Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Boehringer Ingelheim**

2. **Clarification questions and company responses**
   a. Initial clarification response
   b. Additional clarification response

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Action for Pulmonary Fibrosis - *submission written by patient expert Stephen Jones and endorsed by patient expert Bob Bray*
   b. Asthma & Lung UK
   c. British Thoracic Society

4. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre
   a. External Assessment Report
   b. External Assessment Report addendum - PSA analyses

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

6. **Personal statements from experts:**
   a. Dr Felix Chua, Consultant Respiratory Physician – Clinical expert, nominated by Boehringer Ingelheim
   b. Dr Simon Hart, Reader in Respiratory Medicine - Clinical Expert, nominated by Boehringer Ingelheim
   c. Bob Bray – patient expert nominated by Action for Pulmonary Fibrosis

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

Review of TA379: Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of TA379) [ID 4062]

Document A

Company evidence submission summary for committee

Boehringer Ingelheim Ltd confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

June 2022

File name	Version	Contains confidential information	Date
Ofev Document A NICE STA_final	V1	Yes	15th June 2022

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Tables and figures

Submission summary

A.1 Health condition

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial lung disease, conferring substantial disability through deterioration of lung function and ultimately resulting in death (1). In England, current management options for patients with IPF and forced vital capacity (FVC) >80% predicted are limited to best supportive care, pulmonary rehabilitation and lung transplantation (2). Most patients with IPF do not meet the eligibility criteria for lung transplantation due to comorbidities or advanced age (3). The existing NICE guidance for nintedanib recommends use in patients with IPF who have an FVC between 50–80% predicted and for treatment to be stopped if there is a confirmed decline ≥10% in FVC % predicted in any 12-month period (4). UK clinicians and patients with IPF do not support the current treatment threshold and consider the UK to be an outlier internationally for IPF treatment (5,6). There is no clinical basis for the current restrictions given that nintedanib demonstrates comparable efficacy in patients with baseline FVC >80% predicted vs. patients with FVC <80% (7) and that patients whose FVC % predicted value has declined by ≥10% still derive benefit from nintedanib (8). Removing the eligibility restrictions by FVC % predicted would allow the 38% of patients with FVC >80% predicted (almost 4,000 patients) to initiate nintedanib from diagnosis, rather than waiting for disease progression, and potentially save over 12,000 life years (9). As rate of decline in IPF is unpredictable and progression of fibrosis is irreversible, prevention of decline in lung function is key (10).

A.2 Clinical pathway of care

Proposed use of nintedanib in IPF

Nintedanib can meet the current unmet need of IPF patients with FVC >80% predicted to slow the decline in lung function (7). Data in the latest BTS registry report show that of the patients not prescribed antifibrotics at presentation, 63% did not receive them due to being outside of the recommended FVC range (9). The proposed change would allow initiation of nintedanib from the point of diagnosis, or when deemed appropriate by the treating physician without having to wait for further progression until FVC declines to <80% predicted. Nintedanib can also continue to provide benefit to patients who have experienced a decline in FVC ≥10% predicted within a 12-month period to

slow the rate of further decline (8). Should NICE recommend use in this population, the budget impact would reach a maximum of £18.7 million in year 5 and would result in an additional collective 5,000 life years (see section A.17 for the budget impact).

A.3 The technology

Table 1: Technology being evaluated – B.1.2 (page 15)

UK approved name and brand name	Nintedanib (OFEV®)
Mechanism of action	Nintedanib is a small molecule intracellular inhibitor of tyrosine kinases, including PDGFR α and β, FGFR 1-3, and VEGFR 1-3. Nintedanib thereby inhibits several steps in the initiation and progression of lung fibrosis and the proliferation of vascular cells (11).
Marketing authorisation/CE mark status	Nintedanib was granted EMA marketing approval as specified below: o As OFEV®, for the treatment of IPF in January 2015, SSc-ILD in May 2020 and PF-ILD in July 2020 o As VARGATEF®, for the treatment of NSCLC in November 2014
Indications and any restriction(s) as described in the summary of product characteristics	Nintedanib has four approved marketing authorisations: • As OFEV®, it is indicated in adults for the treatment of: o IPF o SSc-ILD o PF-ILD • As VARGATEF®, it is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma tumour histology after first-line chemotherapy Nintedanib is contraindicated in pregnancy, in cases of severe pulmonary hypertension, and in cases of hypersensitivity to nintedanib, to peanut or soya or any of the other ingredients.
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.
List price and average cost of a course of treatment	List price: £2,150.10 for 60 x 150mg capsules. The average cost of a course of treatment is £2,151.10 every 30 days. The average cost of a course of treatment with PAS applied is [redacted] every 30 days. Mean cost of treatment (with PAS): [redacted]
Patient access scheme (if applicable)	A patient access scheme is in place. The patient access scheme is in the form of a simple discount ([redacted]) from the list price. PAS price: [redacted]

Abbreviations: EMA, European Medicines Agency; FGFR, fibroblast growth factor receptor; IPF, idiopathic pulmonary fibrosis; NSCLC, non-small cell lung cancer; PAS, patient access scheme; PDGFR, platelet-derived growth factor receptor; PF-ILD, chronic fibrosing interstitial lung diseases with a progressive phenotype; SSc-ILD, systemic sclerosis associated interstitial lung disease; VEGFR, vascular endothelial growth factor receptor.

A.4 Decision problem and NICE reference case

Nintedanib (OFEV®) is currently recommended by NICE as an option for treating idiopathic pulmonary fibrosis (IPF) if the person has an FVC between 50% and 80% of predicted (TA379) (12). This submission, updated with longer-term survival data, focuses on patients with an FVC above 80% predicted to reflect patient and clinical need not covered by the current NICE guidance. This is in line with clinician consultation comments for the NICE decision review paper of TA379 in 2021, which found that clinicians in the UK do not support the current treatment threshold (5). Patient groups also strongly support, and have been campaigning for, review in this population (13).

Nintedanib has two other licensed indications; for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (PF-ILDs) and of systemic sclerosis associated interstitial lung disease (SSc-ILD) (14). Nintedanib is already recommended by NICE for treating PF-ILD in adults within its marketing authorisation with no restriction on FVC predicted value (TA747) (4).

The company submission is consistent with the final NICE scope and the NICE reference case.

A.5 Clinical effectiveness evidence

Table 2: Clinical effectiveness evidence

Study title	INPULSIS-1 and INPULSIS-2 (Phase III RCTs) (n=1066)	INPULSIS-ON (n=734)
Study design	Replicate 52-week, double-blind, randomised, placebo-controlled trials, evaluating the effect of oral nintedanib, 150 mg twice daily, on annual FVC decline, in patients with IPF	An open-label single-arm extension trial of the long-term safety of oral nintedanib in patients with IPF.
Population	Patients aged ≥40 years with a diagnosis of IPF, confirmed according to standard guidelines†, within 5 years of randomisation.	Patients aged ≥40 years with a diagnosis of IPF, confirmed according to standard guidelines†, within 5 years of randomisation who completed the 52-week treatment period of INPULSIS, and the follow-up visit 4 weeks later.
Intervention(s)	Nintedanib (150 mg twice daily).	Nintedanib (50 mg once a day, 50 mg twice a day, 100 mg twice a day and 150 mg twice a day).
Comparator(s)	Placebo.	None.
Outcomes specified in the decision problem	**Rate of decline in FVC over 52 weeks (primary endpoint)**; change from baseline in SGRQ total score at 52 weeks; **time to first acute IPF exacerbation**; risk of an acute IPF exacerbation over 52 weeks; **time to death over 52 weeks**; AEs, serious AEs; severe AEs.	Incidence of AEs; annual rate of decline in FVC (over 192 weeks); absolute change in FVC (mL and % predicted) from baseline to week 192; time to first acute exacerbation; **time to death.**

Reference to section in submission	B.2.2 (page 26)	B.2.2 (page 27)

Study title	TOMORROW (Phase II RTC) (n=432)	TOMORROW open-label extension (n=198)
Study design	A 52 week, double blind, randomized, placebo-controlled trial evaluating the effect of nintedanib administered at oral doses of 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid on FVC decline during one year, in patients with IPF.	A Phase II open-label, roll-over study of the long-term tolerability, safety and efficacy of oral nintedanib in patients with IPF.
Population	Patients aged ≥40 years with a diagnosis of IPF (received less than 5 years before screening), confirmed according to standard guidelines†.	Patients aged ≥40 years with a diagnosis of IPF (received less than 5 years before screening), confirmed according to standard guidelines† who had completed the TOMORROW study and were willing to continue trial medication.
Intervention(s)	Nintedanib (50 mg qd, 50 mg bd, 100 mg twice a day and 150 mg bd).	Nintedanib (50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid).
Comparator(s)	Placebo.	None.
Outcomes specified in the decision problem	**Rate of decline in FVC over 52 weeks (primary endpoint**); change from baseline in SGRQ total score over 52 weeks; **survival** (**all causes of death** and lung-transplant free) over 52 weeks; number of patients with at least one IPF exacerbation over 52 weeks; **time to first acute exacerbation**; AEs.	Annual rate of decline in FVC (primary endpoint); **overall survival**; incidence of patients with at least one acute IPF exacerbation over time; percentage of patients with at least one AE.
Reference to section in submission	B.2.2 (page 28)	B.2.2 (page 29)

Abbreviations: AE, adverse event; bid, twice daily; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; qd, every day; SGRQ, St George's Respiratory Questionnaire.
†Standard guidelines, refers to criteria published by the American Thoracic Society (ATS), the European Respiratory Society (ERS).

A.6 Key results of the clinical effectiveness evidence

Further detail can be found in section B.2.6.

A.6.1 Annual rate of decline in FVC

Nintedanib has been found to consistently slow disease progression by significantly reducing the annual rate of decline in FVC compared with placebo across multiple RCTs (15–17). No statistically significant treatment-by-subgroup interaction was observed for the primary endpoint in either subgroup analysis in patients with baseline FVC >80% vs. ≤80% predicted or FVC >90% vs. ≤90% predicted (7,18):

- In patients with baseline FVC >80% predicted, the nintedanib vs. placebo difference in the adjusted annual rate of decline in FVC was 128.4 mL/ year (95% CI: 78.0–178.8); in patients with baseline FVC ≤80% predicted, it was 94.8 mL/ year (95% CI: 48.3–141.4); p=0.4959.

