.9
Vomiting	17	5.1	61	18.4
Abdominal pain	8	2.4	34	10.2
Abdominal pain upper	6	1.8	30	9.0
Constipation	25	7.6	23	6.9
Infections and infestations	185	55.9	177	53.3
Nasopharyngitis	40	12.1	44	13.3
Bronchitis	47	14.2	41	12.3
Upper respiratory tract infection	19	5.7	24	7.2
Urinary tract infection	13	3.9	20	6.0
Pneumonia	20	6.0	19	5.7
Respiratory, thoracic and mediastinal disorders	144	43.5	128	38.6
Dyspnoea	44	13.3	36	10.8
Cough	44	13.3	33	9.9
Interstitial lung disease	39	11.8	16	4.8
Investigations	56	16.9	114	34.3
Alanine aminotransferase increased	12	3.6	43	13.0
Weight decreased	11	3.3	41	12.3
Aspartate aminotransferase increased	12	3.6	38	11.4
Gamma-glutamyltransferase increased	7	2.1	19	5.7
General disorders and administration site conditions	85	25.7	86	25.9
Fatigue	20	6.0	33	9.9
Asthenia	10	3.0	18	5.4
Oedema peripheral	20	6.0	12	3.6
Musculoskeletal and connective tissue disorders	87	26.3	77	23.2
Back pain	16	4.8	19	5.7
Arthralgia	20	6.0	10	3.0
Metabolism and nutrition disorders	38	11.5	69	20.8
Decreased appetite	17	5.1	48	14.5
Nervous system disorders	54	16.3	69	20.8
Headache	23	6.9	35	10.5
Hepatobiliary disorders	10	3.0	38	11.4
Hepatic function abnormal	3	0.9	19	5.7

Source data: Table 15.3.1.1.2.1: 2

Adverse events occurring in greater than 5% of patients and at least 1.5 times higher than in the control arm were as follows:

- Gastrointestinal disorders (predominantly diarrhoea, nausea and vomiting)
- Urinary tract infections
- Investigations (alanine aminotransferase increase, weight decrease, aspartate aminotransferase increase, Gamma-glutamyltransferase increase)
- Fatigue
- Asthenia
- Decreased appetite
- Headache
- Abnormal hepatic function.

The selection of events included in the model was considered appropriate as no serious or severe adverse events occurred in greater than 5% of nintedanib patients and the overall incidence of severe adverse events (22.1% vs 18.1%) or serious adverse events (33.2% vs 32.2%) was slightly higher in the placebo arm than in the nintedanib arm of the INBUILD study. The assumption that all adverse events would be resolved without treatment should not bias the cost estimates in favour of nintedanib because the most commonly occurring events of diarrhoea, nausea and vomiting can be treated with low-cost generic medicines or treatment interruption/ dose reductions of nintedanib.

B26. PRIORITY QUESTION: In TA379, the CS stated that patients received oxygen supplementation if their FVC% predicted was lower than 80%. The CS in TA 379 also stated that patients with FVC% predicted above 80% would be in relative good health and would not require oxygen supplementation.

a. **Please explain whether the assumption that patients receive oxygen supplementation only if their FVC% predicted is lower than 80% also applies to patients with PF-ILD.**

b. **Please provide the option in the model to only apply the costs of oxygen supplementation to patients with an FVC% predicted that is lower than 80%.**

Two clinical experts working in specialist ILD centres in the UK confirmed that patients with FVC % predicted above 80% could still require oxygen supplementation, and that this does happen in clinical practice for patients with PF-ILD (see documents provided in response to question A4, page 7). An example of this could be where a patient has a significantly reduced transfer factor, but a preserved FVC, leading to requirement for oxygen supplementation.

Since clinical experts confirmed that oxygen supplementation is given to patients with FVC % predicted >80%, the option to only apply the costs of oxygen supplementation to those with an FVC % predicted <80% has not been applied in the model.

B27. As shown in Table 52 of the CS, all costs of outpatient visits were sourced from PSSRU 2019. Please explain whether cost estimates as provided by the NHS Reference costs 2018 / 2019 were considered, and replace costs sourced from PSSRU 2019 with those from the NHS Reference costs 2018 / 2019 where available from the latter (e.g. for nurse and physiotherapist).

It was assumed that patients would attend outpatient visits within primary care. Therefore, cost estimates as provided by the NHS Reference costs 2018/19 were not considered. However, as requested the following unit costs have been updated in the model using the NHS Reference costs 2018 / 2019 and the updated costs are presented in Table 12. This change had very little impact on the ICER.

Table 12: Updated outpatient unit costs (NHS Reference Costs 2018/19)

Outpatient visit	Value	Source
Specialist	£158.02	Consultant led, weighted average between respiratory physiology and respiratory medicine (codes 340 and 341)
Nurse	£124.37	Non-consultant led, weighted average between respiratory physiology and respiratory medicine (codes 340 and 341)
Physiotherapist	£57.66	Physiotherapy, weighted average between consultant led and non-consultant led (code 650)
Occupational therapy	£70.96	Occupational therapy, weighted average between consultant led and non-consultant led (code 651)

B28. As stated on p. 114 of the CS, a cost estimate of £4384 was used for the total exacerbation costs. However, the model uses a value of £4368.83 for this. Please explain what is the correct value and change the value in the model if it currently uses an incorrect value.

We apologise for this confusion, which was caused by uncertainty regarding the price year of initial unit costs included in the analysis from the source paper. Upon further consideration, it is understood that the source paper used a price year of 2012/2013. Therefore, the unit cost of £4,134 has been inflated from the 2012/2013 price year to 2018/19, equating to a cost of £4,424. This value has been updated accordingly within the model and the alternative values should be discarded. This update led to a very minimal change of the cost-effectiveness results.

B29. Please provide data regarding the intensity of health care resource use (i.e. hospital, ER, visits, and procedures) for each FVC% predicted group.

The monthly probability of a patient requiring each of the resource use categories, stratified by FVC% predicted group is presented in Table 13. These resource use values are taken directly from the available INBUILD data.

Table 13: Monthly probability of resource use by FVC% predicted group

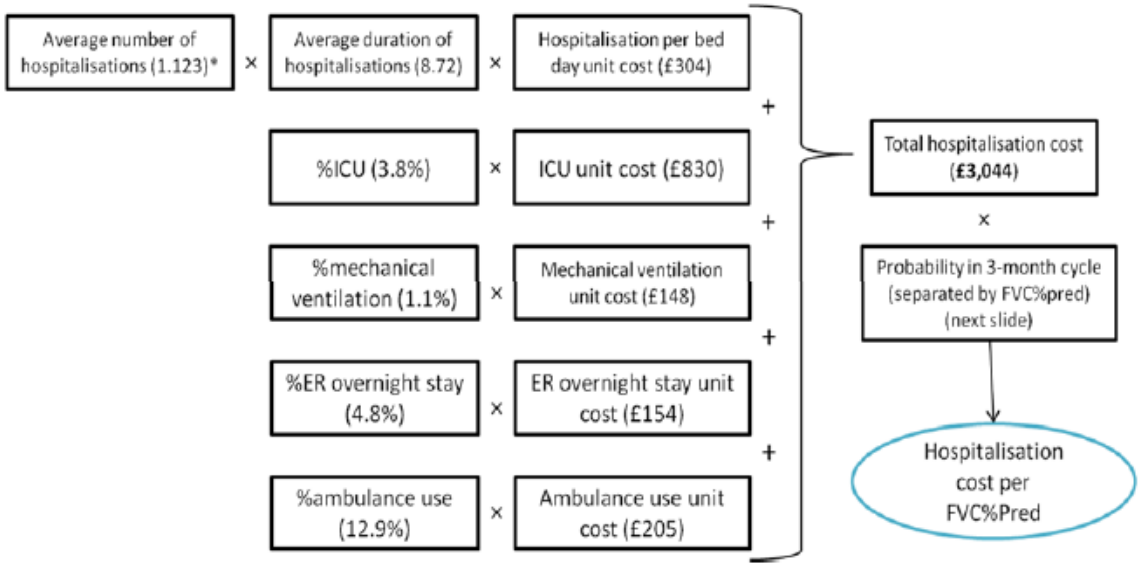
Event	FVC%Pred							
	≥110	100-109.9	90-99.9	80-89.9	70-79.9	60-69.9	50-59.9	40-49.9
Hospitalisation	3.94%	1.81%	1.82%	1.63%	1.67%	3.03%	3.14%	4.51%
ER	3.16%	1.45%	0.83%	1.39%	1.12%	1.81%	1.99%	1.59%
GP visit	3.94%	3.23%	5.36%	5.99%	10.35%	6.19%	5.54%	5.08%
Specialist visit	2.38%	4.63%	8.31%	6.83%	8.78%	7.64%	5.90%	5.71%
Nurse visit	0.80%	0.18%	1.00%	0.74%	0.97%	0.97%	0.75%	0.53%
Physiotherapist visit	0.40%	0.18%	0.17%	0.49%	1.02%	0.08%	0.13%	0.03%
Other visit	0.80%	0.18%	0.67%	1.47%	0.15%	0.31%	0.63%	0.93%
Occupational therapy	0.80%	0.18%	0.67%	1.47%	0.15%	0.31%	0.63%	0.93%
Oxygen use	4.71%	5.33%	5.52%	4.90%	8.83%	10.96%	15.51%	18.98%

Note: The number of patients in the FVC ≥110 health state was very low during the INBUILD trial, leading to relatively high estimates for resource use in this group. If the resource use values in this state are changed to match those in the 100-110 health state the ICER changes by <£100 per QALY.

B30. The annual hospitalization costs, as shown in Figure 32 of the CS, are substantially higher than those in TA379. Please explain the rationale for this difference.

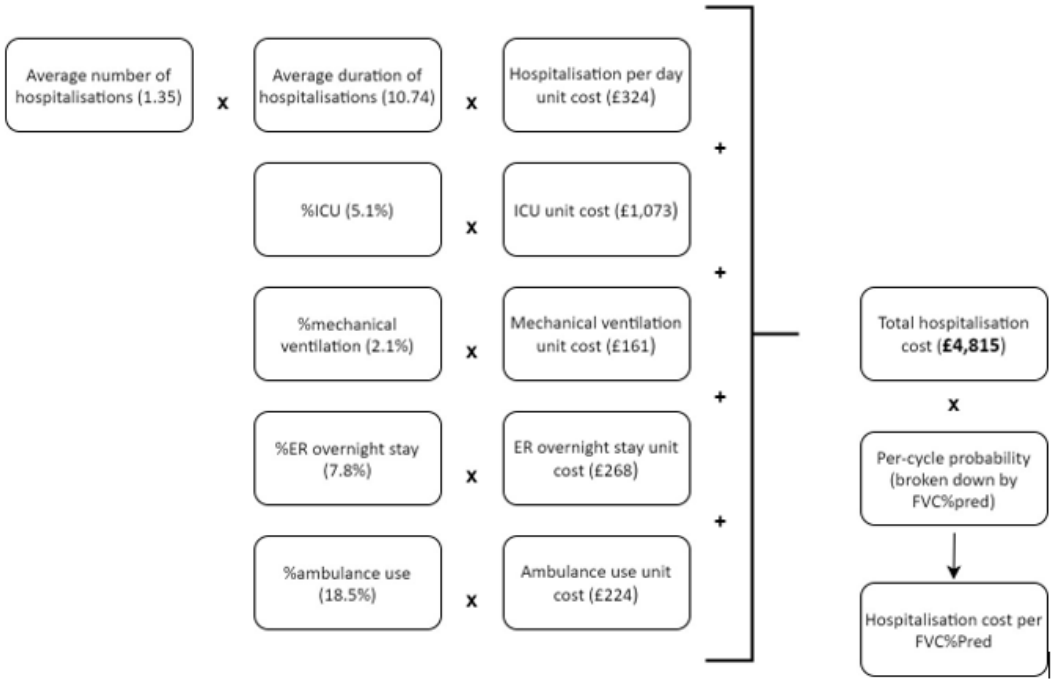
The higher costs applied in the CS, compared with those adopted in TA379, are due to a combination of higher resource use values and higher unit costs. In particular, the cost per hospitalisation episode applied in TA379 was £3,044, as opposed to £4,815 in the current CS. Figure 53 from the CS during TA379 has been replicated below, along with the equivalent Figure from the current submission. As can be seen, both the unit costs and resource use values are consistently higher in the current submission. The unit costs are taken from a more up-to-date version of NHS Reference Costs, thereby indicating that these costs have increased since TA379. In terms of resource use values, these were taken from the INPULSIS and INBUILD studies for TA379 and the current submission respectively. Therefore, the distinctions across the two submissions can be explained by differences in the resources recorded in the two studies.

Figure 53: Cost synthesis: hospitalisation



Source: CS from TA379

Figure 31: Cost synthesis: hospitalisation



Abbreviations: ER, emergency room; FVC%pred, forced vital capacity; ICU, intensive care unit

Source: CS from ID1599

Additionally, in terms of the conversion to annual hospitalisation costs, the 3-month probability of hospitalisation was generally higher in the current submission, as opposed to TA379. Table 14 has been included below to show the probabilities that were applied in the two submissions to illustrate this difference. Again, these values were based on data from the INPULSIS and INBUILD studies for TA379 and the current submission respectively.

Table 14: A comparison of the 3-month hospitalization probabilities from the current submission [ID1599] and the previous nintedanib submission for IPF [TA379].

FVC% pred group	3-month probability of hospitalization	
	Current submission [ID1599]	CS from TA379
>=110	0.12	0.05
100-109.9	0.05	0.04
90-99.9	0.05	0.05
80-89.9	0.05	0.04
70-79.9	0.05	0.05
60-69.9	0.09	0.04
50-59.9	0.09	0.07
40-49.9	0.14	0.16

Adverse events

B31. PRIORITY QUESTION: Please explain the choice for only including AEs with an incidence of > 10% instead of the more usual > 5 % (e.g. in TA379 AEs were included with an incidence of > 5% or 1.5 times greater than in the comparator arm), and provide the options in the model to include AEs with an incidence of > 5%, and AEs with an incidence of > 5% or 1.5 times greater than in the comparator arm.

As noted in response to question B25, only AEs that were severe or serious and with an incidence of > 5% and 1.5 times greater than in the comparator arm were included in the TA379 model. In the current model for PF-ILD an incidence of > 10% was applied for the cut off because adverse events of all severities were included not just serious or severe adverse events. An option to include adverse events with an incidence of > 5% has not been added to the model because no severe or serious adverse events occurred in greater than 5% of patients receiving nintedanib.

Therefore, the overall impact on costs of extending the criteria from a 10% to 5% incidence is expected to be negligible.

Section C: Textual clarification and additional points

Model functionality

C1. PRIORITY QUESTION: Please ensure that the following sets of inputs are included in the PSA:

- **Patient characteristics such as age**
- **The baseline distribution of patients between FVC%Pred health states**
- **AE incidences/risks**

Patient age, the baseline distribution of patients between FVC % predicted health states and AE incidences/risks have been added to the PSA in the model.

C2. PRIORITY QUESTION: Please explain the functionality of the option labelled "Allow progression from FVC%40-49.9Pred to FVC%30-39.9 Pred(Death)" on the "Efficacy" sheet in the model.

This option was left in the model in error as it is not fully functional. Therefore, it has been removed from the latest version of the model.

C3. PRIORITY QUESTION: The model appears to include various options for the implementation of stopping rules in relation to treatment discontinuation, and separate sheets labelled 'MarkovMatrices_CostDiscount' and 'CostDiscount' that seem related to this.

a. **Please explain all the options, their underlying rationale, available evidence and model functionality in relation to stopping rules and the abovementioned sheets.**

The economic model submitted to NICE was not designed solely for the purposes of the appraisal but had multiple purposes. Therefore, this functionality was included to inform internal decision making and was not intended for use in the NICE appraisal.

It was included in error for the version of the model originally submitted to NICE and, therefore, the functionality has been removed in the latest version.

b. Please explain how the various options for stopping rules were implemented in the model and their implications for the interpretation of the cost-effectiveness results.

See response to question C3a.

C4. Please explain the functionality of the button labelled "Change unit costs" on the "Costs" sheet in the model.

This button is simply included to allow navigation to a different sheet in the model. If clicked, this button takes the user to the 'HRCU_Unit_Costs' sheet, which contains all of the unit costs that inform the background costs in the model (e.g. hospitalisations). Therefore, if the user wishes to amend the unit costs they can update the values presented on the 'HRCU_Unit_Costs' sheet. The "Change unit costs" button has no other purpose/function in the model.

Company Submission

C5. **The y-axis of Figure 23 on p. 91 of the CS is labelled "Probability of survival" and has its origin at 65%.**

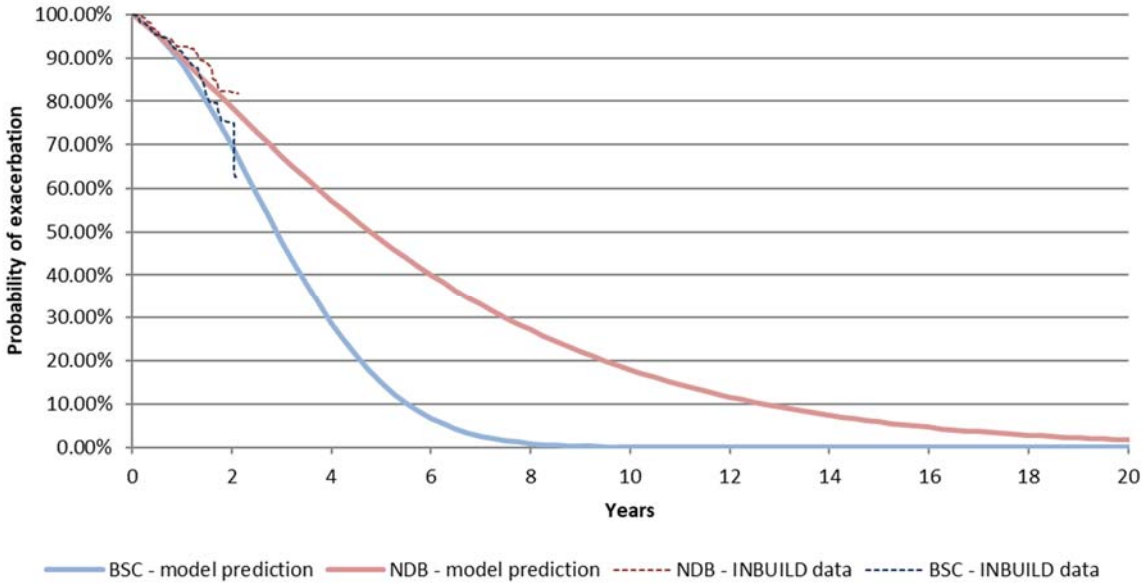
a. Please confirm that the correct label of the y-axis is "Probability of exacerbation" or explain if otherwise.

Yes, the correct label should be "Probability of exacerbation" as stated. This has been corrected in the version shown below.

b. Please replace Figure 23 in the CS with one that has a y-axis from 0 to 100%, and an extended x-axis to show the extrapolated curves beyond the trial duration and reaching a probability that is close to 0%.

An amended version of Figure 23 from the company submission is presented below.

Figure 17: Amended version of Figure 23 from the company submission



C6. A reference is provided for the current prescription records of nintedanib, Ref# 91 in the CS (e.g. see p. 105 of the CS), but it cannot be opened due to the file being damaged or of an unsupported file type. Please provide a copy of the document that pertains to this reference that is undamaged or of the correct file type, so that it can be opened.

Ref#91 is attached below (DoF NIN20-09. 2020). Please note that this reference is likely copied in error from the NCPE submission, but has no implications on the UK model as price for both pack dosages (150mg and 100mg) are the same.

DOF NIN20-09.xlsx

Ireland IPF Pack split.xlsx

C7. Only the abstract was provided for Ref#40 in the CS. Please provide the full poster

The poster is attached below.

Ref 40_Flaherty 2020 poster.pdf

C8. Please provide all documentation for all expert opinion and validation exercises conducted. This should include any documentation shown to or distributed to experts, details of questions asked and all feedback received.

See below for the slides presented during the advisory board, as well as a summary of the meeting discussion.

Summaries of the expert validation exercise conducted to inform our response to the clarification letter are included in the response to question A4 on page 7.


Q-C8 PF-ILD NICE AD board November 202


Q-C8 Slides for UK ad board_23.10.20.pp


Q-C8 - Ad-board concept approval forn


Q-C8 HCPs inclusion rationale.xlsx

References

1. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. International journal of technology assessment in health care. 2012;28(2):138-44.
2. George PM, Spagnolo P, Kreuter M, Altinisik G, Bonifazi M, Martinez FJ, et al. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities. Lancet Respir Med. 2020;8(9):925-34.
3. Boehringer Ingelheim. Clinical Trial Report for the INBUILD trial (study 1199.247). 2019.
4. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. London: National Institute for Health and Care Excellence.; 2013.
5. Flaherty KR, Wells AU, Cottin V, Devaraj A, Inoue Y, Richeldi L, et al. Effects of nintedanib on progression of ILD in patients with fibrosing ILDs and a progressive phenotype: further analyses of the INBUILD® trial. Poster developed for the European Respiratory Society International Congress, 7–9 September 2020.
6. Richeldi L, et al. Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. Thorax. 2018;73(6):581.
7. Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. BMJ Open Respiratory Research. 2019;6(1):e000397.
8. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718-27.
9. Hughes G, Toellner H, Morris H, Leonard C, Chaudhuri N. Real World Experiences: Pirfenidone and Nintedanib are Effective and Well Tolerated Treatments for Idiopathic Pulmonary Fibrosis. Journal of clinical medicine. 2016;5(9).
10. Barratt SL, Mulholland S, Al Jbour K, Steer H, Gutsche M, Foley N, et al. South-West of England's Experience of the Safety and Tolerability Pirfenidone and Nintedanib for the Treatment of Idiopathic Pulmonary Fibrosis (IPF). Frontiers in pharmacology. 2018;9:1480.
11. Noor S, Nawaz S, Chaudhuri N. Real-World Study Analysing Progression and Survival of Patients with Idiopathic Pulmonary Fibrosis with Preserved Lung Function on Antifibrotic Treatment. Adv Ther. 2020.
12. Kreuter M, Koegler H, Trampisch M, Geier S, Richeldi L. Differing severities of acute exacerbations of idiopathic pulmonary fibrosis (IPF): insights from the INPULSIS® trials. Respiratory Research. 2019;20(1):71.
13. BNF price from bnf.nice.org.uk.
14. Kolb M, Bondue B, Pesci A, Miyazaki Y, Song JW, Bhatt NY, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. European Respiratory Review. 2018;27(150):180071.

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Additional ERG requests, 25th February 2021

Please see below for the additional information requested.

- **A table which shows the step-by-step changes required to go from the original base-case to the updated base-case (including details of which cells need to be amended)**

ERG question number	Description of change
B5	**Addition of the following overall survival curves within the model:** Frequentist: exponential, log-normal, gengamma Bayesian: exponential, log-normal, gengamma, Gompertz **Model changes:** Additional options included within drop down menu of the "Efficacy" sheet. Additional coefficients added to the yellow highlighted rows 25:32 of the "SurvivalPooled" sheet. Additional survival curves incorporated into calculations within the "MarkovTraces" sheet.
B8	Functionality has been added to the "Efficacy" sheet, in which the tickbox labelled as “Include recurrent exacerbation risk” can be used to select the option. When ticked, this includes recurrent exacerbations in the model. This is based on 3-month probabilities of a recurrent exacerbation, which are shown to the right of the tickbox.
B10	The model now includes a drop down menu on row 48 of "Efficacy" sheet to enable a choice between an odds ratio or direct regression inputs when modelling the loss of lung function associated with nintedanib. Additional regression outputs were added to the "Progression sheet", with the values in column K feeding through to the calculations in column E of the "MarkovMatrices sheet".
B19	It is already possible to input utilities in the model such that they decline as FVC%pred also declines. This can be achieved by inputting alternative values into cells D8:D14 on the ‘Utilities’ sheet of the model.
B23	Utilities have been converted to disutilities on the "gen. pop utilities" sheet. A tick box has been added to the utility sheet to enable the utility of the population to be adjusted by age.
B24	The unit cost of ventilation from an outpatient procedure to long elective non-stay cost has been updated in cell C33 of the "HCRU_Unit_Costs" sheet.
B27	The unit costs of specialist, nurse, physiotherapist and occupational visits were updated using NHS reference costs 2018/19 - these were previously obtained from the PSSRU. The

ERG question number	Description of change
	updates were made in column C of the "HCRU_Unit_Costs" sheet.
B28	The unit cost of an exacerbation was updated to £4,424. This was updated in cell H98 of the control sheet.
C1	The patient age, the baseline distribution of patients between FVC% pred health states has been added to the PSA using columns O-U (rows 7-15) of the results sheet. AE incidences/risks have been added to the PSA using row 26 of the "Adverse Events" sheet.

- **An explanation of how the age adjustment of utilities has been applied in the model and how the ERG can select to include this in the base-case**

In our response, age adjustment of utilities was applied as a scenario analysis rather than to the base-case. However, we have now included the option of using age-adjusted utilities in the base-case (updated version of the model uploaded separately to NICE Docs). Addition of the age-adjusted utilities option is the only change compared with the last version of the model provided.

While we were adding the functionality to include age adjustment of utilities to the base-case, we noticed a small error in the calculations that had been used previously, which has now been corrected. This has meant that the ICER when age-adjusted utilities are included is now [redacted].

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Additional ERG requests, 2nd March 2021

Please could the company send their intended post-clarification base-case results and a clear summary of how this differs from their original base-case in the CS.

The post-clarification base-case results are presented in Table 1. The following changes have been made compared with the base-case presented in the Company Submission, based on requests from the ERG in their Clarification Letter:

- Included recurrent exacerbation risk (tickbox in the "Efficacy" sheet checked)
- Included age-adjusted utilities (tickbox in the "Utilities" sheet checked)
- Updated the unit cost of ventilation from an outpatient procedure to long elective non-stay cost (cell C33 on the "HCRU_Unit_Costs" sheet)
- Unit costs of specialist, nurse, physiotherapist and occupational visits updated to use NHS reference costs 2018/19 rather than costs obtained from PSSRU (cells C39, C40, C41 and C42 on the "HCRU_Unit_Costs" sheet)
- Unit cost of an exacerbation updated to £4,424 (cell H98 of the "Control" sheet)

Table 1: Post-clarification base-case results

	NDB	BSC	Incremental
Costs			
Treatment costs	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]
Liver panel tests	[redacted]	[redacted]	[redacted]
Patient monitoring and O2 use	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	[redacted]	[redacted]
Exacerbation events	[redacted]	[redacted]	[redacted]
Net monetary benefit	[redacted]	[redacted]	[redacted]
Cost-effectiveness	[redacted]	[redacted]	[redacted]
ICER (per QALY)			**<£20,000** [redacted]
ICER (per LY)			**<£20,000** [redacted]

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Action for Pulmonary Fibrosis (APF)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	APF is a patient-led charity involving a growing community of patients, families, researchers and healthcare professionals striving to find a cure for pulmonary fibrosis so that everyone affected by the disease has a better future. APF supports patients and families and raises awareness of pulmonary fibrosis through campaigning, fundraising and educates GPs and other HCPs about the disease. We advocate for improved treatment and care for those living with pulmonary fibrosis and also shape and fund research to improve quality of life for people living with pulmonary fibrosis and to find a cure. Most of APF's funds are donated by patients and their families, through fundraising events and donations. We also receive limited funding from pharmaceutical companies, for specific projects, and charitable foundations. We do not have members, but we inform, empower and support thousands of patients and their families living with pulmonary fibrosis across the UK to improve quality of life and life expectancy. We do this in the main through a network of patient and carer-led support groups, peer-led telephone support and expert information, co-produced by patients and healthcare professionals, which is available on and off-line.
4b. Has the organisation received any funding from the manufacturer(s) of the	In the last 12 months. APF has received the following grants from Boehringer-Ingelheim: • £52,000 towards support group costs • £4,500 to support production of 5 on-line videos on Covid-19 for pulmonary fibrosis patients

technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	• £1,500 in honoraria for participation of our Chair (Steve Jones) in BI Patient Organisation Advisory group meetings and arranging filming session with patients. We have not received grants from any other organisations on the list.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	APF is in constant touch with patients and carers living with all forms of pulmonary fibrosis, including many living with non-IPF progressive fibrosing interstitial disease (PF/ILD). Most of the support groups in our network (including our carers' and transplant groups) include people with non-IPF PF/ILDs, including chronic hypersensitivity pneumonitis (CHP), auto-immune related connective tissue disease (e.g. Rheumatoid Arthritis-ILD), occupational ILD (e.g., asbestosis) and sometimes other less common disease sub-types. For the specific purposes of this submission, we had discussions with small panels of CHP and RA-ILD patients and also talked to patients with asbestosis and fibrotic sarcoidosis.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Progressive fibrotic ILD is a devastating disease. When you are diagnosed with the condition, you are given a death sentence. You are told that your disease is incurable, is only going to get worse and that you have, on average, only 3-4 years to live. To start with it feels like you have been sent to and open prison – you can do almost everything you used to do. But, within a short time, you start to become more and more breathless. At first, you find it difficult to walk up slopes or to the climb the stairs at home, without becoming severely breathless. In time, even walking on the flat becomes a challenge and you have to stop frequently to catch your breath. The cough, which some two-thirds of patients suffer from often becomes debilitating and some patients are so embarrassed by it that they are reluctant to see friends or family. Eventually the prison walls close in even more and you find yourself stuck at home and dependent on supplementary oxygen to move about and – eventually - to stay alive. You are seriously disabled and need help from your carer with even basic tasks like taking a shower or getting dressed. In time, you will sadly die from respiratory failure or a related illness, like pneumonia. As the disease progresses, you lose your independence and become increasingly dependent on your loved ones. As you become anxious and worried about the future, and possibly depressed, so do they. Your whole family suffers with you. As your symptoms become worse, it is all you can do just concentrate on managing in the face of the disease – on getting through the day. The strain is taken by your carer, if you have one, who has to both stay strong for you and manage the home and links with family and the health care system. Many PF/ILD patients and carers feel isolated and alone. Although there are 45-50,000 people in the UK living with the disease (32,500 with IPF and APF estimates about 15,000 with the other types of PF/ILD, which are the focus of this NICE appraisal), this equates to only 5-6 people per GP surgery. Also, public awareness of the disease is low. This lack of awareness makes it very difficult for patients and carers to talk to friends and relatives or get support from them and increases their sense of isolation.

	Although the prognosis for people with PF/ILD is worse than that of most cancer patients (only pancreatic and lung cancer, among the major cancers, will kill you quicker), people living with PF/ILD do not receive the same level of support as cancer patients. There is no accelerated, timebound pathway to diagnosis, only limited nursing and mental health support and no agreed care pathway. The 2018 *APF Patient Survey - Giving patients a voice* shows that implementation of the NICE quality standard for IPF (QS 79) is patchy at best. It is likely to be even worse for other PF/ILD patients, who seem to be treated more often in general hospitals than specialist ILD centres. ***CHP patient [redacted] from Sussex:*** *I first saw a hospital doctor about three and a half years ago. I was eventually diagnosed with chronic hypersensitivity pneumonitis (CHP), though they don't know why I developed the condition. The first year or so I felt a bit breathless but otherwise OK. Since then, I have gone downhill. Look at me now – I can sit on my chair OK but if I want to move around the house, I need to use oxygen. I have had to go into hospital twice with exacerbations and each time I came out I felt more breathless than when I went in. My husband is amazing but I worry about the stress I am putting on him and the children. I also worry about what the future holds.*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients living with PF/ILD (other than IPF) are generally treated with corticosteroids and/or immune suppressants. Both these types of medications can have serious side effects and many patients have to swap treatments many times. A number of patients find they cannot tolerate the medications and have to give up pharmaceutical treatment. Most patients are aware of these challenges and of the risk of side-effects (such as bone fractures and liver damage) but continue with the therapy, because they are advised to do so by their doctors. Despite this, many patients tell us they are not convinced they work.

	[redacted] ***an RA-ILD patient from the East Midlands*** *No, to be frank, I am not convinced that the medications I take work. I am also anxious about side effects like osteo-porosis, diabetes. I am also worried, with Covid-19, that my immune system is weak and I am more open to infection. But what else can I do?* A few of the best-informed patients are also concerned about the scientific evidence. They point out that there have not been any clinical trials (RCTs) to prove the safety and efficacy of the current treatment regime. They are also worried that the PANTHER trial in 2011 was stopped early because the triple therapy then used for IPF (steroid, immune suppressant and anti-oxidant) was found to exacerbate the lung disease.
8. Is there an unmet need for patients with this condition?	Yes. PF/ILD patients are desperate for new medications which directly tackle their lung fibrosis and will slow progression of the disease. Anti-fibrotic treatments like nintedanib have been a 'game changer' for people living with IPF, slowing disease progression and increasing life expectancy. People living with PF/ILD look at IPF patients they meet in support groups and on-line and envy their access to anti-fibrotics, They feel that it is cruel that other PF/ILD patients are denied these medications and feel they deserve this opportunity. They look enviously at the IPF people and ask: why them and not me? [redacted]***, an RA-ILD patient, from Devon*** *When I look around my support group, I see friends with IPF who have been diagnosed much longer than me and seem to be doing much better. They have all been on nintedanib or pirfenidone for a few years. I just wish anti-fibrotic medicines were available for RA-ILD patients like me.*

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients consider the main advantage of the new technology is that it directly targets the problem of lung fibrosis and has been shown in the INBUILD trial to slow progression of the disease, which is a high priority for them. They note that the benefits of nintedanib for PF/ILD patients are similar to those shown in the clinical trial for nintedanib and IPF. They hope, if the technology is approved, it will also be shown to increase life expectancy, as has been found recently for nintedanib for IPF patients. ***[redacted] a CHP patient from London*** *I was really excited when I heard that scientists had shown that nintedanib works for people like me living with CHP. I am crossing fingers and toes that it gets approved soon.*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	PF/ILD patients know that IPF patients taking nintedanib can experience side-effects, especially diarrhoea. But they also know from conversations in support groups, that the drop-out rate is not that high and most IPF patients stay on the drug once prescribed. The vast majority of the PF/ILD patients we have talked to in support groups and at other forums think that the potential benefits of nintedanib outweigh the possibility of side-effects and are keen to be prescribed the drug. ***RA-ILD patient [redacted] from Manchester*** *I know from our PF patient support group that most IPF patients benefit greatly from taking nintedanib. Sure, if I am given the drug, I may be unlucky, get side-effects and have to give up. But other RA-ILD patients will not and will benefit. From what I can see, nintedanib would be a real game-changer for our community.*

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The benefits of antifibrotic medicines to IPF patients are currently limited in two ways, which we suggest should be avoided with the new technology: • the NICE '50/80 rule' means that about 50% of IPF patients (those with FVC>80% and FVC<50% of expected) are denied access to antifibrotic medication, despite evidence that it works for all IPF patients, irrespective of FVC. In our view, this is unjust. We would strongly urge NICE not to introduce such restrictions if it approves this technology. • Currently, in England, antifibrotic drugs for IPF can only be prescribed at one of the 23 ILD Specialist Centres. Although some GPs refer patients directly, most get referred from districts general hospitals (DGH). APF has learnt from patients that DGH clinicians do not always refer elderly patients to specialist centres for antifibrotic drugs, because they are worried about them have to make many trips and because of side effects. In order to ensure that older people tcan access the new technology, models of shared care need to be strengthened so as to minimise the distance patients must travel to receive treatment and the frequency of visits. This could be done, for example, by carrying out all tests at DGHs, use of virtual MDTs and by involving GPs in blood monitoring. In addition, special attention should be paid to the problems faced by people who lack access to the internet, or are isolated for any reason (remoteness, mobility problems, needing to care for others). Special efforts, using printed materials, are needed to ensure they are aware of the medication and they need to be prescribed and monitored as close as possible to where they live.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are no potential equality issues except those mentioned in #11. PF/ILD occurs in men and women, from all socio-economic and ethnic groups, and all regions. While different sub-types of the disease (e.g., CHP, RA-ILD) may be more common among certain groups or in certain areas, PF/ILD is not strongly linked to poverty or disadvantage.
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- PF/ILD is a devastating condition with an average life expectancy of 3-5 years, which is worse than most cancers.
- Current treatments not been shown to work in RCTs but they do have significant adverse side effects
- PF/ILD patients urgently want access to nintedanib because it directly targets their lung fibrosis and has been shown to slow progression, which a high priority for them.

- Patients feel strongly that they are being denied life extending drugs because of the cause of their disease and this is not fair. The symptoms they experience are the same as people with IPF.
- All suitable patients should be given access to the new technology and restrictions such as the '80/50 rule' (in the case of nintedanib for IPF patients) should be avoided.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Scleroderma & Raynaud's UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	SRUK's mission is to improve the lives of everyone affected by Scleroderma and Raynaud's. We do this by investing in research, improving awareness and understanding of the conditions and providing information and support to all those affected. We are the only UK based charity which serves this population. We have 9,900 members and supporters who are signed up to receive charity communications.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	SRUK received £7,323 from Boehringer Ingelheim in the past 12 months. This funding was used to produce information resources to support the community during COVID pandemic.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	At SRUK, we have close ties and a longstanding dialogue with our patient community. To gather information on the specific experiences of living with a fibrosing lung condition SRUK conducted a survey which was promoted via our website and social media channels. The survey was directed towards members of our community living with scleroderma and a fibrosing interstitial lung condition with idiopathic pulmonary fibrosis being given as an exclusion criteria. The survey combined a combination of check box questions, and longer form free text questions. We also engaged with our community through our local support groups.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Scleroderma is a progressive, fibrosing and life limiting condition. The effects of this condition on patients are far reaching and can affect vital organs such as the heart, lungs and kidneys. Scleroderma can be grouped into subtypes, it has been estimated that more than half of patients with diffuse systemic sclerosis subtype will die or develop significant heart, lung, or kidney problems within 3 years of diagnosis (Shand et al.). This contributes to the fact that scleroderma patients are four times more likely to die than average for their age and sex (Nihtyanova et al.) The burden of lung complications relating to scleroderma, such as ILD, is evidenced in our survey. Those living with the scleroderma and progressive fibrosing interstitial lung disease frequently reported breathlessness and fatigue as two of the major symptoms. Other symptoms included low level aches, tight chests, a chronic cough, and systemic sclerosis. Responses focused on the lung aspects of each patients' condition, rather than on the symptoms resulting from scleroderma.

	These symptoms hugely reduce quality of life, largely through the limitations placed upon those with the condition, and their family. Patients expressed frustration and guilt at: • Not being able to work • Not being able to do housework • Constraining their family activities, hobbies, or simply not being able to play with their kids • Not being able to walk for long distances • The mental health toll on both themselves and their families. The experience is similar for those supporting patients of PF-ILD. There is concern over their mental wellbeing, and recognition that most practical tasks became the responsibility of their family / carer. “They find it hard to watch my limitations.” “My limitations dominate their life.” “My wife does 98% of the household work then looks after me too…” “Everyone has to slow down for me.” “They probably feel sad as I am no longer the person I used to be.” References: Shand L, Lunt M, Nihtyanova S, Hoseini M, Silman A, Black CM, Denton CP. Relationship between change in skin score and disease outcome in diffuse cutaneous systemic sclerosis: application of a latent linear trajectory model. Arthritis Rheum. 2007 Jul;56(7):2422-31. PubMed PMID: 17599771. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, Wells AU, Denton CP. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol. 2014 Jun;66(6):1625-35. doi: 10.1002/art.38390. PubMed PMID: 24591477.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Half of those who responded did not feel the drugs they were currently taking benefited the lung aspects of their condition. Individuals frequently reported that the medication they did receive did not appear to be slowing the progression of their disease. In the comments box participants volunteered information such as “My scarring has progressed in my last CT scan.” “I feel that the drugs help everything else related to my scleroderma but not the lungs.” “I still struggle with each breath.” Of the half who did feel that they were benefitting from their current treatments, most participants stated the stabilisation of their condition as the primary reason. With two participants saying that their current medication had reduced the severity of their symptoms although we do not know what treatments these individuals were taking.
8. Is there an unmet need for patients with this condition?	As mentioned above, around half of those surveyed feel that the lung aspects of their condition are not being adequately manged through existing treatments. This indicates that there is an ‘unmet need’ for more effective treatments to slow progression and improve outcomes and quality of life for these patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	97% of those surveyed felt that an anti-fibrotic treatment could benefit them compared to their current treatment(s). Patients felt that a drug which could reduce scarring would be hugely beneficial. Alternative treatments mask symptoms, whereas the potential for an anti-fibrotic to slow progression is the main advantage. In addition, one participant mentioned that the drug delivery method would be an improvement for them: “I take 5 tablets daily which are very large and difficult to swallow” indicating that a treatment

	with fewer, easier to take tablets would be an improvement on current treatments.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	9% of those we surveyed were concerned about the potential for side effects, with a further 41% stating that their enthusiasm for a new treatment would be dependent on the likely severity of side effects, how rare those side effects would be, and the ability to monitor side effects (including liver and kidney function). The tone of each response indicated cautious enthusiasm, so whilst side effects are an evident disadvantage of any drug, as one participant pointed out “all drugs have side effects” suggesting that this would not dissuade people from trying a new treatment if they were supplied with additional information.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Some scleroderma patients do experience difficulties swallowing – this may mean that these may be less likely to benefit from an oral capsule.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Living with PF-ILD and scleroderma negatively impacts the quality of life of the patients, and their family / carers
- Almost 50% of this group are not satisfied with their current treatment options
- A new treatment option would be very positively received
- Side effects are the main concern, but this could be easily alleviated with more information / education
- We look forward to hearing the outcome

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Society**

3. Job title or position	[redacted], **BTS** [redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The British Thoracic Society is the professional society for respiratory health care professionals, funded via membership subscription.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	**No**

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow the rate of deterioration of lung function in patients with progressive fibrotic pulmonary fibrosis. This will likely correlate with reduced disability, use of home oxygen, hospitalisation and death.
7. What do you consider a clinically significant treatment response? (For example, x of decline in forced vital capacity at x week or a reduction in disease activity by a certain amount.)	It is conventionally accepted that a 10% decline in Forced vital capacity (FVC) or a 15% decline in gas transfer (TLco) is a 'clinically'-significant decline. However smaller changes in FVC – a 5% loss has been associated with increased mortality in other forms of PF- ILD where data already exists - e.g. Idiopathic Pulmonary Fibrosis. Any slowing of the loss of FVC is likely to be beneficial to a patient and may reduce mortality. Slowing FVC decline in PF-ILD may also help reduce hospitalisations for ILD, maintain better exercise tolerance and independence and maintain better quality of life. Some of these key endpoints can be difficult to demonstrate however in relatively short clinical trials (1 year or less) particularly in progressive diseases where appropriate tools to capture these measurements may not be readily available.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes very much so. There are no evidenced based therapies currently available in the NHS for patients with PF _ILD.

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Unlicensed/unproven therapies (immunosuppressive drugs) are used without a good evidence base and are often ineffective at treating the fibrotic component of the disease. . Some of the diseases falling into the PF- ILD categories are treated with immunosuppression, at least initially, but this is for any inflammatory component of their disease and does little for any fibrotic components. Some forms of PF-ILD e.g. asbestosis currently are not offered any drug modifying therapy – best supportive care is all that is given due to a lack of effective treatments. Different types of disease in the PF-ILD category have varying amounts of inflammation vs fibrosis initially. Most end up with significant fibrotic components however. In some disease anti-inflammatory treatments (immunosuppression) may hold the disease for a time but often control is then lost as fibrosis ensues. Drugs to combat the fibrotic components of the PF-ILDs are needed and currently lacking. Often immunosuppressive drugs are tried in PF-ILDs where from the start the main process is likely fibrotic e.g. chronic hypersensitivity pneumonitis. As there are no other treatments to offer patients they are often continued for long periods despite lack of efficacy in many cases. This is reminiscent of how we used to treat IPF in the past before anti fibrotic drugs became available. The immunosuppressive drugs used however are not without side effects. Drugs frequently used in these patients include oral corticosteroids, mycophenolate, azathioprine and methotrexate. Side effects of these drugs include obesity, diabetes mellitus, osteoporosis and increased risk of infections that can lead to hospitalisations, reduced quality of life and death. All patients should also be offered best supportive care which includes access to pulmonary rehabilitation, oxygen assessments, symptom management and psychological support.
• Are any clinical guidelines used in the treatment of the	Guidelines are available for ILD management in general the most detailed focus on IPF which is a form of PF-ILD in itself but not included in this assessment as anti-fibrotic drugs are already authorised for that condition. No guideline exists to guide treatment of the fibrotic component of PF-ILDs because until now (outside of IPF) no treatments had been shown in well-designed trials to be effective. ILD guidelines suggest immunosuppressive treatments for some of the PF-ILDs but that is to treat any inflammatory

condition, and if so, which?	component of the disease and has not been shown to be effective against the fibrotic component once that develops or in some of the diseases is present from the start. Immunosuppressive treatments do have a role in some of the diseases that become PF-ILDs but often in the earlier stages or where inflammation is more visible.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No there is not a well-defined pathway. Most ILD regional centre specialists (in the centres that prescribe antifibrotics for IPF) would act fairly similarly in treating diseases that become PF-ILDs but there will be variations. There include which drugs to treat with in some PF-ILDs, when to start the drugs or stop them. The amount of immunosuppression that is used also varies one drug versus two for example. . In many general hospitals treatment is likely to be steroids alone unless specialist centre advice is sought- at least initially unless the disease is a connective tissue disease related ILD where there are some treatment protocols but these are for the inflammatory part of the disease only not really for the fibrotic component.
• What impact would the technology have on the current pathway of care? (would it displace current treatments? If so, which ones?)	This is a new indication. It may displace immunosuppression in some forms of PF-ILD but not all. If prescribing this drug were to be kept at ILD Specialist centre level then it would have a significant impact on workloads at specialist centres.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Nintedanib use is already very established as a drug to treat IPF prescribed by ILD Specialist centres in England. Its use in PF-ILD if authorised would be very similar except the indication and case definitions would be different. Dosing, blood monitoring would all be expected to be the same.
• How does healthcare resource use differ	If Nintedanib were authorised for use in PF-ILDs and only prescribed by specialist centres referrals to centres would increase significantly perhaps by as much as 40%. As referring hospitals would seek advice

between the technology and current care?	about the management of these patients. It is estimated that prescriptions for anti-fibrotic drugs may rise by as much as 20% depending on the exact criteria set by NICE if drug was authorised for use. This would have a significant impact on specialist centre workloads.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	We advise this should be the preserve of 'specialised ILD services' that already prescribe antifibrotics for IPF. These centres are familiar with the drug, side effects,and compliance management of side effects. They have the expertise to follow any case definition laid out by NICE with appropriate radiological support over diagnoses and some staffing resource to ensure blood monitoring guidance is followed appropriately and patients are supported on the treatment. As the drug is of significant cost- getting it to the right patients is important.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There will be significant increase in demand for ILD specialist outpatient appointments and support services (eg radiology, specialist nurse and other MDT team care). Without appropriate infrastructure investments in ILD services waiting times for patients to be seen at specialist centres are likely to rise. Some services are already stretched as it is and this was before the covid pandemic hit. This is being discussed at national level already.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. This is the first proven therapy to slow decline in FVC in various disease that result in a PF-ILD phenotype. In IPF (itself essentially a form of PF-ILD) multiple studies have demonstrated improved outcomes with anti fibrotic drugs.
• Do you expect the technology to increase length of life more than current care?	Yes. We note there was no statistically-significant effect of mortality in the INBUILD study of nintedanib in progressive ILD but had the trial run for a longer period of time it is thought highly likely a mortality benefit would come through. This has been shown already in IPF. Although immunosuppression treatment in some of the diseases that become PF-ILDs does offer benefit in the earlier stages where inflammation is present – later once fibrosis is the major disease component these treatments offer the patients little benefit. It should be noted that in connective tissue ILDs that become PF-ILDs some patients require immunosuppressive drugs to maintain their joint or other organ health and would not be stopped even if their lungs had only a fibrotic component left to their disease process.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes overall. Whilst nintedanib has some side-effects (as well-recognised in current care with IPF), the side-effects of standard therapies (corticosteroids and immunosuppressants) are also marked. In some diseases that become PF-ILDs immunosuppression would likely be stopped if other better therapies were made available and immunosuppression were not deemed to be working. There will inevitably be patients who will not tolerate nintedanib well – this can occur with any drug- at an individual level some patients may find their quality of life is adversely affected and discontinue the drug. It is difficult with progressive disease and where good quality of life measurement tools may not be readily available to sometimes capture quality of life accurately. We would expect a treatment that slows down loss of lung to ultimately improve that patients quality of life however if tolerance to the drug was satisfactory.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population with the condition?	No – not that we are aware of. In IPF where nintedanib has been extensively used, ethnicity, age nor gender appear to have any impact on its effectiveness. The case definition will be important as to who might receive the drug In the ILD community it is generally accepted that the INBUILD study entry criteria were sound and chosen by experienced clinicians in the field who set the criteria well to include those patients with a relevant amount of fibrosis.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Nintedanib is already used via specialised ILD centres. Its wider use is thus not directly of concern except the impact this may have on specialist centre workloads.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	As mentioned above referral rates to specialist centres will increase. Prescribing will increase. Without investment into ILD services wait times to see new cases will increase for all ILDs. Pressures in the system will rise.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The entry criteria in the INBUILD study outline starting criteria that are sensible. Clearly NICE may take its own view re these and amend. In IPF patients NICE introduced a stopping rule for use of anti-fibrotics. This rule is generally not favoured by respiratory physicians and as NICE will know has been challenged in the past. Nationally few patients come off anti fibrotics due to the 'stopping rule' alone. Often with inevitable disease progression and worsening symptoms and quality of life patients come off anti fibrotic drugs in later disease stages probably most often due to significant weight loss and loss of wellbeing. This state of disease progression makes even a small intolerance of many drugs intolerable and patients accept stopping their drugs at this stage. We would prefer and believe patients would also prefer a clinically and quality of life related stopping rule. We feel this would be best for patients. A patient – doctor based discussion on what was best for the patient and what the patient wanted taking into account their quality of life, aims and aspirations. Sometimes a short trial off any drug is needed for the patient to realise how much that drug may have been affecting them.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This is a new indication and this should be factored in. It should also be considered that any effect on mortality may be manifest after a period longer than the period of the INBUILD study (12 months). The natural history of the disease defined in the INBUILD study suggests that it may be appropriate to treat this condition and it's outcome as similar to that of IPF.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Antifibrotic drugs have had a transformative effect on the treatment of IPF and it is hoped this will have a similar effect on progressive fibrotic ILD.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	See above- yes no proven therapies in this field until now.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	We already have experience of the use of nintedanib in IPF and we anticipate this will be similar in this cohort. The only proviso is that some patients who have progressive fibrosis related to rheumatological disease may be on disease-modifying anti-rheumatic drugs (DMARDs) this may impact on side effects due to possible drug- drug interactions and an impact particularly on liver function disturbances. Or possibly gastro intestinal side effects (nausea etc). Blood monitoring is advised however and this should allow us to detect any liver issues and intervene where necessary. Careful management of other side effects should be feasible. With yellow card reporting where needed. . .
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the INBUILD population reflects a well-recognised cohort of patients seen in an ILD service.
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	FVC decline and mortality- yes measured. Mortality however would be expected to take longer to show though – this was the case with IPF.
• If surrogate outcome measures were used, do they adequately predict	FVC is well-accepted in IPF trials and seems to correlate with outcome. We feel this is a good marker.

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No not that we are aware of.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	There is likely to be more discontinuation of nintedanib in real world use than that seen in the trial. Many factors influence patients managing to stay on drugs. One can be the amount of support they receive from clinical teams in dealing with side effects and concerns over their medication. We know that good support from ILD specialist nurses can improve compliance on anti fibrotic drugs in IPF patients. Due to staffing levels some ILD specialist centres cannot always provide the amount of support needed. If referrals increase staffing will be further stretched. This is likely to have an impact on the number of patients staying on drug. There is also the issue of patients on DMARDS to consider. This may lead to higher levels of drug intolerance.
Equality	

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Antifibrotics are likely only to be able to be prescribed by specialised centres due to experience in phenotyping ILD and in the existing use of antifibrotics for IPF. Not all patients will have equal access to specialist services e.g. due to geography, transport issues and local referral rates from clinicians.
21b. Consider whether these issues are different from issues with current care and why.	No these issues are present already for patients with all ILDs
Topic-specific questions	
22. Are methotrexate, infliximab and rituximab used in the NHS to treat PF-ILD?	No strictly not. These immunosuppressive drugs are used to treat any inflammatory component of ILD's. They are not given to treat the fibrotic component of an ILD. They are currently often not stopped however when fibrosis ensues as the main pathology in an ILD. This is because no other treatments were possible in the past. If the patient still has mixed disease i.e. both inflammatory and fibrotic components of disease then anti-inflammatory drugs may still have a role to play. The concept being that if you treat inflammation and stop it, you can reduce fibrosis as the end result of ongoing inflammation. In many ILDs however fibrosis ensues despite treatment with anti-inflammatory drugs.
23. How should best supportive care be defined?	NICE has already defined this well in clinical guideline 163 and quality standard 79 for IPF. BSC for IPF is applied across all ILDs.

Key messages
24. In up to 5 bullet points, please summarise the key messages of your submission. • This is the first proven therapy for this serious condition with high unmet need and poor outcomes currently • The condition represents a proportion of non-IPF ILD • The technology will likely be limited to specialised centres • Healthcare professionals are already experienced in the use of this drug and are familiar with its side effects and their management. • If authorised by NICE workloads for specialist centres will rise significantly and infrastructure needs to be considered seriously if standards of care and safety are to be maintained.

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NHS organisation submission (CCG and NHS England)

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England & Improvement**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? **X**☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Technology appraisals, and the service specification for ILD https://www.england.nhs.uk/publication/interstitial-lung-disease-adults-service-specification/
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for PF-ILD is reasonably well-defined in terms of referral, diagnosis, and monitoring, as per the NICE guidelines above (see 6). However, effective treatments, and an evidence base for existing agents, are currently lacking. Management decisions are therefore usually made at an MDT meeting. This is often but not always in a nationally commissioned ILD centre, bringing together clinicians and radiologists with expertise in ILD, ILD clinical nurse specialists and pharmacists, and, depending on the nature of the condition, rheumatologists, immunologists and/or specialists in pulmonary hypertension. The relentlessly progressive nature of the condition frequently means that once medical treatment fail the options are either referral for lung transplantation (in a very limited number of suitable patients) or palliative care.
8. What impact would the technology have on the current pathway of care?	Between 18 and 32% of patients diagnosed with non-IPF ILDs are thought to develop progressive fibrosis and would therefore be eligible for consideration of nintedanib.[1] Accurate prevalence figures for England/UK are not currently available, but the combined prevalence of ILDs other than IPF with a progressive fibrosing phenotype (PF-ILD) are thought likely to equal or exceed those of idiopathic pulmonary fibrosis (IPF).[2] These additional patients would all need to be discussed at an ILD MDT in a nationally commissioned ILD centre; 1 they would need baseline clinical assessment including bloods, radiology and lung function; 2 the effects and side-effects of nintedanib would need to be explained and written information provided; 3 written consent would need to be obtained for Bluteq registration; 4 patients would need careful follow up with early and regular full blood count, renal and liver profile as well as clinical assessment. These are the same pathways currently adopted for IPF patients, but the additional patients would entail significant additional workload.

	1.Wijsenbeek M et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Curr Med Res Opin 2019: 35: 2015–24 2. Olson AL et al. The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype. Eur Respir Rev 2018; 27: 180077
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Nintedanib is one of two anti-fibrotic drugs currently licensed for treatment of IPF. The other is pirfenidone. They appear to be equally effective in slowing disease progression, but the dosing and common side-effects of each drug vary. Patients referred to one of the nationally commissioned ILD centres will be offered a choice of treatment unless one is preferred based on their individual risk profile. Under current NICE guidelines, patients with IPF are only eligible for antifibrotic mediation if their Forced Vital Capacity (FVC) falls between 50 and 80 % predicted.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We anticipate that nintedanib would be approved for patients with PF-ILD using the same criteria as for IPF (FVC 50-80 % predicted). The upper limit threshold of FVC % predicted may in future be raised to 90% for IPF (and we would assume also for PF-ILD), which would further increase the number of patients eligible for nintedanib.
• How does healthcare resource use differ between the technology and current care?	Current care for PF-ILD patients includes regular clinical monitoring with lung function and radiology. A variety of immunosuppressive medications may be employed including oral and/or intravenous corticosteroids, methotrexate, mycophenolate mofetil, azathioprine, hydroxychloroquine, infliximab and/or rituximab. These patients are therefore already under careful clinical review. However, the additional workload of initiating and monitoring nintedanib, as outlined above, is considerable. Current estimates are that it will represent an increased workload for specialist ILD centres of at least 20%. This is on a background of services which are

	already understaffed. We predict that waiting times for access to antifibrotic medication overall will rise as a result.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Nintedanib can only be prescribed and initiated in one of the nationally commissioned specialist ILD centres in secondary or tertiary care settings. Patients can be monitored locally in their usual secondary care setting, with input from the specialist ILD centre. Blood tests are frequently performed in secondary care but could be performed in primary care provided they are performed at the required intervals and the results are made readily available to the prescriber.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As noted above, we anticipate that nintedanib would be approved for patients with PF-ILD using the same criteria as for IPF patients. The workload will increase in referring centres, as patients with PF-ILD are added to those with IPF to be referred for review at specialist ILD centres. This will entail additional administration and IT support, as clinical details, reports, and imaging need to be transferred to a specialist ILD centre, wherever possible electronically. This will also entail added costs and workload for the specialist ILD centres who are reviewing patients from outside their hospitals, including extra ILD MDT time, administration, IT, and pharmacy costs. Staff training should not be required in specialist ILD centres since the pathways already exist in these centres, but additional consultant, ILD clinical nurse specialist and/or ILD Pharmacist time will be required to review patients and initiate and monitor nintedanib. There will be a requirement for additional resource in respiratory physiology/lung function testing laboratories to measure baseline spirometry including appropriate PPE. This is both to determine eligibility for nintedanib, and to provide a pre-treatment baseline (see below). There will be a need to communicate new guidance for patients with PF-ILD to general practitioners and secondary care respiratory specialists. This can be done through existing channels such as British Thoracic Society communications and local, regional and national educational meetings.

• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Current NICE guidelines are that patients with IPF must stop nintedanib if FVC falls by more 10% in absolute terms in any 12-month period. There is therefore a need to repeat FVC every 12 months to determine stability. Although most patients with PF-ILD will already be undergoing regular lung function testing in secondary care, additional patients with PF-ILD referred to specialist ILD centres for nintedanib are likely to entail an additional burden of testing in the specialist ILD centres.
11. What is the outcome of any evaluations or audits of the use of the technology?	The efficacy of nintedanib in slowing decline in forced vital capacity (FVC) has previously been demonstrated in IPF fibrosis (TOMORROW and INPULSIS trials) and in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS trial).[3-5] A recent double-blind, placebo-controlled phase 3 trial of nintedanib (INBUILD), conducted in 15 countries, treated 332 patients with progressive fibrosing interstitial lung disease (PF-ILD). Annual rate of decline in FVC was significantly lower in patients who received nintedanib than in those who received placebo.[6] The treatment effect was similar in magnitude to that seen in pooled data from the INPULSIS trials in patients with IPF. 3. Richeldi L et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011; 365:1079-87 4. Richeldi L et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2071-83 5. Distler O et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019; 380:2518-28 6. Flaherty KR et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019; 381: 1718-27
Equality	
12a. Are there any potential equality issues that should be	We do not anticipate that those from Black, Asian, and other ethnic minority groups will either have limited access or be disadvantaged if nintedanib is approved for use in patients with PF-ILD. Sarcoidosis, one of the ILDs that may progress to PF-ILD, disproportionately affects Afro-Caribbean and Black populations. Sarcoidosis is also

taken into account when considering this treatment?	often more severe in these groups. Access to nintedanib for PF-ILD would therefore potentially specifically benefit patients in these populations.
12b. Consider whether these issues are different from issues with current care and why.	At present there is no effective treatment for sarcoidosis patients with PF-ILD, so the introduction of nintedanib for this group would potentially benefit Afro-Caribbean and Black patients with severe sarcoidosis.

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4.16

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Nintedanib for progressive fibrosing interstitial lung disease (PF-ILD) excluding idiopathic pulmonary fibrosis (IPF) [ID1599]

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Hannah Penton acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Pim Wetzelaer, Charlotte Ahmadu and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Sean Harrison and Kevin McDermott acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Janine Ross and Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report, and provided general health economic guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

6MWD	Six-minute walking distance
AE	Adverse events
ALAT	Latin American Thoracic Association
ALT	Alanine aminotransferase
aPTT	Activate partial thromboplastin time
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATS	American Thoracic Society
AZA	Azathioprine
Bid	Twice daily
BI	Budget impact
BIC	Bayesian information criterion
BMI	Body mass index
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CrCl	Creatinine clearance
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CTD	Connective tissue disease
CVD	Cardiovascular diseases
DBL	Database lock
DLco	Diffusing capacity of the lung for carbon monoxide
DSU	Decision Support Unit
EMA	European Medicines Agency
EOT	End of trial
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ERS	European Respiratory Society
EUR	Erasmus University Rotterdam
FAD	Final appraisal document
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
FVC %pred	Forced vital capacity percentage predicted
GI	Gastrointestinal
HP	Hypersensitivity pneumonitis
HR	Hazard ratio
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IC	Indirect comparison
ICER	Incremental cost effectiveness ratio
ICH-GCP	International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease

INR	International normalised ratio
iNSIP	Idiopathic nonspecific interstitial pneumonia
IPF	Idiopathic pulmonary fibrosis
ITC	Indirect treatment comparison
ITT	Intention to treat
IVIG	Intravenous immunoglobulin
JRS	Japanese Respiratory Society
K-BILD	King's Brief Interstitial Lung Disease Questionnaire
KSR	Kleijnen Systematic Reviews
L-PF	Living with pulmonary fibrosis
LYs	Life years
LYG	Life years gained
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NAC	N-acetylcysteine
NR	Not reported
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NSCLC	Non-small cell lung cancer
NTD	Nintedanib
OCS	Oral corticosteroids
OS	Overall survival
PAH	Pulmonary arterial hypertension
PAS	Patient access scheme
PFD	Pirfenidone
PFS	Progression-free survival
PF-ILD	Progressive fibrosing interstitial lung disease
PICO	Patients, interventions, comparators, and outcomes
PLB	Placebo
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PT	Prothrombin time
QALY	Quality adjusted life year
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RR	Relative risk; Risk ratio
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SSc	Systemic sclerosis
SSC-ILD	Systemic sclerosis associated interstitial lung disease

STA	Single technology appraisal
TA	Technology assessment
TEAE	Treatment emergent adverse events
TNF	Tumour necrosis factor
TTFAE	Time to first acute exacerbation
TTO	Time trade-off
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Information on key as well as non-key issues are in the main ERG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 to 6 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report sections
1	Relevant comparators are not included in the company submission (CS).	Sections 2.3 and 3.6
2	The comparator included in the CS does not reflect best supportive care (BSC) in the UK.	Sections 2.3 and 3.6
3	The ERG and company differed on their preferred extrapolation for overall survival (OS)	Section 4.2.6.1

BSC = best supportive care; CS = company submission; ERG = Evidence Review Group; OS = overall survival.

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are that the company preferred to extrapolate OS using a Bayesian Weibull curve. However, although clinical experts consulted by the company could not choose between the two curves, the ERG preferred to use the frequentist Weibull curve. This was because the frequentist curve provided a better fit to long term survival data in idiopathic pulmonary fibrosis (IPF) patients taking nintedanib, used by the company to validate the long-term extrapolation. The ERG also made a minor adjustment to the health state utility value (HSUV) for the 80-89 predicted FVC percentage health state in order to maintain a consistent decline in utility with the decline in lung function.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing survival
- Reducing the number of acute exacerbations
- Slowing the decline in lung function

Overall, the technology is modelled to affect costs by:

- its higher unit price than current treatments
- decreasing costs associated with the deterioration of health due to progressive fibrosing interstitial lung disease (PF-ILD)

The modelling assumption that has the greatest effect on the ICER is:

- The extrapolation of overall survival

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, not all relevant comparators as described in the NICE scope are included in the CS (Table 1.2) and the comparator included in the CS (placebo in the INBUILD trial) may not reflect current best practice or best supportive care (BSC) in the UK (Table 1.3).

Table 1.2: Key issue 1: Relevant comparators are not included in the CS

Report section	**Sections 2.3 and 3.6**
Description of issue and why the ERG has identified it as important	The description of the comparators in the NICE scope is: "Established clinical management without nintedanib (may depend on underlying cause of ILD) including, but not limited to: • immunosuppressants, such as azathioprine, cyclophosphamide, mycophenolate (do not currently have a marketing authorisation in the UK for this indication) • corticosteroids (do not have currently have a marketing authorisation in the UK for this indication) • infliximab (does not have currently have a marketing authorisation in the UK for this indication) • rituximab (does not have currently have a marketing authorisation in the UK for this indication) • best supportive care." The company only included one comparator, which they referred to as placebo. This was effectively all treatments received in the placebo arm of the INBUILD trial and which excluded immunomodulatory treatments that would have been current clinical practice.
What alternative approach has the ERG suggested?	The company should have included other relevant comparators as described in the NICE scope. However, given the lack of evidence for most comparators it is not clear how that could have been achieved. Therefore, the ERG has no suggestions for an alternative approach.
What is the expected effect on the cost effectiveness estimates?	The expected change to the ICER is unclear. However, if comparator treatments are more effective than those treatments received in the placebo arm (i.e. excluding immunomodulatory treatments for six months), the ICER will be less favourable for nintedanib.
What additional evidence or analyses might help to resolve this key issue?	The ERG is not aware of any additional evidence that would resolve this issue.

Table 1.3: Key issue 2: The comparator included in the CS may not reflect BSC in the UK

Report section	Sections 2.3 and 3.6
Description of issue and why the ERG has identified it as important	The comparator (placebo) in the company submission (CS) is defined as the treatment patients received in the control arm of the INBUILD trial. As stated by the company, "Due to the lack of availability of specific targeted therapies, immunomodulatory treatments (including azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids) have routinely been used in clinical practice for the treatment of ILD. However, their benefit-risk profiles in PF-ILD have not been established and they are not licensed for the treatment of PF-ILD. In order to avoid the potential impact of these drugs on the assessment of nintedanib in PF-ILD, their use was not allowed at randomisation and during the first 6 months of the treatment period. Patients who had taken these drugs could only participate in the trial if a wash-out period was observed before randomisation" (CS, pages 25-26). Therefore, it is clear that the treatments received in the placebo arm of the INBUILD trial do not represent current best practice or best supportive care (BSC) in the UK.
What alternative approach has the ERG suggested?	Given the evidence presented in the CS, the ERG has no suggestions for an alternative approach.
What is the expected effect on the cost effectiveness estimates?	The expected change to the ICER is unclear. However, if current best practice in the UK, which includes immunomodulatory treatments, is more effective than those treatments received in the placebo arm excluding immunomodulatory treatments, the ICER will be less favourable for nintedanib.
What additional evidence or analyses might help to resolve this key issue?	The ERG is not aware of any additional evidence that would resolve this issue.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG did not identify any other key issues relating to clinical effectiveness.

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issue in the cost effectiveness evidence is discussed in Table 1.4.

Table 1.4: Key issue 3: The selection of the parametric curve for overall survival (OS)

Report section	Section 4.2.6.1
Description of issue and why the ERG has identified it as important	The company preferred to extrapolate OS using a Bayesian Weibull curve given that: the Bayesian analysis was guided by external long-term IPF data, which could increase the accuracy of long-term predictions; clinicians considered the two Weibull options (frequentist or Bayesian) the most plausible in the long-term; the Weibull Bayesian provided a reasonably good fit to external IPF data. The choice of extrapolation of OS is a driver of model results.

Report section	Section 4.2.6.1
What alternative approach has the ERG suggested?	The ERG prefers to extrapolate OS using the frequentist Weibull, given that clinicians could not choose between the frequentist and Bayesian Weibull and the frequentist better fits the long-term nintedanib IPF external validation data presented.
What is the expected effect on the cost effectiveness estimates?	Extrapolating OS using the frequentist instead of the Bayesian Weibull adds approximately £8,000 to the company's post-clarification base-case ICER.
What additional evidence or analyses might help to resolve this key issue?	This issue would be resolved with longer term follow-up data in PF-ILD patients taking nintedanib, but this is not currently available.

1.6 Other key issues: summary of the ERG's view

The ERG did not identify any other key issues relating to cost effectiveness.

1.7 Summary of the ERG's view

The ERG's preferred assumptions are described in detail in Section 6.1.2 of this report and summarised in Table 1.5, with the impact of each assumption (applied independently to the company's post-clarification base-case) on results also shown. The results of the ERG preferred base-case, combining all the above assumptions, are displayed in the final row of the table.

An issue in the model submitted in response to clarification created an imbalance in the results of the probabilistic sensitivity analysis (PSA) compared to the determinist results, which should be fixed by the company in future stages of the appraisal in order to allow for the presentation of reliable PSA results to accompany the ERG base-case.

Scenario analyses conducted by the ERG are displayed in Section 6.2.2. The scenario which had the largest impact on results was extrapolating OS with the frequentist Weibull rather than the Bayesian Weibull.

Table 1.5: Summary of ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company's original CS base-case	[redacted]	[redacted]	[redacted]
Company's post-clarification base-case (including updated/corrected costs from clarification letter, including recurrent exacerbations in the model and including the age-adjustment of utilities)	[redacted]	[redacted]	[redacted]
Extrapolation of OS using the frequentist Weibull instead of the Bayesian Weibull (Key issue 3)	[redacted]	[redacted]	[redacted]
Adjustment of the health state utility value (HSUV) for 80-89 FVC % predicted state to maintain consistent trend in decline.	[redacted]	[redacted]	[redacted]
ERG's preferred base-case	[redacted]	[redacted]	[redacted]

BSC = best supportive care; CS = company submission; ERG = Evidence Review Group; FVC = forced vital capacity; HSUV = health state utility value; ICER = incremental cost effectiveness ratio.

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with progressive-fibrosing interstitial lung disease (excluding idiopathic pulmonary fibrosis)	Adults with progressive-fibrosing interstitial lung disease (excluding idiopathic pulmonary fibrosis)	N/A	The population is not completely in line with the NICE scope.
Intervention	Nintedanib	Nintedanib	N/A	The intervention is in line with the NICE scope
Comparator(s)	Established clinical management without nintedanib including, but not limited to: • immunosuppressants (such as azathioprine, cyclophosphamide, mycophenolate; do not currently have a marketing authorisation in the UK for this indication) • corticosteroids (do not have currently have a marketing authorisation in the UK for this indication) • infliximab (does not have currently have a marketing authorisation in the UK for this indication) • rituximab (does not have currently have a marketing	Placebo	At the trial design stage, there were no approved therapies for the treatment of PF-ILD, other than IPF. Currently, the only approved therapy is nintedanib. When diagnosis of ILD is confirmed, patients receive conventional treatment (such as corticosteroids and immunomodulatory agents) based on the specific type of ILD (see the proposed algorithm in Figure 3, page 19 [of the CS]). If the disease continues to progress despite use of these conventional treatments, a diagnosis of PF-ILD is then confirmed through pulmonary function tests, as well as radiological and clinical assessments. It is at this stage, once PF-ILD has been confirmed, that nintedanib should be considered as a treatment, as it is the only licensed treatment available for PF-ILD.	The comparators are not in line with the NICE scope. Also, placebo cannot be regarded as a comparator because it is not standard care i.e. no-one in actual clinical practice would receive a placebo. The comparator might be regarded instead as all other treatments administered to the patients (See Section 2.3 for further details).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	authorisation in the UK for this indication) • best supportive care		A consensus of clinical experts have advised that, whilst immunomodulatory agents may still be used to treat the inflammatory component of the disease, there are no randomised controlled trials to suggest that these unlicensed treatments have a positive impact on the chronic fibrotic progression of PF-ILD (i.e. delaying disease progression). Patients were eligible to participate in the trial if their ILD had worsened despite treatment with unapproved medications used in clinical practice to treat ILD. To minimise a potential impact on the efficacy and safety assessments, treatment for ILD with unapproved anti-inflammatory or immunomodulatory medications was required to be discontinued and a wash-out period was to be observed before randomisation of the patient. As there is currently no other targeted anti-fibrotic therapy licensed for the treatment of chronic fibrosing ILD with a progressive phenotype, the use of placebo as a control group was considered justified. However, initiation of concomitant immunomodulatory treatment as medically indicated was allowed for the management of worsening of the	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			disease after the first six months of the trial. Some patients received the treatments specified as comparators within the NICE scope, either for treatment of PF-ILD or the underlying condition (see full description on page 51-52 of the CS). Baseline and concomitant medication use are described in Section B.2.2 of the CS.	
Outcomes	The outcome measures to be considered include: • lung function • physical function • exacerbation rate • progression-free survival • mortality • adverse effects of treatment • health-related quality of life	• Rate of decline in FVC at 52 weeks (primary endpoint) • Absolute change from baseline in total score on K-BILD questionnaire at 52 weeks • Time until acute exacerbation of ILD or death at 52 weeks • Death at 52 weeks • Acute exacerbation of ILD or death up to DBL2 • Death up to DBL2 • AEs, serious AEs and severe AEs	N/A	The outcomes are generally in line with the NICE scope.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for	Not reported.	Not reported.	The economic analysis was conducted in line with the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups to be considered	If the evidence allows subgroup analyses by ILD type will be considered.	Not reported	Not reported.	No subgroup analyses were performed.

Based on Table 1 and pages 11 to 12 of the CS.[1]

AE = adverse event; CS = company submission; DBL1 = database lock 1; DBL2 = database lock 2; FVC = forced vital capacity; ILD = interstitial lung disease; K-BILD = King's Brief Interstitial Lung Disease Questionnaire; N/A = not applicable

2.1 Population

The population defined in the scope is: "People with fibrosing interstitial lung disease that has progressed despite treatment (excluding idiopathic progressive fibrosis)".[2] The population in the CS is "Adults with progressive-fibrosing interstitial lung disease (excluding idiopathic pulmonary fibrosis)".[1] The population is not completely in line with the NICE scope, but is in line with the main trial (the INBUILD trial) described in the company submission, which included patients aged ≥18 years if they had a physician-diagnosed fibrosing ILD present with features of diffuse fibrosing lung disease of ≥10% extent on high-resolution computed tomography (HRCT), and met the protocol criteria for progression within 24 months of screening as assessed by the investigator.

Nintedanib has four approved marketing authorisations:

- As VARGATEF®, it is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology after first-line chemotherapy
- As OFEV®, it is indicated in adults for the treatment of:
  - Idiopathic pulmonary fibrosis (IPF)
  - Systemic sclerosis associated interstitial lung disease (SSc-ILD)
  - Other chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD)

Nintedanib was granted EMA marketing approval as VARGATEF®, for the treatment of non-small cell lung cancer in November 2014; and as OFEV®, for the treatment of IPF in January 2015, SSc-ILD in May 2020 and PF-ILD in July 2020. There are no restrictions in place under the current marketing authorisations.

The company claims that "patients with SSc-ILD with the progressing fibrosing phenotype are included in the INBUILD trial and are therefore included in the population considered in this submission, in line with the marketing authorisation for nintedanib" (CS, page 10).[1] However, it is unclear how many patients with SSc-ILD with the progressing fibrosing phenotype are included in the INBUILD trial and what their results were.

2.2 Intervention

The intervention (nintedanib) is in line with the scope.

The recommended dose is 150 mg nintedanib orally twice daily, administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose. In patients with mild hepatic impairment (Child Pugh A), the recommended dose of nintedanib is 100 mg twice daily approximately 12 hours apart.[1]

According to the company, no additional tests or investigations are required prior to the administration of nintedanib (CS, page 14).[1]

2.3 Comparators

The description of the comparators in the NICE scope is as follows: "Established clinical management without nintedanib (may depend on underlying cause of ILD) including, but not limited to:

- immunosuppressants, such as azathioprine, cyclophosphamide, mycophenolate (do not currently have a marketing authorisation in the UK for this indication)

- corticosteroids (do not have currently have a marketing authorisation in the UK for this indication)
- infliximab (does not have currently have a marketing authorisation in the UK for this indication)
- rituximab (does not have currently have a marketing authorisation in the UK for this indication)
- best supportive care".[2]

The company only included one comparator, which they referred to as placebo.[1]

ERG comment: The comparator (placebo) in the CS is defined as the treatment patients received in the control arm of the INBUILD trial. This should not be referred to as placebo because no one receives placebo in actual clinical practice. As stated by the company, "Due to the lack of availability of specific targeted therapies, immunomodulatory treatments (including azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids) have routinely been used in clinical practice for the treatment of ILD. However, their benefit-risk profiles in PF-ILD have not been established and they are not licensed for the treatment of PF-ILD. In order to avoid the potential impact of these drugs on the assessment of nintedanib in PF-ILD, their use was not allowed at randomisation and during the first 6 months of the treatment period. Patients who had taken these drugs could only participate in the trial if a wash-out period was observed before randomisation" (CS, pages 25-26).[1] Lack of license should not be a reason for excluding a treatment as a comparator: the test for inclusion is whether treatments are used in clinical practice, which the company points out is the case for the treatments excluded for the first six months. Therefore, it is clear that the treatment received in the placebo arm of the INBUILD trial does not represent current best practice or best supportive care (BSC) in the UK.

The company did not include rituximab and infliximab as comparators despite NICE explicitly requesting to make this comparison (see NICE Response to comments on draft scope[3]).

2.4 Outcomes

The NICE final scope lists the following outcome measures:[2]

- Measures of disease progression such as:
  - lung function
  - physical function
  - exacerbation rate
  - lung transplantation
- Mortality
- Adverse effects of treatment
- Health-related quality of life.

The following outcomes were assessed in the INBUILD trial:[1]

- Rate of decline in FVC at 52 weeks (primary endpoint)
- Absolute change from baseline in total score on K-BILD questionnaire at 52 weeks
- Time until acute exacerbation of ILD or death at 52 weeks
- Death at 52 weeks
- Acute exacerbation of ILD or death up to DBL2
- Death up to DBL2
- AEs, serious AEs and severe AEs

ERG comment: The outcomes are generally in line with the NICE scope. However, physical function does not seem to be reported. The K-BILD questionnaire is a self-completed health status questionnaire that comprises 15 items and a seven-point Likert response scale.[4] It has three domains: psychological, breathlessness and activities and chest symptoms. The K-BILD domain and total score ranges are 0–100; 100 represents best health status. Therefore, the activities domain from the K-BILD questionnaire might cover physical function. However, only K-BILD total scores have been reported in the CS. Therefore, physical function is not reported in the CS.

2.5 Other relevant factors

According to the company, nintedanib is innovative because until the recent approval of nintedanib for SSc-ILD and PF-ILD, there were no licensed treatments for patients with PF-ILD other than IPF. In addition, the company states that nintedanib is the first pharmacological treatment to show clinical evidence of slowing disease progression in patients with PF-ILD (CS, Section B.2.12).[1]

A simple PAS is in place for nintedanib (applies to current both indications – as VARGATEF in non-small cell lung cancer (NSCLC) and OFEV in IPF) and the company [redacted] for the current appraisal.[5] The PAS price is a [redacted] discount to the list price of £2,151 for both the 100 mg and 150 mg units = [redacted] (CS, page 105).[1]

According to the company, nintedanib is not expected to meet the criteria for end-of-life use (CS, page 54).[1] This is also illustrated by the statement from the company that "it is expected that patients with PF-ILD who are not receiving an anti-fibrotic therapy would have a median post-diagnosis survival of 2 to 5 years" (CS, page 53).[1, 6, 7] Therefore, treatment is not indicated for patients with a short life expectancy (normally less than 24 months).

According to the company, no equality issues related to the use of nintedanib for the treatment of adults with progressive-fibrosing interstitial lung disease are expected (CS, Section B.1.4).[1]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

Appendix D.1.1 of the CS details a systematic literature review (SLR) conducted to provide evidence on the efficacy of treatments for PF-ILDs other than IPF. In D.1.1 it states that the SLR aimed to identify RCTs that have evaluated pharmacological treatments for ILD with a progressive phenotype.

Searches were conducted on 13 August 2019 and were limited to English language publications. Update searches were run on 29 October 2019 and also on 26 May 2020. Databases were searched from date of inception. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

	Resource	Host/source	Date ranges	Dates searched
Electronic databases	Embase	Ovid	1974 - 26/5/20	13/8/19 29/10/19 26/5/20
	Cochrane CDSR Cochrane CENTRAL	Cochrane library.com	Inception - 26/5/20	13/8/19 29/10/19 26/5/20
	MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations MEDALL	Ovid	1946 - 26/5/20	28/6/20
Clinical Trial Registries	ClinicalTrials.gov		01/01/2010 to 13/08/2019 13/08/2019 to 26/05/2020	13/8/19 26/5/20
	The WHO International Clinical Trials Registry Platform		01/01/2010 to 13/08/2019	13/8/19
Conference proceedings	American Thoracic Society (ATS)	Online abstracts	2019	28/6/20
	British Thoracic Society (BTS)	Online abstracts	2018 2019	13/8/19 26/5/20
	European League Against Rheumatism (EULAR) - European Congress of Rheumatology	Online PDF abstract book	2019 2020	13/8/19 26/5/20
	European Respiratory Society (ERS) International Congress	Not reported	Not reported	Not reported
CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Central Register of Controlled Trials				

ERG comments:

- A single set of searches was undertaken to identify clinical effectiveness and adverse events data. The CS provided sufficient details for the ERG to appraise the literature searches. Several databases and a good range of conference proceedings were searched, and reference checking was conducted. Searches were generally well documented, making them transparent and reproducible.
- The ERG was concerned that limiting the searches to English language may have introduced potential language bias. Current best practice states that that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication" [8] and that "research related to language bias supports the inclusion of non-English studies in systematic reviews".[9, 10]
- Study design filters were appropriately used but were not referenced.
- Separate adverse events (AE) searches were not performed. The clinical effectiveness searches incorporated a methodological filter intended to limit the search to RCTs. Guidance by the Centre for Reviews and Dissemination (CRD)[11] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used.
- MeSH terms were used in the initial Embase searches but these were corrected in subsequent updates and efforts were made to ensure no studies were missed from the mistakes in the previous searches.

3.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs which was guided by expert clinical opinion on PF-ILD is presented in Table 3.2.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Criteria	Inclusion criteria	Exclusion criteria
Population	Patients with ILD and progressive fibrosing phenotype	Patients with IPF
Interventions	Any dose of the following: • Nintedanib • Pirfenidone • Azathioprine • Cyclophosphamide • Rituximab • Mycophenolate mofetil • Corticosteroids • Methotrexate • Tocilizumab • Abatacept • Infliximab • Etanercept • Adalimumab	None
Comparators	Any	None

Criteria	Inclusion criteria	Exclusion criteria
Outcomes	Primary outcomes: • FVC • Progression-free survival/time to progression • Overall survival • Disease-related survival • Acute exacerbation of fibrosis / acute respiratory worsening Secondary outcomes: • FEV1 • FEV1/FVC • VC • TLC • DLco • HRCT • Corticosteroid sparing/corticosteroid use • AEs • Hospitalisation • Activity measures including, but not restricted to 6MWD test • HRQoL measures including, but not restricted to: • SGRQ • K-BILD • EQ-5D • SF-36 • HAQ-DI • VAS	None
Study design	RCTs	All other types of study designs
Language restrictions	English Language only	None
Date	No limits	None
Source: CS, Appendix D, Table 74, pages 161-162.[1] 6MWD = 6-minute walk distance; AE = adverse effect; DLco = diffusing capacity of the lung for carbon monoxide; EQ-5D = EuroQol-5 dimensions questionnaire; FVC = forced vital capacity; HAQ-DI = health assessment questionnaire disability index; HRCT = high-resolution computed tomography; HRQoL = health related quality of life; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; K-BILD = King's brief interstitial lung disease questionnaire; RCT = randomised controlled trial; SF-36 = 36-item short form health survey; SGRQ = St George's respiratory questionnaire; TLC = total lung capacity; VAS = visual analogue scale; VC = Vital Capacity; TLC = total lung capacity.		

ERG comment: Given the final scope issued by NICE, the PICO (patients, interventions, comparators, and outcomes) inclusion criteria seem appropriate. However, it must be noted that two restrictions were placed on study design and language, respectively. Although an RCT is the gold standard for evaluating the effectiveness of an intervention or device, observational studies can contribute to the evidence base

for effective interventions, of a condition that has no current market authorisation. Additionally, the restriction to English language studies only, could mean that all relevant studies may not have been retrieved.

3.1.3 Critique of data extraction

Data extraction was carried out by one reviewer, and checked for consistency and accuracy by another reviewer.[1]

ERG comment: To minimise error during data extraction, it is usually advised that data extraction is carried out independently by two reviewers.

3.1.4 Quality assessment

Quality assessment of included studies was carried out by one reviewer, and checked by another.[1] The INBUILD trial was subjected to risk of bias assessment and judged to be of a low risk of bias.[1] Cost utility studies were assessed using the Drummond checklist and the NICE Decision Support Unit Recommendations were used to assess the quality of studies reporting utilities.[1]

ERG comment: The formal scale used to assess the risk of bias for the INBUILD trial was not described explicitly. However, we assume the company used the University of York, Centre for Reviews and Dissemination criteria.[11]

3.1.5 Evidence synthesis

The company notes and justifies the unfeasibility of conducting a quantitative evidence synthesis, despite there being the possibility of an indirect comparison between nintedanib and pirfenidone. This was due to the heterogeneity of patient and trial characteristics, and lack of comparable outcome reporting of pirfenidone vs. placebo, and nintedanib vs. placebo trials.[1] In addition, pirfenidone was not listed as a comparator in the NICE scope.

ERG comment: The ERG has no further comment regarding evidence synthesis (see also Section 3.3 in this report).

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Details of the included trial: the INBUILD trial

The main evidence for the clinical effectiveness of nintedanib was from the INBUILD trial.[1, 12, 13] This trial (n=663) was a phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study with follow-up at 52 weeks followed by a variable treatment period, where patients continued on blinded, randomised assigned treatment until the end of the trial or until a reason for treatment withdrawal was met. In both arms, patients could not be taking any immunomodulatory treatment at randomisation and for the first six months of the trial, but could do so for the remainder of the trial after six months. Immunomodulatory treatments included: azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids. The INBUILD trial was undertaken in 15 countries in North America, South America, Western Europe, and East Asia, including five centres (22 patients) in the UK. The purpose the INBUILD trial was to investigate the efficacy and safety of nintedanib for treating progressive-fibrosing lung disease.

Patients aged ≥18 years were eligible for enrolment if they had a physician-diagnosed fibrosing interstitial lung disease (ILD, such as connective tissue disease-associated ILD, rheumatoid arthritis-

associated ILD, systemic sclerosis–associated ILD, chronic fibrosing hypersensitivity pneumonitis, idiopathic non-specific interstitial pneumonia, unclassifiable idiopathic interstitial pneumonia, environmental/occupational lung disease, sarcoidosis and other ILDs), present with features of diffuse fibrosing lung disease of ≥10% extent on high-resolution computed tomography, and met the protocol criteria for progression within 24 months of screening as assessed by the investigator. In addition, patients were also required to have a forced vital capacity (FVC) >45% of predicted value and a diffusing capacity of the lungs for carbon monoxide (DLco) of >30% and <80% of predicted at randomisation. Patients who had taken immunomodulatory treatments as outlined above could participate in the trial if they observed a washout period before randomisation. Full inclusion and exclusion criteria are available in the company submission (CS, Table 5).[1]

Primary efficacy endpoint was the rate of decline in FVC as assessed over 52 weeks.

A summary of the methodology of the INBUILD trial is presented in Table 3.3 below.