- In patients with baseline FVC >90% predicted, the nintedanib vs. placebo difference in the adjusted annual rate of decline in FVC was 133.1 mL/ year (95% CI: 68.0–198.2); in patients with baseline FVC ≤90% predicted, it was 102.1 mL/ year (95% CI: 61.9–142.3); p=0.5300.

The rate of decline in FVC observed in the nintedanib 150 mg twice daily group was maintained across the open-label extension trials (TOMORROW open-label extension and INPULSIS-ON), suggesting the effect of nintedanib on slowing the progression of IPF persists beyond 4 years (15,17,19).

A.6.2 Time to first acute exacerbation

There were no statistically significant treatment-by-subgroup interactions in patients with baseline FVC >80% vs. ≤80% predicted or baseline FVC >90% vs. ≤90% predicted for the secondary endpoint time to first acute exacerbation (18,20):

- The hazard ratios (HR) for time to first acute exacerbation in patients with baseline FVC >80% predicted and with baseline FVC ≤80% predicted were 0.49 (95% CI 0.17–1.35) and 0.72 (95% CI 0.41–1.27), respectively, in favour of nintedanib; p=0.6505.

- The HRs for time to first acute exacerbation in patients with baseline FVC >90% predicted and with baseline FVC ≤90% predicted were 0.46 (95% CI 0.09–2.48) and 0.66 (95% CI 0.39–1.11), respectively, in favour of nintedanib; p=0.956.

The incidence of acute exacerbations in INPULSIS-ON were similar to that in patients treated with nintedanib in the INPULSIS trials, supporting the results of the INPULSIS trials, which suggested that treatment with nintedanib might reduce the risk of acute exacerbations in patients with IPF (15).

A.6.3 Change in St George's Respiratory Questionnaire (SGRQ) score from baseline

There were no statistically significant treatment-by-subgroup interactions in patients with baseline FVC >80% vs. ≤80% predicted or baseline FVC >90% vs. ≤90% predicted for the secondary endpoint change in SGRQ score from baseline (18,20):

- The nintedanib vs. placebo differences in adjusted mean change from baseline in SGRQ total score at week 52 in patients with baseline FVC >80% predicted

and with baseline FVC ≤80% predicted were -1.07 (95% CI -3.45–1.32) and -1.66 (95% CI -3.97–0.64), respectively; p=0.5814.

- The nintedanib vs. placebo differences in adjusted mean change from baseline in SGRQ total score at week 52 in patients with baseline FVC >90% predicted and with baseline FVC ≤90% predicted were -0.87 (95% CI -3.97–2.24) and -1.65 (95% CI -3.60–0.32), respectively; p=0.3382. (A negative SGRQ score indicates an improvement in HRQoL.)

A.7 Evidence synthesis

No new randomised clinical trials using nintedanib in IPF were identified during the SLR, so the NMA has not been updated from the original submission (TA379). Only results relevant to the scope of the decision problem are presented.

In the present submission, the overall survival data has been updated based on the TOMORROW open-label extension trial and INPULSIS-ON. For the cost-effectiveness model, mortality has been calculated by fitting individual parametric models to extrapolate the overall survival for both the nintedanib and placebo arms. Therefore, the odds ratios (ORs) from the NMA, which were employed in TA379, are no longer used to estimate the treatment effect for mortality.

For acute exacerbations, loss of lung function, serious cardiac events, serious gastrointestinal events and overall treatment discontinuation, the NMA values from the original analysis are used to derive the treatment effect in the cost-effectiveness model. The NMA was implemented in a Bayesian framework, using both fixed-effect and random-effect models.

Table 3: Results of NMA, scenario 1 analysis

Acute exacerbations		
	FIXED-EFFECTS (DIC=78.0, tot res dev 21.8)	**RANDOM-EFFECTS (DIC=75.50, tot res dev 14.6)**
Comparison	**Median OR (95% CrI)**	**Median OR (95% CrI)**
nintedanib vs. placebo	0.56 (0.35, 0.89)	0.47 (0.01, 15.96)
placebo vs. nintedanib	1.79 (1.12, 2.85)	2.13 (0.06, 78.2)
Loss of lung function		
	FIXED-EFFECTS (DIC=74.7, tot res dev 10.3)	**RANDOM-EFFECTS (DIC=75.2, tot res dev 9.3)**
Comparison	**Median OR (95% CrI)**	**Median OR (95% CrI)**
nintedanib vs. placebo	0.54 (0.42, 0.69)	0.54 (0.11, 2.70)
placebo vs. nintedanib	1.87 (1.45, 2.41)	1.86 (0.37, 9.39)
Serious cardiac events		
	FIXED-EFFECTS (DIC=50.3, tot res dev 10.7)	**RANDOM-EFFECTS (DIC=48.1, tot res dev 7.6)**
Comparison	Median OR (95% CrI)	Median OR (95% CrI)
nintedanib vs. placebo	0.76 (0.45, 1.27)	0.42 (0, 21.16)
placebo vs. nintedanib	1.32 (0.79, 2.2)	2.41 (0.05, 234.9)
Serious GI events		
	FIXED-EFFECTS (DIC=42.4, tot res dev 8.2)	**RANDOM-EFFECTS (DIC=42.5, tot res dev 7.7)**
Comparison	**Median OR (95% CrI)**	**Median OR (95% CrI)**
nintedanib vs. placebo	2.35 (1.05, 5.88)	3.52 (0.08, 429.92)
placebo vs. nintedanib	0.43 (0.17, 0.95)	0.28 (0, 12.09)
Overall discontinuation		
	FIXED-EFFECTS (DIC=81.9, tot res dev 9.6)	**RANDOM-EFFECTS (DIC=83.6, tot res dev 10.1)**
Comparison	**Median OR (95% CrI)**	**Median OR (95% CrI)**
nintedanib vs. placebo	1.42 (1.08, 1.87)	1.43 (0.79, 2.63)
placebo vs. nintedanib	0.71 (0.54, 0.93)	0.70 (0.38, 1.26)

Abbreviations: AE, adverse event; CrI, credible interval; DIC, deviance information criterion; GI, gastrointestinal; OR, odds ratio; tot res dev, total residual deviance.

A.8 Key clinical issues

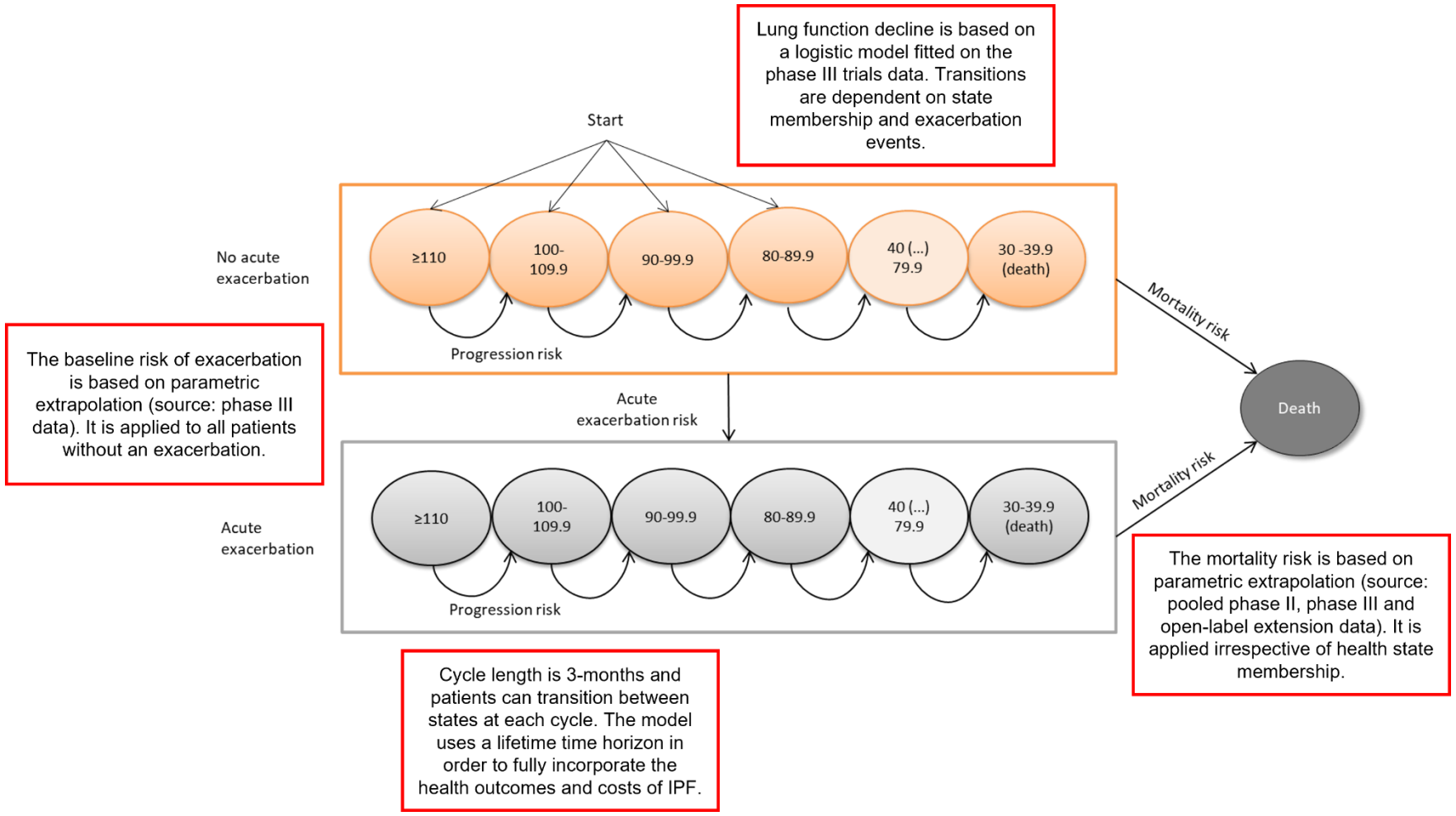
- Subgroup analyses were based on group averages and the subgroups may have included some patients who had no FVC decline during the trial period that could be stabilised with therapy (18). Because the INPULSIS trials were not designed specifically to assess the treatment effect of nintedanib in subgroups, the interaction tests may have been underpowered, and as such, lack of significance does not necessarily imply the absence of a true, underlying difference (21). There is a numerically greater reduction in the primary endpoint of annual rate of decline in FVC (mL/year) in the group with FVC >80% predicted (128.4 mL vs. 94.8 mL in the group with FVC ≤80% predicted), but this is not statistically significant.