Table 3.3: Summary of the methodology of the INBUILD trial

Trial design	Phase 3, multicentre, international, randomised, double-blind, placebo-controlled, 52-week study.
Participant eligibility criteria	Patients aged ≥18 years if they had a physician-diagnosed fibrosing ILD (such as connective tissue disease-associated ILD, rheumatoid arthritis- associated ILD, systemic sclerosis – associated ILD , chronic fibrosing hypersensitivity pneumonitis, idiopathic non-specific interstitial pneumonia, unclassifiable idiopathic interstitial pneumonia, environmental/occupational lung disease, sarcoidosis and other ILDs) present with features of diffuse fibrosing lung disease of ≥10% extent on HRCT, and met the protocol criteria for progression within 24 months of screening as assessed by the investigator.
Settings and locations where the data were collected	15 countries in North America, South America, Western Europe, and East Asia. The trial was run in the UK (22 patients enrolled in five centres).
Intervention	Oral nintedanib 150 mg twice daily (n=332)
Comparator	Oral placebo twice daily (n=331)
Primary outcome	Primary endpoint: annual rate of decline in FVC (mL/year) over 52 weeks in two co-primary populations (overall population and patients with UIP-like pattern on HRCT). Main secondary endpoints: change from baseline K-BILD total score at week 52; time to first acute ILD exacerbation or death over 52 weeks; time to death over 52 weeks.
Other outcomes used in the economic model / specified in the scope	• Acute exacerbation of ILD or death up to DBL2 • Death up to DBL2 • AEs, serious AEs and severe AEs Safety endpoints: • AEs over 52 weeks • Physical examination over 52 weeks • Vital signs over 52 weeks • Bodyweight over 52 weeks
Source: company submission [1]	

AEs = adverse events, DBL2 = database lock 2, FVC = forced vital capacity, HRCT = high-resolution computed tomography, HRQoL = health-related quality of life, ILD = interstitial lung disease, K-BILD = King's Brief Interstitial Lung Disease Questionnaire, L-PF = living with pulmonary fibrosis, UIP = usual interstitial pneumonia

ERG comment: The CS states that the INBUILD trial is likely to be reflective of clinical practice in England and Wales, given the trial endpoints, study population and comparators, and that five centres (22 patients) were located in the UK.[1] The primary endpoint, rate of decline in FVC, is a validated endpoint for studies of IPF.[14]

There are few registries for PF-ILD: in the UK, there is only the BTS ILD registry, which includes the UK IPF registry.[15] There were some differences between patients in the INBUILD trial and patients in the UK IPF registry: 54% of patients in INBUILD were male vs 79% in the registry; mean age was 66 years in INBUILD and 73.5 years in the registry; and 51% of INBUILD were former or current smokers vs 66% in the registry. However, the effects of these differences on the cost effectiveness analysis is unknown, and there is limited evidence of subgroup differences in the INBUILD trial, though there is a lack of power to detect even large differences. The UK IPF registry includes patients other than those with PF-ILD, so some differences are expected. Additionally, 22 patients in INBUILD (3.5%) were from the UK. As such, the cost effectiveness analysis is unlikely to be materially affected by the differences between INBUILD and the UK PF-ILD population.

However, one issue with the generalisability of results to a UK population is that the INBUILD trial did not allow off-label use of immunomodulatory treatments for the first six months of the trial in either arm. From six months into the trial, all participants were allowed to have immunomodulatory treatments in addition to nintedanib or placebo, and some patients were prescribed these. The CS states this "*reflects clinical opinion that treatment for worsening CTD or ILD was required and is reflective of the underlying treatment that would be seen in UK clinical practice*".[1] As such, while the INBUILD trial reflects UK clinical practice after six months, it does not necessarily reflect it during the first six months. However, as there is little evidence from trials for the effectiveness of off-label treatments for PF-ILD it is unknown how much this could affect the cost effectiveness analysis.

3.2.2 Statistical analyses of the INBUILD trial

The INBUILD trial was a superiority trial designed to demonstrate that nintedanib 150 mg twice daily was superior to placebo. The primary endpoint was reduction in FVC from baseline to 52 weeks, see Table 3.4. The initial 52 weeks of the trial were followed by a variable treatment period, where patients continued their blinded, randomised assigned treatment until the end of the trial or until a reason for treatment withdrawal was met. There were two primary co-populations: all patients, and patients with high-resolution computed tomography (HRCT) with usual interstitial pneumonia-like (UIP-like) fibrotic pattern only.

The analysis used all observations over 52 weeks and a random coefficient regression model. The analysis was performed on the intention to treat population, defined as all patients who were randomised and received at least one dose of study treatment. Continuous secondary endpoints were analysed using mixed effects models for repeated measures. Time-to-event secondary endpoints were analysed using Cox proportional hazards models and Kaplan-Meier plots; binary secondary endpoints were analysed using logistic regressions.

Table 3.4: Summary of statistical analyses in the INBUILD trial

Hypothesis objective	**Null hypothesis**: There is no difference in either of the co-primary populations (all patients and patients with HRCT with UIP-like fibrotic pattern only) in the annual rate of decline in FVC from baseline until 52 weeks between nintedanib 150 mg bid and placebo. **Alternative hypothesis**: There is a difference in the annual rate of decline in FVC between nintedanib 150 mg bid and placebo over 52 weeks, in either or both co-primary populations.
Statistical analysis	Primary analysis of the primary endpoint was based on all measurements taken over 52 weeks using a random coefficient regression model. Continuous secondary endpoints were analysed using Mixed Effects Models for Repeated Measures. Time-to-event secondary endpoints were analysed using Cox proportional hazards models and Kaplan-Meier plots; binary secondary endpoints were analysed using logistic regressions. Formal statistical testing was performed on both co-primary populations, and statistical significance declared if the analysis in both populations was significant at the two-sided 5% level, or if the analyses in either population were statistically significant at the two-sided 2.5% level. A Hochberg procedure was used to maintain an overall type 1 error rate of 5%.
Sample size, power calculation	A sample size of 600 patients (300 per randomised treatment group with 400 patients with UIP-like HRCT pattern) was expected to provide adequate power to demonstrate a clinically important treatment benefit on the primary endpoint, according to three scenarios (see CS, Table 13).[1] This included a scenario where the effect on the primary endpoint in both co-primary populations is lower than observed for IPF patients in the INPULSIS trials.
Data management, patient withdrawals	To reduce the amount of missing data, patients who discontinued the trial drug prior to completing the 52 week treatment period were asked to attend all visits as planned. In addition, for patients who prematurely discontinued trial medication and were unable to complete the scheduled visits, every attempt was made to collect information on vital status at week 52, at the time of data cut-off for the primary analysis and at the end of the trial. All aspects of data handling were performed according to guidelines and safety procedures established by the company for safety, completeness, consistency, accuracy, plausibility, legibility and adherence to the Clinical Trial Plan.

Source: company submission [1]
Bid = twice daily, FVC = forced vital capacity, HRCT = high-resolution computed tomography, IPF = idiopathic pulmonary fibrosis, UIP = usual interstitial pneumonia

ERG comment: The analysis of the INBUILD trial used appropriate statistical methods and the ERG has no concerns.

3.2.3 Baseline characteristics of the INBUILD trial

Table 3.5 shows the baseline characteristics of the participants in the INBUILD trial.

Briefly, the INBUILD trial had a total of 663 participants, n=332 received nintedanib and n=331 received placebo. The mean age of participants in the trial was 66 years. Both female and male

participants were included, and 54% of participants were male. The trial was conducted in 15 countries in North America, South America, Western Europe, and East Asia, and 74% of participants were white, 25% were Asian, and 1.5% were Black of African American. Fifty-one per cent of participants were former or current smokers, and 62% had UIP-like fibrotic pattern on HRCT while 38% had other fibrotic patterns. All participants matched at least one criterion for disease progression in the 24 months prior to screening: approximately 50% of participants had a relative decline in FVC ≥10% predicted; 31% had a relative decline in FVC ≥5–<10% predicted combined with worsening of respiratory symptoms and/or increased extent of fibrosis on HRCT; and 19% had worsened respiratory symptoms and increased extent of fibrosis on HRCT only. At baseline, participants had an average of 69% of their predicted FVC.

Table 3.5: Baseline characteristics in the INBUILD trial

	Nintedanib (n=332)	**Placebo (n=331)**
Male – no. (%)	179 (53.9)	177 (53.5)
Age – years	65.2±9.7	66.3±9.8
Former or current smoker – no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on HRCT – no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in 24 months before screening (grouped) – no. (%)		
Relative decline in FVC ≥10% predicted	160 (48.2)	172 (52.0)
Relative decline in FVC ≥5–<10% predicted combined with worsening of respiratory symptoms and/or increased extent of fibrosis on HRCT	110 (33.1)	97 (29.3)
Worsened respiratory symptoms and increased extent of fibrosis on HRCT only	62 (18.7)	61 (18.4)
FVC		
Mean value – mL	2,340±740	2,321±728
% of predicted value	68.7±16.0	69.3±15.2
DLco, mmol/min/kPa†	3.5±1.2	3.7±1.3
DLco, % of predicted value†	44.4±11.9	47.9±15.0
K-BILD questionnaire total score‡	52.5±11.0	52.3±9.8

Source: CS, Table 10, page 31.[1]

DLco = diffusion capacity of the lungs for carbon monoxide, FVC = forced vital capacity, HRCT = high-resolution computed tomography, K-BILD = King's Brief Interstitial Lung Disease, kPa = kiloPascal, UIP = usual interstitial pneumonia.

* Plus–minus values are means ± SD. † The DLco value was corrected for the haemoglobin level. ‡ K-BILD questionnaire total score ranges from 0–100, with higher scores representing better health status.

ERG comments: There was a balanced number of men and women in the INBUILD trial. Despite this, there was limited statistical power to detect differences in the effectiveness of nintedanib between genders. As such, although there was little evidence of a difference in effect between genders, there could still be a meaningful difference in the effectiveness of nintedanib between the genders. This may be relevant if the gender distribution of PF-ILD is not balanced in the UK: in the UK IPF registry 79% of the patients were male, though this includes patients who do not have PF-ILD. It should be noted, however, that patients on nintedanib had smaller declines in FVC at 52 weeks in both genders compared with placebo (male = 145.2 ml, 95% CI: 88.5 ml to 201.9 ml; female: 64.2 ml, 95% CI: 3.9 ml to 124.6

ml), and assuming that females are generally smaller than males, the relative rather than absolute changes in FVC may be more equal.

Further subgroup analyses showed little evidence for differences by age (<65 years versus ≥65 years, with patients ≥65 years having a slightly higher point estimate), by baseline FVC percentage predicted (≤70% versus >70%), by underlying ILD diagnosis (hypersensitivity pneumonitis, idiopathic nonspecific interstitial pneumonia, unclassifiable idiopathic interstitial pneumonia, autoimmune ILDs or other ILDs), or by race (White, Asian or Black or African American; though there was very little evidence for African Americans: 222.5 ml, 95% CI: -143.1 ml to 588.1 ml). As such, even though the participants were younger in the INBUILD trial compared with the UK IPF registry, this is unlikely to substantially affect the cost effectiveness analysis. Lung function (percentage FVC predicted) at presentation in the UK IPF registry was similar to INBUILD at recruitment, with 38% of patients having a predicted FVC of >80%, 57% of patients having a predicted FVC of 50 to 80%, and 5% of patients having a predicted FVC of <50%.[16] Race and underlying ILD diagnosis were not available in the UK IPF registry.

3.2.4 Risk of bias assessment of the INBUILD trial

The company assessed the quality of the INBUILD trial using the University of York, Centre for Reviews and Dissemination criteria.[11] Elements assessed were randomisation, allocation concealment, baseline comparability, care provider, participant and outcome assessor blinding, dropout imbalances, selective outcome reporting, use of intention to treat analysis and conflicts of interest. No information was provided on the number of reviewers who assessed the quality of the INBUILD trial, although it seems likely only one reviewer assessed the quality given the use of "*reviewer's judgement*" rather than "*reviewers' judgement*". The company concluded that all elements had been appropriately addressed in all three of the trials.

Table 3.6: Quality assessment of the INBUILD study

	How is the question addressed in the study?	Company	ERG
Was randomisation carried out appropriately?	Randomisation was performed using an IRT system.	Yes	Yes
Was the concealment of treatment allocation adequate?	Randomisation was performed by IRT, and trial packaging and labelling were identical. Colour, size and shape of nintedanib and placebo capsules were indistinguishable within dose strength but were different between dose strengths.	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Participants in all populations had similar baseline characteristics and treatment arms were well balanced.	Yes	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained blinded with regard to the randomised treatment assignments until after DBL1.	Yes	Yes

	How is the question addressed in the study?	Company	ERG
Were there any unexpected imbalances in dropouts between groups?	Although there were some differences, these were consistent with the known safety profile of nintedanib in IPF and other indications.	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All pre-specified outcomes have been reported.	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy and safety analyses were performed based on the treated set, which included all randomised patients who received ≥1 dose of trial medication; however, since all patients who were randomised received treatment with nintedanib or placebo this included all randomised patients. To reduce the amount of missing data, patients who discontinued trial drugs for any reason prior to completing the 52-week treatment period were asked to attend all visits and undergo all examinations as previously planned. In addition, for all patients who prematurely discontinued trial medication and were unable to complete the scheduled visits, every attempt was made to collect information on vital status at week 52, at the time of data cut-off for the primary analysis and at the end of the trial. The statistical model used for the primary analysis allowed for missing data, assuming they were missing at random.	Yes	Yes
Did the authors of the study publication declare any conflicts of interest?	All authors have clearly declared any conflicts of interest, and these are not considered to have biased the reporting or results of the study.	Yes	Yes
Source: CS, Appendix D, Table 90, page 224.[1] DBL1 = database lock 1; IRT = Interactive Response Technology.			

ERG comments:

- It is normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error.
- The ERG examined the clinical study report for the INBUILD trial and assessed it against the above criteria.[1, 12, 13] Randomisation and allocation concealment procedures appeared to be appropriate. Methods to ensure blinding of care providers, participants and outcome assessors also appeared to be appropriate. All outcomes appeared to be reported. Data from all participants who received at least one treatment dose were included, which is appropriate. The patients in the nintedanib and placebo arms appear similar, based on baseline demographics. Therefore, the ERG agrees the INBUILD trial was well conducted.

3.2.5 Efficacy results of the INBUILD trial

The results presented in the CS have been taken from two published manuscripts (Flaherty et al, 2019[12] and Wells et al, 2020[17]) and the clinical trial report[18]. Data from database lock 2 (DBL2) of INBUILD have been taken from a poster developed for the European Respiratory Society International Congress, 7-9th September 2020.[19]

The analysis of the INBUILD trial considered two co-primary analysis populations, the overall population (including all patients) and all patients with high-resolution computed tomography (HRCT) with usual interstitial pneumonia (UIP)-like fibrotic pattern only. In this report, we will only present data for the overall population.

The primary endpoint, annual rate of decline in FVC over 52 weeks, was met (see Table 3.7). Treatment with nintedanib reduced the adjusted annual rate of decline in FVC by 107.0 mL (p<0.001) in the overall population vs. placebo.

Table 3.7: Efficacy endpoint results in the INBUILD trial

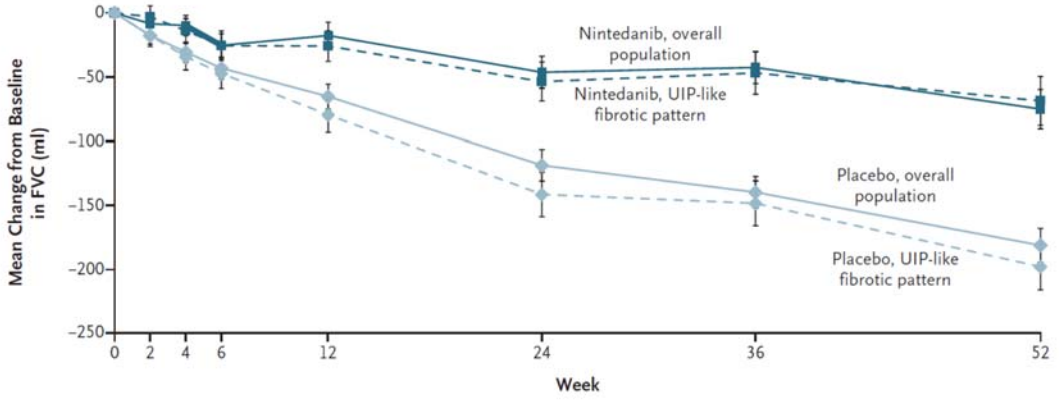
Endpoint	Nintedanib (N = 332)	Placebo (N = 331)	Difference vs. placebo (95% CI; p-value)
Primary endpoint			
Rate of decline in FVC at 52 weeks (mL/year)[†]			
Overall population	−80.8±15.1	−187.8±14.8	107.0 (65.4, 148.5; p<0.001)
Annual rate of decline in FVC (mL/ year) over the whole trial period up to DBL2			
Overall population	−118.14±11.4	−175.67±11.2	57.5 (26.1–89.0)
Main secondary endpoints			
Absolute change from baseline in total score on K-BILD questionnaire at 52 weeks[§]			
Overall population	0.55±0.60	−0.79±0.59	1.34 (−0.31, 2.98; p=0.1115)[‡]
Acute exacerbation of ILD or death at 52 weeks (no. with event/total no. [%])			
Overall population	26/332 (7.8)	32/331 (9.7)	0.80 (0.48, 1.34; p=0.3948)[‡¶]
Time to first acute ILD exacerbation or death over the whole trial period up to DBL2 (no. with event/total no. [%])			
Overall population	46/332 (13.9)	65/331 (19.6)	0.67 (0.46 to 0.98)[¶]
Death at 52 weeks (no. with event/total no. [%])			
Overall population	16/332 (4.8)	17/331 (5.1)	0.94 (0.47, 1.86; p=0.8544)[‡¶]
Time to death over the whole trial period up to DBL2 (no. with event/total no. [%])			
Overall population	36/332 (10.8)	45/331 (13.6)	0.78 (0.50 to 1.21)[¶]
Other secondary endpoints assessed until DBL2 in the overall population (no. with event/total no. [%])			
Time to progression (≥10% absolute decline in FVC % predicted) or death	134/332 (40.4)	181/331 (54.7)	0.66 (0.53 to 0.83)[¶]
Time to death due to a respiratory cause	21/332 (6.3)	30/332 (9.1)	0.68 (0.39 to 1.18)[¶]

Source: CS, Table 15, page 39-40.
FVC = forced vital capacity; ILD = interstitial lung disease; K-BILD = King's Brief Interstitial Lung Disease Questionnaire; NR = not reported; UIP = usual interstitial pneumonia.

Endpoint	Nintedanib (N = 332)	Placebo (N = 331)	Difference vs. placebo (95% CI; p-value)
† For the primary end point, the patients with a UIP-like fibrotic pattern included 206 in each treatment group. The patients with other fibrotic patterns included 126 in the nintedanib group and 125 in the placebo group. ‡ The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects. § For the analysis of the scores on the K-BILD questionnaire, 332 patients were included in the nintedanib group and 330 in the placebo group in the overall population; among the patients with a UIP-like fibrotic pattern, included were 206 patients and 205 patients, respectively. ¶ The difference was assessed as a hazard ratio. Data are taken from Flaherty 201912 and the Clinical Trial Report18. DBL2 data have been taken from the Clinical Trial Report18 and a poster developed by Flaherty et al for the European Respiratory Society International Congress, 7-9th September 2021.19			

The curves of observed change from baseline in FVC in the nintedanib and placebo groups separated early and continued to diverge up to 52 weeks follow-up (Figure 3.1).

Figure 3.1: Decline from baseline in FVC at 52 weeks



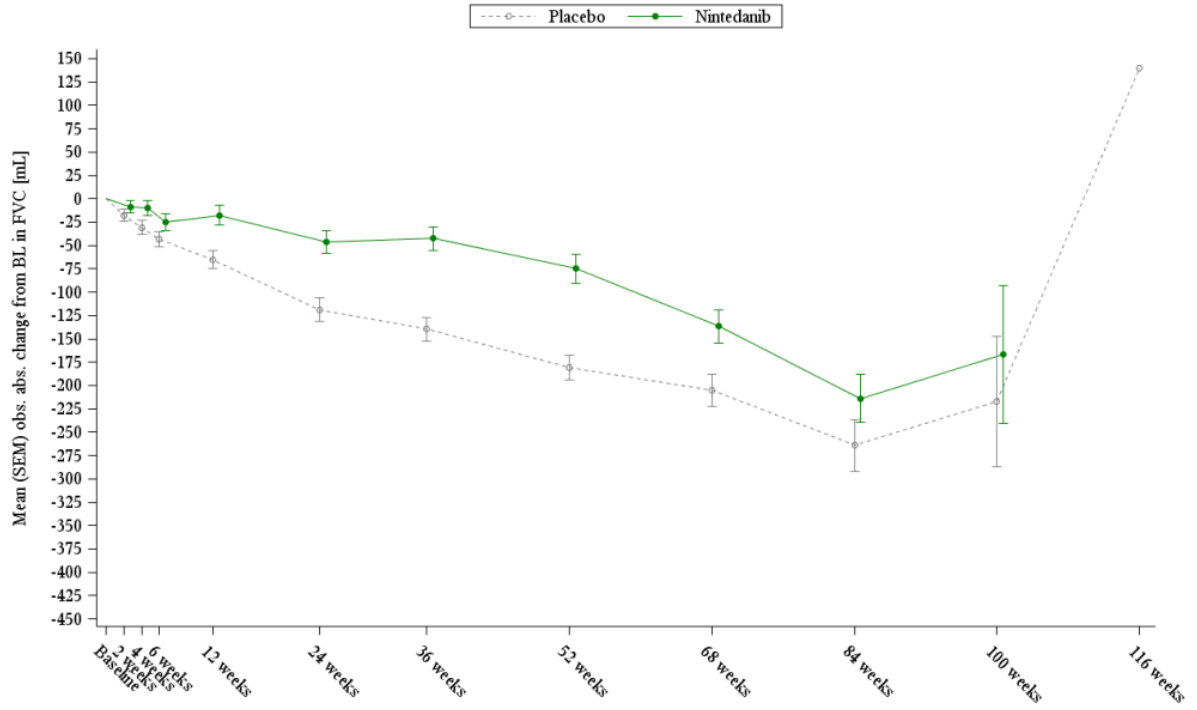
No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

Source: CS, Figure 6, page 41.[1]
Abbreviations: FVC, forced vital capacity; UIP, usual interstitial pneumonia

As can be seen from Table 3.7, the difference in the annual rate of decline in FVC (mL/year) between nintedanib and placebo is smaller over the whole trial period up to DBL2 (difference vs. placebo: 57.5 (95% CI: 26.1to 89.0)) than it is at 52 weeks (difference vs. placebo: 107.0 (95% CI: 65.4 to 148.5)). Therefore, it is likely the curves converge after 52 weeks. In order to see what happens to the curves after 52 weeks, the ERG asked the company to provide a figure such as Figure 6 in the CS for the 'Annual rate of decline in FVC (mL/year) over the whole trial period up to DBL2' (Response to clarification, Question A5, page 11).[3] In response, the company provided Figure 3.2 below. As can be seen from Figure 3.2, the curves of observed change from baseline in FVC in the nintedanib and placebo groups separated early and continued to diverge up to 52 weeks follow-up. However, after 52 weeks follow-up the curves move closer together again. The company does warn that "The analysis of annual rate of decline in FVC (mL/year) including data over the whole trial should be interpreted with caution.

Because of the trial design with a variable duration of Part B, many patients had missing FVC assessment values after week 52" (Response to Clarification, Question A5, page 11).[3]

Figure 3.2: Mean of observed absolute change from baseline in FVC (mL) over the whole trial – treated set, overall population



Source: Response to Clarification, Question A5, Figure 2, page 12.[3]
Abbreviations: FVC, forced vital capacity

In the overall population, treatment with nintedanib did not show a significant difference in health-related quality of life (HRQoL) as measured by the King's Brief Interstitial Lung Disease (K-BILD) questionnaire compared with placebo (adjusted mean difference 1.34; 95% CI: -0.31 to 2.98); the change from baseline total score was small in both treatment groups.

The hazard ratio (HR) for time to first acute ILD exacerbation or death also showed no significant difference between nintedanib and placebo (HR 0.80; 95% CI: 0.48 to 1.34); nor did the HR for time to death over 52 weeks (HR 0.94; 95% CI: 0.47 to 1.86).

Over the whole trial (up to DBL2), in the overall population, a lower proportion of patients in the nintedanib group (13.9%) than in the placebo group (19.6%) had an event of first acute ILD exacerbation or death; this difference was statistically significant (HR 0.67; 95% CI: 0.46 to 0.98) (Table 3.7).

In the overall population, the percentage of patients who died over 52 weeks was similar between treatment groups (%; n/N, nintedanib: 4.8%; 16/332, placebo: 5.1%, 17/331). The HR for time to death over 52 weeks was 0.94 (95% CI: 0.47 to 1.86). Over the whole trial (up to DBL2), in the overall population, a lower proportion of patients died in the nintedanib group (10.8%) than in the placebo group (13.6%). However, this difference was not statistically significant (HR 0.78; 95% CI: 0.50 to 1.21).

In the overall population, over the whole trial period (up to DBL2), a lower proportion of patients in the nintedanib group (40.4%; n/N, 134/332) than in the placebo group (54.7%; n/N, 181/331) progressed

(defined as ≥10% absolute decline in FVC % predicted) or died. Most of these patients had an event of progression (34.3% nintedanib vs. 48.3% placebo). Treatment with nintedanib reduced the risk of progression or death by 34% compared with placebo, as indicated by the HR of 0.66 (95% CI: 0.53 to 0.83). In the overall population, over the whole trial period (up to DBL2), a lower proportion of patients died due to respiratory cause in the nintedanib group (6.3%; n/N, 21/332) than in the placebo group (9.1%; n/N, 30/331). However, this difference was not statistically significant (HR 0.68; 95% CI: 0.39 to 1.18).

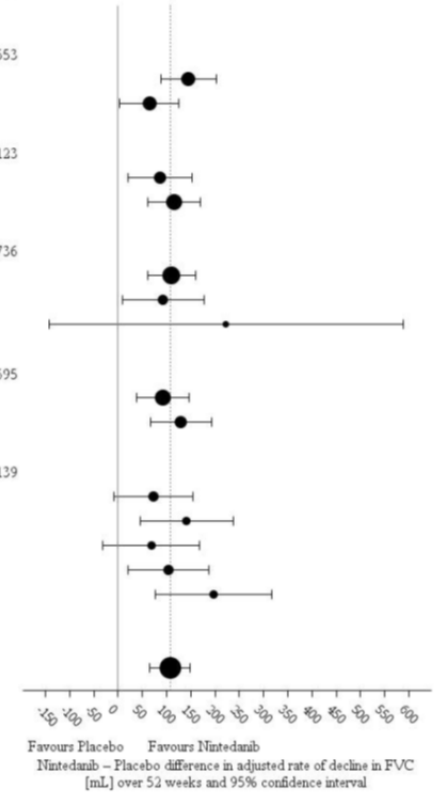
3.2.5.1 Subgroup analyses

The NICE scope specified that if the evidence allows subgroup analyses by ILD type, these should be considered.[2] The company performed subgroup analyses for the description of the trial population, the primary endpoint and safety endpoints in the following pre-planned groups: gender, age (<65 years vs. over 65 years), race, baseline FVC percentage predicted (≤70% vs >70%) and underlying clinical ILD diagnosis in groups.

According to the company, none of the demographics nor clinical characteristics had a substantial influence on the treatment effect of nintedanib vs. placebo in the overall population (Figure 3.3). All point estimates were in favour of nintedanib vs. placebo. An additional analysis investigated the impact of the underlying ILD diagnoses by employing the method of excluding ILD diagnosis groups one by one, thus exploring the influence of the excluded ILD diagnosis group on the overall treatment effect. The point estimates and CIs were very similar in these analyses, showing that the treatment effect was not driven by one of the ILD diagnosis groups.

Figure 3.3: Forest plot for the primary endpoint analysis in subgroups (overall population)

	N analysed Placebo	N analysed Nintedanib	Estimate [95% CI]	Treatment-by-subgroup-by-time interaction p-value
Gender				0.0553
Male	177	179	145.20 [88.47; 201.93]	
Female	154	153	64.21 [3.87; 124.55]	
Age group				0.5123
<65 years	121	139	86.87 [21.53; 152.21]	
>=65 years	210	193	115.13 [61.41; 168.84]	
Race				0.7736
White	246	242	110.59 [61.97; 159.20]	
Asian	80	84	92.98 [9.30; 176.67]	
Black or African American	5	5	222.48 [-143.09; 588.05]	
Baseline FVC % predicted				0.3695
<=70%	193	196	91.68 [37.36; 145.99]	
>70%	138	136	129.98 [66.22; 193.73]	
Underlying ILD Diagnosis in Groups				0.4139
Hypersensitivity pneumonitis	89	84	73.12 [-8.57; 154.81]	
Idiopathic nonspecific interstitial pneumonia	61	64	141.61 [46.04; 237.17]	
Unclassifiable idiopathic interstitial pneumonia	50	64	68.33 [-31.43; 168.10]	
Autoimmune ILDs	88	82	104.02 [21.11; 186.92]	
Other ILDs	43	38	197.13 [77.57; 316.70]	
ALL	331	332	106.96 [65.42; 148.50]	



3.2.6 Adverse events

The CS reported adverse events (AEs) that occurred in both the nintedanib and placebo groups over the course of 52 weeks in the INBUILD trial (CS, page 47, Table 19 – see also Table 3.8 below) and data presented was consistent with that in the published study.[13] The CS reported that overall, the percentages of patients with any AEs (nintedanib: 95.5% v placebo: 89.4%) and serious AEs (nintedanib: 32.2% v placebo: 33.2%) were similar in both groups.

Table 3.8: AEs in the INBUILD trial (overall population, 52 weeks)

AE	Nintedanib	Placebo
Any (n [%])	317 (95.5)	296 (89.4)
Any except for progression of interstitial lung disease	317 (95.5)	295 (89.1)
Most frequent AEs		
Diarrhoea	222 (66.9)	79 (23.9)
Nausea	96 (28.9)	31 (9.4)
Bronchitis	41 (12.3)	47 (14.2)
Nasopharyngitis	44 (13.3)	40 (12.1)
Dyspnoea	36 (10.8)	44 (13.3)
Vomiting	61 (18.4)	17 (5.1)
Cough	33 (9.9)	44 (13.3)
Decreased appetite	48 (14.5)	17 (5.1)
Headache	35 (10.5)	23 (6.9)
Alanine aminotransferase increased	43 (13.0)	12 (3.6)
Progression of ILD	16 (4.8)	39 (11.8)
Weight loss	41 (12.3)	11 (3.3)
Aspartate aminotransferase increased	38 (11.4)	12 (3.6)
Abdominal pain	34 (10.2)	8 (2.4)
Severe AEs	60 (18.1)	73 (22.1)
Serious AEs	107 (32.2)	110 (33.2)
Fatal AE		
Any	11 (3.3)	17 (5.1)
Any except for progression of ILD	10 (3.0)	14 (4.2)
AE leading to discontinuation	65 (19.6)	34 (10.3)
AE leading to permanent dose reduction	110 (33.1)	14 (4.2)

Source: CS, Table 19, pages 47-48.[1]
AE = adverse event; ILD = interstitial lung disease

AEs which were most frequently reported by System Organ Class (SOCs with a frequency >20% in either treatment group) were described in the CS. These included gastrointestinal disorders (nintedanib: 80.7%; placebo: 45.0%); infections and infestations (53.3% vs. 55.9%); respiratory, thoracic and mediastinal disorders (38.6% vs. 43.5%); investigations (34.3% vs. 16.9%); general disorders and administration site conditions (25.9% vs. 25.7%); musculoskeletal and connective tissue disorder (23.2% vs. 26.3%); nervous system disorders (20.8% vs. 16.3%); and metabolism and nutrition disorders (20.8% vs. 11.5%).

It is of note that gastrointestinal disorders occurred more frequently (80.7% vs 45.0%) in the nintedanib group than the placebo group while respiratory, thoracic and mediastinal disorders (38.6% vs. 43.5%) occurred more frequently in the placebo group.

The CS provided frequency detail on occurrence of specific AEs in each treatment group and where a >5%-point difference between groups exists it is noteworthy and included here. The following AEs were more frequent in the nintedanib group than the placebo group; diarrhoea (66.9% versus 23.9%); nausea (28.9% versus 9.4%); vomiting (18.4% versus 5.1%); decreased appetite (14.5% versus 5.1%); alanine aminotransferase increases (13.0% versus 3.6%); weight loss (12.3% versus 3.3%); aspartate aminotransferase increases (11.4% versus 3.6%); and abdominal pain (10.2% versus 2.4%). Furthermore, there was an increased frequency of AEs leading both to discontinuation (19.6% versus 10.3%) and to permanent dose reduction (33.1% versus 4.2%) in the nintedanib group; however, progression of ILD occurred more frequently in the placebo group (11.8% versus 4.8%).

The CS elaborated on the frequency of reported AEs leading both to discontinuation and dose reduction and data demonstrated that diarrhoea (nintedanib: 5.7%, placebo: 0.3%), was the most frequently reported AE leading to treatment discontinuation, while the most frequently reported AEs leading to permanent dose reduction were diarrhoea (nintedanib: 16.0%, placebo: 0.9%) and alanine aminotransferase increased (5.4% vs. 0.6%). The CS also reported that these were the most common other significant AEs (diarrhoea: 19.9% vs. 1.2%, alanine aminotransferase increased: 6.6% vs. 0.6%, and aspartate aminotransferase increased: 5.4% vs. 0.3%).

Investigator-defined drug related AEs were more frequently reported in the nintedanib group and were consistent with increased reporting by SOC of gastrointestinal disorder, these included diarrhoea (nintedanib: 59.0%, placebo: 17.8%), nausea (23.8% vs. 5.7%), and vomiting (12.3% vs. 2.1%).

There were broadly similar results (<5%-point difference) in the frequency of serious adverse events (SAEs) with the noticeable exception of interstitial lung disease which was more common in the placebo group (9.4% vs. 3.3%).

Overall, the data presented in the CS demonstrated that in the described 52 weeks, the groups are similar with respect to frequency of any and serious adverse events. Gastrointestinal discomfort, and in particular diarrhoea, was the most common adverse event and was most frequently reported in those who had taken nintedanib. Administration of nintedanib was associated with increased frequency of indicators of hepatic injury, and gastrointestinal disorder that required a permanent reduction in dosage.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company state that "as an exercise of due diligence, the feasibility of a quantitative evidence synthesis, such as an NMA or Bucher's indirect comparison with available treatments used in clinical practice, was assessed based on evidence identified in the SLR described in Appendix D" (of the CS).[1]

Six studies were explored by the company in the feasibility assessment as they met the criteria for inclusion in the SLR and reported results. Only one of these studies was deemed suitable for an indirect comparison according to the company.

Therefore, the company concluded that "an indirect comparison at 24 weeks was technically possible between nintedanib and pirfenidone, based on INBUILD[12] and NCT03099187[20]. However, since PF-ILD is a chronic condition, this comparison is expected to be immature. As a result, no indirect treatment comparisons were undertaken."[1]

ERG comments: The ERG agrees with the company that none of the studies identified in the systematic literature review performed by the company are suitable for an indirect comparison; mainly because pirfenidone is not a relevant comparator according to the NICE scope.

However, as described in Section 2.3 of this report, this means that none of the comparators described in the NICE scope have been included in the CS.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company concluded that "it was not possible to conduct any indirect or mixed treatment comparisons due to lack of published evidence for comparator treatments".[1] Therefore, no indirect comparison and/or multiple treatment comparison have been described in the CS.

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG

3.6 Conclusions of the clinical effectiveness section

The population is not completely in line with the NICE scope but is in line with the main trial (the INBUILD trial) described in the company submission, which included patients aged ≥18 years if they had a physician-diagnosed fibrosing ILD present with features of diffuse fibrosing lung disease of ≥10% extent on HRCT and met the protocol criteria for progression within 24 months of screening as assessed by the investigator.

The company only included one comparator, referred to as placebo. The comparator (placebo) in the CS was defined as the treatment patients received in the control arm of the INBUILD trial. As stated by the company, "Due to the lack of availability of specific targeted therapies, immunomodulatory treatments (including azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids) have routinely been used in clinical practice for the treatment of ILD. However, their benefit-risk profiles in PF-ILD have not been established and they are not licensed for the treatment of PF-ILD. In order to avoid the potential impact of these drugs on the assessment of nintedanib in PF-ILD, their use was not allowed at randomisation and during the first 6 months of the treatment period. Patients who had taken these drugs could only participate in the trial if a wash-out period was observed before randomisation" (CS, pages 25-26).[1] Therefore, it is doubtful that the placebo group in the INBUILD trial represents current best practice or best supportive care (BSC) in the UK.

The company did not include rituximab and infliximab as comparators despite NICE explicitly requesting to make this comparison (see NICE Response to comments on draft scope[3]).

The main evidence for the clinical effectiveness of nintedanib was from the INBUILD trial.[1, 12, 13] This trial (n=663) was a phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study with follow-up at 52 weeks followed by a variable treatment period, where patients continued on blinded, randomised assigned treatment until the end of the trial or until a reason for treatment withdrawal was met. In both arms, patients could not be taking any immunomodulatory treatment at randomisation and for the first six months of the trial, but could do so for the remainder of the trial after six months. Immunomodulatory treatments included: azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids. The INBUILD trial was undertaken in 15 countries in North America, South America, Western Europe, and East Asia, including five centres (22 patients) in the UK. The purpose the INBUILD trial was to investigate the efficacy and safety of nintedanib for treating progressive-fibrosing lung disease.

The primary endpoint, annual rate of decline in FVC over 52 weeks, was met. Treatment with nintedanib reduced the adjusted annual rate of decline in FVC by 107.0 mL ($p<0.001$) in the overall population vs. placebo. In the overall population, treatment with nintedanib did not show a significant difference in HRQoL as measured by the K-BILD questionnaire compared with placebo (adjusted mean difference 1.34; 95% CI: -0.31 to 2.98); the change from baseline total score was small in both treatment groups.

The hazard ratio (HR) for time to first acute ILD exacerbation or death also showed no significant difference between nintedanib and placebo (HR 0.80; 95% CI: 0.48 to 1.34); nor did the HR for time to death over 52 weeks (HR 0.94; 95% CI: 0.47 to 1.86).

Over the whole trial (up to DBL2), in the overall population, a lower proportion of patients in the nintedanib group (13.9%) than in the placebo group (19.6%) had an event of first acute ILD exacerbation or death; this difference was statistically significant (HR 0.67; 95% CI: 0.46 to 0.98).

In the overall population, the percentage of patients who died over 52 weeks was similar between treatment groups (%; n/N, nintedanib: 4.8%; 16/332, placebo: 5.1%, 17/331). The HR for time to death over 52 weeks was 0.94 (95% CI: 0.47 to 1.86). Over the whole trial (up to DBL2), in the overall population, a lower proportion of patients died in the nintedanib group (10.8%) than in the placebo group (13.6%). However, this difference was not statistically significant (HR 0.78; 95% CI: 0.50 to 1.21).

Overall, the data presented in the CS demonstrated that over the 52 weeks follow-up, the groups were similar with respect to frequency of any and serious adverse events. Gastrointestinal discomfort, and in particular diarrhoea, was the most common adverse event and was most frequently reported in those who had taken nintedanib. Administration of nintedanib was associated with increased frequency of indicators of hepatic injury, and gastrointestinal disorder that required a permanent reduction in dosage.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Appendix G.1.1 of the CS details an SLR which was conducted to identify published cost-effectiveness studies, health-related quality-of-life studies, and costs and healthcare resource use.

Searches were conducted on 9 June 2020. and were limited to English language publications. Databases were searched from date of inception. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the cost effectiveness systematic review (as reported in CS)

	Resource	Host/source	Date range	Date searched
Electronic databases	Embase	Ovid	1974 - 9/6/20	9/6/20
	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)	Ovid	1946 - 9/6/20	9/6/20
	Cochrane CDSR Cochrane CENTRAL	Cochranelibrary.com	Inception - 29/6/20	9/6/20
	NIHR Centre for Reviews and Dissemination (CRD; including NHS EED, DARE, and HTA)	CRD website	Inception - 29/6/20	9/6/20
	Econlit	Ovid	1886-9/6/20	9/6/20
Conference proceedings	ATS	via database searches	2018 onwards	9/6/20
	BTS			
	ISPOR			
	ERS			
	EULAR	Online abstract archive		
Additional resources	Clinicaltrials.gov	No details provided	No details provided	9/6/20
	The WHO International Clinical Trials Registry			

	Resource	Host/source	Date range	Date searched
	Tufts Medical Center Cost Effectiveness Analysis registry			
	SCHARR health utilities database			
	HERC utilities database			
NHS EED = NHS Economic Evaluation Database; HTA Database = Health Technology Assessment database; CRD - Centre for Reviews and Dissemination; ATS = American Thoracic Society; BTS = British Thoracic Society; EULAR = European League Against Rheumatism; ERS = European Respiratory Society; ISPOR = International Society for Pharmacoeconomics and Outcomes Research				

ERG comments:

- A single set of searches were undertaken for economic evaluations and healthcare resource use and cost studies, quality of life and health state utility value studies.
- Several databases and a good range of conference proceedings were searched, and reference checking was conducted. Searches were well documented, making them transparent and reproducible. There were no searches of health technology assessment organisation websites.
- The ERG was concerned that limiting the searches to English language may have introduced potential language bias (please see comments in Section 3.1.1 of this report regarding language bias.
- Study design filters were appropriately used but were not referenced.

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	Studies including any proportion of patients with ILD and progressive fibrosing phenotype defined as: • FVC – any decline in FVC percentage predicted at baseline • DLco – any decline in DLco at baseline • HRCT – worsening of fibrotic features on imaging; images identifying progression of disease • Reference to the progression of lung fibrosis (without any disease specific criteria) are to be included.	Patients with IPF
Intervention	No limits applied in searching. No limits applied during screening for costs, HCRU, or utilities.	
Comparator		

	Inclusion criteria	Exclusion criteria
	Economic evaluation studies limited to the following specific treatments during screening: • Nintedanib • Pirfenidone • Azathioprine • Cyclophosphamide • Rituximab • Mycophenolate mofetil • Prednisone • Prednisolone • Tocilizumab • Abatacept • Methotrexate • Etanercept • Infliximab • Adalimumab	
Outcomes - Economic evaluations	Cost utility analysis.	
Outcomes - Utility studies	• Utility values. • Mapping algorithms.	
Outcomes -Cost/resource use studies	• Direct and indirect costs. • Direct and indirect resource use.	
Study design	Any	• Case reports and case studies. • Editorials. • Retracted studies/ data.
Geography	No geographic limits.	Studies not conducted in Ireland and England will be considered only where no data specific to Ireland and England are identified.
Language	English Language abstracts	Non-English language

Source: Table 97 of the CS.[1]
DLco = Diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; HCRT = high-resolution computed tomography; HCRU = healthcare resource use; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis.

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The restriction to only include consider cost utility analyses (CUAs) in the economic evaluation SLR may have caused some relevant literature to have been missed.

4.1.3 Conclusions of the cost effectiveness review

Appendices G-I of the CS provide an overview of the results of the cost effectiveness, utility and resource use and costs SLRs. No cost effectiveness or HRQoL studies were included in the review. Four publications reporting on two studies were included for cost and resource use, but these were not used in the model.

Eligibility criteria were suitable for the SLR performed and the review was conducted appropriately. However, the English language restriction may have caused relevant literature to be missed.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.3 provides the ERGs comments on how well this submission aligns with the NICE reference case.

Table 4.3: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case
Synthesis of evidence on health effects	Based on systematic review	As per the reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects are expressed in QALYs. HRQoL was measured in the INBUILD trial using the EQ-5D.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	HRQoL was measured directly in patients in the INBUILD trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The UK cross-walk value set was used to value the EQ-5D HRQoL data collected in INBUILD
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per the reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be	As per the reference case

Element of health technology assessment	Reference case	ERG comment on company's submission
	valued using the prices relevant to the NHS and PSS	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case

Source: Information provided in the CS.[1]
EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; NHS = national health service; PSS = personal social services; QALY = quality-adjusted life year.

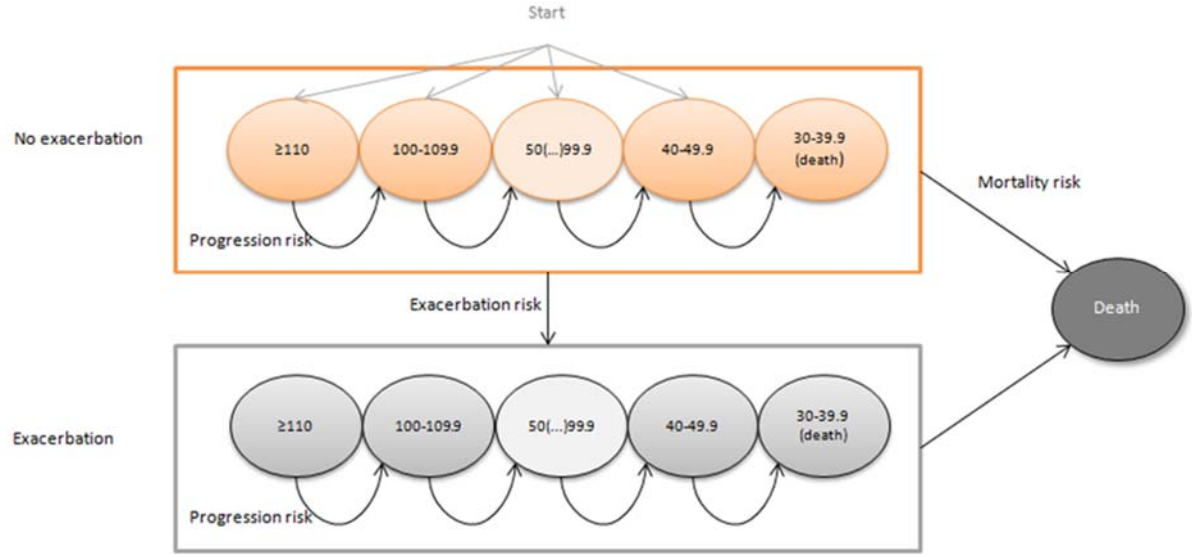
4.2.2 Model structure

The company developed a Markov model in Microsoft Excel and adopted the same model structure as for the nintedanib submission for IPF in TA379.[21] The company considered this appropriate given the equivalent disease trajectories for IPF and PF-ILD and because it was previously considered to be appropriate by the NICE committee and ERG in TA379.[21]

In preparation for their submission for TA379 in 2015,[21] the company performed a targeted review of the literature that identified no other relevant economic analyses within IPF and consulted with Irish clinicians who validated the model structure for IPF.[22] The model structure for PF-ILD was validated by UK clinicians in 2020.[23] For the development of the model for IPF in TA379, the company considered FVC percentage predicted (FVC%Pred) as the most appropriate outcome for incorporation in the Markov model as an indicator of disease progression. FVC is commonly used as a measure of disease status and as an endpoint in clinical trials in IPF and ILD, whilst FVC%Pred is considered as a better indicator of general disease status than FVC since it does not reflect patient heterogeneity in terms of body capacity, age, gender and height that are determinants of absolute FVC. Analogous to TA379,[21] FVC%Pred was also used to define the model health states in the current submission for PF-ILD. Also in line with TA379,[21] a 10-point categorisation of FVC%Pred was used to define the model health states in the current submission for PF-ILD.

In addition to lung function, acute exacerbations of ILD are dramatic, singular events that are often fatal and a major cause of mortality and morbidity in ILD. In line with the model for IPF in TA379,[21] the model structure for PF-ILD in the current submission was designed with health states that describe the patient condition as a combination of lung function, as indicated by FVC%Pred, and exacerbation. The structure of the model is shown in Figure 4.1.

Figure 4.1: Schematic representation of the model structure



Source: Figure 8 in the CS.[1]
Note: numbers in diagram relate to FVC%Pred.

The model structure is thus the same as the one used for IPF in TA379,[21] with its input parameter values updated to correspond to PF-ILD and to the application of nintedanib in this population.

The cohort of patients enters the model at different FVC%Pred health states without exacerbation. Patients can then either remain in the same health state or transition to one of the following other health states: health state with the same FVC%Pred with exacerbation, health state with 10-point lower FVC%Pred without exacerbation, health state with 10-point lower FVC%Pred with exacerbation, or Death. It is assumed that patients cannot transition to a health state with higher FVC%Pred. Similarly, it is assumed that following an exacerbation, patients cannot transition to a health state without exacerbation for the remainder of the time horizon. Transitions to Death can occur from any health state based on survival analysis of clinical trial data, or by reaching a level of FVC%Pred below 40% at which point it is assumed that the level of lung function is unsustainable. The latter was provided as an option in the model that was not used by the company.

The model uses a cycle length of three months, consistent with the clinical trial intervals between observations. The company considers this to be a balanced interval for model outcomes. The same cycle length was also used in TA379 and was considered as appropriate by the ERG of that appraisal.[21]

ERG comments: The company's description of the model provides two routes for patients to transition to Death; one is mortality based on OS, the other is the transition to an FVC%Pred lower than 40%, which the company assumed to be an unsustainable level of lung function. However, in the model, only the first of these two options were used. This implies that mortality is modelled as independent from lung function decline, even for patients with the lowest level of lung function which is assumed to be unsustainable. A similar independence between mortality and rate of acute exacerbations is also assumed in the model, despite the fact that the company report that acute exacerbations are often fatal and a major cause of mortality in ILD.[1] The ERG assumes that this decision was made to avoid double counting, as the overall survival (OS) data already includes all deaths, and obviously agrees that deaths should not be double counted. Therefore, no change was made to these assumptions in the model, but the ERG notes that this can produce implausible results in relation to discontinuation in the model as further discussed in section 4.2.6.5.

The ERG considers the other aspects of model structure appropriate given the similarities between IPF and PF-ILD, validation by UK clinicians, and the ERG and committee in TA379 having considered it appropriate.[21]

4.2.3 Population

Nintedanib has marketing authorisation for adults with chronic fibrosing ILD with a progressive phenotype, i.e. PF-ILD, based on the results of INBUILD. The model population was based on this trial and included patients within the marketing authorisation. The baseline characteristics of this patient population and the extent to which these match the characteristics of the relevant UK population are reported in Section 3.2.3.

4.2.4 Interventions and comparators

The intervention under investigation is continuous treatment with nintedanib oral capsules, in a dosage of 150 mg twice daily (i.e. 300 mg per day). In case of tolerability issues, the dosage can be reduced to 100 mg twice daily. The latter dosage is also recommended for patients with mild hepatic impairment (Child Pugh A).

The company considered that there are no relevant comparators for the treatment of adults with PF-ILD in the UK, therefore the model implements a comparison of nintedanib versus BSC. In the model, BSC was based on the placebo arm of INBUILD that the company considered as a close match to BSC for adults with PF-ILD in UK clinical practice.

ERG comments: The ERG cannot confirm that that there are no relevant comparators for the treatment of adults with PF-ILD in the UK, considering the consensus among the UK clinicians that were consulted by the company during the advisory board meeting of 11 November 2020 that there are other treatment options: steroids, immunosuppressants (i.e. both can be used as part of current best supportive care in clinical practice, but not in INBUILD; see below) and possibly off-license use of pirfenidone, especially when it goes off patent (class effect).[23]

As noted in Sections 2.3 and 3.6, the ERG has concerns regarding the representativeness of the placebo arm of the INBUILD trial for best supportive care. This is because patients in INBUILD were not permitted to receive immunomodulatory treatments (including azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids) at randomisation and during the first six months of the treatment period in INBUILD.

4.2.5 Perspective, time horizon and discounting

The model was constructed from the perspective of the NHS and Personal Social Services (PSS), in line with the NHS Reference case.[24] A lifetime horizon was adopted to capture all relevant costs and health-related utilities, with all costs and utilities discounted at a rate of 3.5% per year, in line with the NHS Reference case.[24]

4.2.6 Treatment effectiveness and extrapolation

The INBUILD trial was the main source of evidence for model parameters including: overall survival, time-to-first acute ILD exacerbation, loss of lung function, time-to-treatment discontinuation, utility values and healthcare resource use.[1] A 52-week analysis of INBUILD has previously been published, however a second database lock, taken approximately three months after the first lock was used to populate the parameters listed above as it provides longer follow-up.

The model requires evidence for three types of transitions related to treatment efficacy: mortality, acute ILD exacerbations and decline in lung function (based on FVC%Pred).

4.2.6.1 Overall survival

The mortality risk in the model is based on parametric extrapolation of OS data and is applied irrespective of health state or model events. OS extrapolation was undertaken using two different approaches: a standard frequentist approach with standard parametric distributions fitted independently to each arm and an exploratory Bayesian approach, undertaken with the aim of improving the accuracy and precision of the extrapolated OS estimates by estimating priors using available long-term data from other sources.

Goodness of fit was assessed using the Akaike information criterion and Bayesian information criterion (AIC and BIC), with models considered to be suitable candidates for inclusion in the economic model if they were within three points of the parametric model with the lowest AIC or BIC.[1] After excluding any models which did not meet this criteria, the results of the remaining parametric models were compared with evidence from the literature (visual inspection/face validity and comparison with published cohorts).

For the standard frequentist extrapolation approach, six parametric distributions were explored, as shown in Table 4.4. The exponential, lognormal and generalised gamma were considered to have a poor fit and were excluded. Therefore, the loglogistic, Gompertz and Weibull distributions were adopted for the frequentist approach.

Table 4.4: Goodness of fit frequentist OS

FVC%Pred Health state	Distribution	AIC	BIC	Decision
Placebo	Exponential	842.1154	845.9175	Excluded
	Weibull	822.3554	829.9597	
	Lognormal	825.7844	833.3886	Excluded
	Loglogistic	822.5821	830.1864	
	Gompertz	823.3835	830.9878	
	Generalised gamma	824.2238	835.6302	Excluded
Nintedanib	Exponential	690.9068	694.712	Excluded
	Weibull	687.0584	694.6687	
	Lognormal	690.5765	698.1868	Excluded
	Loglogistic	687.4335	695.0438	
	Gompertz	685.4074	693.0177	
	Generalised gamma	688.7022	700.1176	Excluded

Source: Table 25 of the CS.[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; FVC%Pred = forced vital capacity % predicted; OS = overall survival.

For the Bayesian OS analysis, additional data sources were required to generate informative priors.[1] The company used data from several trials conducted in IPF patients. The company stated that "*While IPF is the classic fibrosing ILD, PF-ILD patients demonstrate a number of similarities to IPF, with their disease being defined by the presence of progressive pulmonary fibrosis, worsening respiratory symptoms, declining lung function, resistance to immunomodulatory therapies and, ultimately, early mortality.*"[1] Given these similarities the company hypothesised that the trajectory of the survival of IPF patients could be used to inform survival estimates for PF-ILD patients.

Long term survival data were available from one phase 2 study (TOMORROW), two phase 3 IPF trials (INPULSIS I and INPULSIS II) and a combined long-term extension of these studies, known as INPULSIS-ON which monitored OS for more than eight years in IPF patients taking nintedanib.[25-27]

These IPF data were used to generate informative priors to inform the Bayesian survival analysis of the PF-ILD data. The IPF patients were matched to PF-ILD patients using propensity score matching to ensure that these patients had similar baseline characteristics. Survival data were then generated for the matched, weighted IPF patients.

Study linking and cleaning

The following data from the aforementioned trials were used:

- TOMORROW (phase II) study: patients receiving nintedanib (300mg) or placebo; patients from TOMORROW who did not receive the 300mg dose of nintedanib were excluded.[25]
- INPULSIS 1 and 2 (phase III studies): all patients.[26]
- INPULSIS-ON (open-label extension [OLE] from phase II and III studies): patients previously receiving nintedanib (300mg) who continue treatment; patients who were on placebo and then went on to receive nintedanib in the OLE were censored on initiation of nintedanib.[27]

These data were merged for the purpose of this analysis using the following censorship rules:

- Placebo patients were censored at the last contact date recorded in the phase II/III studies, or on the date they entered the OLE study, whichever happened first.
- Nintedanib patients who did not enter the OLE study were censored at the last contact date recorded in phase II/III.
- Nintedanib patients who entered the OLE study were censored at the last contact date recorded in the OLE.

A total of 1,239 IPF patients were included in this global dataset; 726 patients were treated with nintedanib and 513 with placebo. Data from the INBUILD trial were used in this analysis to incorporate PF-ILD patients. The INBUILD dataset contained 663 patients with PF-ILD; 332 patients were treated with nintedanib and 331 with placebo.

Propensity score matching

Patients from the IPF dataset were matched to PF-ILD patients from the INBUILD trial using propensity score matching, with the aim of ensuring that the IPF patients used to inform the Bayesian priors had similar baseline characteristics and disease severity to the PF-ILD patients.[1]

Baseline characteristics were assessed to determine which patient characteristics reported across the PF-ILD and IPF trials would be most relevant in the propensity score matching analysis. Baseline characteristics were assessed according to whether they were widely reported and clinically meaningful. The following baseline characteristics were used in the patient matching:

- Age
- Gender
- Race (coded in this analysis as Asian versus other)
- Time since IPF or PF-ILD diagnosis
- Percent predicted diffusing capacity for carbon monoxide (DLco) corrected for haemoglobin
- Percent predicted forced vital capacity (FVC) at baseline
- Smoking status (coded in this analysis as never smoked, used to smoke, currently smokes)

This selection of variables led to the upfront exclusion of nine PF-ILD patients with a missing baseline percent predicted DLco, and 140 IPF patients (129 had missing race, three missing baseline percent predicted DLco and eight had no baseline characteristics). The final analysis dataset therefore contained 654 PF-ILD patients (326 nintedanib patients and 328 placebo patients) and 1,099 IPF patients (640 nintedanib patients and 459 placebo patients).

Kernel and Radius matching algorithms with radii of 0.1 and 0.05 were considered. Balance was checked and the common support assumption was assessed after patients' propensity scores had been generated to determine whether there was overlap between the scores generated by the IPF and PF-ILD patients to enable matching.

The validity of the matching was assessed using common diagnostic statistics and plots.[1] The balance of covariates after the matching and weighting of control observations was checked by examining standardised differences and a summary of the mean and median bias across all covariates before and after matching, as well as Rubin's B (absolute standardised difference of the means of the linear index of the propensity scores between the two groups) and Rubin's R (ratio of the variances of the propensity score index in the two groups) indicators. Ideally, the bias (expressed as a percentage) should be below 5, Rubin's B less than 25 and Rubin's R between 0.5 and 2. The distribution of the propensity scores was also plotted. Separate analyses were conducted for each treatment arm.

Generating survival data

IPF patients who received nintedanib in both a clinical trial and (optionally) an open-label extension were of interest in this analysis. IPF patients who received placebo at the start of a clinical trial and then went on to receive nintedanib in an open-label extension were censored on initiation of the open-label extension when they started treatment with nintedanib. Overall survival was estimated as time from a patient's first baseline visit to the date of the last recorded visit. Patients were censored on their last visit if they had not been recorded as having died during the trial period. The survival analysis was performed using OpenBUGS (version 3.2.3 rev 1012).[28]

Generating informative priors

Standard frequentist survival models were fit to the matched, weighted IPF patient data using the "flexsurv" package in R (version 3.6.1).[29, 30] The three models with the lowest AIC and BIC (i.e. the best fitting models of the matched IPF data) were used to generate informative priors for the shape parameter of the Bayesian PF-ILD model. The best fitting model of the IPF data dictated the extrapolation models that were fit to the PF-ILD data.

The distribution of the shape parameter generated using the matched IPF data was used to inform the shape parameter of the PF-ILD model. Following the methodology outlined in Soikkeli 2019,[31] the Bayesian shape parameter prior was modelled using a gamma (α,β) distribution. A vague (noninformative) prior was used for the scale parameter throughout all analyses. Convergence was assessed, and a sufficient number of iterations for burn-in selected, for all analyses conducted in OpenBUGS. Autocorrelation was also evaluated and a thinning factor was applied when required.

OS estimates informing Bayesian priors

The AIC and BIC of the IPF survival models are presented in Table 4.5. Across the nintedanib and placebo cohorts, the Weibull, log-logistic and gamma distributions produced the lowest overall AICs and BICs. Given the small differences in fit between these models, all three were considered in Bayesian survival analysis. The exponential distribution produced the lowest BIC value for the nintedanib group but produced unrealistic long-term survival estimates for the placebo cohort and was therefore not considered further.

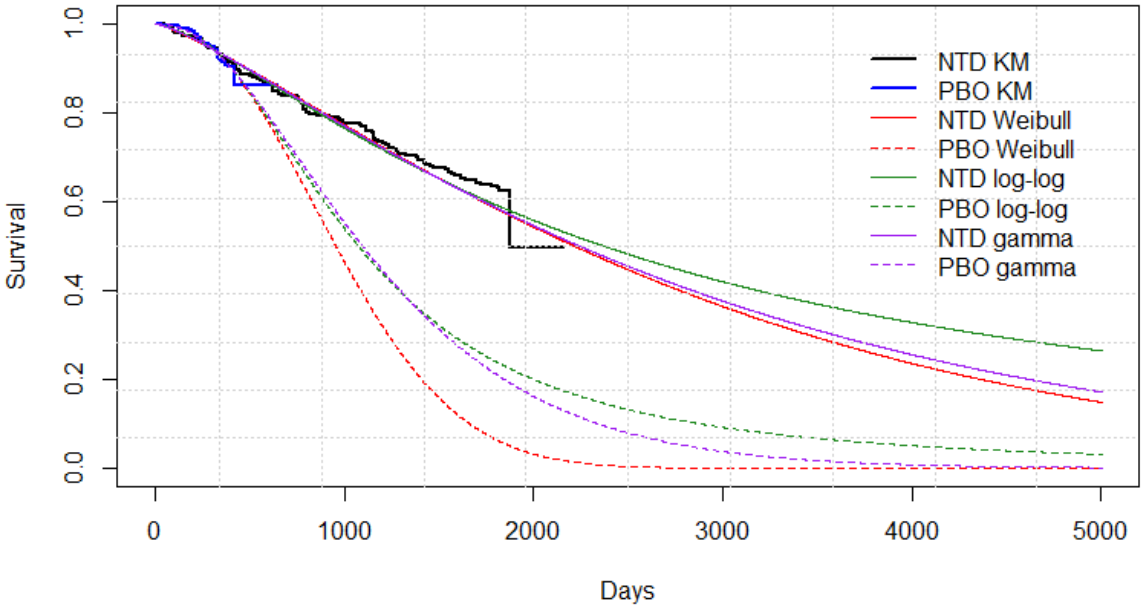
Table 4.5: AIC and BIC values for matched IPF survival models used to generate analysis prior

	Nintedanib		Placebo	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Weibull	1468.961	1476.535	567.0736	574.6227
Exponential	1471.934	1475.721	580.1805	583.9613
Generalised gamma	1470.677	1482.037	569.1665	580.4714
Log-logistic	1469.346	1476.920	567.0456	574.5948
Log-normal	1470.437	1478.010	568.6821	576.2312
Gompertz	1470.285	1477.859	568.4749	576.0240
Gamma	1468.814	1476.388	567.2287	574.7778

Note: The three lowest AIC and BIC values are shaded in grey.
Source: Table 28 of the CS.[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; IPF = idiopathic pulmonary fibrosis.

The three survival models that produced the lowest overall AIC and BIC across the nintedanib and placebo cohorts were plotted against the corresponding Kaplan-Meier curves produced by the matched IPF data in Figure 4.2.

Figure 4.2: Matched IPF Kaplan-Meier curves for placebo and nintedanib plotted alongside the three best survival models



Source: Figure 12 of the CS.[1]
IPF = idiopathic pulmonary fibrosis; KM = Kaplan-Meier; log-log = log-logistic; NTD = nintedanib; PBO = placebo.

The three best fitting survival models of the matched IPF data were used to inform the shape parameter priors in the Bayesian analysis of the PF-ILD data for both nintedanib and placebo. For each IPF model, the same survival model was fit to the PF-ILD data. The results from fitting the gamma, log-logistic and Weibull models are described below. The standard frequentist results produced by modelling survival using the matched IPF data and the PF-ILD data (with no informative prior) were also plotted against the Bayesian survival analysis results for comparison.

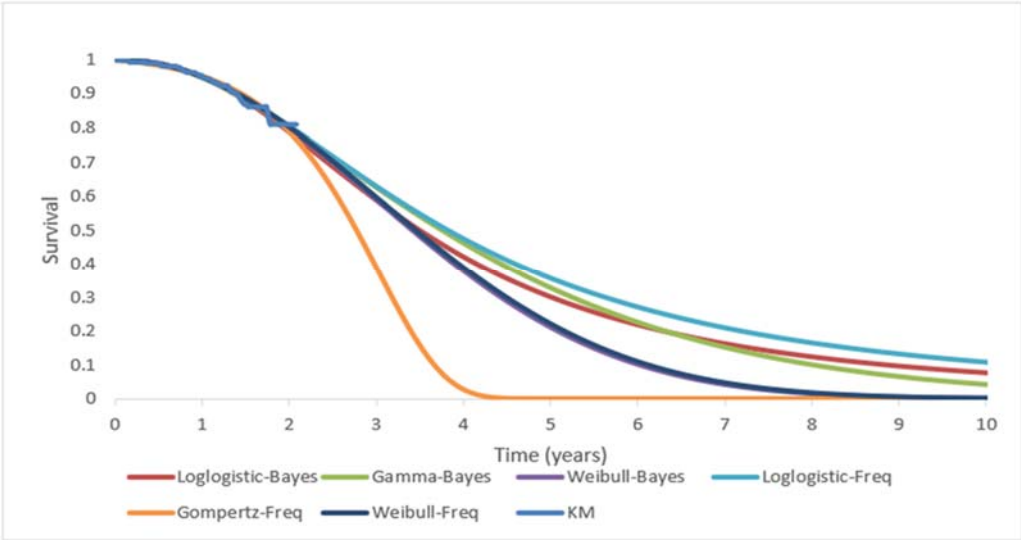
The company included three frequentist distributions (i.e. based on PF-ILD data alone) and three Bayesian survival curve distributions in the model. Figures 4.3 and 4.4 present all six distributions, and the Kaplan-Meier (KM) curves from the INBUILD trial, for placebo and nintedanib, respectively. The OS estimates produced by the three included Bayesian survival models are displayed in Table 4.6.

Table 4.6: OS estimates produced by Bayesian survival models

	Median OS (years)		Five-year survival (%)	
Distribution	**Nintedanib**	**Placebo**	**Nintedanib**	**Placebo**
Log-logistic	6.39	3.51	59	30
Gamma	6.50	3.76	60	32
Weibull	6.45	3.42	60	21

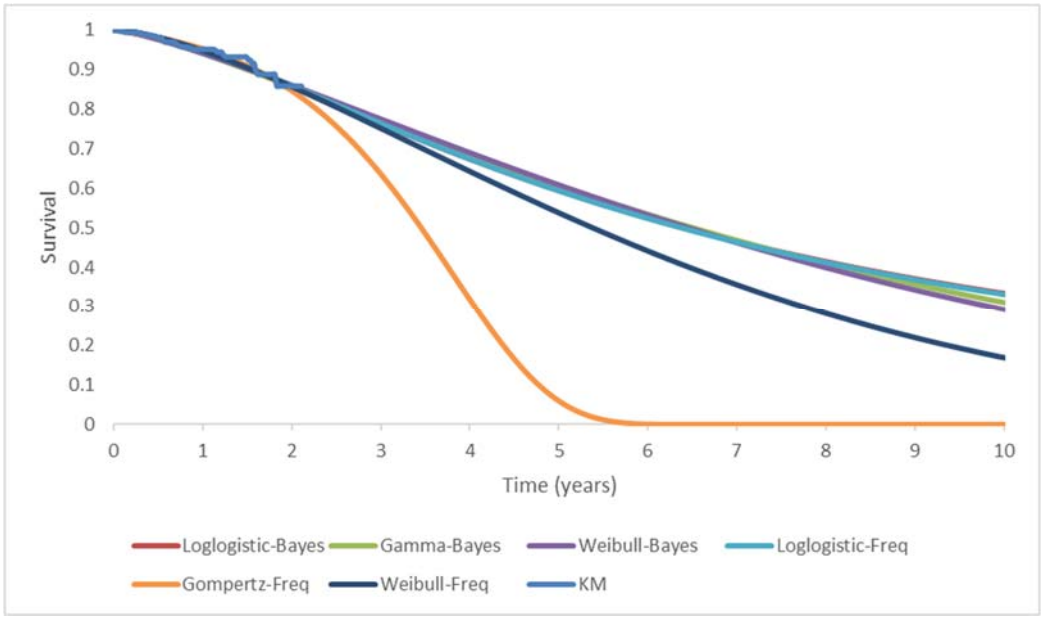
Source: Table 29 of the CS.[1]
OS = overall survival.

Figure 4.3: OS models fit versus INBUILD clinical trial KM – placebo arm



Source: Figure 16 of the CS.[1]
Bayes = Bayesian; Freq = frequentist; KM = Kaplan-Meier; OS = overall survival.

Figure 4.4: OS models fit versus clinical trial KM – nintedanib arm



Source: Figure 17 of the CS.[1]
Bayes = Bayesian; Freq = frequentist; KM = Kaplan-Meier; OS = overall survival.

External validation

Five clinical experts were approached to validate the assumptions within the model during a two-hour teleconference held on 11 November 2020. The advisory board was facilitated by company representatives and details of the attendees are available in Section B3.3 of the CS. During the teleconference, the clinical assumptions of the model were checked and discussed between the clinicians, with a particular focus on the long-term overall survival predictions of the model for PF-ILD patients.

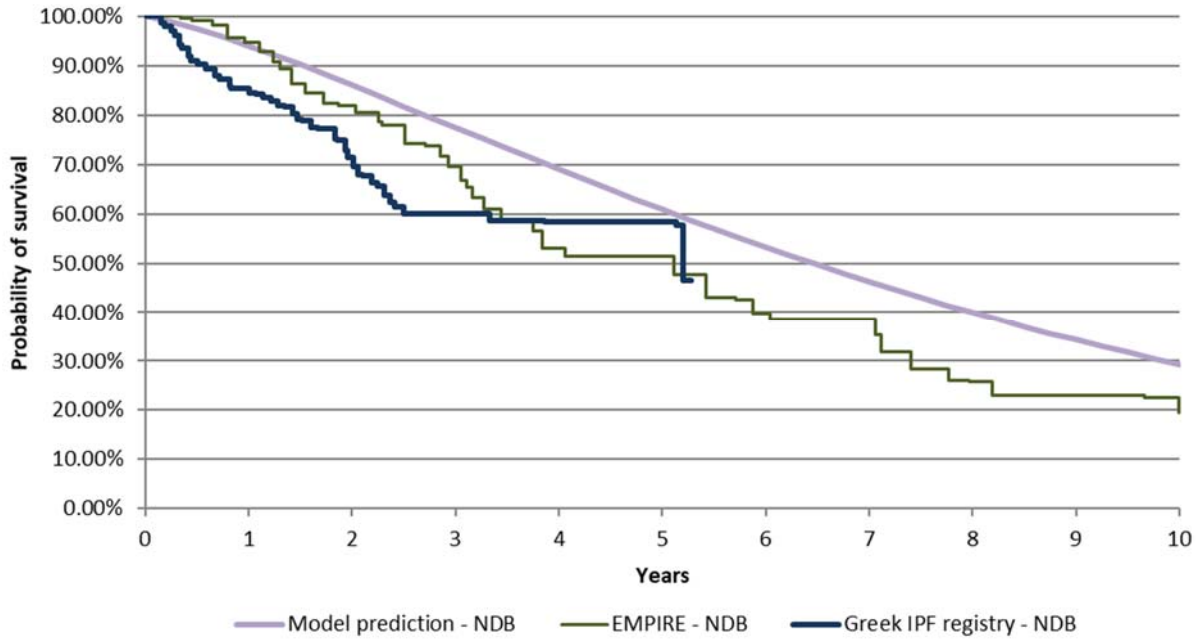
The clinicians were presented with the overall survival extrapolations presented in Figures 4.3 and 4.4 and were able to provide more commentary on the curves for BSC given the limited knowledge on the

long-term impact of nintedanib in the PF-ILD population. The clinicians agreed that for both curves the frequentist Gompertz curve was likely to underestimate survival as they would expect a proportion of patients to live beyond five years; these were therefore removed from further consideration. They also considered that both loglogistic curves appeared to overestimate survival as nearly all ILD patients with the progressive fibrosing phenotype would be dead by 10 years without any anti-fibrotic treatment. The clinicians agreed that either of the Weibull (frequentist or Bayesian) curves could be plausible for BSC.

When choosing between the Weibull curves, the company expected that the Bayesian analysis should provide more robust estimates of long-term survival, given the inclusion of longer-term IPF data to support to use of immature PF-ILD data. Therefore, the Bayesian Weibull curves were adopted for both nintedanib and BSC in the base-case.

The company used two sources of real-word data, both in IPF populations, in an attempt to validate the Weibull Bayesian curve for nintedanib, The EMPIRE study provides approximately 10 years of follow-up in 637 IPF patients taking nintedanib and a study by Antoniou et al, 2020 reports five-year survival data in 244 Greek IPF patients receiving nintedanib.[32, 33] The survival data from these studies were compared to the Weibull Bayesian extrapolation for nintedanib by the company in Figure 4.5 below. The company recognised that, in comparison to the EMPIRE study, the Weibull Bayesian extrapolation follows the KM curve for the first year or so, but then overpredicts survival and survival is consistently overpredicted by the extrapolation compared to the Greek IPF registry study.

Figure 4.5: OS models fit versus clinical trial KM – nintedanib arm

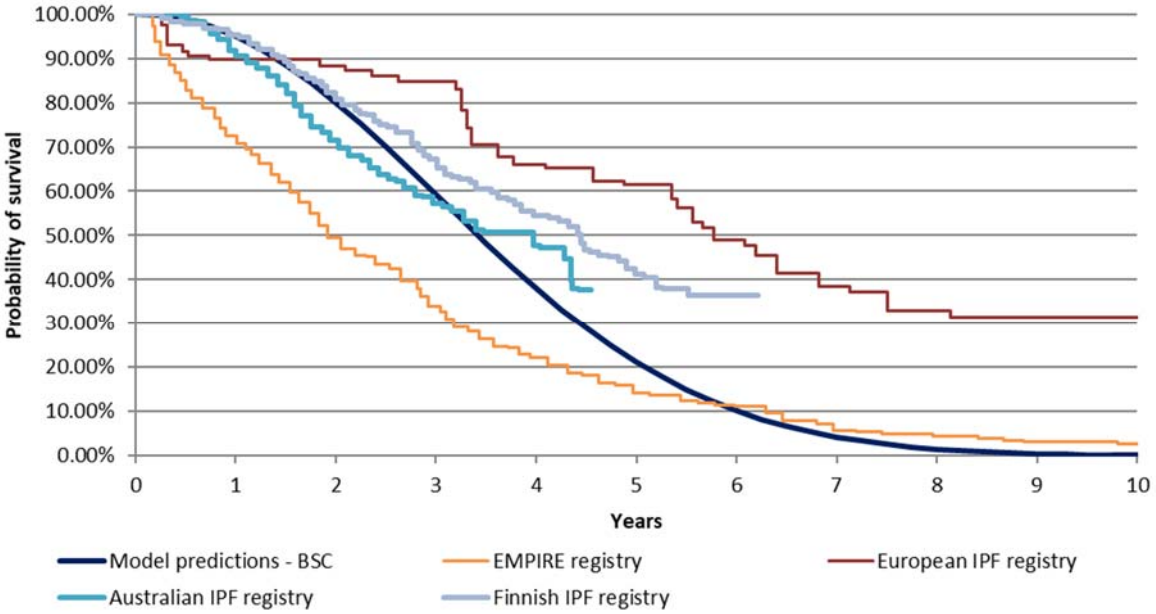


Source Figure 20 of the CS.[1]
IPF = idiopathic pulmonary fibrosis; NDB = nintedanib.

KM data from the treatment arms with no anti-fibrotic treatment in the EMPIRE study, Australian IPF registry, European IPF registry and Finnish IPF registry were used to validate the BSC survival extrapolations. Figure 4.6 shows a lack of consistency in survival between these sources. The clinicians considered the Australian registry most appropriate due to similarities between UK and Australian

clinical practice.[34] However it should be noted that as shown in Table 35 of the CS, patients in the INBUILD study were younger with lower FVC percentage than in the Australian study.

Figure 4.6: OS models fit versus clinical trial KM – BSC arm



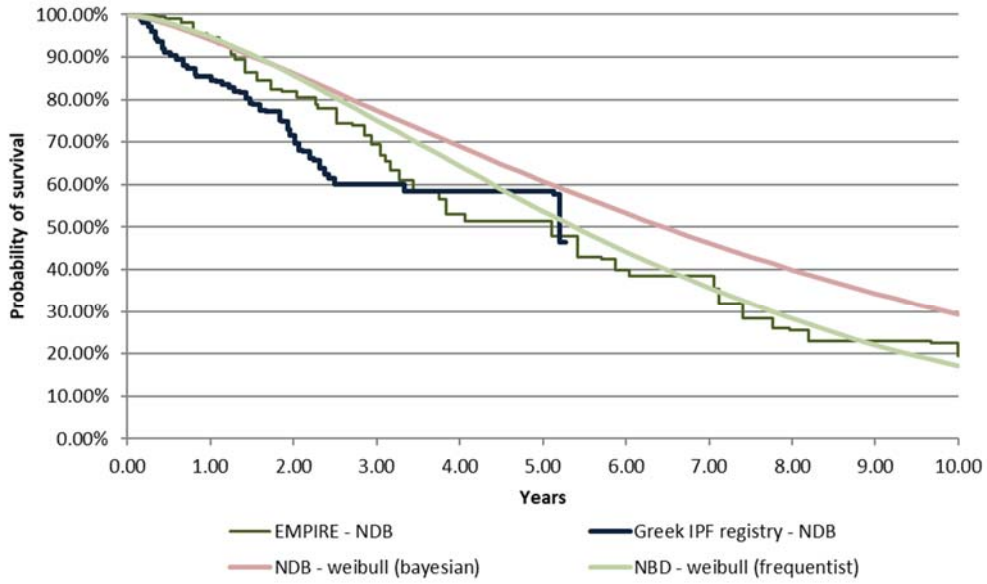
Source: Figure 21 of the CS.[1]
BSC = best supportive care; IPF = idiopathic pulmonary fibrosis; KM = Kaplan-Meier; OS = overall survival.

ERG comments: The ERG does not agree with the immediate exclusion of survival curves which may produce plausible long-term extrapolations due to arbitrary AIC and BIC difference cut-offs. Therefore, at clarification the ERG requested to see all extrapolations and have them included in the model for potential use. The company complied with this request.[3] Figures including all tested extrapolations can be seen in Figures 8 and 9 of the clarification response.[3]

The use of the Bayesian analysis adds uncertainty by requiring the use of propensity score matching and an assumption that IPL and PF-ILD patients have equivalent survival. It is not clear whether the benefits of having long-term data with which to generate priors and guide the extrapolations outweighs the additional uncertainty incorporated into the survival analysis when using the Bayesian method.

The clinicians consulted by the company to validate the survival curves considered that either of the Weibull curves (frequentist or Bayesian) could be plausible for BSC.[1] Given that the company's external validation in Figure 4.5 above shows that the Bayesian curve appears to overpredict survival compared to real-world data, the ERG requested that the company add the Weibull frequentist curve to this external validation figure, which resulted in Figure 4.7 below. This shows that the Weibull frequentist provides a better fit to the long-term KM data from the real-world data. Therefore, the ERG considers the Weibull frequentist curve more appropriate and hence has included it in their base-case.

Figure 4.7: Comparison of data on long-term survival with nintedanib in the IPF population (EMPIRE study and Greek IPF registry) versus the model predictions



Source Figure 11 of the Clarification Response.[3]
IPF = idiopathic pulmonary fibrosis; NDB = nintedanib.

4.2.6.2 Time to first acute exacerbation

Time to first acute exacerbation (TTFAE) was a secondary endpoint in the INBUILD trial. Standard parametric models were also considered to extrapolate TTFAE, resulting in AIC scores as shown below in Table 4.7.

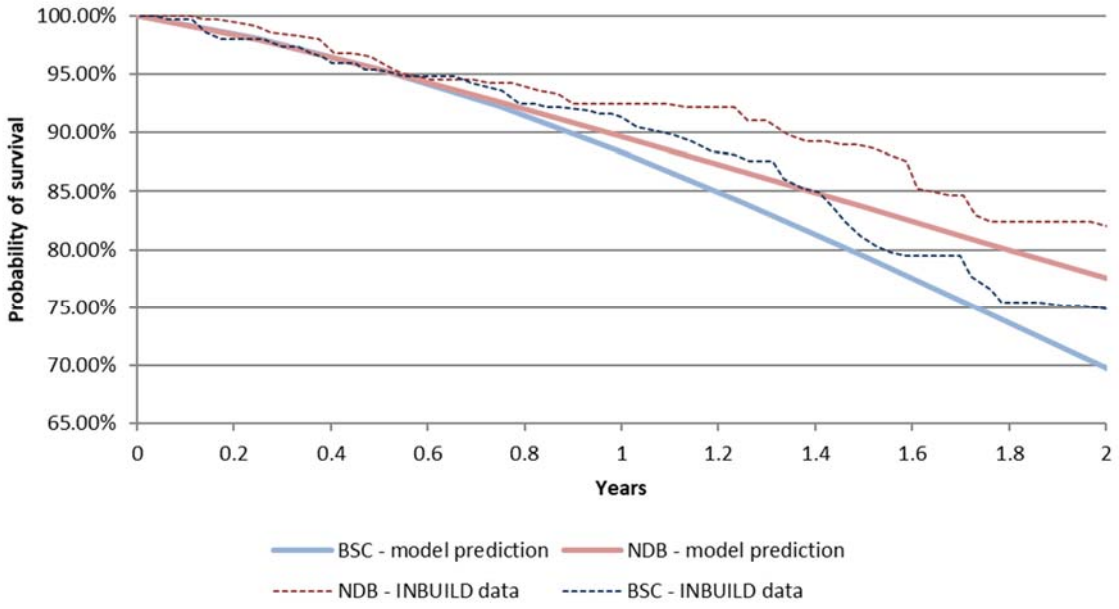
Table 4.7: Goodness of fit: time to first acute exacerbation

Treatment arm	Exponential	Generalised Gamma	Gompertz	Log logistic	Log normal	Weibull
Nintedanib	461.81	458.98	463.48	463.64	462.02	463.79
Placebo	670.14	673.82	672.14	672.15	671.82	672.11

Source: Table 36 of the CS[1]
Grey highlighted values represent the best fit

The exponential curve was associated with the lowest AIC score for the placebo arm and the second lowest for the nintedanib arm. Use of the exponential curve also facilitated a simpler modelling approach allowing the use of a fixed transition probability. Therefore, the exponential curve was used in the model. The coefficients for each arm are shown in Table 37 of the CS.[1] These coefficients resulted in a per-cycle risk of exacerbation of 1.76% and 1.12% for patients receiving BSC and nintedanib respectively. The company presented Figure 4.8 below, to demonstrate the fit of the exponential curves to the INBUILD KM data for TTFAE.

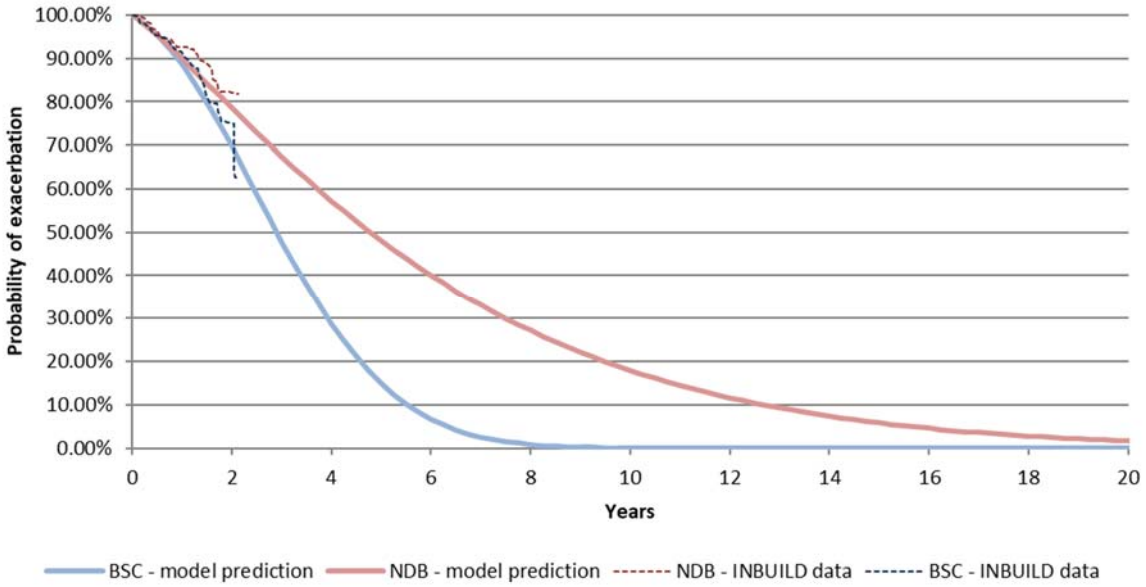
Figure 4.8: Exacerbation model fit vs. clinical trial Kaplan-Meier



Source: Figure 23 of the CS.[1]
BSC = best supportive care; NDB = nintedanib.

ERG comment: Figure 4.8 above suggests that the model is overpredicting the risk of acute exacerbation after approximately eight months, but the extrapolations beyond two years are not shown, so the long-term plausibility could not be examined. The ERG requested to see the long-term extrapolations and these were provided in the clarification response and are displayed below in Figure 4.9.

Figure 4.9: Amended exacerbation model fit vs. clinical trial Kaplan-Meier



Source: Figure 17 of the clarification response.[3]
BSC = best supportive care; NDB = nintedanib.

The ERG considered that this updated Figure provides quite a different view on the long-term difference between nintedanib and BSC which is modelled using these exponential extrapolations. The sharp drop

in the KM observed in BSC towards the end of follow-up, which is likely to be quite uncertain at the tail of the KM, has a substantial influence on the BSC extrapolation, substantially increasing the difference observed between the treatments.

The company did not include any other extrapolation options in the model or include an option for time varying risks of exacerbation which may better reflect the KM data. The company reported that they ran a scenario analysis where the rate of exacerbation with nintedanib was varied from 1.12% to 20% per cycle, which resulted in only a small increase to the incremental cost effectiveness ratio (ICER) of £3,000 per quality adjusted life year (QALY) and therefore exacerbations were not a driver of results. The ERG considered that this is likely due to the fact that mortality is not directly linked to the occurrence of acute exacerbation in the model. The ERG will explore scenarios regarding the assumed constant risk of exacerbation to explore the impact that this overprediction in both arms and the potential overestimation of the difference between arms has on results.

4.2.6.3 Recurrent exacerbations

The company base-case in the company submission assumed that patients could experience one acute exacerbation in the model. They reported that since the outlook of patients with an acute ILD exacerbation is generally very poor, this is probably a conservative assumption and the low overall frequency of exacerbations combined with the limited remaining lifetime of the patients in the model results in a very low risk for recurrent exacerbation.

ERG comment: At clarification, the ERG requested data on the occurrence of recurrent exacerbations in the INBUILD trial. The company responded that 1.5% and 1.2% of placebo and nintedanib patients experienced a recurrent exacerbation during the 52-week follow-up period of INBUILD, equating to 9/663 patients (1.36%) with a recurrent exacerbation overall. The breakdown of the number of exacerbations experienced per patient is shown in Table 4.8.[3]

Table 4.8: Exacerbations reported in the INBUILD trial up to 52 weeks

Number of exacerbation episodes	Nintedanib		Placebo	
0	311	93.7%	297	89.7%
1	17	5.1%	29	8.8%
2	1	0.3%	3	0.9%
3	3	0.9%	2	0.6%
>=4	0	0.0%	0	0.0%
Source: Table 4 of the clarification response.[3]				

The company added functionality to the model to allow the inclusion of recurrent exacerbations according to the rates of 1.5% and 1.2% for placebo and nintedanib respectively, converted to three-month probabilities. This had a limited impact of <£100 on the ICER and was included in their post-clarification base-case. The ERG agrees with the inclusion of the risk of recurrent exacerbation in the model. The ERG notes that the impact of recurrent exacerbation on patients in the model is limited to utility and costs but does not further increase the probability of loss of lung function beyond that of the first exacerbation.

4.2.6.4 Loss of lung function

Patients start the model in different FVC%Pred health states, according to the distribution of patients at baseline in the INBUILD trial, as shown in Table 4.9 below.[1, 3]

Table 4.9: Patient distribution at the start of the model

FVC%Pred Health state	Distribution (%)
110 and above	1.25%
100-109.9	1.88%
90-99.9	7.34%
80-89.9	13.59%
70-79.9	20.16%
60-69.9	25.00%
50-59.9	21.41%
40-49.9	9.38%
Source: Table 38 of the CS FVC%Pred = forced vital capacity % predicted	

Probabilities of decline in lung function per cycle for the BSC arm were estimated from the INBUILD data using a multivariate mixed effects logistic regression model including predictors of lung function decline.[1] This allowed for the analysis of recurrent events and the incorporation of additional covariates that could influence the probability of decline. Candidate predictors were:

- Age (continuous)
- Gender (male or female)
- Race (white, Asian, or other)
- Methotrexate use at baseline (yes or no)
- High-resolution computed tomography (HRCT) results (i.e. UIP-like pattern only, other fibrosis patterns)
- Underlying ILD diagnosis (e.g. autoimmune ILDs, hypersensitivity pneumonitis)
- Group criteria for progressive ILD [PGGR1] (i.e. clinically significant decline in FVC%Pred >=10%, marginal decline in FVC %Pred (>=5-<10%) combined with worsening of respiratory symptoms or increasing extent of fibrotic changes on chest imaging, worsening of respiratory symptoms and increasing extent of fibrotic changes on chest imaging only)
- FVC%Pred at the start of the time period (continuous)
- Exacerbation during the analysed three-month period (whether it occurred or not)

A p-value of 0.2 was used to determine which variables had a univariate association. The final model included the following variables: age, HRCT pattern, group criteria for progressive ILD, FVC at start of interval, and exacerbation variable. Further details of the model coefficients are available in Table 39 of the CS.[1]

The resulting three-monthly probabilities of progressing for each FVC%Pred category are shown in Table 4.10. Separate values are used for patients prior to and after an acute exacerbation as exacerbation was found to be a statistically significant predictor of lung function, with lung function decline expected

to occur more quickly after exacerbation and a diminishing effect in progression as lung function was lost observed.