- The open-label extension trials did not have a comparator and patient numbers decreased over time. Patients who completed the parent trials and then entered the extension trials may have been more likely to have experienced a favourable disease course or to have better tolerated nintedanib so there is a degree of selection bias, as with all extension trials (15,17).

A.9 Overview of the economic analysis

The cost-effectiveness analysis is based on the model submitted to NICE in TA379 and similar to that reviewed in TA747 (4,12). The original model structure was maintained, as this allowed the inclusion of survival evidence from longer-term follow-up studies without modification of the original structure. Additionally in the decision problem meeting held on 12th April 2022, it was requested that the original model assumptions were kept where appropriate. In alignment with the NICE final scope, the model population included patients with a starting FVC predicted >80%.

Figure 1: Model diagram – B.3.2 (page 91



A.10 Incorporating clinical evidence into the model

The model captured three types of transitions related to treatment efficacy: mortality (overall survival [OS]), acute IPF exacerbations, and decline of lung function (progression based on FVC % predicted).

Overall survival

The risk of mortality was extrapolated beyond the observed trial follow-up period using parametric survival models fitted independently for nintedanib and placebo (PBO) (representing BSC; as is usual for a placebo-controlled clinical trial, the protocol of the INPULSIS 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 “best supportive care” in this disease). The data used was derived from TOMORROW (phase II trial and open-label extension [OLE]), INPULSIS-1 and -2 (phase III trials), and INPULSIS-ON (OLE from phase II and III INPULSIS trials) (15,17,22). Parametric models were fitted to make best use of the available long-term survival data for nintedanib and BSC. Therefore, it was no longer considered appropriate to include the assumption that patients die when they reach FVC predicted <40%, since deaths are accounted for already in the survival analysis.

The base-case analysis assumes the parametric extrapolation model is applied for the full duration of the economic model; that also includes the period of the analysis where clinical trial data were available. This allows uncertainty to be formally explored via a probabilistic sensitivity analysis (PSA). More detail about selection of the parametric model can be found in B.3.3.

The log-logistic model was selected for the base-case based on having the lowest AIC/BIC score for the nintedanib arm, indicating the best fit to the existing data. The log-logistic model was also used for the BSC arm as the NICE DSU technical support document recommends using the same model for both arms (23). Additionally, the decision to base the parametric model choice on the nintedanib arm was due to longer-term survival data being available, which would provide more plausible long-term projections of survival and also the sudden drop due to censoring after the end of the randomised period in the placebo arm likely explains the fit of the Gompertz model. Face validity of long-term extrapolations was confirmed using an Australian IPF

registry, which clinical experts and the NICE committee agreed in TA747 to be representative of UK clinical practice (4).

Acute exacerbation

The baseline and PBO arm probability of exacerbation was implemented using an exponential model, which provides a constant hazard over time, using data on time to first adjudicated acute exacerbation from INPULSIS-1 and -2 in the base-case analysis. An exponential model was used to ensure model parsimony as the difference in AIC between other parametric models was very small.

Loss of lung function

The baseline and PBO arm probability of loss of lung function was derived from a logistic regression model, assuming a constant probability. The goal of this analysis was to estimate the probability of experiencing a drop of 10% in FVC % predicted during any 3-month cycle and control for any other parameter that could influence progression. A logistic regression was selected as this allows the analysis of recurrent events and the incorporation of additional covariates that may influence the probability.

The trial data were separated into four 3-month time intervals (cycle length) and assessed whether a 10-points drop was observed during each interval. The logistic regression model was built by trying several covariates, before fine tuning it to the ones used (FVC % predicted value at start of interval, treatment) based on significance.

Treatment discontinuation

The baseline probability of treatment discontinuation was implemented as an exponential model fitted to PBO trial data, which assumes a constant hazard over time. The exponential and Gompertz parametric models provided the best fit to the discontinuation data, but to ensure model parsimony the exponential model was used. Overall discontinuation was used, which accounts for safety/ tolerability and does not cover stopping rules.

Safety

Safety in the model was analysed by selecting events (individual or grouped in classes) that satisfied certain criteria relating to severity and incidence in at least one

of the clinical studies considered (see section B.3.3 page 129). Two AEs met all criteria; serious cardiac events and serious gastro-intestinal (GI) events.

The serious AE risk for nintedanib was estimated by applying the OR obtained from the NMA to the trial-based placebo risk. The NMA scenario implemented in the model for serious cardiac events and serious GI events included Richeldi et al. 2011 (19) and Richeldi et al. 2014 (16). Serious AE NMA scenarios using just INPULSIS data from Richeldi et al. 2014 were explored in the sensitivity analyses (see Section B.3.11 in Document B). In addition to the adverse events presented above, GI perforation events and mild/ moderate diarrhoea were also implemented in the model as clinically important events.

Sensitivity analyses were also performed on mortality, costs and utilities detailed in Table 7 and section B.3.11 in Document B.

Nintedanib treatment effect

For the risk of acute exacerbation, loss of lung function and overall treatment discontinuation, the treatment effect of nintedanib was obtained by applying to the baseline risk the odds ratios from the NMA (detailed in Table 3).

For TA379, Boehringer Ingelheim selected clinical experts to review assumptions within the model on the basis they have a track record of peer-reviewed publications in IPF and were involved in clinical trials and guidelines and guidance development. Two clinical experts (Dr Gisli Jenkins and Dr Toby Maher) attended an advisory board held on the 23rd of April 2014. The meeting was facilitated by both members of Boehringer Ingelheim and Symmetron, the health economic consultancy who developed the model (24).

Clinicians were aware that the advisory board was to discuss aspects of nintedanib in relation to the IPF HTA submission, and they had knowledge of the nintedanib clinical trials. During the advisory board, the clinical assumptions of the model were checked and discussed between the clinicians. The details and minutes of the advisory board were recorded (24). The clinicians were in agreement of the model structure and assumptions made.

A similar model was also submitted to NICE as part of TA747, and assumptions were separately validated by clinicians at an Advisory Board held in November 2020. This model was considered acceptable for decision making by the committee.

A.11 Key model assumptions and inputs

Given that FVC "*is a widely used measure of disease status and a common endpoint in clinical trials in IPF*" (25), it was selected to be the main factor of disease progression. The MCID for FVC % predicted has been reported as a 2–6% change (25). A 5–10% change has been suggested to predict long-term outcomes including survival. In NICE TA379 (12), after consultation with clinical experts (26) and consideration of the literature, it was decided that a 10-point categorisation of FVC % predicted was appropriate.

The economic model assumes that patients who experienced at least one exacerbation event are at risk of recurrent events. Due to lack of evidence on the incidence of recurrent events, the model assumes the same risk as for patients that have not had an exacerbation. Given that in general the outlook of patients with an acute IPF 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.

No stopping rule was included for patients incurring a greater than 10% decline in their predicted FVC, as it was originally implemented to be consistent with pirfenidone, which was a comparator in TA379 (12). Additionally, clinicians at the advisory board meeting for TA379 were highly critical of implementing a stopping rule and considered it difficult to impose (24), and in TA747, the NICE committee reached the conclusion that a formal stopping rule was not required as clinicians would stop treatment with nintedanib if patients continued to experience rapid disease progression (4).

The EuroQol-5D (EQ-5D) values were compiled from the phase III INPULSIS trial by FVC % predicted group (27). The analysis controlled for exacerbation events, i.e., data before exacerbations occurred were used. To incorporate the results of the data analysis into the economic model the assumption was made that for health states with FVC % predicted values above 90% the utility value was the same as for

FVC90%pred. This assumption was made because the values for FVC % predicted ≥90% were all around an EQ-5D value of 0.84.

Table 4: Key model assumptions

Model Input	Assumption	TA379	Source / Rationale
Cycle length	The model cycle length was assumed to be 3 months.	Same assumption.	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 in discussion with clinical experts (24).
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) nintedanib clinical trials.	Same assumption.	Since the purpose of the economic evaluation is to ascertain the incremental cost-effectiveness of nintedanib vs. BSC, it was assumed that the efficacy and safety of BSC is reflected by the observed outcomes of the PBO arm of the trial. Patients were allowed to use certain background therapies in case of acute exacerbations or disease decline after 6 months on therapy, which is similar to current BSC. Concomitant medications at baseline were well balanced between the nintedanib and placebo groups (azathioprine, cyclophosphamide, cyclosporine, N-acetylcysteine, prednisolone).
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.	Long-term survival data was not available at the time of TA379 submission.	This allows uncertainty to be formally explored via a probabilistic sensitivity analysis (PSA).
	Independent survival models for nintedanib and placebo were used for long-term extrapolation of overall survival.	Long-term survival data was not available at the time of TA379 submission.	Patient survival analysis using data from pooled TOMORROW and INPULSIS clinical and long-term extension trial data was conducted. Given signs of non-proportionality, the use parametric models fitted independently to each treatment arm was deemed appropriate. In the nintedanib arm, the log-logistic model had the lowest AIC/BIC, followed by the Weibull and generalised gamma models. To ensure consistency, as recommended by NICE, the log-logistic model was considered the best fitting model for placebo (BSC) (23). Additionally, the sudden censoring at the end of the trial period likely explains the fit of the Gompertz model to the placebo arm and when comparing the Weibull model to real-world data (28), it appeared to provide a less conservative fit compared to the log-logistic model.
Baseline mortality risk	It was assumed that death occurred at the point that patients reached a level of FVC%pred of 30-39.9%; however, the transition from the FVC%pred 40-49.9% health state was not explicitly modelled as	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 Clinical Guidelines (CG163), a threshold of 35% FVC%Pred was applied (2). However, it was assumed that all deaths would be accounted for in the survival analysis and

Model Input	Assumption	TA379	Source / Rationale
	it was assumed that this was captured in the survival analysis.	with patients transitioning from FVC%pred 40-49.9%	including the transition from FVC%pred 40-49.9% to 30-39.9% would result in double counting.
	The model did not consider the statistical interaction or correlation between mortality, exacerbations and progression	Same assumption.	The following interactions and correlations between parameters were tested: a) Treatment-related mortality, treatment-related progression, and treatment-related exacerbation analysed independently. b) Treatment-related exacerbation and treatment-related progression were analysed independently; overall mortality was dependent on exacerbation only. c) Treatment-related exacerbation and treatment-related progression were analysed independently; overall mortality was dependent on progression only. d) Treatment-related exacerbation and treatment-related progression were analysed independently; overall mortality was dependent on exacerbation and progression. The economic model is based on case (a), Case (b) was not selected because after synthesis of the probabilities of exacerbation and mortality, the final mortality risk was illogical (i.e., exacerbations were linked to better survival) therefore the analysis was not pursued further. For case (c) results were not statistically significant and no link was found between overall survival and progression. It was reasoned that either there were not enough data points for progression, or a 10-point decrease in lung function was not enough to influence survival. As a result, this dependency was not pursued any further. The last scenario (d) was problematic due to two reasons: 1. Statistically, the same problems as with the progression were encountered-dependent overall survival. 2. Including this link in the economic model would have rendered it too complicated, and the objective was to keep it simple, transparent, and user-friendly. It would have been too complex to follow patients' survival through health states as they experienced exacerbations. This analysis would have required tunnels for re-setting time and switching to a different survival equation to account for a different survival function when experiencing exacerbations. This modelling approach has been accepted by NICE in two previous submissions (4,12).