Table 4.10: Three-month probabilities of progression, placebo (i.e. BSC)

FVC%Pred at start of interval	No exacerbation at start of interval	Intervals starting after first exacerbation
115	7.35%	41.14%
105	5.34%	33.19%
95	3.85%	26.10%
85	2.77%	20.07%
75	1.99%	15.14%
65	1.42%	11.26%
55	1.01%	8.27%
45	0.72%	6.02%

Source: Table 41 of the CS.[1]
BSC = best supportive care; FVC%Pred = forced vital capacity % predicted.

The risk of loss of lung function for nintedanib was informed by an odds ratio applied to the baseline placebo risk, assuming a constant relationship over time.[1] This odds ratio (shown in Table 4.11) was estimated using a mixed effect logistic regression of data from INBUILD, in which treatment was included as the only predictor. The company note that the 95% confidence interval for the odds ratio contains the value of 1 at the very upper limit of the interval, indicating that there is no statistically significant difference in effect between nintedanib and placebo at the 95% level. However, given this occurs at the highest end of the range it was judged appropriate to model a difference in lung function decline between nintedanib and placebo (or BSC) and explore this uncertainty further in a sensitivity analysis. The modelled three-month probabilities of progression for nintedanib patients are displayed in Table 4.12.

Table 4.11: OR values for loss of lung function

Fixed effects:	Estimate	SE	p-value	Odds ratio	95% CI
Intercept	0.654	0.2405	<0.01		
NDB coefficient	-0.4248	0.226	0.0602	0.654	0.420 – 1.1018

Source: Table 43 of the CS.[1]
CI = confidence interval; NDB = nintedanib; OR = odds ration; SE = standard error.

Table 4.12: Three-month probabilities of progression, nintedanib

FVC%Pred at start of interval	No exacerbation at start of interval	Intervals starting after first exacerbation
115	4.93%	31.37%
105	3.56%	24.52%
95	2.55%	18.76%
85	1.83%	14.10%

FVC%Pred at start of interval	No exacerbation at start of interval	Intervals starting after first exacerbation
75	1.31%	10.45%
65	0.93%	7.66%
55	0.66%	5.57%
45	0.47%	4.02%

Source: Table 41 of the CS.[1]
FVC%Pred = forced vital capacity % predicted.

ERG comment: It is not clear to the ERG why the impact of treatment on the probability of progression was not included in the full model used to estimate the probability of progression in BSC, but instead estimated in a separate model. The ERG requested this to be included in the full model at clarification. The company conducted the requested analysis, which resulted in the following probabilities of loss of lung function shown in Table 4.13 below. The ERG notes that these two different methods produce very different probabilities of loss of lung function after first exacerbation in both placebo and nintedanib patients. The company allowed for the use of these updated probabilities in the model, stating that this had a minimal impact on the ICER (<£20). The ERG was somewhat surprised that changes to the probability of progression had such a small impact on results, but this is likely due to the fact that while the absolute values differ substantially the relative differences between pre and post-exacerbation and between nintedanib and placebo do not differ substantially between the two models. The ERG also notes that in both methods the coefficient for treatment was not statistically significant, with confidence intervals crossing one.

From a methodological point of view the ERG would have preferred that the impact of treatment on the probability of progression was included in the full model, but given the minimal impact on the ICER, no change was made. It is worth noting that both methods assume a lifetime treatment effect while on nintedanib treatment.

Table 4.13: Three-month probabilities of progression (based on new regression output)

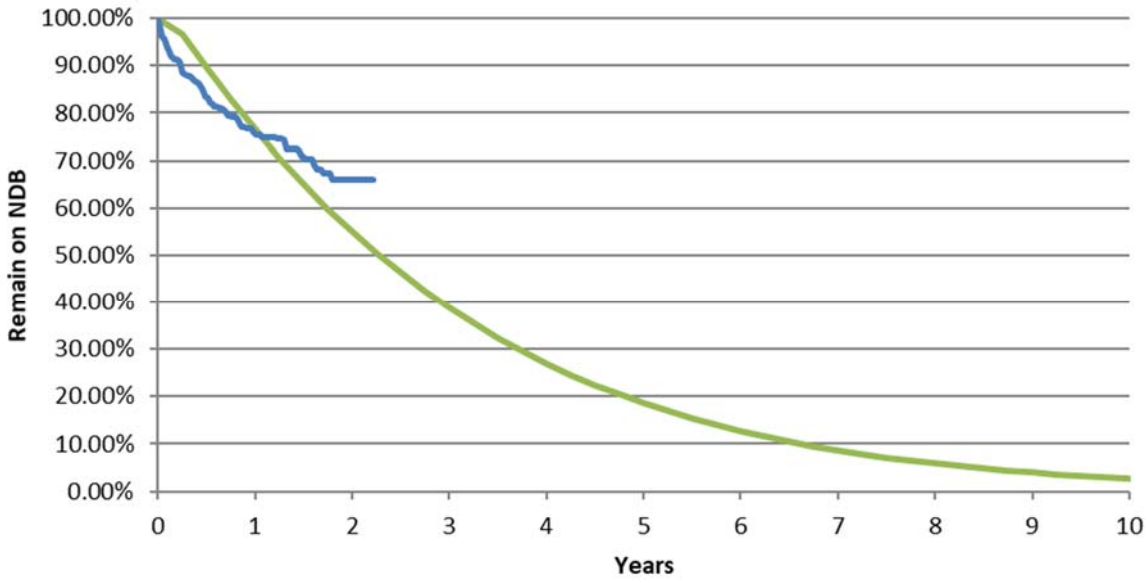
FVC%Pred at start of interval	Nintedanib		Placebo	
	No exacerbation at start of interval	Intervals starting after first exacerbation	No exacerbation at start of interval	Intervals starting after first exacerbation
115	5.57%	16.81%	8.26%	23.56%
105	4.29%	13.31%	6.41%	18.98%
95	3.30%	10.45%	4.94%	15.11%
85	2.53%	8.15%	3.80%	11.92%
75	1.93%	6.31%	2.92%	9.32%
65	1.47%	4.87%	2.23%	7.25%
55	1.12%	3.75%	1.71%	5.61%
45	0.86%	2.87%	1.30%	4.32%

Source: Tables 6 and 7 of the clarification response.[3]
FVC%Pred = forced vital capacity % predicted.

4.2.6.5 Treatment discontinuation

The company reported that up to DBL2, approximately 34% of patients had discontinued treatment in the nintedanib arm of the clinical trial.[1] Overall nintedanib discontinuation risk was estimated by extrapolating INBUILD discontinuation data using an exponential model, as it assumes a constant hazard and therefore a fixed discontinuation rate allowing for simple model implementation.[35] The company noted that this approach was also taken in TA379.[21] Discontinuation due to death was excluded from analysis. The coefficient for the exponential model was 7.270 (SD 1.737, 95% CI 7.083-7.457). This resulted in an overall discontinuation risk for nintedanib of 5.97% per month. The model predictions for time to discontinuation based on this risk, compared to available KM data from INBUILD, are presented in Figure 4.10.

Figure 4.10: Time on treatment with nintedanib



Source: Figure 27 in the CS.[1]
NDB = nintedanib.

This figure shows that the model underestimates discontinuation in the first year, but from approximately 15 months onwards the model appears to overestimate discontinuation. The company validated these predictions using data from Lancaster et al. 2019, which provides long-term data on the safety and efficacy of nintedanib in the IPF population.[36] Lancaster et al. 2019, reported that the median exposure to nintedanib, based on the long-term follow-up data from the nintedanib trials, was 22.5 months with a maximum exposure time of 93.1 months. The exponential model fitted to the INBUILD data predicts median survival of approximately 2.3 years (or 27-28 months), with a proportion of patients remaining on nintedanib after eight years (96 months), which was past the maximum exposure point measured by Lancaster et al. 2019. Therefore, the company acknowledged that the model may underestimate the true rate of discontinuation for nintedanib and conducted a scenario analysis in which a higher rate of discontinuation was applied to more closely match the data reported by Lancaster et al. 2019.

ERG comments: Given that the company's base-case exponential extrapolation of time to discontinuation does not appear to reflect the underlying KM data well, at clarification the ERG requested that the company consider alternative plausible extrapolations, or constant or time dependent discontinuation rates which better represent the INBUILD KM data, for possible use in the model.[37]

The company responded that the inclusion of alternative extrapolations or time dependent discontinuation rates would have required a more complicated and less transparent model structure and therefore these options were not included in the model.[3] Instead they conducted further sensitivity analyses using constant rates of discontinuation determined by the upper and lower bounds of the confidence interval from INBUILD (5.13% – 7.37%) as well as an alternative analysis where the exponential coefficient was varied until a curve was generated that was more consistent with that reported by Lancaster et al. 2019 and lastly a scenario which generated the long-term predictions to more closely match the tail of the INBULD KM curve.

The ERG noted a plausibility concern in the model regarding the impact of discontinuation on model results. When the discontinuation rate from nintedanib is increased in the company's model, the ICER decreases due to substantial treatment cost savings, with the optimal ICER observed when discontinuation is 100%. However, increasing the discontinuation rate had zero impact on life years in the nintedanib group and a minimal impact on QALYs (5.97% discontinuation = [redacted] vs. 100% discontinuation = [redacted]). This would imply that the optimal course of treatment according to the model, would be for all patients to take nintedanib for the first three months and then discontinue. The lack of difference in LYs is due to two modelling aspects: a) the company assumed that patients who had discontinued from nintedanib continued to be represented by the nintedanib survival analysis post-discontinuation, as most patients who discontinued treatment were included in the trial survival analysis; and b) exacerbation events were not directly linked to mortality in the model, meaning the increased risk of exacerbation events after discontinuation (when patients are assumed to have the same risk as BSC patients), does not translate into any difference in LYs. This results in a lifetime treatment effect in terms of OS in the model. Given that a high proportion of patients who discontinued nintedanib in the trial continued to be followed-up, the ERG consider that the OS is likely to reflect the weighted efficacy of patients on and off-treatment over the observed follow-up. However, the impact on efficacy in the longer-term remains uncertain as it is not clear whether the trial follow-up is sufficiently long to fully capture the impact of discontinuation on OS. It is important to note that the way discontinuation has been incorporated into the survival analysis makes it impossible to assess the impact of changes in the discontinuation rate on the ICER, as a new OS curve would be needed.

4.2.7 Adverse events

Data on the frequency of AEs were obtained from the INBUILD trial CSR.[18] The company included those AEs which:

- Had an incidence of >10% in either treatment arm
- Were treatment-related/treatment-emergent.
- Had an incidence at least 1.5 times higher in the treatment arm than in the control arm.

Based on these criteria the AEs shown in Table 4.14 were included in the model.

Table 4.14: Adverse events included in the model

	Nintedanib		Placebo	
AE	**N (%)**	**Risk per cycle**	**N (%)**	**Risk per cycle**
Patients	332 (100.0)	N/A	331 (100.0)	N/A
GI events				
Diarrhoea	196 (59.0)	20.05%	59 (17.8)	4.8%

	Nintedanib		Placebo	
AE	**N (%)**	**Risk per cycle**	**N (%)**	**Risk per cycle**
Nausea	79 (23.8)	6.59%	19 (5.7)	1.47%
Vomiting	41 (12.3)	3.25%	7 (2.1)	0.53%
Investigations				
Alanine aminotransferase increased	36 (10.8)	2.84%	8 (2.4)	0.61%

Source: Table 44 of the CS.[1]
AE = adverse events; GI = gastrointestinal.

ERG comment: At clarification, the ERG requested that the company provide an option in the model to include AEs with an incidence of > 5%, and AEs with an incidence of > 5% or 1.5 times greater than in the comparator arm and to justify their choice of a 10% cut-off. The company clarified that they had chosen an incidence cut-off of > 10% because adverse events of all severities were included and not just serious or severe adverse events. They did not provide a 5% incidence option in the model because no severe or serious adverse events occurred in greater than 5% of patients receiving nintedanib and therefore the overall impact on costs of extending the criteria from a 10% to 5% incidence was expected to be negligible.

4.2.8 Health-related quality of life

The literature review conducted to identify relevant health state utility values (HSUVs) did not identify any values specific to PF-ILD. Therefore the HRQoL data collected from the INBUILD trial was used to estimate HSUVs in the model.[1] EQ-5D HSUVs were estimated for each FVC%Pred health state. Acute exacerbation and AEs were included as utility decrements.[1]

In INBUILD, HRQoL was measured using the EQ-5D-5L on day 1 of treatment and then at weeks 12, 24, 36 and 52 of treatment as well as the end of treatment visit.[35] This HRQoL data was valued using the EQ-5D cross walk value set for the UK to obtain utility values. Table 4.15 shows the mean EQ-5D-5L utility used in the model for each FVC%Pred health state. The analysis only used data before exacerbations so that these events would not affect the HSUVs as the impact of exacerbations is considered separately. The analysis resulted in a lower estimated utility in patients with an FVC%Pred ≥110 than those patients in the 100-109.9 category (0.7028 vs 0.7521). This was considered implausible by two clinicians consulted by the company and given that the ≥110 estimate was based on only 10 patients, utility in the ≥110 category was assumed equal to utility in the 100-109.9 category in the model. It was assumed that the utility was 0 (dead) for FVC%Pred values < 40%.

Table 4.15: EQ-5D utility values used in the model by FVC%Pred group

FVC%Pred Health state	Mean EQ-5D utility	SD	Number of patients
≥110	0.7521	NA.	NA.
100-109.9	0.7521	0.2570	30
90-99.9	0.7287	0.2278	76

FVC%Pred Health state	Mean EQ-5D utility	SD	Number of patients
80-89.9	0.7333	0.2051	148
70-79.9	0.7242	0.2113	214
60-69.9	0.6750	0.2349	271
50-59.9	0.6453	0.2240	256
40-49.9	0.6045	0.2457	137

Source: Table 46 of the CS.[1]
EQ-5D = European Quality of Life-5 Dimensions; FVC%Pred = forced vital capacity % predicted; SD = standard deviation; NA = not applicable

When patients experience an acute exacerbation, this is associated with a utility decrement of 0.167 (SE = 0.050).[1] This decrement was estimated from regression analysis using the EQ-5D collected in the INBUILD trial. Reduction in utility due to acute exacerbation was assumed to last for one month and therefore this disutility was adjusted to 0.0556 per three month cycle, after which utility returned to the relevant FVC%Pred HSUV. The company report that the disutility value estimated from the INBUILD data was likely to be a conservative estimate because it is likely that the worst patients were missing not-at-random from the dataset (as they were unable or unwilling to attend the next study visit).

Disutilities for gastrointestinal (GI) event were based on estimates from TA379 based on the assumption that nintedanib has a similar safety profile regardless of the indication.[1, 21] Post hoc analysis of INPULSIS safety data showed that the EQ-5D change in patients that experienced a serious GI event was -0.068 (-0.201 to 0.065).[38, 39] The company assumed half of this value (-0.034) in this model for GI disutility in patients that experienced a non-serious GI event. The company validated this assumption against results from a phase III trial in recurrent non-small cell lung cancer which estimated a disutility for grade 3/4 diarrhoea of -0.042.[40] If 0.042 is a reasonable disutility for a serious diarrhoea, the company considered their assumed value of 0.034 for any GI event to be plausible. For alanine aminotransferase (ALT) increase the company assumed no disutility as this event is of mild to moderate severity and therefore considered asymptomatic.

ERG comments: The ERG was pleased to see base-case utility values based on EQ-5D trial data from INBUILD. The reversal in the trend that patients with lower FVC%Pred have lower utility for the 80-89 FVC%Pred category is not particularly plausible. Therefore, the ERG requested that the company make some adjustment to this value so that the trend remained consistent. The company responded that this was possible within the model structure but had a minimal impact on the ICER. To ensure that plausible values were used, the ERG incorporated a utility value of 0.7265 for the 80-89 FVC%Pred health state, which equates to a linear decline in utility from the 90-99 and 70-79 health states.

The company updated the model to allow for the age-adjustment of utilities during the clarification stage as the request of the ERG. This was done using UK population norms calculated by Kind et al, 1999.[41]

The ERG identified two other estimates for the impact of acute exacerbations in the first month in TA379.[21] These were estimated from EQ-5D data from the INPULSIS trial in IPF.

The validity of the assumed disutility for all GI events included in the model, estimated as half the value of serious GI events in TA379 is unclear. However, given the limited impact of AEs on model results

this is not a key issue. The disutility estimated from investigator ruled exacerbations was -0.14 in the first month, while the disutility estimated from adjudication committee ruled exacerbations was -0.274. These estimates will be explored as scenarios to examine the impact of the assumed disutility.

4.2.9 Resources and costs

The company included the following costs in the cost effectiveness analysis: drug acquisition costs for nintedanib, liver function test costs, health care resource use costs corresponding to each of the health states in the model, acute exacerbation costs, end of life costs, and costs in relation to adverse events.

4.2.9.1 Drug acquisition costs

The list price for nintedanib is £2,151.10 per pack of 60 capsules, for both the 100 mg and 150 mg formulations. The price that is used in the model includes a Patient Access Scheme (PAS) discount of [redacted] and is [redacted] per pack of 60 capsules. This amounts to a cost of [redacted] per capsule, or a cost of [redacted] per daily dose of two capsules of either 100 or 150 mg. Based on prescription records of nintedanib for IPF, the company assumed that 79% of patients receive the 150 mg formulation and 21% of patients receive the 100 mg formulation. Since the same price applies to both formulations, this has no implications for the calculation of drug acquisition costs. Administration costs are not applicable, because nintedanib is an oral treatment.

4.2.9.2 Liver function test costs

The nintedanib Summary of Product Characteristics states that hepatic transaminase and bilirubin levels should be investigated before treatment initiation and during the first month of treatment, and should be monitored at regular intervals thereafter.[42] The company assumed that all patients on active treatment would incur the cost of a liver function test at a quarterly frequency (i.e. once every three months). The cost per liver panel blood test was estimated at £2.79 (NHS Reference Costs 2018/19, Direct Access: Pathology Services: DAPS05 Haematology).[43]

4.2.9.3 Health state resource use costs

The company used individual patient data from INBUILD on the frequencies of use for the following health care resources: hospitalisations, emergency room (ER) visits, general practitioner visits, specialist visits, nurse visits, physiotherapy visits, occupational therapist visits, other visits, and use of oxygen. These data were grouped into the same 10-point FVC%Pred categories as used to define the model health states. Within each category, the number of observations corresponds to the number of patients multiplied by the number of months spent in that category. These numbers of observations and the three month probabilities of resource use are provided in Table 4.16.

Table 4.16: Three monthly probabilities of resource use for each FVC%Pred group

Health care resource	FVC%Pred group							
	≥110	100 - 109.9	90 - 99.9	80 - 89.9	70 - 79.9	60 - 69.9	50 - 59.9	40 - 49.9
Number of observations	124	274	599	1,215	1,958	2,566	2,386	1,497
Hospitalisation	0.12	0.05	0.05	0.05	0.05	0.09	0.09	0.14
Emergency room visit	0.10	0.04	0.02	0.04	0.03	0.05	0.06	0.05
GP visit	0.12	0.10	0.16	0.18	0.31	0.19	0.17	0.15
Specialist visit	0.07	0.14	0.25	0.21	0.26	0.23	0.18	0.17

Health care resource	FVC%Pred group							
	≥110	100 - 109.9	90 - 99.9	80 - 89.9	70 - 79.9	60 - 69.9	50 - 59.9	40 - 49.9
Number of observations	124	274	599	1,215	1,958	2,566	2,386	1,497
Nurse visit	0.02	0.01	0.03	0.02	0.03	0.03	0.02	0.02
Physiotherapy visit	0.01	0.01	0.01	0.02	0.03	0.00	0.00	0.00
Other visits	0.02	0.01	0.02	0.04	0.01	0.01	0.02	0.03
Occupational therapy visit	0.02	0.01	0.02	0.04	0.01	0.01	0.02	0.03
Oxygen use	0.14	0.16	0.17	0.15	0.27	0.33	0.47	0.57

Source: the electronic model from the CS / Figure 32, Tables 48, 51, 53 and 54 of the CS.[1]
CS = company submission; FVC%Pred = forced vital capacity % predicted; GP = general practitioner.

The estimated cost of hospitalisation was composed of the following: the average number of hospitalisations per patient with at least one hospitalisation (1.35, SE 0.22), the average duration of hospitalisation (10.74 days, SE 0.62), the proportion of hospitalisations associated with an ICU stay (5.1%, SE 1.1%), the proportion of hospitalisations associated with mechanical ventilation use (2.1%, SE 0.8%), the proportion of hospitalisations associated with an ER overnight stay (7.8%, SE 1.4%), and the proportion of hospitalisation associated with ambulance use (18.5%, SE 2.0%). The company considered the number of observations for each of these components too low for an analysis by FVC%Pred group, therefore the averages for each component over all groups was used to calculate the cost per hospitalisation that was applied to all groups. The unit costs and average values for each component of the hospitalisation cost estimate as well as the total cost estimate per hospitalisation are provided in Table 4.17.

Table 4.17: Hospitalisation cost estimate

Health care resource	Unit cost		Number of visits (per patient)	
	Value	Source	Average value (SE)	Source
Hospitalisation	£324	National Schedule of Reference Costs - Year 2017-18 - NHS trusts and NHS foundation trusts; Weighted average of DZ27S, DZ27T and DZ27U (Respiratory Failure without Intubation with CC score 11+, 6-10, 0-5 respectively. Inflated to 2018/2019 price year. Excess bed days are not reported within 2018/2019 NHS reference costs.[44]	Number of visits: 1.35 (0.22); Duration 10.74 days (0.62)	INBUILD trial post hoc analysis [35]
ICU stay	£1,073	Weighted average of XC06Z (Adult Critical Care, 1 organ supported) and XC07Z (Adult Critical Care, 0 organs supported), Adult Critical Care Unit National Schedule of Reference Costs Year 2018/19 - NHS trusts and NHS foundation trusts; Critical Care.[43]	5.1% (1.1%)	

Health care resource	Unit cost		Number of visits (per patient)	
	Value	Source	Average value (SE)	Source
Mechanical ventilation	£1,735	Non-Invasive Ventilation Support Assessment, 19 years and over, Non-Elective Long Stay, DZ37A; NHS Reference Costs 2018/2019.[43]	2.1% (0.8%)	
ER overnight stay	£268	Weighted average across all types (admitted only). Excludes patients that are dead on arrival, dental services and patients with no treatment/investigations. National Schedule of Reference Costs Year 2018/19 - NHS trusts and NHS foundation trusts; Accident and Emergency Services.[43]	7.8% (1.4%)	
Ambulance use	£224	Weighted average of ASH1 (hear and treat or refer), ASS01 (see and treat or refer), ASS02 (see and treat and convey); National Schedule of Reference Costs Year 2018/19 - All NHS trust and NHS foundation trusts - ambulance services.[43]	18.5% (2.0%)	
Total cost per hospitalisation	£4,815			

Based on Table 49 in the CS.[1]
CS = company submission; ER = emergency room; ICU = intensive care unit; NHS = national health service.

The estimated cost of an emergency room visit was composed of the average number of emergency room visits (1.21, SE 0.113), and the proportion of emergency room visits associated with ambulance use (19.4%, SE 2.724%). The unit costs and average values for each component of the emergency room visit cost estimate as well as the total cost estimate per emergency room visit are provided in Table 4.18.

Table 4.18: Emergency room visit cost estimate

Health care resource	Unit cost		Number of visits (per patient)	
	Value	Source	Average value (SE)	Source
ER visit	£182.85	Weighted average across all types. Excludes patients that are dead on arrival, dental services and patients with no treatment/investigations; National Schedule of Reference Costs - Year 2018/19.[43]	1.21 (0.113)	INBUILD trial post hoc analysis[35]
Ambulance use	£224.39	Same as hospitalisation, Table 4.17.[43]	19.4% (2.724)	

Health care resource	Unit cost		Number of visits (per patient)	
	Value	Source	Average value (SE)	Source
Total cost per ER visit	£264			
Based on Table 50 in the CS.[1] CS = company submission; ER = emergency room.				

For general practitioner visits, specialist visits, nurse visits, physiotherapy visits, occupational therapist visits and other visits, the unit costs and average number of visits per patient are provided in Table 4.19.

Table 4.19: Outpatient visits unit costs and average number of visits

Health care resource	Unit cost		Number of visits (per patient)	
	Value	Source	Average value (SE)	Source
GP	£39 per visit	PSSRU 2019[45]	1.497 (0.507)	INBUILD trial post hoc analysis[35]
Specialist	£158.02	Consultant led, weighted average between respiratory physiology and respiratory medicine (codes 340 and 341)[43]	1.613 (0.344)	
Nurse	£124.37	Non-consultant led, weighted average between respiratory physiology and respiratory medicine (codes 340 and 341)[43]	0.181 (0.051)	
Physiotherapist	£57.66	Physiotherapy, weighted average between consultant led and non-consultant led (code 650)[43]	0.068 (0.088)	
Occupational therapy	£70.96	Occupational therapy, weighted average between consultant led and non-consultant led (code 651)[43]	0.133 (0.105)	
Other visits	£158.02	Assumed to be the same as a specialist visit.	0.133 (0.105)	
Source: Table 52 in the CS,[1] and Table 12 in the response to clarification questions.[3] CS = company submission; GP = general practitioner.				

The analysis also included the costs of supportive long-term oxygen supplementation in case of resting hypoxemia. The cost of oxygen supplementation was estimated at £0.21 per hour, based on a £1,600 annual cost (sourced from the UK National Guideline on diagnosis and management of suspected IPF,[46] which was based on NHS Reference Costs 2010/2011[47] and inflated to 2018/2019 costs). The average hours of oxygen use per day and days of oxygen use (per patient) were 12.86 (SE 1.25) and 51.21 (SE 3.89), respectively.[35]

4.2.9.4 Acute exacerbation costs

The unit cost associated with each acute exacerbation was estimated using patient-level data from patients with IPF in INPULSIS who experienced an exacerbation, based on the three month probabilities of visiting the hospital (63.49%, which was combined with an average number of 1.3 hospitalisations and an average duration of 16.3 days), visiting an emergency room (7.49%), visiting a general practitioner (7.94%, which was combined with an average number of 1.59 visits), and visiting a specialist (15.87%, which was combined with an average number of 1.3 visits).[21, 48] The resulting estimate of £4,134 (2012/2013 cost year) was also used in TA379 and Rinciog et al, 2017, [21, 48] and inflated to 2018/2019 it was £4,424 using the NHSCII from PSSRU 2019.[45]

4.2.9.5 End of life costs

The company included end of life costs in the analysis, which were sourced from Georghiou and Bardsley, 2014 and consisted of the costs of secondary (acute) hospital care, local authority-funded social care, district nursing, and GP contacts that were based on patients without a cancer diagnosis.[49] Since the original estimate was largely based on costs from the cost year 2010, the end of life cost estimate was inflated to 2018/2019 values. This resulted in a cost estimate for end of life costs of £6,045.

4.2.9.6 Adverse event costs

The company assumed that all adverse events were resolved without treatment other than a visit to the general practitioner. A unit cost of £39 was sourced from PSSRU 2019 for this, referring to a per patient contact visit lasting 9.22 minutes.[45] The company also noted (in Section B.3.5 'Cost and healthcare resource use identification, measurement and valuation') that the frequencies of patients with adverse events related to increased hepatic enzymes were about four times higher in the nintedanib group (22.6%) than in the placebo group (5.7%).[18] This was not reported in Section B.2.10 'Adverse reactions'.

ERG comments: The ERG considers the health care resource use and costs that were included in the analysis as appropriate. The same approach was used in TA379 and deemed appropriate by the ERG of that appraisal. The CS did not state which source was used to inflate costs from previous cost years, but the ERG can confirm that the inflated costs were in line with those when applying the NHS Cost Inflation Index values from PSSRU 2019.[45]

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's post-clarification base-case deterministic cost effectiveness results are presented in Table 5.1. The total costs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with incremental costs of £[redacted] associated with nintedanib. The total QALYs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with an incremental QALY gain of [redacted] associated with nintedanib. This resulted in an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained.

Table 5.1: Company post-clarification base-case deterministic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
BSC	[redacted]	[redacted]	[redacted]				

Source Post-clarification company's base-case results provided in response to additional ERG requests on March 2nd 2021.[3]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

For consistency with the company's sensitivity analyses results as reported in the original CS that are reported in the next section, the company's original submission deterministic cost effectiveness results are reported in Table 5.2 below as well.

Table 5.2: Company original submission deterministic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
BSC	[redacted]	[redacted]	[redacted]				

Source: Table 58 in the CS.[1]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

5.2 Company's sensitivity analyses

The results of the company's sensitivity analyses based on the post-clarification version of the model were not provided to the ERG. The ERG could also not reproduce these results using the post-clarification version of the model, due to an issue that became apparent from the results of the probabilistic sensitivity analysis (PSA) and an issue with the functionality of the one-way sensitivity analyses (OWSA) in the post-clarification model. Therefore, the ERG reports below the results of the sensitivity analyses that were provided by the company in their original (i.e. pre-clarification) CS.[1]

5.2.1 Probabilistic sensitivity analysis

A PSA with 1,000 iterations was performed to assess the sensitivity of the cost effectiveness results to the uncertainty associated with model input parameters. Random samples were drawn simultaneously

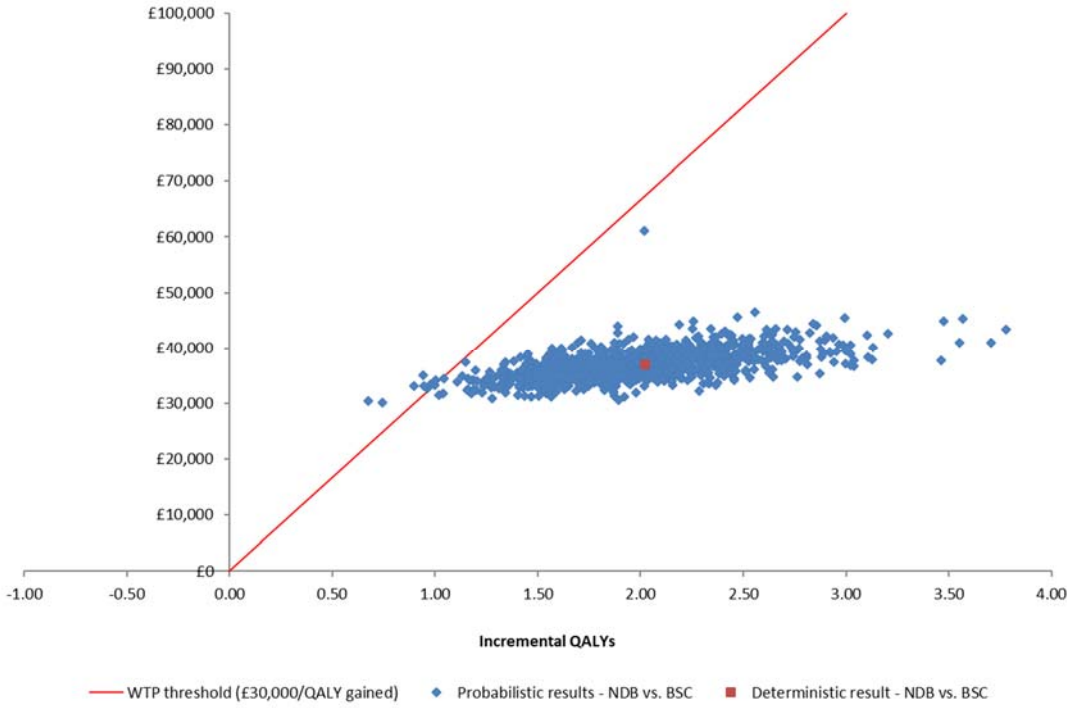
from the probability distributions that were assumed for each input parameter, which are detailed in Table 59 in the CS.[1]The company's PSA results are presented in Table 5.3. The total costs for the nintedanib and BSC arms were £[redacted] and £[redacted] respectively, with incremental costs of £[redacted] associated with nintedanib. The total QALYs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with an incremental QALY gain of [redacted] associated with nintedanib. This resulted in an ICER of £[redacted] per QALY gained. The probability that nintedanib is cost effective in comparison to BSC is 66% and 98% at cost effectiveness thresholds of £20,000 and £30,000 per QALY gained, respectively. The cost effectiveness plane and cost effectiveness acceptability curves are shown in Figures 5.1 and 5.2, respectively.

Table 5.3: Company first submission probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
BSC	[redacted]	[redacted]	[redacted]				

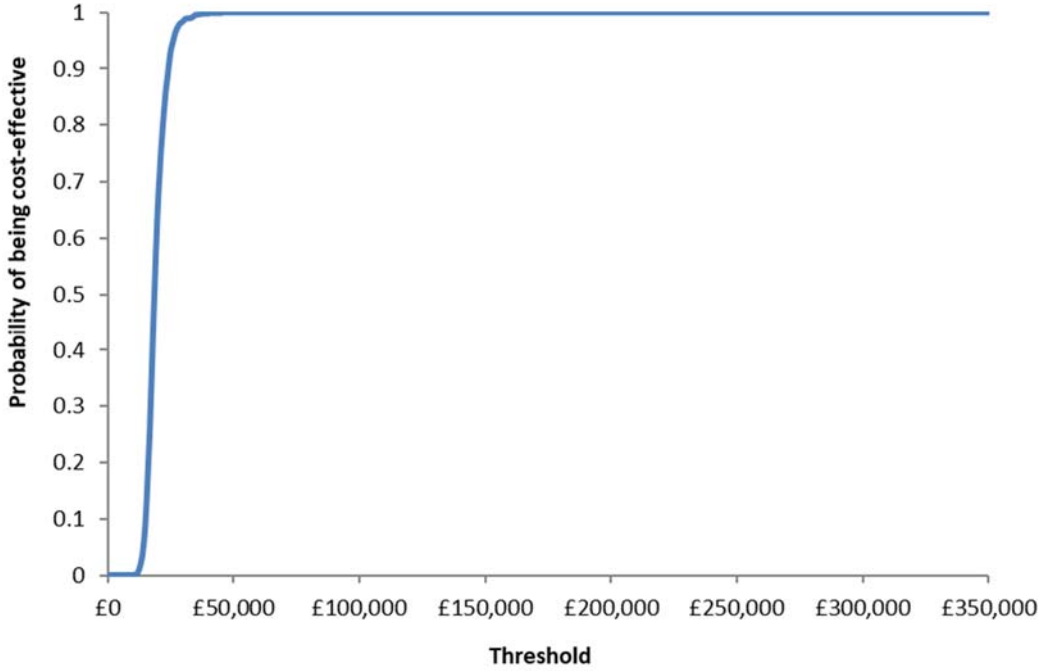
Source: Table 62 in the CS.[1]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

Figure 5.1: Cost effectiveness plane



Source: Figure 35 in the CS.[1]
BSC = best supportive care; NDB = nintedanib; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; WTP = willingness to pay.

Figure 5.2: Cost effectiveness acceptability curve

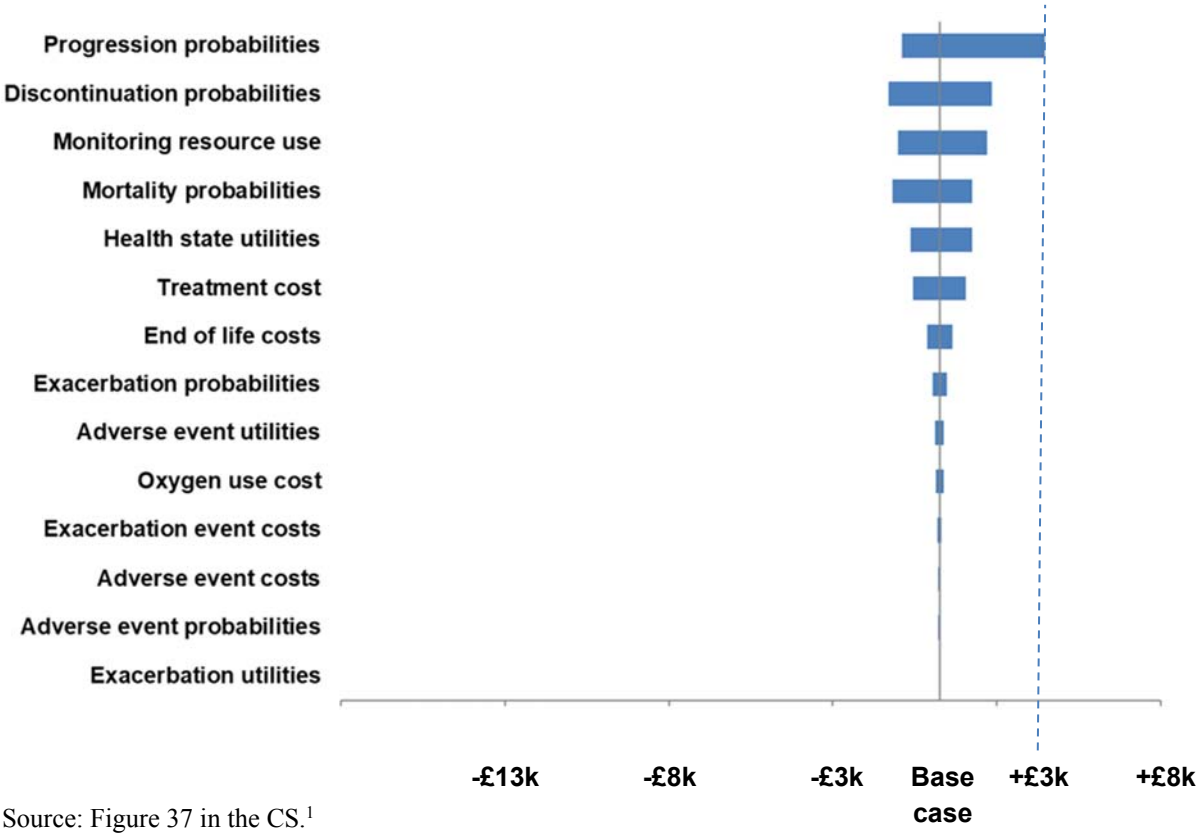


Source: Figure 36 in the CS.[1]

5.2.2 Deterministic sensitivity analysis

The company performed a deterministic, one-way sensitivity analysis (OWSA) to assess the impact of varying each parameter independently at both the upper and lower bounds of the 95% confidence interval that surrounds its mean estimate. The results of the OWSA are shown in Figure 5.3. Varying the progression probabilities caused the most substantial impact on the ICER, increasing it by approximately £3,000 per QALY gained to approximately [redacted] when varied to the highest confidence interval. The discontinuation and mortality probabilities, resource use associated with patient monitoring and health state utilities also cause some variation in the model results. None of the variations in inputs caused the ICER to increase to values higher than £30,000 per QALY gained.

Figure 5.3: Tornado diagram



Source: Figure 37 in the CS.[1]

5.2.3 Scenario analysis

The company performed a series of scenario analyses to assess the impact of alternative parameter inputs and assumptions on the cost effectiveness results. Three sets of scenarios were explored, relating to 1) alternative parametric distributions for OS extrapolations, 2) alternative utility inputs, and 3) alternative discontinuation rates.

For the first set of scenario analyses (i.e. scenarios 1 – 5), alternative parametric distributions were used for the extrapolation of OS. Specifically, the company replaced the Bayesian Weibull OS curves that were used in the base-case for both nintedanib and BSC with Bayesian Gamma OS curves in Scenario 1, Bayesian loglogistic OS curves in Scenario 2, frequentist Weibull OS curves in Scenario 3, frequentist loglogistic OS curves in Scenario 4, and frequentist Gompertz OS curves in Scenario 5.

For Scenario 6, the company replaced the utility values from INBUILD that were used in the base-case with utility values from patients with IPF in INPULSIS. These values were higher for all health states and are shown in Table 5.4.

Table 5.4: Alternative utility values used in scenario 6

FVC%Pred	Utility value	SD
≥110	0.8380	0.1782
100-109.9	0.8380	0.1782
90-99.9	0.8380	0.1782
80-89.9	0.8105	0.2051
70-79.9	0.7800	0.2244
60-69.9	0.7657	0.2380

FVC%Pred	Utility value	SD
50-59.9	0.7387	0.2317
40-49.9	0.6634	0.2552

Source: Table 64 in the CS.[1]
FVC%Pred = forced vital capacity percentage predicted; SD = standard deviation.

For the third set of scenario analyses (i.e. scenarios 7 and 8), the company replaced the discontinuation rate of 5.97% per cycle that was used in the base-case with a discontinuation rate of 7.67% per cycle to match the median time on treatment from the study by Lancaster et al, 2019 in Scenario 7,[36] and with a discontinuation rate of 3.97% in Scenario 8. The latter was considered by the company to provide a better fit to the tail of the INBUILD KM curve (i.e. only the last few months of available data), while noting that it did not fit the first two years of those data well.

The results of the scenario analyses are provided in Table 5.5.

Table 5.5: Results of the company's scenario analyses

Scenario #	Description	Incremental costs	Incremental QALYs	ICER
1	Bayesian gamma OS curves	[redacted]	[redacted]	<£25,000 [redacted]
2	Bayesian loglogistic OS curves	[redacted]	[redacted]	<£20,000 [redacted]
3	Frequentist Weibull OS curves	[redacted]	[redacted]	<£30,000 [redacted]
4	Frequentist loglogistic OS curves	[redacted]	[redacted]	<£20,000 [redacted]
5	Frequentist Gompertz OS curves	[redacted]	[redacted]	>£30,000 [redacted]
6	Alternative utility values	[redacted]	[redacted]	<£20,000 [redacted]
7	Discontinuation to match Lancaster et al, 2019[36]	[redacted]	[redacted]	<£20,000 [redacted]
8	Discontinuation to match tail of INBUILD KM data	[redacted]	[redacted]	<£25,000 [redacted]

Source: Table 65 in the CS.[1]
ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; OS = overall survival; QALYs = quality adjusted life years.

Nintedanib was associated with higher incremental costs and incremental QALYs than BSC in all of the scenarios considered. Scenarios two, six and seven resulted in a reduction in the ICER compared to the company's base case results. Nintedanib is not cost effective compared to BSC when the frequentist Gompertz OS curves are used, as this scenario produced an ICER >£30,000 ([redacted]) per QALY gained. However, based on clinician input the results from using the frequentist Gompertz OS curves were considered as implausible since they resulted in overly pessimistic extrapolations for both treatment arms.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The face validity of the model was examined during the UK Advisory Board.[1] This was achieved by describing the model structure and inputs to UK clinical experts to ensure the suggested approach appropriately captured costs and outcomes for UK clinical practice. Specific revisions were made to the model upon the advice received.

As described in Section 4.2.6.1, five clinical experts were asked to validate the model assumptions during a teleconference held on 11 November 2020. The company stated that clinicians validated the overall survival extrapolations and agreed that the Weibull Bayesian may be the most appropriate choice for both treatment arms. The overall survival curves were also compared with relevant data identified in the wider literature.

Due to a lack of previous economic models in this indication, it was not possible to examine the external validity of the model by comparing the results.

5.3.2 Technical verification

The company examined the internal validity of the model via a two-step process. First, they performed a cell-by-cell check of all model formulae to ensure they were both correct and appropriately applied. Second, a model verification checklist including a range of tests and sense checks, for instance, changing certain inputs to zero and checking that the observed effect was as expected (i.e. illogical results were not generated) was used. This internal validation process was undertaken by a health economist who was not directly involved in the conceptualisation and development of the model.

5.3.3 Comparisons with other technology appraisals

The company stated that due to a lack of previous economic models in this indication, it was not possible to examine the external validity of the model by comparing the results.

5.3.4 Comparison with external data

Extrapolations were compared with external data for OS and discontinuation as described in Sections 4.2.6.1. and 4.2.6.5.

ERG comments: The company report that clinicians validated the overall survival extrapolations and agreed that the Weibull Bayesian may be the most appropriate choice for both treatment arms, but in fact clinicians could not choose between the two Weibull options. The company stated that the model was sense checked during technical verification, but this did not pick up the implausible relationship between discontinuation, the ICER and LYs.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

6.1.1 Explanation of the company adjustments after the request for clarification

In response to the clarification letter, the company supplied an updated version of the model with the following changes:

- The company updated/corrected several costs at the request of the ERG during clarification, including the cost of mechanical ventilation, cost of outpatient visits and cost of acute exacerbation in response to clarification questions B24, B27 and B28.[3]
- Recurrent exacerbations were included in the model and in the company base-case
- The company incorporated age-adjustment of utilities into the model and included these in their base-case.
- The baseline distribution of patients, baseline age and AE incidences were included in the PSA.