Model Input	Assumption	TA379	Source / Rationale
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).	Same assumption.	According to many studies the MCID for FVC%pred ranged between a 2-6% change (29). Therefore, it was decided after consultation with clinical experts (24) that a 10-point categorisation of FVC%Pred was a balanced range to capture granularity of outcomes without overcomplicating the model. Additionally, a 10% change was adopted in previous IPF NICE submissions (4,12,30).
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).	Same assumption.	Similar assumptions were made in previous NICE UK models (4,12,30). For TA379, clinical expert opinion validated the assumptions (24). It was conservatively assumed that any treatment effect would cease as soon as treatment was discontinued.
Definition of baseline exacerbation risk (PBO arm)	The model used the adjudication committee defined exacerbations as base-case, and explored the investigator reported exacerbations in sensitivity analysis.	The investigator assessed exacerbations were used for consistency with trials for other comparators.	An indirect comparison between clinical trials that used investigator-reported exacerbations was not necessary. The adjudication committee estimates were used as they were confirmed by an independent committee and were therefore considered to be more reliable.
Exacerbation risk	Exacerbation was assumed to be a constant hazard every three months (exponential model).	Same assumption.	Several parametric models were considered based on INPULSIS trial data. Considering the AIC values and model parsimony, the exponential model was selected.
Recurrent exacerbation risk	Patients who experienced at least one exacerbation event were at risk of recurrent events, which was assumed to be the same risk as for patients that have not had an exacerbation.	Same assumption.	It was considered that this is a reasonable assumption given the lack of other relevant evidence on the incidence of recurrent exacerbation events. The assumption (inclusion/exclusion of recurrent events) was tested in deterministic scenario analysis and had a minimal effect on the cost-effectiveness results.
Overall discontinuation risk	Baseline discontinuation (PBO risk) was assumed to be a constant hazard every three months (exponential model).	Same assumption.	Several parametric models were considered based on INPULSIS trial data. Considering the AIC values and model parsimony, the exponential model was selected. Stopping rules are not covered by the time-to-discontinuation analysis, as this was based on safety and tolerability.
IPD analysis on discontinuation to separate from death events	In INPULSIS, in some cases it was impossible to separate discontinuation due to death from actual treatment discontinuation; it was assumed that an event counted as death rather than study discontinuation if the date of discontinuation	Same assumption.	Simplifying assumption.

Model Input	Assumption	TA379	Source / Rationale
	coincided with the date of death or if it was the very next day.		
Discontinuation for the BSC arm	Assumed no discontinuation from BSC.	Same assumption.	Simplifying assumption – no other treatment to cycle to.
Applying OR values to the baseline (PBO) risk – relative treatment effects (nintedanib)	The relative effect of nintedanib was assumed to be informed by an NMA using a fixed effects model	Same assumption.	Nintedanib was found to be significantly superior to placebo in terms of loss of lung function ($p < 0.001$).
	The same relative effects (OR) were applied to the baseline risks, independent of time.	Same assumption.	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).	Same assumption.	This was consistent with the assumptions made regarding a constant relationship of relative effects over time.
Adverse events	AEs with a significant impact on costs and QALYs were assumed to be those that were severe or serious, or frequent and of clinical significance.	Same assumption.	This was to focus on adverse events that had the potential to have a meaningful impact on the overall cost-effectiveness results.
Liver enzyme evaluations	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.	Same assumption.	Simplifying assumption; in clinical practice patients would discontinue treatment – an outcome analysed separately in the model.
BSC daily treatment cost	No treatment cost was assumed for the BSC arm.	Same assumption.	An analysis on concomitant medications on INPULSIS showed a small difference between trial arms (PBO and nintedanib).
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 cycle).	Same assumption.	Frequency schedule was the same with the maintenance test frequency recommended by the pirfenidone summary of product characteristics (31).
Oxygen use	It was assumed that patients with an	Same assumption.	Simplification assumption due to lack of alternative guidance on this parameter.

Model Input	Assumption	TA379	Source / Rationale
	FVC%Pred of 80% would not require oxygen.		
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 cost for the last year of patients' life.	Same assumption.	Clinical experts advised that palliative care is an important aspect of people's end of life care.
Use of clinical trial EQ-5D and HCRU data	The correlation of lung status and patient condition (health state) with HRQoL (in the form of EQ-5D) and resource use was based on INPULSIS 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.	Same assumption.	This was the only available evidence to perform such an analysis for IPF patients. All other known HRQoL analyses were based on mapping from other instruments.
Baseline EQ-5D value for FVC%Pred ≥110 and 100-109.9	Assumed the same utility value as for FVC90%Pred (0.8380).	Same assumption.	This assumption was made because the values for FVC%Pred ≥90% were all around an EQ-5D value of 0.84.
Baseline EQ-5D value for FVC%Pred 30-39.9	Assumed the utility is 0 (dead).	Same assumption.	This assumption was made after discussion with experts, who agreed it was reasonable to assume life was unsustainable with FVC<40% pred.
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.	Same assumption.	This assumption was supported by the analysis of INPULSIS EQ-5D data [INPULSIS post-hoc analysis] (32). The analysis of INPULSIS data showed the following trend in disutility following an acute exacerbation: • There was a severe change in the 1st month after the exacerbation, followed by a recovery and smaller and longer-lasting disability in the subsequent months. Note that the data were too limited to permit the analysis of 2-, 3-, or 4-months decrements [INPULSIS post-hoc analysis] (32). • Adjudicated exacerbations had a more severe impact than the investigator-reported ones. Values were assumed to be conservative estimates, as it was likely that the most severely affected patients were not missing at random (as they were unable or unwilling to attend the next study visit).

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; BSC, best supporting care; EQ-5D, EuroQol-5D; FVC, forced vital capacity; HCRU, health care resource utilisation; HRQoL, health-related quality of life; IPF, idiopathic pulmonary fibrosis; MCID, minimal clinically important difference; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; pred, predicted; QALY, quality-adjusted life year; UK, United Kingdom

A.12 Base-case ICER with PAS applied (deterministic)

Table 5: Base-case results (deterministic) – B.3.10 (page 183)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
BSC	19,262.35	4.0791	3.2056	-	-	-	Baseline	-
Nintedanib	[redacted]	**7.3959**	**5.6942**	[redacted]	**3.3168**	**2.4886**	[redacted]	**-**
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

A.13 Probabilistic sensitivity analysis – with PAS applied

See section B.3.11 (page 182) in the main submission Document B for discussion of the underlying methodology.

Table 6: Base-case results (probabilistic) – B.3.11 (page 190)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. Costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
BSC	19,926.93	4.167	3.263	-	-	-	Baseline	-
Nintedanib	[redacted]	**7.404**	**5.693**	[redacted]	**3.237**	**2.430**	[redacted]	**-**
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Figure 2 Scatterplot of probabilistic results (with PAS) – B.3.11 (page 191)

In the probabilistic sensitivity analysis, nintedanib was cost-effective in 90.4% of simulations with a willingness-to-pay (WTP) threshold of £20,000 and 98.5% of simulations with a WTP threshold of £30,000.

A.14 Key sensitivity and scenario analyses (with PAS applied)

Figure 3 Tornado diagram – B.3.11 (page 197)

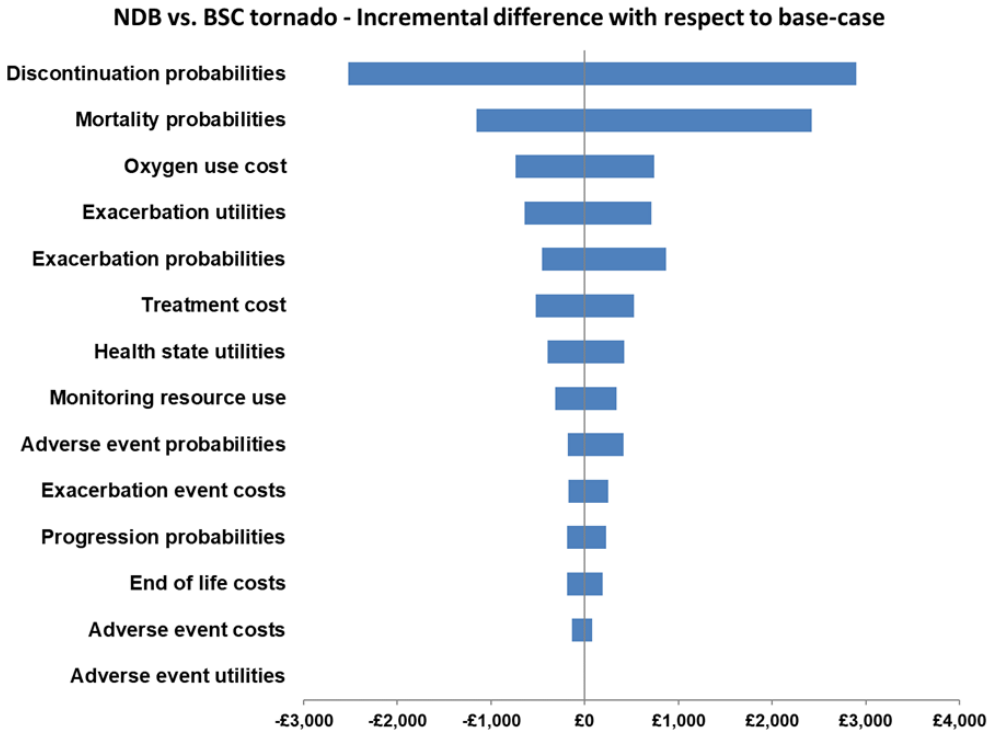


Table 7: Key scenario analyses (with PAS applied)