6.1.2 Explanation of the ERG adjustments

Based on these model updates and all considerations in the preceding Sections of this ERG report, the ERG defined an alternative base-case. The ERG base-case included the above changes made during the clarification stage. Further adjustments made by the ERG were subdivided into three categories (derived from Kaltenthaler 2016)[50]:

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Adjustments made by the ERG, to derive the ERG base-case (using the post-clarification base-case as starting point) are listed below.

6.1.2.1 Fixing errors

After clarification no further errors were identified.

6.1.2.2 Fixing violations

After clarification no further violations were identified.

6.1.2.3 Matters of judgement

1. Extrapolation of OS (Key Issue 3, Section 4.2.6.1)
   The ERG preferred to extrapolate OS using the frequentist Weibull curve, given that it appeared to fit long-term nintedanib IPF survival data used for external validation better than the company's preferred Bayesian Weibull curve and clinicians considered both curves plausible.

2. Adjustment of HSUV for 80-89 FVC%Pred health state (Section 4.2.8)
   The ERG adjusted this value (assuming a linear decline between the neighbouring categories) to maintain the consistent trend between decline in lung function and decline in HRQoL.

6.1.3 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base-case.

6.1.3.1 Exploratory scenario analyses

1. Extrapolation of OS (Key Issue 3, Section 4.2.6.1)
   The ERG compared results obtained from extrapolating OS using their preferred frequentist Weibull curves, compared to the company's preferred Bayesian Weibull approach.

2. Time to first acute exacerbation, recurrent exacerbations and loss of lung function (Sections 4.2.6.2-4.2.6.4)
   The ERG examined the impact of adjusting the time to first acute exacerbation and removing the possibility of recurrent exacerbations. The ERG also examined the impact of using the probabilities of loss of lung function generated using the coefficients of the alternative model provided at clarification.

3. Health state utility values and disutilities (Section 4.2.8)
   A scenario will be conducted showing the HSUVs applied as they are in the company base-case. Several scenarios exploring alternative disutilities for acute exacerbations and AEs were conducted to examine the impact of these disutilities on results.

6.1.4 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

6.2.1 Results of the ERG preferred base-case scenario

The ERG's base-case deterministic cost effectiveness results are presented in Table 6.1. The total costs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with incremental costs of [redacted] associated with nintedanib. The total QALYs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with an incremental QALY gain of [redacted] associated with nintedanib. This resulted in an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained.

Table 6.1: ERG base-case deterministic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
BSC	[redacted]	[redacted]	[redacted]				
Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[3] BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).							

The ERG's probabilistic cost effectiveness results are presented in Table 6.2. The total costs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with incremental costs of £[redacted] associated with nintedanib. The total QALYs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with an incremental QALY gain of [redacted] associated with nintedanib. This resulted in an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained. These PSA results are not

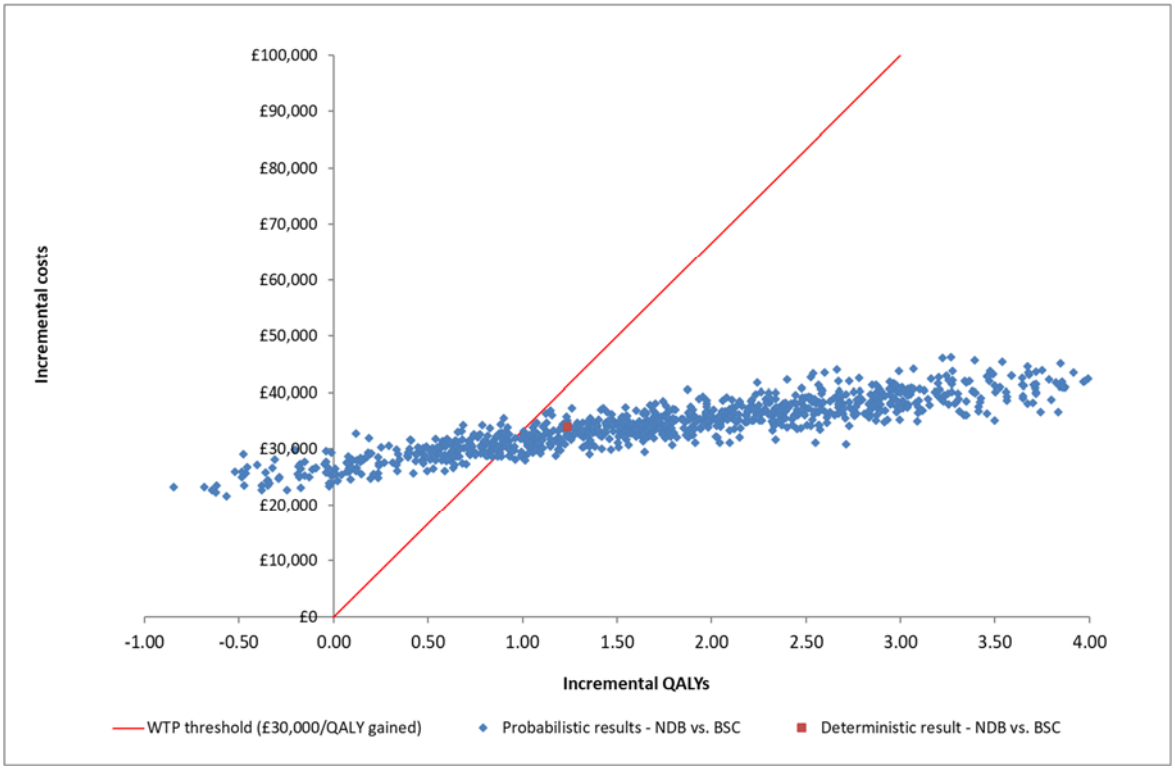
in line with the deterministic base-case results, with the difference being due to a discrepancy in the estimates for total QALYs per treatment. This misalignment is presumably caused by an issue with the PSA that the ERG could not resolve within the time that was available to them. Therefore, the ERG advises that this issue is resolved by the company at Technical Engagement so that the correct probabilistic results can be provided. The CE-plane and CEAC that are provided below in Figures 6.1 and 6.2 also pertain to the results from the PSA that includes this technical issue.

Table 6.2: ERG base-case probabilistic cost effectiveness results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nintedanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
BSC	[redacted]	[redacted]	[redacted]				

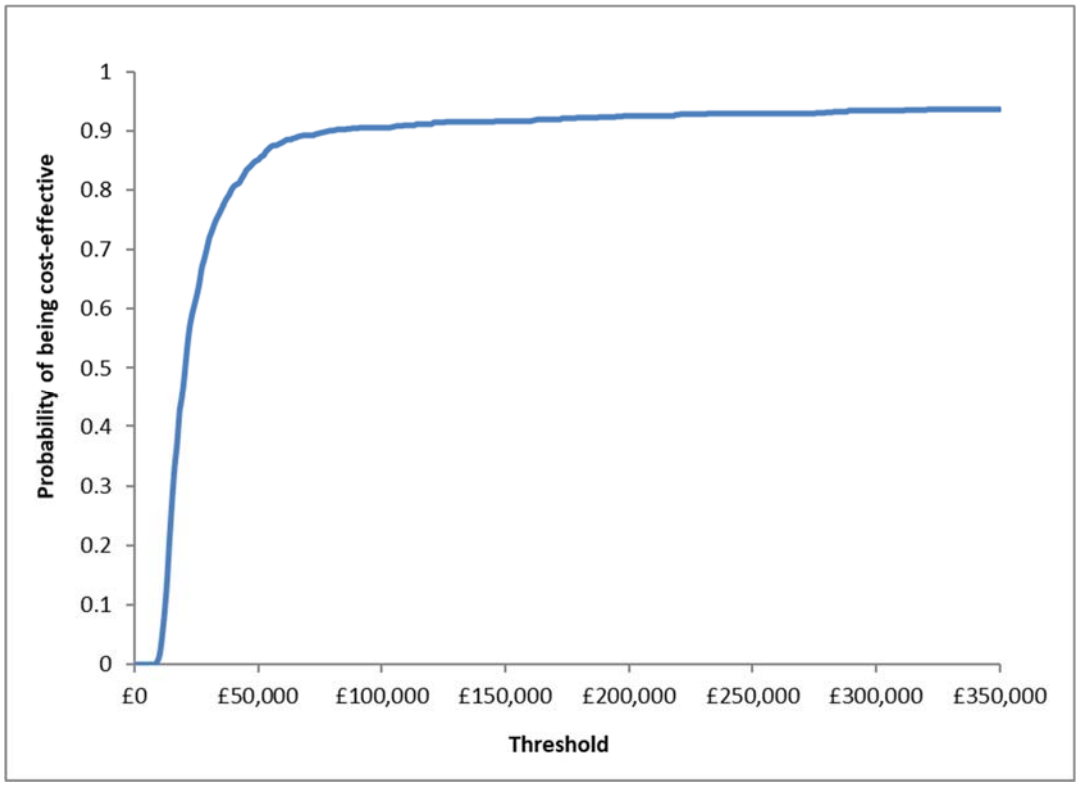
Source: The ERG preferred version of the electronic model provided in response to clarification questions.[3]
BSC = best supportive care; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY(s) = quality adjusted life year(s).

Figure 6.1: Cost effectiveness plane (ERG preferred, includes PSA issue)



Source: The ERG preferred version of the electronic model provided in response to clarification questions.[3]
BSC = best supportive care; ERG = evidence review group; NDB = nintedanib; PSA = probabilistic sensitivity analysis, QALY(s) = quality-adjusted life year(s); WTP = willingness to pay.

Figure 6.2: Cost effectiveness acceptability curve (ERG preferred, includes PSA issue)



Source: The ERG preferred version of the electronic model provided in response to clarification questions.[3]
ERG = evidence review group; PSA = probabilistic sensitivity analysis.

Based on the PSA results that substantially underestimated the ICER due to a technical issue, the probability that nintedanib is cost effective relative to BSC is 48.8% and 72.0% at ICER thresholds of £20,000 and £30,000 per QALY gained respectively.

6.2.2 Results of the ERG scenario analyses

6.2.2.1 Scenario set 1: Overall survival

Table 6.3 shows that extrapolating OS with the Bayesian Weibull, as per the company's base-case, reduces the ICER by approximately £7,500.

Table 6.3: OS scenarios

OS	Nintedanib		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Bayesian Weibull (company BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
Frequentist Weibull (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[3]
BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; OS = overall survival; QALYs = quality adjusted life years.

6.2.2.2 Scenario set 2: Time to first acute exacerbation, recurrent exacerbations and loss of lung function

The results in Table 6.4 demonstrate that assumptions regarding time to first acute exacerbation, the inclusion of recurrent exacerbations and the method used to estimate the decline in lung function in nintedanib patients have a small impact on results. The largest impact was seen for TTFAE, but this scenario assumed that nintedanib had no impact on TTFAE, which is likely to be overly conservative.

Table 6.4: Scenarios regarding TTFAE, recurrent exacerbations and loss of lung function

TTFAE, recurrent exac. and lung function	Nintedanib		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
TTFAE							
TTFAE BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
TTFAE BSC= NDB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
Recurrent exacerbation							
Recurrent exacerbation included (ERG and Company post-CL BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
No recurrent exacerbation (CS BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
Loss of lung function nintedanib							
Estimated from OR (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
Estimated directly from regression results	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[3]
BC = base-case; BSC = best supportive care; CL = clarification letter; CS = company submission ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NDB = nintedanib; OR = odds ratio; QALYs = quality adjusted life years; TTFAE = time to first acute exacerbation.

6.2.2.3 Scenario set 3: Health state utility values and disutilities

Table 6.5 indicates that the adjustment to the HSUV for the 80-89 FVC%Pred health state had minimal impact on the ICER. Doubling the assumed disutility for GI AEs increased the ICER by approximate £1,500, but all other changes had less than £600 impact.

Table 6.5: Health state utility values and disutilities

HRQoL	Nintedanib		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Health state utility values							
HSUVs company BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
HSUVs ERG BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
Disutilities							
Disutility for GI AEs 0.068 (TA379)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
Disutility for GI AEs 0.042	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
Disutility for acute exacerbation 0.14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
Disutility for acute exacerbation 0.274	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[3]
AEs = adverse events; BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; GI = gastrointestinal; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; Incr. = incremental; OS = overall survival; QALYs = quality adjusted life years.

6.3 ERG's preferred assumptions

Table 6.6 below displays the step-by-step changes made by the company during clarification, followed by the changes made by the ERG, alongside the cumulative impact of each change, added to the previous changes, on results. This clearly shows that the only change which had a substantial impact on the ICER was modelling OS using the frequentist Weibull rather than the Bayesian Weibull and (increased the ICER by approximately £8,000). All other changes had less than £1,000 impact on the ICER.

Table 6.6: ERG's preferred model assumptions (cumulative)

Preferred assumption	Section in ERG report	Nintedanib		BSC		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company CS original base-case	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
Updating/correction of several costs	6.1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
Inclusion of recurrent acute exacerbations	4.2.6.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
Age adjustment of utilities	4.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
Company post-clarification base-case	6.1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<20,000 [redacted]
Extrapolate OS using Weibull frequentist	4.2.6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
Adjustment of HSUV for 80-89 FVC%Pred to maintain consistent trend in decline.	4.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]
ERG base-case	6.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	<30,000 [redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.[3]
AE = adverse event; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PD = progressed disease; QALY = quality-adjusted life year.

6.4 Conclusions of the cost effectiveness section

The cost effectiveness analysis was based on a model with the same structure as the one used in TA379,[21] which was validated by UK clinicians and deemed appropriate by the ERG and committee in TA379. The current ERG notes that mortality is modelled, both in the company base-case and the ERG base-case, based solely on OS and independent of the rate of exacerbations and lung function decline even for patients with the lowest sustainable lung function who are at risk of a further decline. Although the model provides the option to also allow patients with the lowest sustainable lung function to transition to Death upon further decline, the ERG did not use this option since this would imply a double counting of mortality. Nevertheless, the ERG has concerns about the assumption that mortality is assumed to be independent of exacerbation rate and lung function decline.

The clinical effectiveness inputs for the model are based on the results of the INBUILD trial. As noted in Sections 2.3 and 3.6, the ERG has concerns regarding the representativeness of the placebo arm of the INBUILD trial for best supportive care in UK clinical practice. This is because patients in INBUILD were not permitted to receive immunomodulatory treatments (including azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids) at randomisation and during the first six months of the treatment period in INBUILD, though these treatments are part of mainstream best supportive care.

A key source of uncertainty in the model is survival. The survival data from INBUILD is fairly immature and therefore relies heavily on extrapolation. The company chose to extrapolate OS using a Bayesian Weibull curve given that: 1) the Bayesian analysis was guided by external long-term IPF data, which could increase the accuracy of long-term predictions; 2) clinicians considered the two Weibull options (frequentist or Bayesian) the most plausible in the long-term; 3) the Bayesian Weibull provided a reasonably good fit to external IPF data. However, the ERG considers that the incorporation of external long-term data into the survival analysis potentially added more uncertainty than it solved given that the long-term data was in an IPF rather than a PF-ILD population and required the use of matching. Additionally, while clinicians considered both extrapolations plausible, the frequentist Bayesian actually fit the long-term nintedanib IPF survival data better than the Bayesian. For these reasons, the ERG preferred the frequentist Bayesian for the extrapolation of OS.

Discontinuation from nintedanib treatment in the model was extrapolated using an exponential distribution to allow a simple constant risk of discontinuation. However, the extrapolation did not fit the data well. Additionally, the model structure and assumptions made created an implausible relationship between discontinuation and the ICER whereby a discontinuation rate of 100% produced the most cost effective ICER and had no impact on LYs. This is because in the company base-case, it was assumed that patients who had discontinued from nintedanib continued to be represented by the nintedanib survival analysis post-discontinuation, as most patients who discontinued treatment were included in the trial survival analysis, and mortality was modelled as independent from the rate of acute exacerbations and decline in lung function. Therefore, increasing the discontinuation rate had no impact on LYs and a very minor impact on QALYs, while leading to large cost savings in terms of treatment costs. Given that a high proportion of patients who discontinued nintedanib in the trial continued to be followed-up, the ERG consider that the OS is likely to reflect the weighted efficacy of patients on and off-treatment over the observed follow-up. However, the impact on efficacy in the longer-term remains uncertain as it is not clear whether the trial follow-up is sufficiently long to fully capture the impact of discontinuation on OS. The way discontinuation has been incorporated into the survival analysis makes it impossible to assess the impact of changes in the discontinuation rate on the ICER, as a new OS curve would be needed.

Other more minor uncertainties relating to treatment effectiveness relate to the estimation of time to first acute exacerbation, the inclusion of recurrent exacerbations in the model and the method used to estimate loss of lung function. The company included the risk of recurrent exacerbation in their base-case during clarification, which had a very minor impact on results. Uncertainties surrounding the extrapolation of TTFAE and the model used to estimate loss of lung function also have a minor impact on results as exacerbations are not drivers of results and therefore no base-case changes were made.

The company included those treatment related/emergent AEs which had an incidence of >10% in either treatment arm and an incidence at least 1.5 times higher in the treatment arm than in the control arm. The ERG requested that the 10% cut-off be amended to 5%, but the company refused stating that events of all severities were included and not just serious or severe adverse events and given that no severe AEs occurred in >5% of patients receiving nintedanib, the overall impact on costs of extending the criteria to 5% was expected to be negligible. HRQoL was measured using the EQ-5D-5L during the INBUILD trial and valued using the UK cross-walk value set, as preferred by NICE. FVC%Pred HSUVs were estimated from this data and resulted in a largely consistent trend between decline in lung function and lower HRQoL. The ERG adjusted one HSUV for the 80-89 FVC%Pred health state to ensure a plausible trend in their base-case, but this had minimal impact on results. Disutilities were applied for the GI AEs included in the model, assuming a utility value from TA379 and for acute exacerbations based on the estimated impact of acute exacerbations on utility from the INBUILD data.

The company used a similar approach as in TA379 for the inclusion of resource use and costs in the model, with the inclusion of the following costs: drug acquisition costs for nintedanib, liver function test costs, health care resource use costs corresponding to each of the health states in the model, acute exacerbation costs, end of life costs, and costs in relation to adverse events. The ERG agrees that the company's approach to model resource use and costs is appropriate, in line with the assessment performed by the ERG in TA379.

The company's base-case deterministic cost effectiveness results, based on their post-clarification model indicated total costs for nintedanib and BSC of [redacted] and [redacted] respectively, with incremental costs of [redacted] associated with nintedanib, and total QALYs for nintedanib and BSC of [redacted] and [redacted] respectively, with an incremental QALY gain of [redacted] associated with nintedanib. This resulted in an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained. The same model was used by the ERG in an attempt to provide post-clarification PSA results, at which point a technical issue with the PSA surfaced due to the QALY results not being comparable to the deterministic results. The ERG advises that the company resolves the PSA issue at Technical Engagement.

The ERG base-case differed from the company's post-clarification base-case in two ways: 1) OS was extrapolated using the frequentist Weibull; and 2) the HSUV for the 80-89 FVC%Pred health state was adjusted to ensure a plausible trend in HSUVs. The ERG's base-case deterministic cost effectiveness results indicate total costs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with incremental costs of [redacted] associated with nintedanib. The total QALYs for the nintedanib and BSC arms were [redacted] and [redacted] respectively, with an incremental QALY gain of [redacted] associated with nintedanib. This resulted in an incremental cost effectiveness ratio (ICER) of [redacted] per QALY gained. The larger ICER in the ERG base-case is largely due to the different approach for OS extrapolation. Assumptions around the extrapolation of OS also had the largest impact on results of all scenarios explored by the ERG.

The key uncertainties in the model are the long-term efficacy of nintedanib and BSC. Short-term trial data resulted in immature survival data, and therefore the model relies heavily on extrapolation. Different potentially plausible extrapolations produce substantially different results, making the base-case ICER uncertain. Uncertainty in the treatment effect is further increased by uncertainty regarding the extent to which the comparator arm in the trial truly reflects BSC in clinical practice, particularly given the observed treatment restrictions in the first six months of INBUILD. Without more data in these areas, these uncertainties cannot be resolved, and the results of the model remain somewhat speculative.

7. REFERENCES

[1] Boehringer Ingelheim. *Nintedanib for the treatment of adults with progressive fibrosing interstitial lung disease (PF-ILD): Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*: Boehringer Ingelheim, 2021. 259p.

[2] National Institute for Health and Care Excellence. *Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]. Final scope*: NICE, 2020. 5p.

[3] Boehringer Ingelheim. *Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599] – Response to request for clarification from the ERG*: Boehringer Ingelheim, 2021. 54p.

[4] Patel AS, Siegert RJ, Brignall K, Gordon P, Steer S, Desai SR, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. *Thorax* 2012;67(9):804-810.

[5] Boehringer Ingelheim. *Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]. Company decision problem form*: Boehringer Ingelheim, 2020. 14p.

[6] Meltzer EB, Noble PWC. Idiopathic pulmonary fibrosis. *Orphanet J Rare Dis* 2008;3:8.

[7] Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183(6):788-824.

[8] Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care* 2012;28(2):138-44.

[9] Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997;350(9074):326-9.

[10] Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, et al. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane, 2019. Available from: http://www.training.cochrane.org/handbook

[11] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 23.3.11] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[12] Flaherty KR, Brown KK, Wells AU, Clerisme-Beaty E, Collard HR, Cottin V, et al. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. *BMJ Open Respir Res* 2017;4(1):e000212.

[13] Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019;381(18):1718-1727.

[14] Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011;377(9779):1760-9.

[15] British Thoracic Society. BTS ILD Registry Annual Report 2019. 2019.

[16] British Thoracic Society. *BTS ILD Registry Annual Report 2019*: British Thoracic Society, 2019. 31p. Available from: https://www.brit-thoracic.org.uk/document-library/quality-improvement/ild-registry/bts-ild-registry-annual-report-2019/

[17] Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med* 2020;8(5):453-460.

[18] Boehringer Ingelheim. *Clinical trial report for the INBUILD trial (study 1199.247)*, 2019

[19] Flaherty KR, Wells AU, Cottin V, Devaraj A, Inoue Y, Richeldi L, et al. Effects of nintedanib on progression of ILD in patients with fibrosing ILDs and a progressive phenotype: further analyses of the INBUILD® trial. Poster developed for the European Respiratory Society International Congress, 7–9 September 2020.

[20] Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2019;27:27.

[21] National Institute for Health Care Excellence. *Nintedanib for treating idiopathic pulmonary fibrosis [TA379]*. Manchester, UK: NICE, 2016 Available from: https://www.nice.org.uk/guidance/ta379/

[22] Boehringer Ingelheim. *Advisory board minutes. Data On File NIN15-04*, 2015

[23] National Institute for Health and Clinical Excellence. *Boehringer Ingelheim (BIL) PF - ILD NICE Advisory Board. Wednesday 11 November 2020. Minutes of Meeting*, 2020. 5p.

[24] National Institute for Health Care Excellence. *Guide to the methods of technology appraisal 2013*. London: National Institute for Health and Care Excellence., 2013 Available from: http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf

[25] Richeldi L, et al. Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. *Thorax* 2018;73(6):581.

[26] Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370(22):2071-82.

[27] Crestani B, Huggins JT, Kaye M, al e. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. *Lancet Respir Med* 2019;7:60-68.

[28] Lunn D, Spiegelhalter D, Thomas A, et al. The BUGS project: Evolution, critique and future directions. *Stat Med* 2009;28:3049-3067.

[29] R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2019 Available from: https://www.R-project.org/

[30] Jackson CH. flexsurv: a platform for parametric survival modeling in R. *Journal of Statistical Software* 2016;70.

[31] Soikkeli F, Hashim M, Ouwens M, et al. Extrapolating survival data using historical trial-based a priori distributions. *Value Health* 2019;22:1012-1017.

[32] Vasakova M, Sterclova M, Mogulkoc M, et al. Long-term overall survival and progression-free survival in idiopathic pulmonary fibrosis treated by pirfenidone or nintedanib or their switch. Real world data from the EMPIRE registry. *Eur Respir J* 2019;54:PA4720.

[33] Antoniou K, Markopoulou K, Tzouvelekis A, Trachalaki A, Vasarmidi E, Organtzis J, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study. *ERJ Open Res* 2020;6(1):00172-2019.

[34] Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J* 2017;49(2).

[35] Boehringer Ingelheim. *INBUILD phase III trial (no. 1199.247) post-hoc analysis. Data on file*, 2019

[36] Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. *BMJ Open Respir Res* 2019;6(1):e000397.

[37] National Institute for Health and Care Excellence. *Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]: Clarification letter*. London: NICE, 2021. 13p.

[38] Guenther A, Prasse A, Kreuter M, Neuser P, Rabe K, Bonella F, et al. Exploring Efficacy and Safety of oral Pirfenidone for progressive, non-IPF Lung Fibrosis (RELIEF). *European Respiratory Journal. Conference: 29th International Congress of the European Respiratory Society, ERS. Spain.* 2019;54.

[39] EMC. Summary of Product Characteristics Ofev 150mg. 2020.

[40] Homma S, Azuma A, Taniguchi H, Ogura T, Mochiduki Y, Sugiyama Y, et al. Efficacy of inhaled N-acetylcysteine monotherapy in patients with early stage idiopathic pulmonary fibrosis. *Respirology* 2012;17(3):467-77.

[41] Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D*. York: Centre for Health Economics, University of York, 1999

[42] EMA. *Ofev: EPAR product information*: European Medicines Agency, 2020 Available from: https://www.ema.europa.eu/documents/product-information/ofev-epar-product-information_en.pdf

[43] NHS Improvement. National schedule of NHS costs 2018/19. 2019.

[44] NHS Improvement. National schedule of NHS costs 2017/18. 2018.

[45] Curtis L, Burns A. *Unit Costs of Health and Social Care*, 2019

[46] National Clinical Guideline Centre. *Diagnosis and management of suspected idiopathic pulmonary fibrosis: idiopathic pulmonary fibrosis*. London: National Clinical Guideline Centre, 2013. 307p.

[47] Department of Health and Social Care. *NHS reference costs 2010-2011 [Internet]*. London: Department of Health and Social Care, 2011 [accessed 12.3.21] Available from: https://www.gov.uk/government/publications/2010-11-reference-costs-publication

[48] Rinciog C, et al. A cost-effectiveness analysis of nintedanib in idiopathic pulmonary fibrosis in the UK. *Pharmacoeconomics* 2017;35(4):479-491.

[49] Georghiou T, M B. *Exploring the cost of care at the end of life*. London, UK, 2014

[50] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 30 March 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Infliximab and rituximab as comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report states that "The company did not include rituximab and infliximab as comparators despite NICE explicitly requesting to make this comparison (see NICE Response to comments on draft scope3)." (pages 21 and 39) Although rituximab was excluded for the first 6 months of the trial, it could be resumed after 6 months of trial treatment if patients were deteriorating with their ILD or connective tissue disease (CTD). Rituximab was used in two patients in the comparator arm (0.6%) and 3 patients in the nintedanib arm (0.9%) over the whole trial to database lock 2 (DBL2), as shown in Table 10.4.6.1:2 of the Clinical Trial Report. Use of infliximab was not restricted in the INBUILD trial, and was reported in two patients in the placebo arm (0.6%) at baseline.	We suggest removing this statement from the ERG report, as it is not accurate.	This inaccuracy suggests a deviation from the NICE scope, when this is not the case.	Not a factual error. Rituximab and infliximab were explicitly listed as comparators in the final NICE scope; but they were not included as comparators in the company submission.

Issue 2 Patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report states that the population included in the Company Submission is not completely in line with the NICE scope (pages 16, 20 and 39). We do not see any difference between the NICE	We suggest that this statement should be changed as below: • Page 16: "The population is in line with the NICE scope"	This inaccuracy suggests a deviation from the NICE scope, when this is not the case.	Not a factual error. The difference is in the age of the population. The NICE scope inferred all ages,

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
scope "adults with progressive-fibrosing interstitial lung disease (excluding idiopathic pulmonary fibrosis)" and the population included in the submission, which includes patients aged ≥18 years with physician-diagnosed fibrosing ILD present with features of diffuse fibrosing lung disease of ≥10% extent on high-resolution computed tomography and meeting the protocol criteria for progression within 24 months of screening as assessed by the investigator. The protocol criteria for progression have been adopted by key tertiary centres (as noted in a recent publication by George et al), so this population is equivalent to adult patients with progressive fibrosing lung disease. Patients with IPF were not included in the INBUILD trial or the population covered by the Company Submission.	• Pages 20 and 39: "The population is in line with the NICE scope, as well as the main trial (the INBUILD trial) described in the company submission…"		while the company submission only focussed on adults. This is explained in the ERG report.

Issue 3 Population with SSc-ILD

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 20 section 2.1 includes the statement "The company claims that "patients with SSc-ILD with the progressing fibrosing phenotype are included in the INBUILD trial and are therefore included in the population considered in this submission, in line with the marketing authorisation for nintedanib" (CS, page 10).[1] However, it is unclear how many patients with	We suggest removing this statement from the ERG report.	This inaccuracy relates to the treatment effectiveness of nintedanib in a specific group of patients, and is therefore important to address.	Not a factual error. As far as the ERG is aware, the company did not mention the Supplementary Appendix of the INBUILD publication in the company

SSc-ILD with the progressing fibrosing phenotype are included in the INBUILD trial and what their results were." This statement is inaccurate because the Supplementary Appendix of the INBUILD publication (page 27) gives a breakdown on SSc-ILD patients in the study (6.9% in the nintedanib and 4.8% in the placebo arms). Subgroup analyses presented in Appendix E of the Company Submission shows that the subgroup of patients with autoimmune ILDs, including SSc-ILD, showed no evidence of difference in treatment effect vs. the overall population.			submission, nor was it included in the reference pack with the submission. Appendix E of the CS does not provide data for patients with SSc-ILD. Therefore, based on the CS, it is unclear how many patients with SSc-ILD with the progressing fibrosing phenotype are included in the INBUILD trial and what their results were We thank the company for explaining where these data can be found.

Issue 4 Use of concomitant therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report states that "the INBUILD trial did not allow off-label use of immunomodulatory treatments for the first 6 months of the trial in either arm" (page 28). This is not quite accurate, as low-dose steroids were allowed during the first 6 months of the trial; 28.5% of patients received corticosteroids and 68.5% received corticosteroids for systemic use over the first 52 weeks (see Table 10.4.6:1 of the Clinical Trial Report).	We suggest that the statement on page 28 is changed to "the INBUILD trial allowed restricted use of off-label immunomodulatory treatments for the duration of the trial. The INBUILD trial allowed use of stable doses of approved medication to treat autoimmune diseases, with the exception of azathioprine, cyclosporine, mycophenolate	The broad statement that immunomodulatory treatments were excluded is not accurate. It should be clarified that use of specific immunomodulatory medications (azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, oral	Not a factual error. The ERG stands by the conclusion that the treatment received in the placebo arm of the INBUILD trial does not represent current best practice or best supportive care (BSC) in

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 10.4.6:3 of the Clinical Trial report states that 13.6% of patients received restricted corticosteroids, showing that some corticosteroid use over this period was not restricted medications. Other related statements include: • "The company only included one comparator, which they referred to as placebo. This was effectively all treatments received in the placebo arm of the INBUILD trial and which excluded immunomodulatory treatments that would have been current clinical practice." (page 12) • "…treatments received in the placebo arm (i.e. excluding immunomodulatory treatments for six months)" (page 13) • "In both arms, patients could not be taking any immunomodulatory treatment at randomisation and for the first six months of the trial, but could do so for the remainder of the trial after six months." (page 39)	mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids at a dose of >20 mg/day which were not permitted for the first six months of the trial. Initiation of these medications was allowed after 6 months of the trial in cases of deterioration of ILD or autoimmune disease." For the remaining statements we suggest that the medications that were restricted are specifically listed: • Page 12: The company included one comparator, which they referred to as placebo. This was effectively all treatments received in the placebo arm of the INBUILD trial and which excluded some immunomodulatory treatments (azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, oral corticosteroids >20 mg per day) at randomization and for the first 6 months of the treatment period. These	corticosteroids >20 mg per day) were not allowed at randomisation and during the first 6 months of the treatment period. Other immunomodulatory treatments were permitted throughout the trial and use of the specific restricted immunomodulatory treatments was permitted after the first 6 months in both treatment arms.	the UK.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
	treatments are not licensed for PF-ILD but may at times be used in current clinical practice." • Page 13: …treatments received in the placebo arm (i.e. excluding specific immunomodulatory treatments (azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, oral corticosteroids > 20 mg per day) at randomization and for the first 6 months of the treatment period. • Page 39: In both arms, patients could not be taking specific immunomodulatory treatments which are not licensed for PF-ILD (azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, oral corticosteroids >20 mg per day) at randomisation or for the first six months of the trial, but could do so for the remainder of the trial after		

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
	six months.		

Issue 5 Impact of discontinuation on treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG report states that "the company assumed that discontinuation from nintedanib had no impact on survival" (page 11). A similar statement is made on page 14. This is not accurate, as the overall survival analysis from INBUILD did not include censoring for patients who had discontinued nintedanib, and every effort was made to continue follow-up with patients who discontinued. In other words, unless patients were lost to follow-up, those who discontinued treatment were included in the overall survival analysis. Over the whole trial up to DBL2, very few patients who had prematurely discontinued from the trial were lost to follow-up (two patients, or 0.3% of the overall trial population, both in the placebo arm). Only three patients in the nintedanib group (0.9%) did not complete the planned observation time due to being lost to follow-up, and 12 nintedanib patients (3.6%) withdrew themselves. 17 nintedanib patients (5.1%) did not complete the planned observation time for 'other' reasons (see Table 10.1.1:1 in the Clinical Trial Report).	We suggest changing this statement to "the company assumed that patients who had discontinued from nintedanib continued to be represented by the nintedanib survival analysis post-discontinuation, as most patients who discontinued treatment were included in the trial survival analysis". We also request that this scenario is removed from the ERG base case.	This assumption has an impact on key issue 4 noted by the ERG, and their subsequent decision to include a limited period of post-discontinuation efficacy in their base case. This issue has a considerable impact on the ICER for nintedanib, and is therefore highly important to address.	The ERG thanks the company for providing additional clarification on the proportion of patients who discontinued, but continued to be followed-up within the INBUILD trial. Given this clarification, the ERG is satisfied that the OS data for nintedanib patients in the INBUILD trial is likely to be fairly representative of the combined group of patients who remain on treatment and who discontinue. The ERG has removed their adjustment for post-discontinuation efficacy from their base-case. Given the short-term nature of the trial data the ERG would argue that there is

Therefore, the overall survival curve for nintedanib used to inform the survival modelling does include a high proportion of patients who discontinued nintedanib treatment. We consider that this undermines the use of the limited period of post-discontinuation efficacy used by the ERG in their base case, as this scenario is effectively double counting the impact of discontinuation.			remaining uncertainty regarding the long-term impact of discontinuation on OS, which is unlikely to have been fully captured in the existing KM data and have commented on this in the report. The ERG would like to note that the way discontinuation has been modelled makes it impossible to assess the impact of changes in the discontinuation rate on the ICER, as then a new OS curve would be needed.

Issue 6 Minor errors in information taken from the Company Submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
There are some minor errors in the information taken from the Company Submission. • Table 4.5 of the ERG report states that the source of information is Table 25 of the Company Submission. This should be Table 28. • Table 4.12 of the ERG report states that the source of information is Table 41 of the Company Submission. This should be Table 43. • Page 63 of the report states that the Company conducted "sensitivity analyses using constant rates of discontinuation determined by the upper and lower bounds of the confidence interval from INBUILD (5.00% – 7.11%)". The 95% confidence interval used was 5.13 – 7.37%, as reported in Table 56 of the Company Submission and the control sheet of the Company model. • There are some rounding errors in Table 4.16 of the ERG report. Please see corrections in the table below.	We suggest amending to reference the correct information in the CS, as stated in the first column.	To allow readers to cross-reference the correct information in the CS.	The ERG thanks the company for noting these errors and has corrected the confidence interval on p63 of the ERG report, the rounding errors in Table 4.16 and the sources for Tables 4.5 and 4.12.

No inaccurate confidential marking was noted.

Table 0.1: Three monthly probabilities of resource use for each FVC%Pred group

Health care resource	FVC%Pred group							
	≥110	100 - 109.9	90 - 99.9	80 - 89.9	70 - 79.9	60 - 69.9	50 - 59.9	40 - 49.9
Number of observations	124	274	599	1,215	1,958	2,566	2,386	1,497
Hospitalisation	0.12	0.05	0.05	0.05	0.05	0.09	0.09	0.14
Emergency room visit	0.09	0.04	0.02	0.04	0.03	0.05	0.06	0.05
GP visit	0.12	0.10	0.16	0.18	0.31	0.19	0.17	0.15
Specialist visit	0.07	0.14	0.25	0.21	0.26	0.23	0.18	0.17
Nurse visit	0.02	0.01	0.03	0.02	0.03	0.03	0.02	0.02
Physiotherapy visit	0.01	0.01	0.01	0.01	0.03	0.00	0.00	0.00
Other visits	0.02	0.01	0.02	0.04	0.00	0.01	0.02	0.03
Occupational therapy visit	0.02	0.01	0.02	0.04	0.00	0.01	0.02	0.03
Oxygen use	0.14	0.16	0.17	0.15	0.26	0.33	0.47	0.57

Source: the electronic model from the CS / Figure 32, Tables 48, 51, 53 and 54 of the CS.[1]
CS = company submission; FVC%Pred = forced vital capacity % predicted; GP = general practitioner.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5pm, Friday 14 May**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Abby Tebboth
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Boehringer Ingelheim
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Relevant comparators are not included in the company submission	**NO**	The ERG report states that the company "should have included other relevant comparators as described in the NICE scope. However, given the lack of evidence for most comparators it is not clear how that could have been achieved. Therefore, the ERG has no suggestions for an alternative approach". The report also states that "the expected change to the ICER is unclear. However, if comparator treatments are more effective than those treatments received in the placebo arm (i.e. excluding immunomodulatory treatments for six months), the ICER will be less favourable for nintedanib". **Opinion from patient, clinical and NHS organisations is that current conventional unlicensed treatments have very limited efficacy in treating the fibrotic component of disease. The definition of the population in scope also means that patients have progressed despite treatment. Therefore, this issue is not expected to have any meaningful impact on the ICER.** Responses to NICE from the British Thoracic Society, Action for Pulmonary Fibrosis and NHS England all agree that the current treatments have very limited efficacy on the fibrotic component of disease (see pages 323-324, 340 and 352 of the technical engagement papers). Therefore, it is unlikely that the efficacy of these unlicensed treatments used in clinical practice will differ significantly from those used in the best supportive care arm of the INBUILD trial.

		Further to this, the population defined in the scope is “people with fibrosing interstitial lung disease that has progressed despite treatment (excluding idiopathic pulmonary fibrosis)”. Therefore, by definition, these patients will not be receiving any benefit from conventional therapies such as immunosuppressants. As noted in response to key issue 2 below, clinical experts and professional groups agree that current conventional therapies are used for the extrapulmonary, or non-lung, component of patients’ underlying disease, not the progressive fibrotic component. Therefore, while patients with progressive fibrosing interstitial lung disease (PF-ILD) may be receiving immunomodulatory treatments for the extrapulmonary aspects of their disease, these are not expected to treat the fibrotic component that is addressed by nintedanib. It is also incorrect to state that all immunosuppressants were not allowed during the first six months of the trial. Only azathioprine, cyclosporine, tacrolimus, high dose corticosteroids, rituximab, cyclophosphamide and mycophenolate mofetil were restricted during the first six months of the trial; other immunosuppressant therapies were allowed provided they were given at stable doses prior to randomisation. For all of these reasons, we do not believe that this key issue represents any meaningful risk to the cost-effectiveness of nintedanib in this population.
Key issue 2: The comparator included in the company submission does not reflect best supportive care in the UK.	**NO**	The ERG report states that “the treatments used in the placebo arm of the INBUILD trial do not represent current best practice or best supportive care (BSC) in the UK”, although there were no suggestions for an alternative approach. The report also states that “if current best practice in the UK, which includes immunomodulatory treatments, is more effective than those treatments received in the placebo arm excluding immunomodulatory treatments, the ICER will be less favourable for nintedanib”.

		According to expert and clinical groups, these unlicensed current conventional therapies are being used for the extrapulmonary component of patients' underlying disease, not the progressive fibrotic component, and therefore do not represent best supportive care in the UK. The ERG's main concern seems to be that the restriction of certain medications in the INBUILD trial (azathioprine, cyclosporine, tacrolimus, high-dose corticosteroids, rituximab, cyclophosphamide and mycophenolate mofetil) means that the comparator in the company submission is not reflective of clinical practice in the UK. Infliximab also appears to be of specific interest to the ERG. The submission from the British Thoracic Society states that drugs frequently used in clinical practice include oral corticosteroids, mycophenolate, azathioprine and methotrexate. However, they also state that methotrexate, infliximab and rituximab are not used in the NHS to treat the progressive fibrosing component of interstitial lung disease: "these immunosuppressive drugs are used to treat any inflammatory component of ILDs. They are not given to treat the fibrotic component of an ILD" (page 348 of the technical engagement papers). Therefore, while patients with PF-ILD may be receiving immunomodulatory treatments for the extrapulmonary aspects of their underlying disease, these treatments are not prescribed to treat the progressive fibrotic component. Clinicians treating IPF in tertiary centres in the UK have also specifically reported that infliximab and rituximab are not relevant treatments for ILD in the UK. Although mycophenolate and other immunomodulatory treatments are sometimes used in early disease, clinicians have raised concerns around their continued use in patients with progressive fibrotic disease based on the results of the PANTHER-IPF trial, which studied the efficacy of prednisone, azathioprine and N-acetylcysteine (NAC) triple therapy in patients with idiopathic pulmonary fibrosis (IPF).(1) The trial found increased risks of death and hospitalisation in patients with IPF who were treated with a combination of prednisone, azathioprine and NAC compared with placebo, with no benefit in improving lung function, therefore

		providing evidence against use of this treatment in patients with impaired pulmonary function in clinical practice. These comments are consistent with the lack of observed use of infliximab, rituximab and other immunomodulatory medications in the INBUILD trial. Less than 1% of patients in the placebo arm received infliximab during the trial period. Infliximab use was reported at baseline in two patients in the placebo arm (0.6%) and no patients in the nintedanib arm even though use was not restricted. This low level of usage does not allow a comparative assessment of nintedanib vs. the placebo plus infliximab subgroup and implies that infliximab is not really in routine use in patients with PF-ILD. Use of rituximab was more restricted than infliximab in the INBUILD trial, as noted above. However, less than 1% of patients received rituximab over the whole trial period. Similarly, use of immunomodulatory medications for ILD, including mycophenolate, azathioprine, tacrolimus and cyclosporine, was low over the whole trial. This demonstrates that these treatments are not considered or used as routine care even after the six-month restriction was lifted for patients who had experienced clinically significant deterioration of their disease. **Clinical experts and professional organisations agree that the restriction of certain medications for the first six months of the INBUILD trial does not mean that the trial is not relevant to UK clinical practice.** The lists showing use of concomitant and restricted therapies over the course of the INBUILD trial were shared with two clinical experts working in tertiary centres in the UK as part of our response to clarification questions. Both experts consulted agreed that these were broadly in line with what they would expect to see in clinical practice in the UK. The British Thoracic Society also state in their submission to NICE that the INBUILD trial does reflect UK clinical practice (page 346 of the technical engagement papers).