Scenario and cross reference (B.3.11)	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			[redacted]
Overall survival (Page 199)	Parametric distribution: Weibull parametric model (NDB and BSC)	To analyse the variation in cost-effectiveness results when alternative independent parametric distributions are used.	[redacted]
	Parametric distribution: Generalised gamma parametric model (NDB and BSC)		[redacted]
	Allow progression from FVC%Pred 40-49.9% to FVC%Pred 30-39.9% (death)		[redacted]
Exacerbation (Page 199)	Baseline risk: use investigator estimates	To test assumptions regarding the acute exacerbation parameters	[redacted]
	Baseline risk: exclude recurrent exacerbation risk		[redacted]
	Relative risk: NMA results, scenario 4 excluding Richeldi 2011 (OR=0.62)		[redacted]
Loss of lung function (Page 199)	Baseline risk: include exacerbation coefficient	To examine the robustness of using transition probabilities derived from the whole population and test assumptions regarding acute exacerbations and ORs	[redacted]
	Relative risk: NMA results, scenario 3, excluding Richeldi 2011 (OR=0.53)		[redacted]
	Transition probabilities for FVC%Pred >80%		[redacted]
	Transition probabilities and OR for FVC%Pred >80% (OR=0.50)		[redacted]
Safety (Page 199)	Relative risk: serious cardiac events, NMA results, scenario 2 excluding Richeldi 2011 (OR=0.92)	To examine OR from INPULSIS trials only and test uncertainty in disutility values	[redacted]
	Relative risk: serious GI events, NMA results, scenario 2 excluding Richeldi 2011 (OR=1.88)		[redacted]
	Use alternative disutility value for serious cardiac events (-0.00825)		[redacted]
	Use alternative disutility value for GI perforation (-0.0021)		[redacted]
	Extreme disutility value for serious AEs - serious cardiac events value for serious GI events		[redacted]
Costs	Cost of right heart catheterisation. Cost for Respiratory physiology (£96.68)	Cost was substantially lower than Respiratory medicine	[redacted]
Discontinuation (Page 199)	Relative risk: NMA results, scenario 3, excluding Richeldi 2011 (OR=1.39)	To examine OR from INPULSIS trials only	[redacted]
FVC%Pred values (Page 199)	Lowest value of each FVC%Pred category (e.g., 80 for the 80-89.99) as starting point	To test assumption that people will have an FVC in the middle of the range	[redacted]
	Use the highest value of each FVC%Pred category (e.g., 89.9 for the 80-89.9) as starting point		[redacted]

BSC, best supportive care; FVC%Pred, force vital capacity percent predicted; GI, gastrointestinal; NDB, nintedanib; NMA, network meta-analysis; OR, odds ratio

A.15 Benefits not captured in the QALY calculation

A qualitative study carried out in the US demonstrated that IPF incurs a substantial caregiver burden, as informal caregivers struggle to find balance between providing emotional, and often physical, support, while maintaining their own emotional and physical wellbeing, freedom, and identity (33). Impact on carers has not been captured in the QALY calculation. Some patients are also paying large amounts of their own money to access antifibrotics in the absence of NICE recommendation. This is also not captured in the QALY calculation.

A.16 Severity

Nintedanib was not considered for a severity weight.

A.17 Budget impact

Table 8: Budget impact (Budget impact document – Page 14)

	Company estimate	**Cross reference**
Number of people in England who would have treatment	Year 1 - 478 Year 2 - 717 Year 3 - 955 Year 4 - 1,194 Year 5 - 1,505	England and Wales population – 59,720,000 (34) IPF Prevalence – 0.0136% (35) IPF incidence – 0.0029% (35) Target subpopulation (FVC >80% predicted) – 38% (36) Patients remaining on treatment – 64.06%† Estimated market share uptake‡: Year 1 – 20%, Year 2 – 30%, Year 4 – 40%, Year 5 – 63%
Average treatment cost per person	[redacted] per person per year (PAS Price including VAT)	Nintedanib cost including PAS is [redacted] per person per course of treatment per day Including VAT (72% homecare and 28% secondary care), cost is [redacted] The cost for 365 days is [redacted]. No additional costs were assumed.
Estimated annual budget impact on the NHS in England	Year 1 - [redacted] Year 2 - [redacted] Year 3 - [redacted] Year 4 - [redacted] Year 5 - [redacted]	

†Patients whose FVC drops below 80% predicted are excluded from the calculation, as treatment is already recommended and therefore funded in these patients (12). The proportion of patients remaining in the target population (FVC >80% predicted) after 1 year has been taken from the cost-effectiveness model.
‡Market share estimates are assumed to peak at 63%, as this is the number of patients currently not receiving treatment due to having an FVC out of the recommended range in the BTS Registry Annual Report (9)

A.18 Interpretation and conclusions of the evidence

The results demonstrate the cost-effectiveness of nintedanib compared with BSC: currently the only treatment option in England for patients affected by IPF with an FVC >80% predicted. Nintedanib at list and discounted price was more costly but more effective (for life years and QALYs gained), with the ICER being below the threshold of £20,000-30,000/QALY. With the PAS, this result was consistent across all the deterministic sensitivity analyses. In a PSA, nintedanib was cost-effective in 98.5% of simulations. In the pairwise comparison with BSC, the ICER for nintedanib (discounted price) was [redacted] /QALY gained.

The deterministic sensitivity analysis showed that the ICER was sensitive to the discontinuation probabilities (min: [redacted], max: [redacted]). The choice of a survival model for the mortality risk (log-logistic, Weibull or generalised gamma), was important (min: [redacted], max: [redacted]).

Data from the INPULSIS (16) and TOMORROW trials (19) informed the model, which enrolled patients with FVC >80% predicted and were reflective of the English population. The long-term life expectancy was estimated from the OLE trials (15,17). Survival analysis was validated against data from real-world registries, including the Australian registry (37), which clinicians and the committee for TA747 deemed close to UK clinical practice. Extensive scenario analyses were carried out to ensure the cost-effectiveness estimate was robust. The model assumptions were consistent with two previous NICE assessments (4,12), which were accepted, and the analysis was built on the previous model structure with longer-term survival data (15,17). HRQoL and resource use data from the INPULSIS trials informed the model (38) and are therefore relevant to the target population.

The methodology for costing each of the inputs provided a sufficient level of granularity to inform cost parameters of the English population. Overall, nintedanib addresses an unmet need and was demonstrated to represent a cost-effective use of NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Clarification questions

July 2022

File name	Version	Contains confidential information	Date
ID4062 nintedanib clarification questions to PM_company response	V1	Yes	22/7/22

Notes for company

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Section A: Clarification on effectiveness data

Systematic literature review

A1. Priority question. 'Identification and selection of relevant studies'

a) **CS Appendix D Table 137 lists the 89 publications that were included in the updated systematic literature review of which nine clinical trials are further described in Table 136 (Overview of the identified clinical trials). Only 5 of the 9 clinical trials in Table 136 were considered relevant to the decision problem; please give reasons why the other 4 studies are not included. (NB. see also question B2 below)**

b) **The EAG assumes that the remaining publications in Table 137 were excluded because they were not relevant to the decision problem, but we also note that this table includes several observational studies of nintedanib. Please provide reasons for exclusion of the remaining publications in this table.**

a) The four trials that were not considered relevant to the decision problem together with the reasons are listed below:

NCT02788474 (INMARK, Maher, 2019): While the population included in this trial had a FVC of 80% predicted or higher, the primary endpoint of this study was rate of change in C-reactive protein degraded by matrix metalloproteinases 1 and 8 (CRPM), an endpoint that was not considered relevant to the decision problem. Patients were also treated for 12 weeks with either placebo or nintedanib, therefore the trial design differed to that of TOMORROW and INPULSIS where the randomised period was 52 weeks.(1)

However, the results of the secondary endpoints in this study are consistent with the results of the INPULSIS trials. The adjusted rate of change in FVC over 12 weeks was 5.9 mL in the nintedanib group (n=116) and -70.2 mL in the placebo group (n=231) (difference 76.1 mL/12 weeks [31.7 to 120.4]. This difference was statistically significant, as was observed for the difference in FVC between the nintedanib and placebo groups at week 12 in post-hoc analyses of the INPULSIS trials. Participants in the INMARK trial could continue in an open-label extension for a further 40 weeks. The adjusted annual rate of change in FVC was -88.8 mL/year (SE 23.9) in the nintedanib group, which is comparable to the adjusted annual rate of change in FVC observed in patients with baseline FVC >80% predicted in the INPULSIS trials (-99.6 mL/year). No survival data was reported. These data provide additional support that the efficacy of nintedanib is favourable in the patient subgroup with FVC >80% predicted.(1,(2))

NCT01979952 (Lancaster, 2020): The primary endpoint of this trial was change from baseline in quantitative lung fibrosis score. While the secondary endpoints examined in this study were relevant to the decision problem, due to enrolment difficulties, the planned sample size of the study was reduced, and the primary endpoint was analysed at 6 months as opposed to 52 weeks in the TOMORROW and INPULSIS trials. As a result, all efficacy analyses were deemed exploratory, and the trial was not powered to show significant difference between treatment groups. Protocol amendments resulted in patients receiving double-blind treatment for varying periods beyond month 6. Findings at month 6, and particularly at month 12, are biased by premature discontinuations that were more frequent in the placebo group.

Nevertheless, the findings from this study are supportive of the results of the TOMORROW and INPULSIS trials showing that nintedanib reduces disease progression in patients with IPF. The adjusted mean absolute change from baseline in FVC at month 6 was -14.2 mL in the nintedanib group (n=56) and -83.2 mL in the placebo group (n=57) (difference 69.0 mL [-8.7 to 146.8]), a reduction in decline in FVC which is consistent with the findings of the INPULSIS trials. At 6 months, 1 patient had died in the nintedanib group, and 4 patients had died in the placebo group. However, due to the size of the study and the protocol amendments needed during the trial, we did not consider this trial in the decision problem. We believe that inclusion of this study would have a minimal impact on the overall results for this submission.(3)

NCT01136174: This trial was a safety and PK study comparing nintedanib and placebo conducted at a number of sites in Japan. Since this trial was conducted in Japanese patients, it was considered that the results may not be generalisable to the UK patient population.(4)

UMIN0000020682: This trial is ongoing, and no results have been posted. For this reason, it was not considered as part of the decision problem.(5)

b) Publications that underwent full text review were assessed for inclusion in the SLR according to the PICO criteria. Reasons for exclusion of the publications in Table 137 are listed according to the PICO criteria. For clarity, the publications and reasons for exclusion are listed below:

Publications excluded due to not meeting patient population criteria:

Cottin V, Ryerson CJ, Flaherty KR, Lee JS, Corte TJ, Schinzel B, et al. Effects of nintedanib in subgroups based on combined pulmonary fibrosis and emphysema (CPFE) index at baseline. American journal of respiratory and critical care medicine. 2020;201(1).
Galli JA, ya A, Vega-Olivo M, Dass C, Zhao H, Criner GJ. Pirfenidone and nintedanib for pulmonary fibrosis in clinical practice: Tolerability and adverse drug reactions. Respirology.22(6):1171-8.
Maher TM, Bendstrup E, Kreuter M, Martinez FJ, Sime PJ, Stowasser S, et al. Decline in Forced Vital Capacity as a Surrogate for Mortality in Patients with Fibrosing Interstitial Lung Diseases. American Thoracic Society (ATS)2021.
Pappalardo F, Pieraccini F, Gavioli B, Carnaccini F, Fantini L, Rossi L. Safety profile of pirfenidone and nintedanib in a real life setting: Assessment of suspected adverse drug reactions in the Emilia Romagna Region, Italy. European Journal of Hospital Pharmacy.27:A180-A1.
Richeldi L, Wells A, Cottin V, Crestani B, Molina M, Goeldner R, et al. Does excluding subjects with features similar to IPF affect the results of the INBUILD trial of nintedanib? European Respiratory Society - Virtual Congress2020.

Efficacy and Safety of Nintedanib in Patients With Progressive Fibrosing Interstitial Lung Disease (PF-ILD) https://ClinicalTrials.gov/show/NCT02999178

Publications excluded due to Intervention/ Comparator:

Costabel U, Behr J, Crestani B, Stansen W, Schlenker-Herceg R, Stowasser S, et al. Anti-acid therapy in idiopathic pulmonary fibrosis: insights from the INPULSIS® trials. Respiratory research. 2018;19(1):167.
Fujimoto K, Inomata M, Ito Y, Matsumoto H, Saiki A, Sakamoto K, et al. Efficacy and safety of combination therapy of antifibrotic agents in patients with idiopathic pulmonary fibrosis. Respirology.26:490.
Huh J, Lee J, Song J. Efficacy and safety of combined use of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis. European Respiratory Society - Virtual Congress 2021.
Safety and Tolerability Study of Pirfenidone in Combination With Nintedanib in Participants With Idiopathic Pulmonary Fibrosis (IPF) https://ClinicalTrials.gov/show/NCT02598193
IPF Italian Observational Study (FIBRONET) in Idiopathic Pulmonary Fibrosis https://ClinicalTrials.gov/show/NCT02803580
Evaluate the Safety and Efficacy of FG-3019 (Pamrevlumab) in Participants With Idiopathic Pulmonary Fibrosis (IPF) https://ClinicalTrials.gov/show/NCT01890265
Safety and PK Study of BIBF 1120 in Japanese Patients With IPF: Follow up Study From 1199.31(NCT01136174) https://ClinicalTrials.gov/show/NCT01417156
Study of Pulmonary Rehabilitation in Patients With Idiopathic Pulmonary Fibrosis (IPF) https://ClinicalTrials.gov/show/NCT03717012
Long-term Effect of Pulmonary Rehabilitation under Nintedanib treatment in Idiopathic Pulmonary Fibrosis https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000030312
Efficacy and Safety of Nintedanib Co-administered With Sildenafil in Idiopathic Pulmonary Fibrosis Patients With Advanced Lung Function Impairment https://ClinicalTrials.gov/show/NCT02802345

Publications excluded due to Outcome:

Arai N, Matsuyama M, Nakajima M, Yazaki K, Nonaka M, Sakai C, et al. Search for host factors that predict the therapeutic effect of nintedanib for idiopathic pulmonary fibrosis (ipf). American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2021;203(9).
Cilli A, Uzer F, Sevinc C, Coskun F, Ursavas A, Oner, et al. Tolerability and efficacy of second-line antifibrotics in patients with idiopathic pulmonary fibrosis. Pulmonary Pharmacology and Therapeutics. 2021;71.
Perelas A, Glennie J, van Kerkhove K, Li M, Scheraga RG, Olman MA, et al. Choice of antifibrotic medication and disease severity predict weight loss in idiopathic pulmonary fibrosis. Pulmonary Pharmacology & Therapeutics. 2019;59:101839.
Polito G, Limodio M, Ferraro M, Ferrante F. Pirfenidone and nintedanib for the treatment of the idiopathic pulmonary fibrosis: An italian hospital experience. European Journal of Hospital Pharmacy. 2021;28:A74.
Safety, Tolerability and PK of Nintedanib in Combination With Pirfenidone in IPF https://ClinicalTrials.gov/show/NCT02579603

Publications excluded due to timeframe:

Goyard C, Cottin V. Does emphysema influence the effect of nintedanib in IPF?. French. Revue des Maladies Respiratoires Actualites. 2015;7:146-7.

Goyard C, Crestani B. The effect nintedanib on lung function decline according to the initial FVC in idiopathic pulmonary fibrosis: Results of INPULSIS studies. French. Revue des Maladies Respiratoires Actualites. 2015;7:151-3.
Highland K, Distler O, Gahlemann M, Azuma A, Fischer A, Mayes M, et al. Safety profile of nintedanib in patients with systemic sclerosis-associated interstitial lung disease and idiopathic pulmonary fibrosis. Annals of the Rheumatic Diseases. 2019;78:200.
Huggins J, Kaye M, Bailes Z, Esser D, Conoscenti C, Flaherty K. Efficacy and safety of nintedanib in US and NonUS patients with Idiopathic Pulmonary Fibrosis (IPF) in the INPULSIS trials. Chest. 2015;148(4).
Huggins J, Meyer K, Stansen W, Quaresma M, Kreuter M. No effect of dose adjustments on long-term reduction in FVC decline with nintedanib in patients with idiopathic pulmonary fibrosis (IPF). Chest. 2017;152:A452.
Kolb M, Collard HR, Stowasser S, Girard M, Schlenker-Herceg R, Richeldi L. Sensitivity analyses from the INPULSISTM trials of nintedanib. Eur Respir J. 2014;44.
Kolb M, Kimura T, Stowasser S, Hallmann C, Richeldi L. Effect of baseline fvc on decline in lung function with nintedanib in patients with IPF: results from the inpulsis trials. Respirology. 2015;20:84.
Kolb M, Kimura T, Stowasser S, Hallmann C, Richeldi L. Effect of baseline FVC on decline in lung function with nintedanib in patients with IPF: Results from the INPULSIS trials. Thorax. 2015;3:A62.
Kolb M, Richeldi L, Kimura T, Stowasser S, Hallmann C, Du Bois RM. Effect of baseline FVC on decline in lung function with nintedanib in patients with IPF: Results from the inpulsis trials. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2015;191.
Koschel DS, Lancaster L, Hern, ez P, Inoue Y, Wachtlin D, et al. Safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): Pooled data from six clinical trials *. Pneumologie Conference. 2019;60.
Kreuter M, Koegler H, Trampisch M, Geier S, Richeldi L. Efficacy of nintedanib on acute exacerbations reported as serious adverse events in the INPULSIS trials in idiopathic pulmonary fibrosis (IPF). Pneumologie Conference. 2017;58.
Lancaster LH, Conoscenti CS, Ilowite J, Trampisch M, Mogulkoc N, Homik L, et al. Effect of nintedanib on exercise capacity in patients with idiopathic pulmonary fibrosis (IPF): results from a phase iiib trial. American journal of respiratory and critical care medicine. 2018;197.
Lancaster LH, Hern, ez P, Inoue Y, Wachtlin D, Loaiza L, et al. Safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): Pooled data from six clinical trials. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2018;197.
Maher T, Flaherty KR, Inoue Y, Richeldi L, Selman M, Stansen W, et al. No effect of baseline diffusing capacity of lung for carbon monoxide on benefit of nintedanib. European respiratory journal Conference: european respiratory society annual congress 2016 United kingdom. 2016;48.
Maher TM, Flaherty KR, Noble PW, Vancheri C, Wuyts WA, Kimura T, et al. Effect of baseline FVC on lung function decline with nintedanib in patients with IPF. European respiratory journal (varpagings). 2015;46.
Maher TM, Inoue Y, Case AH, Sakamoto W, Stowasser S, Wuyts WA. Effect of dose reductions and/or interruptions on the efficacy of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): Subgroup analysis of the inpulsis trials. Thorax. 2017;72:A253.
Maher TM, Inoue Y, Case AH, Sakamoto W, Stowasser S, Wuyts WA. Effect of dose reductions and/or interruptions on the efficacy of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): Subgroup analysis of the inpulsis trials. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2017;195.
Moreno Q, Garcia V, Miarons M, Marin S, Camps M, Sanchez A, et al. Evaluation of the effectiveness and safety of pirfenidone and nintedanib in idiopathic pulmonary fibrosis. European Journal of Hospital Pharmacy. 2016;23:A151.
Mulholl, SA, Al Jbour K, Steer H, Gutsche M, Foley N, et al. Real world experience of pirfenidone and nintedanib for the treatment of idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2018;197.
Munoz Burgos M, Mejias Trueba M, Desongles Corrales T. Antifibrotics in idiopathic pulmonary fibrosis management: Pirfenidone and nintedanib. European Journal of Hospital Pharmacy. 2019;26:A125-A6.
Neurohr C, Richeldi L, Azuma A, Selman M, Tang W, Capapey J, et al. Twenty-four week decline in forced vital capacity (FVC) predicts mortality at week 52 in the INPULSIS trials. Pneumologie Conference. 2017;58.
Nishioka Y, Song JW, Kondoh Y, Kim YW, Nishiyama O, Stowasser S, et al. Biomarkers of disease progression in Asian subjects with idiopathic pulmonary fibrosis treated with nintedanib: subgroup analysis of the INMARK trial. Respirology (Carlton, Vic). 2019;24:83-.

Noor S, Nawaz S, Garfoot T, Greaves M, Hayton C, Margaritopoulos G, et al. What happens to patients with idiopathic pulmonary fibrosis who are not eligible for antifibrotic treatment due to current nice guidelines. Thorax. 2019;74:A119-A20.
Noth I, Wijsenbeek M, Kolb M, Bonella F, Moros L, Wachtlin D, et al. Cardiovascular safety of nintedanib in subgroups by cardiovascular risk at baseline in the tomorrow and inpulsis trials. American journal of respiratory and critical care medicine Conference: american thoracic society international conference, ATS 2017 United states. 2017;195.
Richeldi L, Selman M, Kirsten AM, Wuyts W, Bernois K, Stowasser S, et al. Long-term efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): results from the tomorrow trial and its open-label extension. QJM : monthly journal of the association of physicians. 2016;109:S45-S6.