		Current conventional therapies have limited impact on the fibrotic component of disease; therefore, this key issue is not expected to have any meaningful impact on the ICER. As stated in response to key issue 1 above, submissions to NICE from the British Thoracic Society, Action for Pulmonary Fibrosis and NHS England and Improvement all agree that current treatments have very limited efficacy on the fibrotic component of disease (pages 323-324, 340 and 352 of the technical engagement papers). *"Many patients are aware of these challenges and of the risk of side-effects (such as bone fractures and liver damage) but continue with the [current] therapy, because they are advised to do so by their doctors. Despite this, many patients tell us they are not convinced they work." (Action for Pulmonary Fibrosis)* *"Unlicensed/unproven therapies (immunosuppressive drugs) are used without a good evidence base and are often ineffective at treating the fibrotic component of the disease." (British Thoracic Society)* *"However, effective treatments, and an evidence base for existing agents, are currently lacking." (NHS England and Improvement)* Therefore, it is unlikely that the efficacy of treatments used in clinical practice will differ significantly from those used in the best supportive care arm of the INBUILD trial. Further to this, the population defined in the scope is those with "fibrosing interstitial lung disease that has progressed despite treatment (excluding idiopathic pulmonary fibrosis)". Therefore, by definition, these patients will not be receiving any benefit from conventional therapies such as immunosuppressants. For these reasons, we do not believe that this key issue represents any meaningful risk to the cost-effectiveness of nintedanib in this population

Key issue 3: The ERG and company differed on their preferred extrapolation for overall survival	**NO**	The ERG's preferred base case uses the frequentist Weibull curve to extrapolate survival, rather than the Bayesian Weibull curve. The ERG believes that the incorporation of long-term data into the survival analysis "potentially added more uncertainty than it solved given that the long-term data was in an IPF rather than a PF-ILD population and required the use of matching. Additionally, while clinicians considered both extrapolations plausible, the frequentist [Weibull] actually fit the long-term nintedanib IPF survival data better than the Bayesian. For these reasons, the ERG preferred the frequentist [Weibull] for the extrapolation of OS". **Use of the Bayesian analysis reduced the overall variability of survival estimates compared to the frequentist analysis.** We found that use of the Bayesian analysis actually reduced the overall variability of survival estimates, and resulted in greater consistency compared to the frequentist analysis, rather than increasing uncertainty. Due to immature data, the PF-ILD frequentist survival estimates were uncertain and varied widely across different survival models, despite similar AICs and BICs. For example, the frequentist Weibull and frequentist log-logistic PF-ILD nintedanib survival models had similar fits (Weibull nintedanib: 687.0584 [AIC] and 694.6687 [BIC]; log-logistic nintedanib: 687.4335 [AIC] and 695.0438 [BIC]). However, the frequentist log-logistic nintedanib model was more aligned with the Bayesian survival analysis results, whereas the frequentist Weibull nintedanib model produced substantially lower survival estimates. The Bayesian survival estimates for the top three best-fit models were consistent and produced similar survival estimates (median OS range for nintedanib: 6.39-6.50 years). **Use of propensity score matching is appropriate to ensure that the Bayesian analysis did not overestimate survival.** The ERG suggests that the use of propensity score matching may add uncertainty in the Bayesian analysis. Propensity score matching was conducted to ensure that the priors generated using the IPF data were realistic and did not overestimate

		survival due to differences in patient baseline characteristics. In the unmatched IPF trial dataset, FVC % predicted was 79.3 in the nintedanib arm, compared with 68.6 in the PF-ILD trial dataset. If propensity score matching had not been used to address this imbalance before conducting the Bayesian analysis, then the IPF prior may have overestimated survival due to patients in the unmatched IPF dataset having a much higher FVC % predicted. **All available evidence suggests that patients with IPF and PF-ILD have similar survival, therefore this aspect is not expected to add any meaningful uncertainty.** The ERG stated that the use of Bayesian analysis adds uncertainty due to the assumption that IPF and PF-ILD patients have equivalent survival (page 55 of the ERG report). Given the absence of long-term PF-ILD data, it was not possible to use PF-ILD data to inform the prior in the Bayesian analysis and so the long-term IPF trial data were selected as the best alternative. This assumption is supported by evidence in the literature that IPF and PF-ILD patients follow similar survival trajectories. For example, survival estimates in a real-world analysis by Simpson et al showed consistent survival for IPF and PF-ILD patients in the UK (hazard ratio, 1.06; 95% confidence interval, 0.84 –1.35; P = 0.6; measured up to approximately 2.5 years).(2) This is consistent with analysis published by Brown et al based on clinical trial data, showing that PF-ILD and IPF patients who don't receive antifibrotic treatment have similar disease trajectories.(3) Additionally, the ERG believed that the use of IPF data to inform the prior added uncertainty to the Bayesian analysis (page 55 of the ERG report), but stated that the frequentist Weibull model was preferred and better fits the long-term nintedanib IPF external validation data presented (page 77). It is not clear why the ERG believed the use of an IPF-informed prior was inappropriate but based their argument for selecting the frequentist overall survival analysis on the long-term IPF registry data.

		The frequentist analysis did not match the long-term clinical trial data for nintedanib in the IPF population very well, and can therefore be considered to be pessimistic. Real-world and long-term clinical trial data from the IPF population show that the survival curves separate after around 18 months, with a clear survival benefit for nintedanib vs. the comparator that is maintained for the remaining follow-up time.(4-6) For example, the TOMORROW trial, a long-term clinical trial in patients with IPF, reported a descriptive hazard ratio of 0.7 (95% CI 0.46 to 1.08; p=0.0954) for nintedanib vs. the comparator.(5) A combined analysis of 6 IPF trials estimated median survival of 8.5 years in the nintedanib group compared with 3.3 years in the placebo group.(6) The frequentist analysis did not match this long-term data very well, and is therefore considered to be pessimistic. **There are some differences between the reported registries and UK clinical practice as well as the INBUILD trial.** The EMPIRE and Greek registries were selected to validate the modelled nintedanib survival curves, as there are no long-term data available for PF-ILD patients, and other more appropriate sources for validation, such as the long-term INPULSIS-ON and TOMORROW clinical trials in IPF patients, were used to generate the informative prior. However, it should be noted that there is heterogeneity between these registries and the PF-ILD and IPF clinical trials, as well as what might be expected in UK clinical practice. A key difference between the clinical trials and the EMPIRE study is that OS is estimated as time from IPF diagnosis rather than time from treatment initiation. It is unlikely that patients began treatment with nintedanib straight after IPF diagnosis, and so these survival data may not be an accurate reflection of actual survival after treatment initiation. The EMPIRE registry also includes a number of countries with varied and different healthcare systems to the UK (Austria, Bulgaria, Croatia, Czech Republic, Hungary, Israel, North Macedonia, Poland, Serbia, Slovakia and Turkey). FVC % predicted at baseline is reported to be between 72-79% in the EMPIRE registry, which is lower than the point at which antifibrotic treatment is

		allowed to start in UK clinical practice (the upper limit of restriction for nintedanib and pirfenidone is FVC 80% of predicted). In the Greek registry, patients spent a mean 23.6±15.0 months on nintedanib (7), which is lower than that of the unmatched IPF long-term clinical trial population (mean: 27.7 months; SD: 20.5).(6) Additionally, patients in the Greek registry were generally older compared to INBUILD (mean age: 71.80 years vs. 65.75), and more patients were smokers (78.2% vs. 51%; see Table 35 of the Company Submission). These differences could have led to patients in the Greek registry having decreased survival compared to INBUILD or the IPF clinical trial.
Issue with the probabilistic results in the model submitted in response to clarification (not a key issue)	**NO**	The ERG noted an issue in the model submitted in response to clarification that created an imbalance in the results of the probabilistic sensitivity analysis compared to the deterministic results. We have looked into this issue, and found a small error in the way disutilities were included (a negative sign was missing from the health state values, meaning they were applied as a utility rather than a disutility). This issue has been corrected in the new version of the model uploaded alongside this response.
Alternative extrapolations for discontinuation (not a key issue)	**YES**	The ERG report correctly notes that the company was asked to consider alternative plausible extrapolations, or constant or time dependent discontinuation rates which better represent the INBUILD Kaplan Meier (KM) data. There was insufficient time to provide these with our clarification response, however we have now been able to conduct an exploratory analysis of the impact of selecting a different curve for discontinuation (considering generalised gamma, Gompertz, log logistic, log normal and Weibull as alternatives to the exponential distribution used in the base case). Plots of these curves against the KM data from INBUILD over 3 years suggest that the Gompertz curve may be closest to the KM data, however over the long term

		this produces unrealistically optimistic rates of discontinuation for nintedanib (see Figure 1 and Figure 2 below). Over the long term, the generalised gamma, log logistic, log normal or Weibull curves give more realistic estimates of discontinuation. These updated extrapolations were used to calculate the costs of nintedanib treatment, which were then combined with the outputs from the cost-effectiveness model (QALYs for nintedanib and placebo, total costs for placebo and non-treatment costs for nintedanib) to generate exploratory ICERs. This exploratory analysis assumes that the choice of discontinuation distribution does not have an impact on the QALYs and non-treatment costs for nintedanib, In reality, there will be some variation in these outcomes based on the distribution chosen, as once a patient has discontinued they revert to the transition probabilities for best supportive care, so will transition faster through the FVC states. However, as described in the submission, the transition probabilities for lung function decline are not a key driver of results. Therefore, it is expected that the choice of discontinuation distribution will not have a large impact on the nintedanib QALYs or background costs and they should remain relatively stable. Using the generalised gamma, log logistic, log normal or Weibull curves for discontinuation gives an estimated ICER between ‘academic/commercial in confidence information removed’ and ‘academic/commercial in confidence information removed’ when using the company base case distribution for overall survival (Bayesian Weibull) (see Table 1 below).

Figure 1: Alternative extrapolations for distribution (over 3 years)

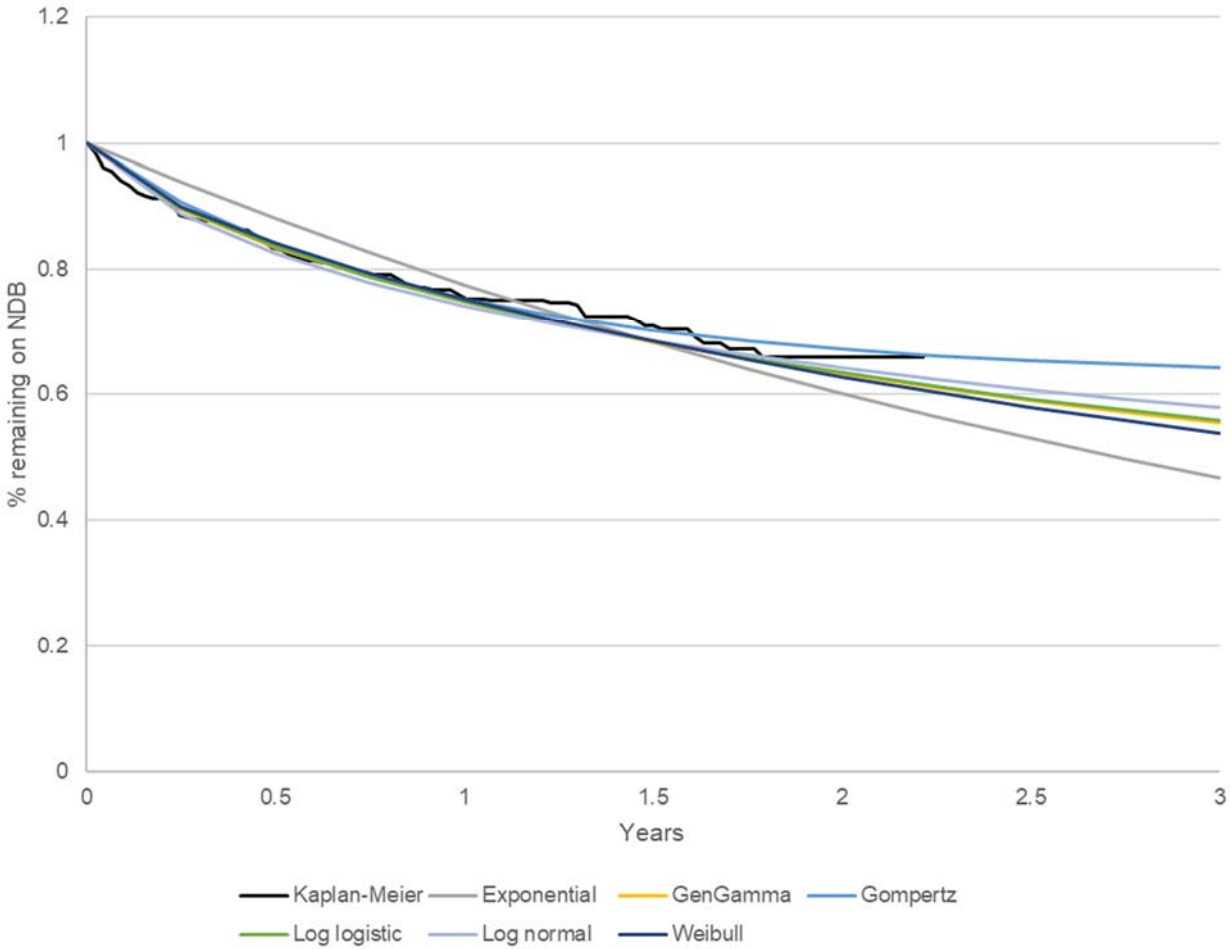

Figure 2: Alternative extrapolations for discontinuation (full model time horizon)

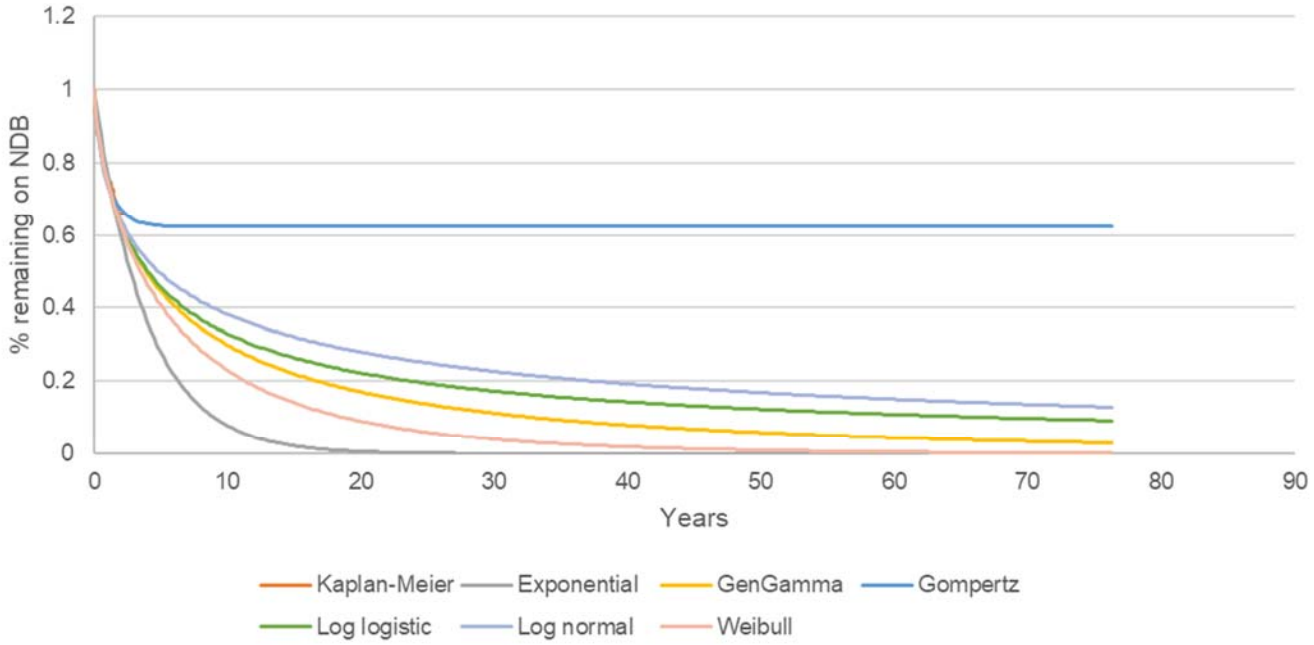

Table 1: Estimated impact of different discontinuation distributions on the ICER

OS distribution	Discontinuation distribution	ICER
Bayesian Weibull	Generalised Gamma	Academic/commercial in confidence information removed
	Gompertz (clinically implausible)	Academic/commercial in confidence information removed
	Log logistic	Academic/commercial in confidence information removed
	Log normal	Academic/commercial in confidence information removed
	Weibull	Academic/commercial in confidence information removed

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

No changes have been made to the company base case following technical engagement.

References

1. The Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. New England Journal of Medicine. 2012;366(21):1968-77.
2. Simpson T, Barratt SL, Beirne P, Chaudhuri N, Crawshaw A, Crowley LE, et al. The burden of Progressive Fibrotic Interstitial lung disease across the UK. European Respiratory Journal. 2021:2100221.
3. Brown KK, Martinez FJ, Walsh SLF, Thannickal VJ, Prasse A, Schlenker-Herceg R, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J. 2020.
4. Vasakova M, Sterclova M, M M, et al. Long-term overall survival and progression-free survival in idiopathic pulmonary fibrosis treated by pirfenidone or nintedanib or their switch. Real world data from the EMPIRE registry. European Respiratory Journal. 2019;54:PA4720.
5. Richeldi L, et al. Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. Thorax. 2018;73(6):581.
6. Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. BMJ Open Respiratory Research. 2019;6(1):e000397.
7. Antoniou K, Markopoulou K, Tzouvelekis A, Trachalaki A, Vasarmidi E, Organtzis J, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study. ERJ Open Res. 2020;6(1):00172-2019.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 14 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with progressive fibrosing interstitial lung disease and current treatment options	
About you	
1. Your name	**Dr Lisa Spencer**
2. Name of organisation	**I work at Aintree Hospital, Liverpool University Hospitals NHS FT**
3. Job title or position	**Consultant Respiratory Physician**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X**☐ a specialist in the treatment of people with progressive fibrosing interstitial lung disease? ☐ a specialist in the clinical evidence base for progressive fibrosing interstitial lung disease or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X**☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation	☐ yes

submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NONE**
The aim of treatment for progressive fibrosing interstitial lung disease	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow disease progression and prolong life with better quality of life and mobility than without treatment
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity	Slowing disease progression as measured by breathing tests, prolonging life compared to those not on treatment

by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in progressive fibrosing interstitial lung disease?	Yes absolutely. There are no funded treatments available currently in the NHS for PF-ILD. These patients progress and die.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Best supportive care is offered this helps manage some of the symptoms but does not offer patients disease modification. Best supportive care for ILD patients is outlined in IPF NICE document Quality standard 79 and covers oxygen, drugs for breathlessness and pulmonary rehabilitation. There are no disease modifying therapies available in the NHS for PF-ILD. Immunosuppressant drugs e.g. steroids, mycophenolate mofetil are given to some of the diseases that end up as PF-ILDs but these drugs are to treat any inflammatory components of the disease not the fibrotic component.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	No. There are no clinical guidelines for the disease group PF-ILD. PF-ILD is the end place where many forms of ILD end up it's a bit like lung failure or impending lung failure…... Consider heart failure which can be caused by many different heart diseases which all end up in same place. If you have an MI as the cause for your heart failure your MI has specific treatments but by time your MI results in heart failure the treatment for heart failure from many different causes is the same often diuretics regardless of what disease you started with. Sometimes some aspects of your MI treatment may continue once you hit heart failure 'end' point some of the treatments you had for your MI might be stopped or start to cause side effects and need to be stopped. Heart failure has other causes like valve disease or heart muscle disease (cardiomyopathies) and others but they can all end up in heart failure. PF-ILD can be thought of as lung failure or impending lung failure with many routes or diseases into it. Diseases becoming PF-ILD's may come into PF-ILD category on different treatments some

	which may be good to continue but others which need to be stopped due to treatment failure or side effects. Some guidelines exist for the disease management PRE the development of PF-ILD (lung failure , the final pathway) but none once end point PF-ILD is reached. Just to note that technically IPF is a form of PF-ILD and there are several NICE documents relevant to IPF but this technology appraisal is about PF-ILDs that are not IPF.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Patients developing PF-ILD will usually be located in secondary care hospital clinics of respiratory doctors or rheumatologists in either district general hospitals or in 'specialised ILD' or Connective Tissue Disease (CTD) service clinics which are regional services. The complexity of the patients case or their address will determine where they end up being looked after. By address it means some patients will live near a hospital that houses a specialised ILD or CTD service 'by chance' i.e. that is their local hospital so that is where they are seen. Other patients will have been referred into a specialised service from another smaller hospital usually due to case complexity and the smaller hospital seeking help re management from larger specialised service. Care is sometimes shared between the specialist centre and the DGH. In my opinion the care pathway is not well defined and many of these patients would benefit from at least one visit to a specialised centre (ILD or CTD depending on disease type) to ensure their management is optimised. It does depend a bit on the local expertise however in smaller hospitals. We do not have any specialised drugs to treat PF-ILD within the NHS yet (hence this NICE TA) so currently no pathway into specialist centres is encouraged or required specifically. Whether a patient gets seen at a specialist centre or not is determined by their local consultant team and /or patient preference/willingness to travel to a specialist centre. Within specialist ILD doctor or specialist Rheumatology teams opinions re managing PF-ILD are fairly consistent in my view- i.e. there are no effective treatments currently available in the NHS. Immunosuppressive drugs given to treat ILDs pre them becoming PF-ILDs phenotypes stop working, patients progress with a fibrotic disease type. Please be aware a significant proportion of patients with PF-ILD from a CTD background currently sit in rheumatology not chest clinics. Particularly those with rheumatoid arthritis related ILD. The numbers of patients sitting there need to be taken into account.
• What impact would the technology have on the current pathway of care?	If nintedanib was NICE approved for use in PF-ILD we would anticipate that prescriptions would be issued only from specialised ILD or CTD services by respiratory or rheumatology consultants. This is the current case for use of nintedanib in Idiopathic Pulmonary Fibrosis (IPF) where only respiratory consultants' in specialised centres can prescribe the drug. For IPF it is a respiratory disease only so only lung doctors involved whereas PF-ILD can arise from a number of ILDs including CTDs which are looked after by rheumatologists –hence both specialists might be involved in providing the drug.

	Assuming the drug was limited to specialist centres only – yes this technology would impact pathway of care. All PF-ILD cases would need to be assessed at least virtually in an ILD MDT by specialised centre services. This is different to the current situation outlined above where some PF-ILD cases sit only in DGH clinics. This would have a significant impact on workloads for specialised services. Not only in the number of referrals received but if new drug was given there are significant blood monitoring responsibilities that the specialised centres would also have to provide as aftercare. The workload impact is large. The overall standard of care for this patient group however would be expected to improve/increase as they have entered a speciality commissioned service.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Nintedanib is already an established treatment for IPF (a different ILD type) and is used regularly in specialised ILD services. Its use in PF-ILD would be the same. What may be new is consultant rheumatologists in specialised CTD services prescribing the drug. A significant proportion of these PF-ILD patients sit in rheumatology services and from personal discussions of myself with rheumatologists many would wish to be able to prescribe this drug if it were approved for use for their CTD patients with fibrotic ILD. Anti fibrotic drugs for IPF can only be given within certain FVC criteria - 50-80% predicted. Most ILD specialists accept the lower FVC limit here as patients with FVCs in that area are quite ill and do not tolerate new drugs with potential side effects well. They are often losing weight by that point. The INBUILD study used FVC >45% as their lower limit. A choice would need to be made at what level was appropriate. The upper limit of 80% predicted FVC for use of drugs in IPF however is contested by ILD doctors as being 'the best choice' for patients. It has been unsuccessfully challenged in the past as NICE will be aware. INBUILD had no upper FVC limit. I would request that NICE consider again what is the best/right upper FVC limit choice for use of these drugs. We think this may currently be under consideration with NICE following a further more recent challenge. There is also a '10% rule review' in place with IPF at 12 months of treatment. This is also questioned by ILD doctors. However in effect few patients come off drug due to that rule alone its usefulness is thus questioned.
• How does healthcare resource use differ between the technology and current care?	I feel I have covered this above really. Increased workloads to specialised centres – clinic visits, cases to be assessed at ILD MDTs, pharmacy input re dispensing, ILD nursing support and subsequent blood monitoring duties. Sometimes drugs patients were on pre development of PF-ILD may be stopped (see heart failure analogy above) reducing a little resource. This would be immunosuppression drugs.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialised ILD or CTD service clinics are advised to ensure the correct diagnosis is made re any PF-ILD. This is hospital based tertiary care. ILD is a very complex and potentially confusing area of respiratory medicine. Few DGH lung consultants have the expertise, confidence and support locally e.g. nursing and radiology support to assess and diagnose these patients accurately and provide the aftercare needed e.g. blood monitoring. Few would take this on.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Specialised ILD services in England have expanded from previously no services over a relatively short period of time. They were commissioned from ~ 2014 by NHSE depending on which region is being considered to improve care for ILD patients and ensure sometime costly drug prescriptions were appropriate. They have expanded rapidly at a time when the financial constraints on the NHS were marked. This means many services are currently understaffed as staff expansion request were denied due to finances. Although the approval of nintedanib for the treatment of PF-ILD would be welcomed by the ILD community to provide an unmet need the implications on the services are significant in terms of increased referrals, drug start ups, nursing and pharmacy support. Ideally increased sessions for all ILD staff would be required to maintain service waits for patients. Waits were already quite long in some areas (pre COVID19), post COVID 19 backlogs are large. This technology being approved will create a new backlog. Ideally a review of staffing by NHSE would help to identify services of greatest need with NHSE encouraging trusts to provide new posts where needed. No new equipment is needed. Training of new staff could be delivered. Pressure on clinic space would go up but ILD services are such a small part of overall chest clinics we would expect trusts to hopefully be able to sort that out. A number of extra CT scans/breathing tests may be needed to assess fibrosis progression but this could be spread between DGHs and centres so impact on one place relatively small to me.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Studies assessing the efficacy of nintedanib (and pirfenidone - a drug in same class) have demonstrated in clinical trials a slowing of the loss of lung function (FVC) over 12 months compared to placebo. The impact of anti – fibrotic drugs in the PF-ILD studies is similar to their impact in IPF another form of progressive lung fibrosis. The loss of lung over time in lung fibrosis equates to dying. We expect patients in whom the drug slows FVC loss will live longer and maintain independence for longer. 'Current care' for PF-ILD is best supportive care which has little, if any impact on survival although it does improve quality of life. PF-ILD patients could have BSC and drugs to modify their disease if nintedanib was approved for use.
• Do you expect the	Yes.

technology to increase length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. You would be advised to have a *specialised ILD centre* confirmed diagnosis of PF-ILD (ensuring diagnosis correct) You would have to show evidence of disease progression – the criteria in the INBUILD study are very good, wide and clinically appropriate. They allow patients who cannot do breathing tests for example (some find it very hard to do them) would not be excluded from being considered for treatments. Currently there is a caution for the use of nintedanib in patients on full dose anticoagulation e.g for treatment of pulmonary embolism, atrial fibrillation etc due to a theoretical increased bleeding risk. Caution needs to be applied in this patient group.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	I have covered these points above. Drug is already well known in specialised centres.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	INBUILD study criteria very clinically sensible to start. See point 12 above please some relevant comments there. Suggest abandon stopping rule. Base decision to stop on patients wishes and any side effects being experienced. Patients are already monitored with breathing tests and occasional CTs so expect little impact re tests.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There is not enough data yet re any suspected improved mortality outcomes with this drug. If that were available it would have been very helpful to have that data.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need	The drug is not new its use in this disease group would be. Yes I believe it will make a significant impact in patient care. PF-ILD patients currently have no disease modifying therapies on offer to them to treat the fibrotic component of their disease.

is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. No treatment to treatment is a step change.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. As outlined above. No treatment currently for fibrotic component of their disease.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main, common side effects of nintendanib are well known due to its use international use for several years for treatment of IPF. ~25 -30% of patients may not tolerate the drug in the longer term. Side effects mainly centre around gastrointestinal system i.e. diarrhoea, weight loss, nausea, altered taste. Some side effects can be managed satisfactorily for the patient. Others cannot and the patient chooses to stop the drug. Significant side effects will clearly impact on quality of life but tend to stop if the drug is paused or stopped. A serious side effect can be derangement of patients liver function. This is uncommon ~3% in studies (and clinical practice). This normalises usually on pausing drug and ~1% cannot take drug over longer term due to this issue. If the patient attends advised blood monitoring harm rarely occurs via this route. There are few important interactions with nintedanib and other drugs. Drugs that interact are fortunately rarely used. If the patient has a CTD ILD that becomes a PF-ILD they may be on rheumatological disease modifying drugs like mycophenolate mofetil (MMF). MMF itself can cause diarrhoea and nausea so being on nintedanib in addition could worsen those types of symptoms in a patient meaning drug is not tolerated. Symptoms usually subside if nintedanib or MMF is stopped however. There is enough clinical experience in UK and other countries now to know what was found in clinical trials assessing nintedanib (in terms of side effects and issues) is very similar to what is seen in clinical practice.

Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. It has been mentioned that placebo is not a relevant comparator. I think it is. Immunosuppressant drugs these patients are on for their disease pre developing the PF-ILD phenotype or for their joint disease management if have a CTD-ILD and they do not address the fibrotic component of their disease. Once fibrosis sets in these PF-ILD patients get worse and die over time. Consider rheumatoid arthritis patients on methotrexate for years who develop progressive fibrotic ILD. The methotrexate does not 'stop' their ILD developing and it does not stop them dying of their lung disease. I have yet to see a chronic hypersensitivity pneumonitis patient survive more than 10 years on steroids and /or mycophenolate. Once the fibrosis sets in nothing we have available stops its relentless progression. Nintedanib would only be considered if patients on any immunosuppressant drugs continued to progress and fibrose down. If patients were doing well on immunosuppressant drugs we would not wish to alter or add other therapies in.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	I feel the most important outcome is that the patient survives longer with a quality of life that is acceptable/accepted by them. That is what most patients want in my clinic where I cannot make them better or hold them where they are. I cannot make their fibrosis better with current therapies and even this therapy cannot hold the patient stable. In the INBUILD study mortality could not be fully assessed because the trial was only 12 months long. No study in lung fibrosis has really shown that any drug treatment has drastically improved quality of life. This may indicate that we do not have the right tools to assess quality of life well in this patient group. The group receiving the drugs however do not usually report worse symptoms to those in placebo group.

	INBUILD measured all relevant outcomes – yes. FVC, mortality, quality of life, Dlco, exacerbation rate, etc.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	FVC is used in ILD to monitor disease progression- this is very established practice now. It does predict worsening and a trajectory towards inevitable death sadly. FVC was primary outcome of INBUILD study.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None of which I am aware.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. How do data on real-world experience compare with the trial data?	We have not had access to nintedanib to treat patients with PF-ILD yet so no real world data in that disease group. There is plenty of real world data published however in IPF patients who are very similar to the PF-ILD group in fact IPF is by definition a type of PF-ILD itself. Real world data is similar to trial published data.
Equality	
23a. Are there any potential equality issues that should be taken into account when	If authorised it is thought that prescription of nintedanib may be held at specialist centres only. This means patients who decline for various reasons to travel to specialised centres may not be able to access this treatment unless it is supported/advised that remote start-ups after e.g. telephone and ILD MDT assessments are safe. Some patients

considering this treatment?	may decline due to transport issues (lack of it) or financial (costs of travel) or difficulty in travelling (due to disability). Remote startups require blood monitoring still which may not be agreed locally for various reasons with GPs or hospitals. Equality issues therefore may arise depending on how drug prescriptions are controlled. The situation currently for access to anti fibrotic drugs for IPF is similar. It is difficult to get around this issue.
23b. Consider whether these issues are different from issues with current care and why.	Yes different to current care for PF-ILD which maybe solely at their local hospital. Care currently available however is best supportive care only access to this drug would be a new treatment.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Relevant comparators are not included in the company submission	Comparators are appropriate. See above. Concerns have been raised over stopping immunosuppression (IS) drugs prior to trial entry. There is no evidence base however that IS drugs have any significant role to play once a PF-ILD picture develops in most conditions. In clinical practice if patients progress on IS treatments e.g. in chronic hypersensitivity pneumonitis , IS treatments may be stopped any way particularly if patients are experiencing side effects. In asbestosis no IS treatments are given at all.
The comparator included in the company submission does not reflect best supportive care in the UK.	Comparators are appropriate.
The ERG and company differed on their preferred	This part of the assessment is highly technical and involves complex statistics of which I do not have the expert knowledge to comment in detail. The important question is whether the two different survival

extrapolation for overall survival	models take the decision re the drug to be viable or not viable.
Are there any important issues that have been missed in ERG report?	Not that I can see its extremely thorough.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- PF-ILD is a serious area of unmet need with no treatment, that leads to premature death in the UK
- ILD clinicians are familiar with the drug nintedanib
- Workloads towards specialist centres will rise significantly if drug approved leading to delays in ILD care unless staffing levels in ILD centres are improved
- The INBUILD study accurately reflects UK ILD practice in my view on many levels
- I believe both ILD patients and ILD healthcare staff would welcome the opportunity to have access to this drug and it will bring benefits to patients

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Friday 14 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with progressive fibrosing interstitial lung disease and current treatment options	
About you	
1.Your name	**Debbie Roots**
2. Are you (please tick all that apply):	☐ a patient with progressive fibrosing interstitial lung disease? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with progressive fibrosing interstitial lung disease? ☐ a patient organisation employee or volunteer? x other (please specify):
3. Name of your nominating organisation.	Association of respiratory nurse specialists
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) x Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement x Yes, I authored / was a contributor to my nominating organisations submission x I agree with it and **do not wish to** complete this statement x I agree with it and **will be** completing
5. How did you gather the information included in your	**x** I am drawing from personal experience.

statement? (please tick all that apply)	**x** I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I am a respiratory nurse consultant and have cared for ILD patients **x** I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with progressive fibrosing interstitial lung disease? If you are a carer (for someone with progressive fibrosing interstitial lung disease) please share your experience of caring for them.	My personal experience is from my father who had IPF. He was diagnosed at least 10 years before he died and his condition did not progress much over the time period. He had no medication for the pulmonary fibrosis except for antibiotics for the chest infections he was prone to. He would get very breathless on exertion. Sadly he passed away in Dec 20 following developing COVID 19
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for progressive fibrosing interstitial lung disease on the NHS?	There is no treatment available on the NHS other than for the underlying conditions treatment. Drugs that are currently used are prednisolone, Mycophenolate, Azathioprine or Pirfenidone but these are off license. Oxygen may be used and lung transplantation is sometimes an option.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	If someone is diagnosed with IPF then they can access Nintedanib so there is a precedent. Those with Progressive ILD need to also be able to try this drug that evidence says may benefit them. Patients with PF-ILD with usual interstitial pneumonia (UIP)-like fibrotic pattern are expected to have a similar survival to patients with IPF and patients with PF-ILD with other fibrotic patterns
9a. If there are advantages of nintedanib over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does nintedanib help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe	Nintedanib has been shown to slow progression of the fibrosis, giving patients a better quality of life and increasing their life expectancy. This would enable them to be able to participate in activities more-including work depending on what they do.

these.	
Disadvantages of this treatment	
10. If there are disadvantages of nintedanib over current treatments on the NHS please describe these? For example, are there any risks with nintedanib? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Nintedanib may cause serious side effects, including liver problems, diarrhoea, nausea, vomiting, heart attack, stroke, bleeding problems or gastric ulceration. The risks are mitigated by testing bloods and monitoring. Nintedanib would be discontinued if side effects intolerable or unsafe.
Patient population	
11. Are there any groups of patients who might benefit more from nintedanib or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	There are different variants that are causing of the fibrosis. I don't think this is something that was looked into. Initial treatment will vary depending on what the underlying cause of the PF ILD is

Equality	
12. Are there any potential equality issues that should be taken into account when considering progressive fibrosing interstitial lung disease and nintedanib? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-	It will give progressive pulmonary fibrosis patients equal opportunity to access this evidence based treatment with others pulmonary fibrosis patients y of life and extending the life expectancy. This would need to be initiated by specialist centres. This is current practice with other in pulmonary fibrosis conditions To the best of my knowledge this is not something that would effect equality in that a diagnosis of PF ILD is the criteria and lung function are the deciding factors.

rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	If people with IPF can get this drug then those with PF ILD should also have the opportunity to try this treatment. We have a precedent set already. I do think we need more research into the benefits against usual treatment but that also needs to be reviewed.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
13) Issues have been raised in the ERG report around a) Relevant comparators are not included in the	The comparator against usual care-albeit off license is correct. .The comparison with current treatment for very similar conditions is also relevant.

company submission b) The comparator included in the company submission does not reflect best supportive care in the UK c) The ERG and company differed on their preferred extrapolation for overall survival	The study would have been more relevant if there was a stream on best current practice without and with Nintedanib however as off license this would have not passed the ethics committee The company have responded to the request for other extrapolations to be made available since the report
14a. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured? 14b. What are the benefits of	This is 1 of 2 anti fibrotic drugs that have been shown to slow down progression of the disease. During the Inbuild trial, the annual rate of decline in the FVC was significantly lower among patients who received Nintedanib than among those who received placebo. This change in physiological outcomes was not accompanied by meaningful changes in measures of quality of life, which is suprising. To have your loved one able to enjoy life and participate is so valuable. It could benefit both carer and patients mental health. It can support the patient to be more independent, reducing the demand on the

this treatment for carers?	carer
15. Are there any important issues that have been missed in ERG report?	In my opinion further study is required into this. Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities-George et al :-Lancet resp medicine2020 8 925-934 This paper recommends further study but that Nintedanib be used as a second line therapy
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • Nintedanib has been shown to slow progression of the fibrosis, giving patients a better quality of life and extending the life expectancy. • More research needed • There needs to be equity with IPF patients • Evidence based practice • Only initiated by specialist tertiary centres	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

x☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 14 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with progressive fibrosing interstitial lung disease and current treatment options	
About you	
1.Your name	**Stephen Jones**
2. Are you (please tick all that apply):	☐ a patient with progressive fibrosing interstitial lung disease? ☒ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with progressive fibrosing interstitial lung disease? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	**Action for Pulmonary Fibrosis**
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ **Yes, I was lead author of my nominating organisation's submission** ☐ I agree with it and **do not wish to** complete this statement ☒ **I agree with it and will be completing to provide supplementary information**

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: I lived with IPF for 8 years before my lung transplant in 2016. I have met scores of PF/ILD patients over the past 3 years as Chair of Action for Pulmonary Fibrosis and President of the European Pulmonary Fibrosis Federation (EUIPFF). APF has a network of 80 support groups across the UK, which include IPF and PF/ILD patients. For the purposes of this submission, I organised focus group discussions in December 2020 and January 2021 with RA-ILD and CHP patients and also interviewed patients living with pleuro-parenchymal fibroelastosis, asbestosis and fibrotic sarcoidosis. ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with progressive fibrosing interstitial lung disease?	I lived with Idiopathic Pulmonary Fibrosis (IPF) for eight years and experienced the devastating progression of the disease (increasing breathlessness, debilitating cough, dependence on supplementary oxygen, increasing isolation and disability) before fortunately receiving a lung transplant 5 years ago. I was prescribed pirfendidone, for 6 months, and nintedanib for 9 months. I stopped taking nintedanib after receiving my transplant.

If you are a carer (for someone with progressive fibrosing interstitial lung disease) please share your experience of caring for them.	
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for progressive fibrosing interstitial lung disease on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Patients living with PF/ILD (other than IPF) are generally treated with corticosteroids and/or immune suppressants. Both these types of medications can have serious side effects and many patients have to swap treatments many times. Some patients find they cannot tolerate the medications and have to give up pharmaceutical treatment. Most patients are aware of these challenges and of the risk of side-effects (such as bone fractures and liver damage) but continue with the therapy, because they are advised to do so by their doctors. Despite this, many patients I have spoken to say they are not convinced they work. A few of the best-informed patients I spoke to are also concerned about the scientific evidence. They point out that there have not been any clinical trials (RCTs) to prove the safety and efficacy of the current treatment regime. The above views are based on my frequent discussions with PF/ILD patients as Chair of Action for Pulmonary Fibrosis (see answer to Q.5, above).
8. If there are disadvantages for patients of **current NHS treatments** for progressive fibrosing interstitial lung disease (for example how nintedanib is given or	Your question is confusing. The disadvantages of current treatments (corticosteroids and immune suppressants) are given in response to Q7. In Q8, in parentheses, you mention nintedanib but this is not yet a current treatment for PF/ILD. It is, however, a treatment for IPF so I have answered the question accordingly.

taken, side effects of treatment etc) please describe these	The main side-effect of nintedanib, of which PF-ILD patients are well aware, is diarrhoea, nausea and other gastro-intestinal issues. I experienced these side effects when taking nintedanib for IPF. The vast majority of the PF-ILD patients I have talked to in support groups, focus groups and on-line think that the potential benefits of nintedanib outweigh the risk of these side-effects and are keen to be prescribed the drug. They have spoken to IPF patients, who take the drug, at support group meetings and know, while a significant but still small percentage of patients gives up the drug, most manage to live with the side effects using travel diarrhoea pills and other medicines prescribed by their doctor
Advantages of this treatment	
9a. If there are advantages of nintedanib over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does nintedanib help to overcome/address any of the listed disadvantages of current treatment that you	**9a**. PF-ILD is a devastating disease for patients, their families and carers. As the disease progresses, patients become more and more dependent on their carers and loved ones for support. As the patient loses his or her independence so do the family members, who support them. While patients often need physical support (fetching and carrying, assistance with dressing and showering in late stages of the disease) they often also become very anxious and depressed, which impacts on the whole family. It is often a very difficult journey for carers and supporting family members. Advantages: 1. Nintedanib directly targets fibrosis and slows progress of the disease, 2. It might also extend life (as has been found with IPF patients) 3. Nintedanib is administered orally and monitoring blood tests can be done locally by the GP, with the results sent to the hospital. This should reduce the care burden with fewer clinic/hospital visits for treatment.

have described in question 8? If so, please describe these.	4. Another significant advantage is that the new treatment would give the patient community and their families hope - something the PF-ILD community curently lacks - and reduce anxiety. **9b. Most important advantage:** Nintedanib would slow the progress of the disease for many patients prescribed the treatment. This would be experienced by patients as remaining less breathless for longer. They would remain active and independent for longer and the time when they will need supplementary oxygen would be postponed. It is also possible that nintedanib could extend life (as recent research indicates for IPF). It would also have a positive impact on family members and carers, who would keep their own independence for longer. **9c.** See my comment in red, above. Nintedanib would give doctors another treatment to use for patients with PF/ILD, if the current, stand treatment of corticosteroids and/or immune suppressants does not work. PF-ILD patients are desperate for new medications which directly tackle their lung fibrosis and will slow progression of the disease. Anti-fibrotic treatments like nintedanib have been a 'game changer' for people living with IPF, slowing disease progression, maintaning quality of life for longer and increasing life expectancy. Patients expect that nintedanib, by slowing the progress of the disease, will slow their worsening breathlessness and delay the time when they become dependent on supplementary oxygen. People living with PF-ILD look at IPF patients they meet in support groups and on-line and envy their access to anti-fibrotics. They feel that it is cruel that other PF-ILD patients are denied these medications and feel they deserve this opportunity. They look enviously at the IPF people and ask: why them and not me?

	Patients consider the main advantage of the new technology is that it directly targets the problem of lung fibrosis and has been shown in the INBUILD trial to slow progression of the disease, which is a high priority for them. They note that the benefits of nintedanib for PF-ILD patients found in the INBUILD study are similar to those shown in the clinical trial for nintedanib and IPF. They hope, if the technology is approved, it will also be shown to increase life expectancy, as has been found recently for nintedanib for IPF patients.
Disadvantages of this treatment	
10. If there are disadvantages of nintedanib over current treatments on the NHS please describe these? For example, are there any risks with nintedanib? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	See response to Q.8, above.
Patient population	
11. Are there any groups of patients who might benefit more from nintedanib or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with	Nintedanib would potentially benefit all patients living with non-IPF progressive pulmonary fibrosis.

mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering progressive fibrosing interstitial lung disease and nintedanib? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-	1. **Inequality with IPF Patients**. See response to Q 9c, above. People living with PF-ILD look at IPF patients they meet in support groups and on-line and envy their access to anti-fibrotics. They feel that it is cruel that PF-ILD patients are denied these medications and feel they deserve this opportunity. They look enviously at the IPF people and ask: why them and not me? 2. **PF/ILD patients are more diverse than IPF patients.** IPF patients are generally white and mainly men 60-80 years old. PF/ILD patients are generally younger (40-60 years of age), roughly equal numbers of women and men, and more ethnically diverse (i.e., include more people of south Asian and Afro-Caribbean heritage. 3. **Inequality with cancer patients.** Life expectancy from diagnosis for PF/ILD patients is worse than for most common cancers. Only lung cancer and pancreatic cancer will kill you quicker than PF/ILD. Yet IPF and PF/ILD patients receive less comprehensive care than cancer patients. PF/ILD patients do not have the same time bound 62-day pathway to diagnosis and treatment, which cancer patients have, nor do they have the same level of access to specialist and MacMillan nurses. With cancer patients, there is a hope of remission but for PF/ILD patients the only hope is a lung transplant, which only 1% of patients receive.

read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	1. It is important to appreciate that the benefit of nintedabib is that it slows progress of the disease so that patients will in future feel better than they would have done if they had not taken the drug. It does not make the patient feel better immediately. 2. **Patient experience supports the idea of a progressive pulmonary fibrosus 'phenotype'.** In arguing for nintedanib to be made available to all PF/ILD patients, clinicians and researchers argue there is a **progressive lung fibrosis 'phenotype'**. **Patient experience supports this view.** In talking to scores of PF/ILD patients over the last few years, it is clear to me and colleagues at Action for Pulmonary Fibrosis that IPF and PF/ILD patients (e.g. RA-ILD, CHP and other sub-types) experience a very similar patient journey, involving increasing breathlessness, often a debilitating cough, dependence on supplementary oxygen, increasing disability and death due to respiratory failure, or a related condition. The time from diagnosis to death varies both within and between different sub-types of progressive pulmonary fibrosis (the course of the disease is variable) but the way patients experience and talk about their disease is the same, whatever the sub-type of disease.