Publications excluded due to Publication type:

Abe M, Tsushima K, Sakayori M. Corrigendum: Utility of nintedanib for severe idiopathic pulmonary fibrosis: A single-center retrospective study(Drug Des Devel Ther., 2018, 12, (3369-3375), 10.2147/DDDT.S179427). Drug Design, Development and Therapy. 2019;13:807-8.
Anonymous. Erratum: Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis (New England Journal of Medicine (2014) 370 (2071-2082)). New England Journal of Medicine. 2015;373:782.
Anonymous. Nintedanib (Ofevdegree) and idiopathic pulmonary fibrosis. Prescrire International. 2016;25(173):177.
Anonymous. Corrigendum to: Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia: Treatment of IPF (Respirology, (2017), 22, 7, (1436-1458), 10.1111/resp.13146). Respirology. 2018;23:116.
Bouvry D, Jouneau S. Idiopathic pulomonary fibrosis: Nintedanib, pirfenidone, beyond the randomised clinical trials. French. Revue des Maladies Respiratoires Actualites. 2015;7:256-62.
Costabel U, Stansen W, Stowasser S. Reply: Effect of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis. American Journal of Respiratory & Critical Care Medicine. 2017;195(9):1275.
Laurenson S, Sidhu R, Goodall M, Adler AI. NICE guidance on nintedanib for treating idiopathic pulmonary fibrosis. The Lancet Respiratory Medicine. 2016;4(3):176-7.

Publications excluded due to duplicate:

Cottin V, Spagnolo P, Bonniaud P, Nolin M, Dalon F, Kirchgassler K, et al. Outcomes in patients receiving nintedanib or pirfenidone for idiopathic pulmonary fibrosis. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2020;201(1).
Gao J, Kalafatis D, Carlson L, Li CX, Pesonen I, Skold M. Baseline characteristics and survival of patients with idiopathic pulmonary fibrosis (IPF): analysis from the Swedish IPF registry. European Respiratory Journal Conference: European Respiratory Society International Congress, ERS. 2020;56.
Glaspole I, Bonella F, Bargagli E, Glassberg MK, Caro F, Stansen W, et al. Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis and multiple comorbidities. American Journal of Respiratory and Critical Care Medicine Conference: American Thoracic Society International Conference, ATS. 2020;201(1).
Jprn U. The comparison of the efficacy and safety of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis. 2016 https://trialsearchwhoint/Trial2aspx?TrialID=JPRN-UMIN000020682
Jprn U. Long-term Effect of Pulmonary Rehabilitation under Nintedanib treatment in Idiopathic Pulmonary Fibrosis. 2017 https://trialsearchwhoint/Trial2aspx?TrialID=JPRN-UMIN000026376
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.
NCT. A Study to Test How Well a Medicine Called Nintedanib Helps People in China With Progressive Lung Fibrosis. 2021 https://clinicaltrialsgov/show/NCT05065190

Taniguchi H, Xu Z, Azuma A, Inoue Y, Li H, Fujimoto T, et al. Subgroup analysis of Asian patients in the INPULSIS^R trials of nintedanib in idiopathic pulmonary fibrosis. Respirology. 2016;21(8):1425-30.

Reporting trial follow-up and missing data

A2. The CS (Table 15) provides a risk of bias assessment for the TOMORROW and INPULSIS trials which the EAG assumes is based on the total trial populations (rather than baseline FVC % predicted subgroups). Please provide evidence to show that there were no unexpected differences in drop-out rates or missing data between respective trial arms for the FVC > 80% predicted subgroup.

It is not clear whether this question concerns the number of patients who did not complete the planned observation time (planned observation time was considered as completed if all visits until week 52 and the following follow-up visit were performed), or it refers to missing data for analysis purposes. Missing data in relation to data analysis may vary according to the type of endpoint, its timepoint of measurement, and the criteria for patients' inclusion in the analysis. We therefore address this question in relation to both these interpretations.

<u>Interpretation 1: Non-completers (drop-out rates) of planned observation period</u>

In the pooled INPULSIS-1 and INPULSIS-2 trials, 487 patients were enrolled with an FVC>80% predicted and randomised at a 3:2 ratio (nintedanib: placebo) into the trial (295 nintedanib; 192 placebo). A total of 485 patients were treated in the trial (295 nintedanib; 190 placebo). Overall, 423 (87.2%) of patients completed planned observation time: 252 in the nintedanib arm (85.4%); 171 in the placebo arm (90%). The difference in treatment completers is not unexpected, because the main reason for patients prematurely discontinuing from trial medication was an adverse event (22.4% nintedanib; 8.4% placebo), and the proportion of patients prematurely discontinuing from trial medication was higher in the nintedanib group as expected. Consequently, overall, 62 patients (12.8%) did not complete the observation time (planned observation time was considered as completed if all visits until week 52 and the follow-up visit were performed according to the flow chart). (Source: Table

28.1.2.1 Disposition of patients by FVC% predicted at baseline ,<=80%, >80% - Studies 1199.32 and 1199.34 pooled. Date: 19AUG2014).(6)

We will provide the drop-put rates for the FVC>80% predicted subgroup in TOMORROW by 1st August, as agreed at the clarification meeting.

Interpretation 2: Missing data for analysis purposes

In TOMORROW, the primary outcome was the annual rate of decline in FVC, measured as the difference of 0.1 litres in the annual decrease in FVC between patients receiving nintedanib and those receiving placebo. The primary analysis for the primary outcome was done on the randomised set but including only on-treatment evaluations. To be included in the analysis, a patient needed to have at least two on-treatment FVC evaluations performed. For the estimation of this slope no replacement of missing data was done. For the primary analysis, the slope of decline of FVC was included also discontinued patients, but only based on their on-treatment evaluations provided they had at least two on-treatment FVC evaluations performed; missing values were not otherwise replaced. The data for the FVC>85% predicted subgroup are provided in Table 1; these did not show any unexpected differences between placebo and nintedanib. The table updated with the missing data by FVC 80% predicted threshold subgroups will be provided by 1st August, as agreed at the clarification meeting.

Table 1. TOMORROW trial (NCT00514683). Missing data for the analysis of rate of decline in FVC (L/yr) at 52 weeks – OC* – randomized and analysed sets by treatment arm; FVC≥85% pred. subgroup

Subgroup with FVC≥85% predicted at baseline	Placebo	Nintedanib 50mg qd	Nintedanib 50mg bid	Nintedanib 100mg bid	Nintedanib 150mg bid
Number of patients in randomised set	33	27	30	39	31
Number of analysed patients	31	27	30	39	30
Proportion with missing data	6.06%	0	0	0	3.23%

*OC, observed cases

Source: Source: Table 15.2.12.1.1: 9 Rate of decline in FVC (L/yr) at 12 months* by FVC% pred at baseline <=85% − OC − randomised set, Clinical Trial Report Trial no. 1199.30, page 851 (7)

In INPULSIS-1 and -2, the primary efficacy endpoint was the annual rate of decline in FVC (expressed in mL over 52 weeks). The efficacy analysis was based on the treated set, which consisted of patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. For

the primary endpoint specifically, all data (including baseline) up to, but not including (except for some specific cases), the follow-up visit were taken into account. Follow-up visit data were excluded, except for patients who prematurely discontinued trial medication and did not complete the planned observation time (8,9) .

For the pooled INPULSIS-1 and -2 datasets, the proportion with missing data for the FVC>80% subgroup is presented in Table 2. The number of analysed patients in relation to the primary efficacy endpoint has been derived from the number of patients reported in Figure 'Change from baseline in FVC' in Maher et al study (2015) as part of their post-hoc subgroup analyses of patients with baseline FVC >80% versus ≤80% of predicted value. The size of the treated sets has also been obtained from Maher et al.(2) There were no unexpected imbalances between arms.

Table 2. INPULSIS-1 and -2 pooled dataset (NCT01335464 and NCT01335477). Missing data for the analysis of rate of decline in FVC (L/yr) at 52 weeks – OC* – randomized and analysed sets by treatment arm; FVC>80% pred. subgroup

Subgroup with FVC>80% predicted at baseline	Placebo	Nintedanib 150mg bid
Number of patients in treated set	190	295
Number of analysed patients	188	288
Proportion with missing data	1.05%	2.37%

*OC, observed cases
Source: Maher 2015, page 13 (2)

A3. Please clarify whether the multiple imputation sensitivity analysis to assess alternative missing data assumptions (described in CS Table 14) was also conducted for the FVC > 80% predicted subgroup in the INPULSIS trials and, if so, provide a summary of the results.

The multiple imputation sensitivity analysis was undertaken in relation to the whole dataset. We have not performed these analyses separately in relation to any of the subgroups, due to the low power in these groups.

A4. Please report how many patients had missing data for the primary outcome in the TOMORROW trial, by treatment arm and by FVC % predicted subgroup.

The number of TOMORROW trial patients with missing data in relation to the primary outcome is provided in Table 3 by treatment arm, and in Table 4 by baseline FVC 85% predicted threshold subgroups. The table updated with the missing data by FVC

80% predicted threshold subgroups will be provided by 1st August, as agreed at the clarification meeting.