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
13) Issues have been raised in the ERG report around a) Relevant comparators are not included in the company submission b) The comparator included in the company submission does not reflect best supportive care in the UK	**I have nothing to add on these 3 issues raised in the ERG report, over and above what was stated in the Expert Engagement Meeting and summarised in the minutes of the meeting. I reviewed the changes proposed by the Clinical Expert (Dr L Spencer) before she submitted them and agree with them.**

c) The ERG and company differed on their preferred extrapolation for overall survival	
14a. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured? 14b. What are the benefits of this treatment for carers?	**See answers to questions 9(a), 9(b) and 9(c) above.**
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- **PF/ILD is a devastating disease**, in which the patient becomes increasingly breathless, often suffers from a debilitating cough, becomes dependent on supplementary oxygen, isolated and disabled and generally dies from respiratory failure, or a related cause, within 3-7 years of diagnosis (a worse prognosis than most common cancers).
- There are **currently no evidence-based treatments for PF/ILD** – existing treatments of corticosteroids and immune suppressants have serious side effects and patients often have to give up pharmaceutical treatment.
- **Patients are desperate for new medications, such as nintedanib**, which will directly target their lung fibrosis and slow progression of the disease.
- **Nintedanib has been a game changer for people living with IPF**: slowing disease progression, maintaining quality of life for longer, and increasing life expectancy
- **People living with PF/ILD envy IPF patients' access to nintedanib** and think: **why them and not me?** - they experience the same symptoms as IPF patients and cannot understand why they are denied to the medication.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Friday 18 June 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with progressive fibrosing interstitial lung disease and current treatment options	
About you	
1. Your name	**Voon Ong**
2. Name of organisation	**Royal Free Hospital**
3. Job title or position	**Consultant Rheumatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with progressive fibrosing interstitial lung disease? ☐ a specialist in the clinical evidence base for progressive fibrosing interstitial lung disease or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosure**
The aim of treatment for progressive fibrosing interstitial lung disease	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Primarily to halt disease progression specifically decline in FVC as marker of chronic disease progression across all progressive ILD of autoimmune origin – including systemic sclerosis and rheumatoid arthritis.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Stabilisation of lung function parameters, improvement in quality of life, improvement in symptom score and/or reduction in oxygen requirement. As decline of FVC has been shown to be associated with mortality in SSc related ILD, slowing the FVC decline would contribute to improved survival.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in progressive fibrosing interstitial lung disease?	Among the group of conditions of progressive ILD, systemic sclerosis-associated ILD has significant mortality of up to 50% and early development of lung fibrosis is associated with aggressive clinical course. With no evidence based therapeutics specifically targeting fibrosis, this is an important area of unmet need with significant impact on quality life with appreciable morbidity and mortality.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	In progressive ILD, the current approach is primarily immunosuppressives with non-specific agents cyclophosphamide, mycophenolate, azathioprine, tacrolimus and B-cell directed rituximab (for those with coexisting inflammatory myositis) in addition to symptomatic supportive therapies with oxygen. Referral for consideration for lung transplant is undertaken for selected patients.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines in management of systemic sclerosis that includes ILD led by British Society for Rheumatology with NICE accreditation Christopher P. Denton, Michael Hughes, Nataliya Gak, Josephine Vila, Maya H. Buch, Kuntal Chakravarty, Kim Fligelstone, Luke L. Gompels, Bridget Griffiths, Ariane L. Herrick, Jay Pang, Louise Parker, Anthony Redmond, Jacob van Laar, Louise Warburton, Voon H. Ong, on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group, BSR and BHPR guideline for the treatment of systemic sclerosis, *Rheumatology*, Volume 55, Issue 10, October 2016, Pages 1906–1910, https://doi.org/10.1093/rheumatology/kew224
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	With some variation, there is designated service organisation and care framework for patients with progressive ILD with specialist centres for connective tissue diseases and interstitial lung diseases. As an example, the BSR guidelines for scleroderma advises that patients with scleroderma should be managed within an integrated system of primary, secondary and tertiary level care with access to specialist care in rare autoimmune diseases with joint care with local specialist team (Denton CP… Ong VH Rheumatology 2016). In complex rheumatic diseases including scleroderma, this model of patient service delivery is instrumental in organisation of specialists input with access in

state if your experience is from outside England.)	investigations, therapeutics, development of NHS-England commissioning policy for therapeutics (including Bosentan for digital vasculopathy; http://allcatsrgrey.org.uk/wp/download/commissioning/1911-Sildenafil-Bosentan-Policy-updated-2021.pdf) and clinical trials.
• What impact would the technology have on the current pathway of care?	As the first antifibrotic for ILD without risk of infection, this will complement the current care pathway focussing on immunosuppressive agents for progressive lung disease. This will reduce the potential referrals for lung transplant, reduce risk of infections for this high-risk group of patients.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I envisage that this technology will be delivered through specialist centres in connective tissues diseases or respiratory centres with interest in interstitial lung diseases. Specialised centres for rheumatology have existing systems in place for coordination and delivery of biological therapeutics with blueteq to support data-driven care, document outcomes, recording treatment switching and cessation as a result of non-responsiveness or remission with homecare services to ensure effective dispensing and delivery systems.
• How does healthcare resource use differ between the technology and current care?	As above although no specific training of patients is required as Nintedanib is available as oral medication.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinic either respiratory or specialist connective tissue disease experienced in managing patients with connective tissue diseases.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As above, all specialised rheumatology services have systems in place for coordination and delivery of biological therapeutics with blueteq to support introduction of Nintedanib. I envisage similar systems are in place for Nintedanib for idiopathic pulmonary fibrosis in respiratory centres.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – halting decline in FVC should translate to improved survival in addition to improve quality of life scores.
• Do you expect the technology to increase length of life more than current care?	There is no current evidence from current trials to indicate the nintedanib improves mortality. However, trends in FVC decline have consistently predicted mortality in idiopathic pulmonary fibrosis and scleroderma associated lung fibrosis – thus this can be viewed as the best marker of disease progression/stabilisation.
• Do you expect the technology to increase health-related quality of life more than current care?	With change in FVC linked to Impaired functional capacity, oxygen supplementation, and dyspnoea – these elements will translate to an effect on quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None to my knowledge as the evidence suggests effect across different conditions with progressive lung disease.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any	As above, within the specialised rheumatological centres with existing service organisation for biological therapeutics, utilisation of Nintedanib can be effectively managed within this framework with existing blueteq and homecare service delivery. As this is oral formulation, no patient training is required thus this would be considerably

practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	easier to manage by both healthcare and patients. Routine monitoring of bloods is required and this would have minimal impact on service organisation and patient acceptability.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Progressive lung deterioration (based on lung function or imaging with HRCT eg decline of at least 10% FVC over 12-month period) Intolerability to Nintedanib
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and	As a non-immunosuppressive agent, Nintedanib provides a different novel therapeutic strategy in the armamentarium of immunosuppressives for progressive ILD. Importantly it spares the risk of infection in a cohort of

substantial impact on health-related benefits and how might it improve the way that current need is met?	immunocompromised patients with progressive ILD where further respiratory infection increases mortality risk with potential worsening of lung fibrosis.
• Is the technology a 'step-change' in the management of the condition?	Yes – focussing on fibrosis as the key pathogenic sequelae of the disease.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – uniquely focussing on fibrotic pathways.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Gastrointestinal side effects including nausea and diarrhoea. Management of these symptoms is critical as long term continuation of Nintedanib is critical for obtaining maximal therapeutic effects of the medication in lung fibrosis.
The type of ILD patients you see who will develop a progressive phenotype: are they only patients with rheumatoid arthritis? And what is the prevalence of those patients in England?	Progressive ILD occurs in a range of conditions. Evidence for the effect of Nintedanib in an uncommon autoimmune rheumatic disease systemic sclerosis is available via SENSCIS trial (n=580 compared to n=39 in INBUILD study) (Distler O, et al; SENSCIS Trial Investigators. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019). Incidence of SSc 1:10,000, so in England this is approximately 8,000. Up to 40% of SSc patients with develop significant lung fibrosis. INBUILD study also included patients with progressive ILD of

	difference cause including sarcoidosis, systemic sclerosis, mixed connective tissue diseases and other autoimmune-related interstitial lung diseases.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Change in annual rate of decline in FVC as indicator of disease progression.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Change in FVC is the surrogate outcome measure used.
• Are there any adverse effects that were not apparent in clinical trials but	None to my knowledge

have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None to my knowledge
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Relevant comparators are not included in the company submission	
The comparator included in the company submission does not reflect best supportive care in the UK.	
The ERG and company differed on their preferred	

extrapolation for overall survival	
Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • • • • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

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Deadline for comments **5pm, Friday 14 May**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Scleroderma and Raynaud's UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Relevant comparators are not included in the company submission	**YES**	The data presented by the company outlines the INBUILD trial which recruited across all ILDs other than IPF. To be included within the trial 'Participants fulfilled protocol-defined criteria for ILD progression in the 24 months before screening, despite management considered appropriate in clinical practice for the individual ILD.' (Lancet Respiratory, Vol 8 May 2020). In other words, to be included within this study patients had to show progression or worsening of their lung disease despite being on active therapies. A 'comparator' group would not have made sense since: 1. individuals came from diverse counties with differing treatment regimens depending on the ILD and the country or origin; 2. To be included within the trial a patients lung disease was judged to be progressing despite treatment – therefore the treatments the patients were currently on at the time of enrolment were 'ineffective' since they were not adequately controlling lung disease.
Key issue 2: The comparator included in the company submission does not reflect best supportive care in the UK.	**YES/NO**	Taking into consideration the point above patients were randomised to either placebo or nintedanib. There was a wash out period prior to commencing treatment within the trial, this varied depending on the treatment regimen of the patient prior to enrolment. The protocol did not allow for the use of restricted medications at randomisation but initiation of these medications was allowed 6 months after study treatment in cases of significant deterioration of ILD or CTD. Overall, the proportion of patients taking a restricted medication at any time

		over the course of the 52 weeks of the study was lower in the group of patients taking nintedanib (12%) compared to placebo (24%). Demonstrating a beneficial effect of nintedanib. These findings are supported by data from the SENSCIS trial for patients with ILD caused by underlying scleroderma. In this study use of mycophenolate in either the placebo arm or combination with nintedanib was permitted. Analysis of trial data suggests an additive effect of nintedanib to antifibrotic therapy minimising the annual rates of change in FVC **-40.2 mls for MMF and nintedanib, - 66.5 mls nintedanib alone or -63.9mls MMF alone compared to -119.3mls placebo (no MMF or nintedanib).**
Key issue 3: The ERG and company differed on their preferred extrapolation for overall survival	**YES/NO**	Not able to respond to this point.

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Summary of changes to the company's cost-effectiveness estimate(s)

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..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

NICE National Institute for Health and Care Excellence

Technical engagement response form

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Thoracic Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Relevant comparators are not included in the company submission	Yes	There are no evidence based therapies that are approved for the management of non- IPF Interstitial Lung Disease (ILD). The only evidence based therapies are for idiopathic pulmonary fibrosis (IPF) and systemic sclerosis related ILD. This cohort of patients are defined as progressive fibrotic interstitial lung disease (not IPF) – there are no evidence based therapies for this group of ILDs **Therefore the comparator to nintedanib would be best supportive care. 68% of the placebo arm were treated with immunosuppressants with glucocorticoid therapy.** **The company have included the correct comparator** It is not correct for the ERG to request for the company to compare nintedanib to Rituximab or Infliximab as these therapies are not licensed nor approved for the treatment of ILD. Furthermore, aside from a selected group of niche indications where these drugs are of clinical utility in treating extra-pulmonary pathology (for

		example neurosarcoidosis or refractory rheumatoid arthritis associated joint disease), even in a tertiary setting, these drugs are not used to treat progressive fibrotic ILD. In actual fact, the reverse is often true in that for patients in whom there is evidence of progressive fibrosis despite escalation immunosuppression, management often revolves around reduction in such therapies, management of infection and consideration of lung transplantation or with focus on best supportive care as there is an acceptance that (aside from antifibrotic therapy), no currently available treatments can slow the rate of disease progression. Therefore, as per NHS England specifications ILD Clinicians do not, and are not able to use Rituximab or Infliximab for management in progressive fibrotic ILD. This is not a relevant or correct comparator.
Key issue 2: The comparator included in the company submission does not reflect best supportive care in the UK.	**YES/NO**	As expert clinicians in the field of interstitial lung disease we disagree with this assumption by the ERG. The diagnosis of progressive fibrotic interstitial lung disease is based on the progression of disease despite failure of conventional therapies. Conventional therapy includes a number of non evidence based therapies in this cohort. This could include a variety of interventions or therapies: 1. Best supportive care only: Some patients are not be suitable for any immunosuppression due to the risk of infections. This is consistent with the placebo arm of this trial

		2. Glucocorticoid treatment only: again due to the risks of infection. This is consistent with the placebo arm of this trial as 68.6% of patients had glucocorticoid therapy at baseline 3. Combination therapy with glucocorticoid and second line immunosuppression with mycophenolate mofetil or azathioprine. This is consistent with the placebo arm as 39.8% of patients had non steroid anti-inflammatory therapies at baseline for their underlying systemic disease eg connective tissue disease. All three categories as above were included in the placebo arm of the trial as described in the Companies report/submission. The definition of progressive fibrotic ILD is defined as progression despite standard therapy. It is common practice that when patients with predominantly fibrotic ILD decline despite immunosuppression, immunosuppression would be reduced or completely stopped due to lack of effectiveness – we consider this to be treatment failure. It is therefore acceptable that for the first 6 months of the trial that patients are not on second line immunosuppressive therapy for their Interstitial Lung Disease. Please also note patients could be on immunosuppressant therapy at the beginning of the trial for their underlying systemic symptoms particularly for connective tissue diseases

		Indeed, the company state that 68.6% of patients in the INBUILD study were on glucocorticoid therapy and 39.8% had non-steroid anti-inflammatory agents at baseline. The very low rate of reintroduction of immunosuppressant therapy after 6 months as seen in this trial (21% Placebo and 10% Nintedanib arms) reflect the lack of evidence base for the effectiveness of immunosuppression for fibrotic ILDs as well as expert clinician reluctance at using immunosuppressants in this group of fibrotic lung diseases. The majority of reintroductions were glucocorticoids (27.1%) and only approximately 6% were second line agents (1.8% (n=6) Azathioprine, 0.6%(n=2) cyclophosphamide, 3%(n=10) Mycophenolate, 0.6%(n=2) rituximab) The PANTHER study is a cautionary tale when considering the use of non-licenced and non evidence based immunosuppressant therapies for a progressive ILD (IPF) (Ref 1). The use of corticosteroids and Azathioprine for patients with IPF was considered “standard of care” before the PANTHER study demonstrated that this treatment approach was associated with an increased risk of mortality. There are clear overlaps between IPF and progressive fibrotic ILD. For example, in patients with chronic hypersensitivity pneumonitis a study has shown that those treated with immunosuppressants such as azathioprine or mycophenolate had a higher risk of death (Hazard ration 4.9 $p<0.01$) (ref 2). The ILD community is therefore reticent and concerned about using non evidence based immunosuppressant therapy in a cohort of patients that phenotypically behave like

		IPF and have similar radiological features to IPF without appropriate evidence to show efficacy and that we are not doing more harm (as was seen in PANTHER). The ERG commented that in the real world that no-one would actually receive placebo – This is incorrect as per the scenarios set out above. The only therapy that has shown effectiveness in progressive ILD is nintedanib in the INBUILD study. The placebo arm is representative of the UK population as it comprised a group of patients on no therapy, glucocorticoids and/or second line immunosuppression at baseline. References: 1. N Engl J Med. 2012 May 24;366(21):1968-77. Prednisone, azathioprine and N-acetylcysteine for pulmonary fibrosis. Idiopathic Pulmonary Fibrosis Clinical Research Network; Ganesh Raghu, Kevin J Anstrom, Talmadge E King Jr, Joseph A Lasky, Fernando J Martinez 2. ERJ Open Research 2017 3: 00016-2017. Outcomes of immunosuppressive therapy in Chronic Hypersensitivity pneumonitis. Adegunsoye A et al
Key issue 3: The ERG and company differed on their preferred extrapolation for overall survival	**YES/NO**	Unable to comment as out of our remit as expert clinicians in Interstitial Lung Disease. Would be guided by expert statisticians.

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About you

Your name	Abby Tebboth
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Boehringer Ingelheim
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG critique
Key issue 1: Relevant comparators are not included in the company submission	**NO**	The ERG report states that the company "should have included other relevant comparators as described in the NICE scope. However, given the lack of evidence for most comparators it is not clear how that could have been achieved. Therefore, the ERG has no suggestions for an alternative approach". The report also states that "the expected change to the ICER is unclear. However, if comparator treatments are more effective than those treatments received in the placebo arm (i.e. excluding immunomodulatory treatments for six months), the ICER will be less favourable for nintedanib". **Opinion from patient, clinical and NHS organisations is that current conventional unlicensed treatments have very limited efficacy in treating the fibrotic component of disease. The definition of the population in scope also means that patients have progressed despite treatment. Therefore, this issue is not expected to have any meaningful impact on the ICER.** Responses to NICE from the British Thoracic Society, Action for Pulmonary Fibrosis and NHS England all agree that the current	The ERG continue to maintain that those treatments prohibited during the first six months of the INBUILD trial could be regarded as actual clinical practice since they were curtailed. Given that they had been prescribed there must at least have been the belief by the prescriber and patient that they conferred benefit. Therefore, the placebo arm of the INBUILD trial cannot be considered to be consistent with actual clinical practice and the effectiveness of

		treatments have very limited efficacy on the fibrotic component of disease (see pages 323-324, 340 and 352 of the technical engagement papers). Therefore, it is unlikely that the efficacy of these unlicensed treatments used in clinical practice will differ significantly from those used in the best supportive care arm of the INBUILD trial. Further to this, the population defined in the scope is “people with fibrosing interstitial lung disease that has progressed despite treatment (excluding idiopathic pulmonary fibrosis)”. Therefore, by definition, these patients will not be receiving any benefit from conventional therapies such as immunosuppressants. As noted in response to key issue 2 below, clinical experts and professional groups agree that current conventional therapies are used for the extrapulmonary, or non-lung, component of patients’ underlying disease, not the progressive fibrotic component. Therefore, while patients with progressive fibrosing interstitial lung disease (PF-ILD) may be receiving immunomodulatory treatments for the extrapulmonary aspects of their disease, these are not expected to treat the fibrotic component that is addressed by nintedanib. It is also incorrect to state that all immunosuppressants were not allowed during the first six months of the trial. Only azathioprine, cyclosporine, tacrolimus, high dose corticosteroids, rituximab, cyclophosphamide and mycophenolate mofetil were restricted during the first six months of the trial; other immunosuppressant therapies were allowed provided they were given at stable doses prior to randomisation. For all of these reasons, we do not believe that this key issue represents any meaningful risk to the cost-effectiveness of nintedanib in this population.	treatments in clinical practice might be underestimated by using the INBUILD trial data.

Key issue 2: The comparator included in the company submission does not reflect best supportive care in the UK.	**NO**	The ERG report states that "the treatments used in the placebo arm of the INBUILD trial do not represent current best practice or best supportive care (BSC) in the UK", although there were no suggestions for an alternative approach. The report also states that "if current best practice in the UK, which includes immunomodulatory treatments, is more effective than those treatments received in the placebo arm excluding immunomodulatory treatments, the ICER will be less favourable for nintedanib". **According to expert and clinical groups, these unlicensed current conventional therapies are being used for the extrapulmonary component of patients' underlying disease, not the progressive fibrotic component, and therefore do not represent best supportive care in the UK.** The ERG's main concern seems to be that the restriction of certain medications in the INBUILD trial (azathioprine, cyclosporine, tacrolimus, high-dose corticosteroids, rituximab, cyclophosphamide and mycophenolate mofetil) means that the comparator in the company submission is not reflective of clinical practice in the UK. Infliximab also appears to be of specific interest to the ERG. The submission from the British Thoracic Society states that drugs frequently used in clinical practice include oral corticosteroids, mycophenolate, azathioprine and methotrexate. However, they also state that methotrexate, infliximab and rituximab are not used in the NHS to treat the progressive fibrosing component of interstitial lung disease: "these immunosuppressive drugs are used to treat any inflammatory component of ILDs. They are not given to treat the fibrotic component of an ILD" (page 348 of the technical engagement papers). Therefore, while patients with PF-ILD may be receiving immunomodulatory treatments for the extrapulmonary aspects of their	See response to Key issue 1.

		underlying disease, these treatments are not prescribed to treat the progressive fibrotic component. Clinicians treating IPF in tertiary centres in the UK have also specifically reported that infliximab and rituximab are not relevant treatments for ILD in the UK. Although mycophenolate and other immunomodulatory treatments are sometimes used in early disease, clinicians have raised concerns around their continued use in patients with progressive fibrotic disease based on the results of the PANTHER-IPF trial, which studied the efficacy of prednisone, azathioprine and N-acetylcysteine (NAC) triple therapy in patients with idiopathic pulmonary fibrosis (IPF).(1) The trial found increased risks of death and hospitalisation in patients with IPF who were treated with a combination of prednisone, azathioprine and NAC compared with placebo, with no benefit in improving lung function, therefore providing evidence against use of this treatment in patients with impaired pulmonary function in clinical practice. These comments are consistent with the lack of observed use of infliximab, rituximab and other immunomodulatory medications in the INBUILD trial. Less than 1% of patients in the placebo arm received infliximab during the trial period. Infliximab use was reported at baseline in two patients in the placebo arm (0.6%) and no patients in the nintedanib arm even though use was not restricted. This low level of usage does not allow a comparative assessment of nintedanib vs. the placebo plus infliximab subgroup and implies that infliximab is not really in routine use in patients with PF-ILD. Use of rituximab was more restricted than infliximab in the INBUILD trial, as noted above. However, less than 1% of patients received rituximab over the whole trial period. Similarly, use of immunomodulatory medications for ILD, including mycophenolate, azathioprine, tacrolimus and cyclosporine, was low over the whole trial. This demonstrates that these treatments are not considered or used as	

		routine care even after the six-month restriction was lifted for patients who had experienced clinically significant deterioration of their disease. **Clinical experts and professional organisations agree that the restriction of certain medications for the first six months of the INBUILD trial does not mean that the trial is not relevant to UK clinical practice.** The lists showing use of concomitant and restricted therapies over the course of the INBUILD trial were shared with two clinical experts working in tertiary centres in the UK as part of our response to clarification questions. Both experts consulted agreed that these were broadly in line with what they would expect to see in clinical practice in the UK. The British Thoracic Society also state in their submission to NICE that the INBUILD trial does reflect UK clinical practice (page 346 of the technical engagement papers). **Current conventional therapies have limited impact on the fibrotic component of disease; therefore, this key issue is not expected to have any meaningful impact on the ICER.** As stated in response to key issue 1 above, submissions to NICE from the British Thoracic Society, Action for Pulmonary Fibrosis and NHS England and Improvement all agree that current treatments have very limited efficacy on the fibrotic component of disease (pages 323-324, 340 and 352 of the technical engagement papers). *"Many patients are aware of these challenges and of the risk of side-effects (such as bone fractures and liver damage) but continue with the [current] therapy, because they are advised to do so by their doctors. Despite this, many patients tell us they are not convinced they work." (Action for Pulmonary Fibrosis)*	

		"Unlicensed/unproven therapies (immunosuppressive drugs) are used without a good evidence base and are often ineffective at treating the fibrotic component of the disease." (British Thoracic Society) *"However, effective treatments, and an evidence base for existing agents, are currently lacking." (NHS England and Improvement)* Therefore, it is unlikely that the efficacy of treatments used in clinical practice will differ significantly from those used in the best supportive care arm of the INBUILD trial. Further to this, the population defined in the scope is those with "fibrosing interstitial lung disease that has progressed despite treatment (excluding idiopathic pulmonary fibrosis)". Therefore, by definition, these patients will not be receiving any benefit from conventional therapies such as immunosuppressants. For these reasons, we do not believe that this key issue represents any meaningful risk to the cost-effectiveness of nintedanib in this population	
Key issue 3: The ERG and company differed on their preferred extrapolation for overall survival	**NO**	The ERG's preferred base case uses the frequentist Weibull curve to extrapolate survival, rather than the Bayesian Weibull curve. The ERG believes that the incorporation of long-term data into the survival analysis "potentially added more uncertainty than it solved given that the long-term data was in an IPF rather than a PF-ILD population and required the use of matching. Additionally, while clinicians considered both extrapolations plausible, the frequentist [Weibull] actually fit the long-term nintedanib IPF survival data better than the Bayesian. For	**Use of the Bayesian analysis reduced the overall variability of survival estimates compared to the frequentist analysis.** The Bayesian analysis may reduce variability, but providing more precise estimates driven by data from a different population, does not necessarily mean that those more precise estimates

		these reasons, the ERG preferred the frequentist [Weibull] for the extrapolation of OS". **Use of the Bayesian analysis reduced the overall variability of survival estimates compared to the frequentist analysis.** We found that use of the Bayesian analysis actually reduced the overall variability of survival estimates, and resulted in greater consistency compared to the frequentist analysis, rather than increasing uncertainty. Due to immature data, the PF-ILD frequentist survival estimates were uncertain and varied widely across different survival models, despite similar AICs and BICs. For example, the frequentist Weibull and frequentist log-logistic PF-ILD nintedanib survival models had similar fits (Weibull nintedanib: 687.0584 [AIC] and 694.6687 [BIC]; log-logistic nintedanib: 687.4335 [AIC] and 695.0438 [BIC]). However, the frequentist log-logistic nintedanib model was more aligned with the Bayesian survival analysis results, whereas the frequentist Weibull nintedanib model produced substantially lower survival estimates. The Bayesian survival estimates for the top three best-fit models were consistent and produced similar survival estimates (median OS range for nintedanib: 6.39-6.50 years). **Use of propensity score matching is appropriate to ensure that the Bayesian analysis did not overestimate survival.** The ERG suggests that the use of propensity score matching may add uncertainty in the Bayesian analysis. Propensity score matching was conducted to ensure that the priors generated using the IPF data were realistic and did not overestimate survival due to differences in patient baseline characteristics. In the unmatched IPF trial dataset, FVC % predicted was 79.3 in the nintedanib arm, compared with 68.6 in the PF-ILD trial dataset. If propensity score matching had not been used to address this imbalance before conducting the Bayesian analysis, then	are accurate in the population of interest. Therefore the ERG is still uncertain about estimates produced by the Bayesian analysis. **Use of propensity score matching is appropriate to ensure that the Bayesian analysis did not overestimate survival.** The ERG is not suggesting that using PSM to attempt to correct for population differences is more uncertain than an unmatched comparison. The ERG is suggesting that an approach which requires the use of different populations and PSM adds uncertainty compared to an approach which does not require either of these. The ERG therefore prefers to use the frequentist approach, in this case, to avoid the need for PSM altogether. **All available evidence suggests that patients with IPF and PF-ILD have similar survival, therefore this**

		the IPF prior may have overestimated survival due to patients in the unmatched IPF dataset having a much higher FVC % predicted. **All available evidence suggests that patients with IPF and PF-ILD have similar survival, therefore this aspect is not expected to add any meaningful uncertainty.** The ERG stated that the use of Bayesian analysis adds uncertainty due to the assumption that IPF and PF-ILD patients have equivalent survival (page 55 of the ERG report). Given the absence of long-term PF-ILD data, it was not possible to use PF-ILD data to inform the prior in the Bayesian analysis and so the long-term IPF trial data were selected as the best alternative. This assumption is supported by evidence in the literature that IPF and PF-ILD patients follow similar survival trajectories. For example, survival estimates in a real-world analysis by Simpson et al showed consistent survival for IPF and PF-ILD patients in the UK (hazard ratio, 1.06; 95% confidence interval, 0.84 –1.35; P = 0.6; measured up to approximately 2.5 years).(2) This is consistent with analysis published by Brown et al based on clinical trial data, showing that PF-ILD and IPF patients who don't receive antifibrotic treatment have similar disease trajectories.(3) Additionally, the ERG believed that the use of IPF data to inform the prior added uncertainty to the Bayesian analysis (page 55 of the ERG report), but stated that the frequentist Weibull model was preferred and better fits the long-term nintedanib IPF external validation data presented (page 77). It is not clear why the ERG believed the use of an IPF-informed prior was inappropriate but based their argument for selecting the frequentist overall survival analysis on the long-term IPF registry data. **The frequentist analysis did not match the long-term clinical trial data for nintedanib in the IPF population very well, and can therefore be considered to be pessimistic.**	**aspect is not expected to add any meaningful uncertainty.** In response to the company's comment about it not being clear why the ERG believed the use of an IPF-informed prior was inappropriate but based their argument for selecting the frequentist overall survival analysis on the long-term IPF registry data, the ERG has several points to raise. Firstly, as previously stated the ERG does not believe that estimating survival using the survival of another population is a better approach than using the population specific data available. Therefore the decision to prioritise the frequentist Weibull was primarily based on the preference to use a frequentist curve and the fact that the Weibull was preferred by clinical experts. Estimates of clinical plausibility are also helpful in assessing long term plausibility and in the absence of any better data the ERG

		Real-world and long-term clinical trial data from the IPF population show that the survival curves separate after around 18 months, with a clear survival benefit for nintedanib vs. the comparator that is maintained for the remaining follow-up time.(4-6) For example, the TOMORROW trial, a long-term clinical trial in patients with IPF, reported a descriptive hazard ratio of 0.7 (95% CI 0.46 to 1.08; p=0.0954) for nintedanib vs. the comparator.(5) A combined analysis of 6 IPF trials estimated median survival of 8.5 years in the nintedanib group compared with 3.3 years in the placebo group.(6) The frequentist analysis did not match this long-term data very well, and is therefore considered to be pessimistic. **There are some differences between the reported registries and UK clinical practice as well as the INBUILD trial.** The EMPIRE and Greek registries were selected to validate the modelled nintedanib survival curves, as there are no long-term data available for PF-ILD patients, and other more appropriate sources for validation, such as the long-term INPULSIS-ON and TOMORROW clinical trials in IPF patients, were used to generate the informative prior. However, it should be noted that there is heterogeneity between these registries and the PF-ILD and IPF clinical trials, as well as what might be expected in UK clinical practice. A key difference between the clinical trials and the EMPIRE study is that OS is estimated as time from IPF diagnosis rather than time from treatment initiation. It is unlikely that patients began treatment with nintedanib straight after IPF diagnosis, and so these survival data may not be an accurate reflection of actual survival after treatment initiation. The EMPIRE registry also includes a number of countries with varied and different healthcare systems to the UK (Austria, Bulgaria, Croatia, Czech Republic, Hungary, Israel, North Macedonia, Poland, Serbia, Slovakia and Turkey). FVC % predicted at baseline is reported to be between 72-79% in the EMPIRE registry, which is lower than the point	can only use this data. However this criteria was considered the lowest priority given uncertainty regarding population. This point was highlighted by the ERG more to point out that if clinical plausibility and fit to the long-term data were criteria in the company's choice of extrapolation curve, the frequentist Weibull curve should have been chosen, as it provided the better fit to the long-term data in the nintedanib arm and equivalent fit in the BSC arm. Therefore, of the two Weibull curves selected by the clinical experts, the ERG consider the frequentist Weibull should have been chosen. **The frequentist analysis did not match the long-term clinical trial data for nintedanib in the IPF population very well, and can therefore be considered to be pessimistic.** The ERG notes that both the frequentist and Bayesian

		at which antifibrotic treatment is allowed to start in UK clinical practice (the upper limit of restriction for nintedanib and pirfenidone is FVC 80% of predicted). In the Greek registry, patients spent a mean 23.6±15.0 months on nintedanib (7), which is lower than that of the unmatched IPF long-term clinical trial population (mean: 27.7 months; SD: 20.5).(6) Additionally, patients in the Greek registry were generally older compared to INBUILD (mean age: 71.80 years vs. 65.75), and more patients were smokers (78.2% vs. 51%; see Table 35 of the Company Submission). These differences could have led to patients in the Greek registry having decreased survival compared to INBUILD or the IPF clinical trial.	Weibull give substantial treatment effects to nintedanib. The ERG would argue that we cannot be sure to what extent survival using the long-term frequentist Weibull curve can be considered pessimistic as this long-term data is taken from a different population with different characteristics. If the populations were the same, there would not have been need for matching. We also cannot be sure that the long-term treatment effect would be the same across populations. **There are some differences between the reported registries and UK clinical practice as well as the INBUILD trial.** The ERG would like to note that the company had no problem using these registries in the CS to validate the Weibull Bayesian. Additionally, even if the company now considers these registries a poor source of external validation, the ERGs

			preferred approach would not change given their preference for using the frequentist approach in this case, and the clinical experts selecting the Weibull curve.
Issue with the probabilistic results in the model submitted in response to clarification (not a key issue)	**NO**	The ERG noted an issue in the model submitted in response to clarification that created an imbalance in the results of the probabilistic sensitivity analysis compared to the deterministic results. We have looked into this issue, and found a small error in the way disutilities were included (a negative sign was missing from the health state values, meaning they were applied as a utility rather than a disutility). This issue has been corrected in the new version of the model uploaded alongside this response.	The ERG thanks the company for providing this.
Alternative extrapolations for discontinuation (not a key issue)	**YES**	The ERG report correctly notes that the company was asked to consider alternative plausible extrapolations, or constant or time dependent discontinuation rates which better represent the INBUILD Kaplan Meier (KM) data. There was insufficient time to provide these with our clarification response, however we have now been able to conduct an exploratory analysis of the impact of selecting a different curve for discontinuation (considering generalised gamma, Gompertz, log logistic, log normal and Weibull as alternatives to the exponential distribution used in the base case). Plots of these curves against the KM data from INBUILD over 3 years suggest that the Gompertz curve may be closest to the KM data, however over the long term this produces unrealistically optimistic rates of discontinuation for nintedanib (see Figure 1 and Figure 2 below).	The ERG thanks the company for providing these analyses. The ERG agrees that while the Gompertz appears to fit the KM curve best, the long-term extrapolation does not seem plausible and that the generalised gamma, log logistic, log normal or Weibull curves appear more realistic in the long-term. Given the mean age of 65 at baseline in INBUILD, the Weibull model probably gives a more

		Over the long term, the generalised gamma, log logistic, log normal or Weibull curves give more realistic estimates of discontinuation. These updated extrapolations were used to calculate the costs of nintedanib treatment, which were then combined with the outputs from the cost-effectiveness model (QALYs for nintedanib and placebo, total costs for placebo and non-treatment costs for nintedanib) to generate exploratory ICERs. This exploratory analysis assumes that the choice of discontinuation distribution does not have an impact on the QALYs and non-treatment costs for nintedanib, In reality, there will be some variation in these outcomes based on the distribution chosen, as once a patient has discontinued they revert to the transition probabilities for best supportive care, so will transition faster through the FVC states. However, as described in the submission, the transition probabilities for lung function decline are not a key driver of results. Therefore, it is expected that the choice of discontinuation distribution will not have a large impact on the nintedanib QALYs or background costs and they should remain relatively stable. Using the generalised gamma, log logistic, log normal or Weibull curves for discontinuation gives an estimated ICER between [redacted] and [redacted] when using the company base case distribution for overall survival (Bayesian Weibull) (see Table 1 below).	realistic extrapolation of time on treatment than the other more optimistic curves. As explained by the company, exploratory analyses testing the impact of discontinuation on nintedanib treatment costs which were then combined with other existing model outcomes (assuming company base-case settings) were provided in a separate excel file (not within the model). However, when selecting the company's base-case Bayesian Weibull extrapolation and exponential extrapolation, an ICER of [redacted] is obtained, which does not match the company's post-clarification base-case of [redacted] Therefore, while the results obtained from these exploratory analyses can give an idea of the impact of changing the desired base-case discontinuation curve, they do not provide correct ICERs and therefore cannot be used in an updated base-case. However to provide an

			idea of the variation in ICERs when using plausible discontinuation extrapolations alongside the ERG's preferred frequentist Weibull OS extrapolation, ICERs obtained from the company exploratory spreadsheet are presented below. Weibull = [redacted] Gen Gamma = [redacted] Log logistic = [redacted] Log normal = [redacted]

Figure 1: Alternative extrapolations for distribution (over 3 years)

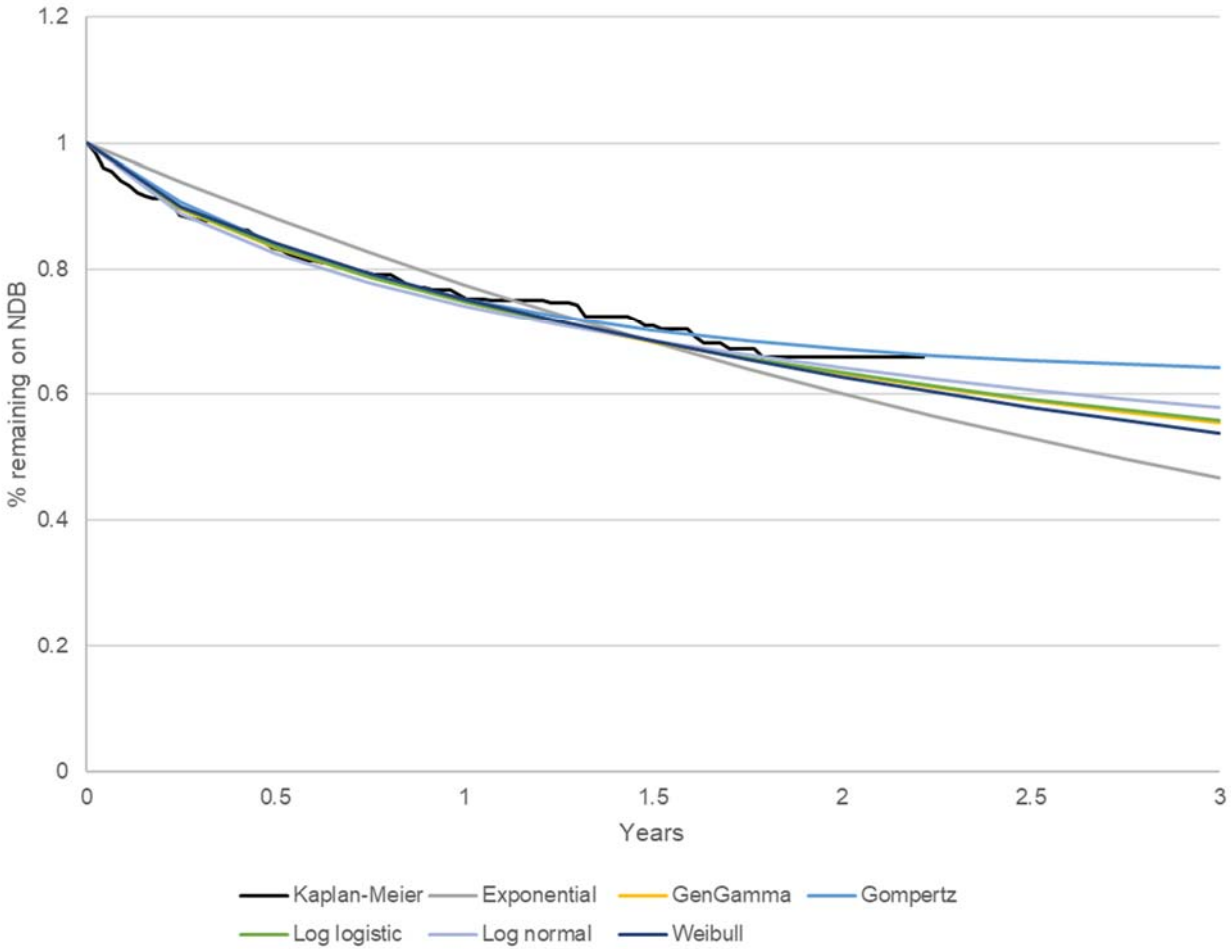

Figure 2: Alternative extrapolations for discontinuation (full model time horizon)

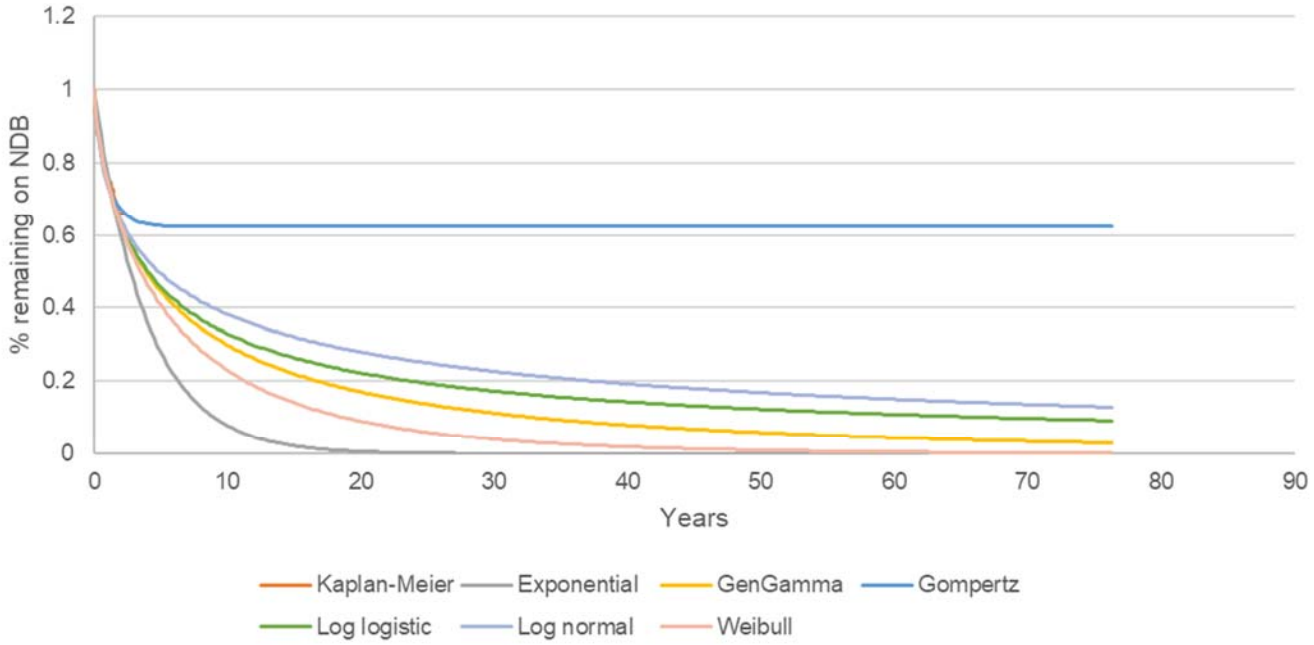

Table 1: Estimated impact of different discontinuation distributions on the ICER

OS distribution	Discontinuation distribution	ICER
Bayesian Weibull	Generalised Gamma	[redacted]
	Gompertz (clinically implausible)	[redacted]
	Log logistic	[redacted]
	Log normal	[redacted]
	Weibull	[redacted]

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

No changes have been made to the company base case following technical engagement.

References

1. The Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. New England Journal of Medicine. 2012;366(21):1968-77.
2. Simpson T, Barratt SL, Beirne P, Chaudhuri N, Crawshaw A, Crowley LE, et al. The burden of Progressive Fibrotic Interstitial lung disease across the UK. European Respiratory Journal. 2021:2100221.
3. Brown KK, Martinez FJ, Walsh SLF, Thannickal VJ, Prasse A, Schlenker-Herceg R, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J. 2020.
4. Vasakova M, Sterclova M, M M, et al. Long-term overall survival and progression-free survival in idiopathic pulmonary fibrosis treated by pirfenidone or nintedanib or their switch. Real world data from the EMPIRE registry. European Respiratory Journal. 2019;54:PA4720.
5. Richeldi L, et al. Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. Thorax. 2018;73(6):581.
6. Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. BMJ Open Respiratory Research. 2019;6(1):e000397.
7. Antoniou K, Markopoulou K, Tzouvelekis A, Trachalaki A, Vasarmidi E, Organtzis J, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study. ERJ Open Res. 2020;6(1):00172-2019.