Table 3. TOMORROW trial (NCT00514683). Missing data for the analysis of rate of decline in FVC (L/yr) at 52 weeks – OC – randomized and analysed sets by treatment arm; overall sample

NCT00514683 (TOMORROW) Rate of decline in FVC (L/yr) at 52 weeks – OC* – randomized and analysed sets by treatment arm					
Overall population	Placebo	Nintedanib 50mg qd	Nintedanib 50mg bid	Nintedanib 100mg bid	Nintedanib 150mg bid
Number of patients in randomised set	87	87	86	86	86
Number of treated patients	85	86	86	86	85
Number of analysed patients	83	85	86	85	84
Number of patients with missing data	4	2	0	1	2

OC, observed cases
Source: Table 11.4.1.1.1:1 Rate of decline in FVC (L/yr) at 52 weeks – OC – randomised set, Clinical Trial Report Trial no. 1199.30, page 147 (7)

Table 4 TOMORROW trial (NCT00514683). Missing data for the analysis of rate of decline in FVC (L/yr) at 52 weeks – OC – randomized and analysed sets by baseline FVC ≤ or > 85% predicted subgroup

NCT00514683 (TOMORROW) Rate of decline in FVC (L/yr) at 52 weeks – OC* – randomized and analysed sets by FVC 85% predicted subgroup										
	FVC≥85% pred. at baseline					**FVC <85% pred. at baseline**				
	Placebo	NDB 50mg qd	NDB 50mg bid	NDB 100mg bid	NDB 150mg bid	Placebo	NDB 50mg qd	NDB 50mg bid	NDB 100mg bid	NDB 150mg bid
Number of patients in randomised set	33	27	30	39	31	54	60	56	47	55
Number of analysed patients	31	27	30	39	30	52	58	56	46	54
Number of patients with missing data	2	0	0	0	1	2	2	0	1	1

OC, observed cases; NDB, nintedanib
Source: Table 15.2.12.1.1: 9 Rate of decline in FVC (L/yr) at 12 months* by FVC% pred at baseline <=85% − OC − randomised set, Clinical Trial Report Trial no. 1199.30, page 851 (7)

A5. Priority question. 'Summary of methodology of the relevant clinical effectiveness evidence'

a) For the INPULSIS-ON study, please clarify whether the baseline is the start of the extension study itself or the start of the parent RCT

(INPULSIS), i.e. do the 192 weeks of observation include or exclude the initial 52 week period from the randomised phase?

b) Further, please clarify whether the baseline characteristics in Tables 11 (INPULSIS-ON) and 13 (TOMORROW extension) represent characteristics at the start of these respective extension studies or at the start of their parent RCTs (i.e. INPULSIS and TOMORROW respectively).

c) Table 19 summarises clinical outcomes for INPULSIS-ON including mortality over 5 years' follow-up (5 years would be approximately 260 weeks). Is this 5 years period the 52-week INPULSIS trial period + the maximum 12 week off-treatment period after the INPULSIS trial + the 192 week INPULSIS-ON follow-up (total 256 weeks)?

a) The 192 weeks follow-up period excludes the initial 52-week trial duration from randomisation in INPULSIS-1 and INPULSIS-2 (Crestani 2019) (10).

b) The baseline characteristics in Tables 11 and 13 respectively represent the characteristics at the start of INPULSIS-ON (please see Table 1 in Crestani 2019 (10)) and TOMORROW OLE (please see Table S3 in the Supplementary material in Richeldi 2018 (11)).

c) The approximated 5 years period relates to the maximum exposure of 68.3 months to nintedanib across both the INPULSIS parent trials and INPULSIS-ON: *"Median exposure time for patients treated with nintedanib in both the INPULSIS and INPULSIS-ON trials was 44·7 months (range 11·9–68·3)"* (Crestani 2019) (10).

A6. In the INPULSIS-ON study did all participants achieve 192 weeks of follow-up (aside from those who died during the open label extension period)? If not, what is the median period of follow-up?

A total of 735 patients were entered into the trial and 734 patients received at least 1 nintedanib dose. Overall, 677 patients started the trial receiving nintedanib 150 mg bid and 57 patients started the trial receiving nintedanib 100 mg bid. By the database lock time for the final analysis, 70.0% of patients had permanently discontinued

nintedanib treatment. At the time of the database lock, 27 patients (3.7%) were still on trial treatment. Patients who left the trial after it was stopped in their country were reported as not having discontinued trial medication (193 patients [26.3%]). The median (min, max) exposure was 31.48 (0, 56.3) months.(Source: INPULSIS-ON CTR, page 5) (12)

Trial subgroups - baseline FVC >80% predicted

A7. Priority question. How many of the 734 participants who entered the INPULSIS-ON extension study have a baseline FVC >80% predicted?

The number of patients who entered the INPULSIS-ON trial was 735. One patient in the ≤80% subgroup was not treated, and therefore 734 patients were treated in the trial, of which 457 (62.26%) were in the FVC ≤80% predicted subgroup and 277 (37.74%) were in the FVC>80% predicted subgroup. (Source: Table 3.1.58.1.1 Disposition of patients by FVC% predicted at baseline (<=80%, >80%) − Study 1199.33 in DOF NIN 22-07a).(13)

A8. CS Section B.2.6 describes how the rate of decline in FVC during the first 52-week period of the INPULSIS trials and the decline observed during the 192-week period during INPULSIS-ON did not differ by a clinically significant amount (22 ml). Please provide evidence to show whether this was similarly observed for the baseline >80/<80 FVC% predicted subgroups.

We did the analysis of annual rate of decline in FVC by subgroup of FVC % predicted (≤80% vs > 80%) for the pooled INPULSIS-1 and -2 datasets; please see the results in Table 5. The corresponding analysis from INPULSIS-ON has now been done based on data from the final database lock (September 2017); these results are presented in Table 6.

The analysis in INPULSIS-ON shows a slightly higher, but still clinically insignificant, rate of decline in FVC for patients with FVC >80% predicted at baseline, compared with that shown in the same subgroup in the parent INPULSIS trials (-99.57 mL in the nintedanib group in the pooled INPULSIS trials vs. -133.60 in INPULSIS-ON, or a difference of 34.03 mL; see Table 5 and Table 6). For comparison, the annual rate of decline in the placebo group for patients with FVC >80% predicted reported over 52 weeks was -228.0 mL. Please also note that the subgroup with FVC >80% predicted

had a numerically lower annual rate of decline in FVC in INPULSIS-1 and -2, and therefore started INPULSIS-ON with a numerically greater lung capacity than the overall population.

Table 5: Rate of decline in FVC (m/yr) over 52 weeks by FVC% predicted at baseline (≤ 80%, > 80%), observed cases, treated set of INPULSIS-1 and -2 pooled

Subgroup	Treatment group	N1 / N2*	Adjusted¥ rate (SE)	Adjusted¥ difference (95%CI)	p-value
FVC≤80% predicted	Placebo	233 / 233	-220.5	94.8 (95% CI 48.3, 141.4)	
	Nintedanib	343 / 343	-125.7		
FVC>80% predicted	Placebo	190 / 190	-228.0	128.4 (95% CI 78.0, 178.8)	
	Nintedanib	295 / 295	-99.6		
Treatment by time by subgroup interaction p-value∞					0.4959

*N1: number of analysed patients; N2: number of patients in each subgroup.
¥ Based on a random coefficient regression with fixed effects for trial, treatment, gender, age, height and random effect of patient specific intercept and time.
∞ Based on a random coefficient regression with fixed effects for trial, treatment, gender, age, height, treatment by FVC% predicted interaction, time by FVC% predicted interaction, treatment by time by FVC% predicted interaction and random effect of patient specific intercept and time.
Source: Maher et al 2015(2)

Table 6: Annual rate of decline in FVC (mL) over the whole study period by FVC % predicted at baseline (≤80%, >80%), observed cases, treated set in INPULSIS-ON (final database lock September 2017)

Subgroup	Treatment group	N1 / N2*	Adjusted¥ rate (SE)	95% CI
FVC ≤80% predicted	Total	457/457	-138.38 (7.905)	-153.96, -122.81
FVC >80% predicted	Total	277/277	-133.60 (8.776)	-150.90, -116.29

*N1: number of analysed patients; N2: number of patients treated in each subgroup.
¥ Adjusted rate based on a random coefficient regression with fixed effects for gender, age, height and random effect of patient specific intercept and time. Within−patient errors are modelled by an Unstructured variance−covariance matrix. Inter−individual variability is modelled by a Variance−Components variance−covariance matrix.
Source: Table 1.5.12.2.1.5.2 Annual rate of decline in FVC (mL) over time including the whole study period by FVC %pred at BL (<=80%, >80%) in total population − OC − Treated Set − Study 1199.33; based on snapshot on 12SEP2017.
Note: The results in Table 6 are currently undergoing validation and we will send confirmation of validation and the Data on File reference for Table 6 by 1st August.

A9. Priority question. Please provide any available subgroup analyses of patients with baseline >80/<80 FVC % predicted for outcomes of the TOMORROW trial.

For TOMORROW trial, subgroup analyses were done based on FVC % predicted above and below 90%, 85% and 70% predicted at baseline. Unfortunately, there is no analysis in patients with FVC above and below 80% predicted. In the subgroup

with FVC ≥90% predicted, the trend was consistent with the trend in the overall population, but did not reach statistical significance due to the small numbers of patients in each group (see Table 7). Similar trends (consistent with the overall population) were observed with baseline FVC % predicted cut-offs at 85% and 70%, and the difference was statistically significant for the nintedanib 150 mg bid in the subgroup of patients with FVC ≥70% predicted at baseline.(7)

Table 7: Rate of decline in FVC (L/year) at 12 months by FVC % predicted at baseline, observed cases, RS (TOMORROW trial)

	Treatment	N patients in RS	N analysed patients	Adjusted rates (SE)	Adjusted rates of difference (SE)	95% CI	p-value
FVC ≥90% predicted							
No	Placebo	60	58	−0.197 (0.043)			
	Nintedanib 50mg qd	66	64	−0.203 (0.044)	−0.007 (0.061)	−0.127, 0.114	0.9149
	Nintedanib 50mg bid	70	70	−0.228 (0.039)	−0.031 (0.058)	−0.145, 0.083	0.5966
	Nintedanib 100mg bid	51	50	−0.184 (0.047)	0.013 (0.063)	−0.111, 0.138	0.8365
	Nintedanib 150mg bid	62	61	−0.079 (0.046)	0.118 (0.063)	−0.005, 0.241	0.0606
Yes	Placebo	27	25	−0.186 (0.067)			
	Nintedanib 50mg qd	21	21	−0.100 (0.070)	0.086 (0.097)	−0.104, 0.276	0.3722
	Nintedanib 50mg bid	16	16	−0.119 (0.081)	0.067 (0.105)	−0.140, 0.274	0.5253
	Nintedanib 100mg bid	35	35	−0.143 (0.053)	0.043 (0.086)	−0.125, 0.212	0.6140
	Nintedanib 150mg bid	24	23	−0.019 (0.072)	0.168 (0.098)	−0.025, 0.360	0.0878
FVC ≥85% predicted							
No	Placebo	54	52	−0.212 (0.046)			
	Nintedanib 50mg qd	60	58	−0.189 (0.046)	0.023 (0.065)	−0.105, 0.150	0.7279
	Nintedanib 50mg bid	56	56	−0.271 (0.044)	−0.059 (0.064)	−0.184, 0.066	0.3519
	Nintedanib 100mg bid	47	46	−0.197 (0.049)	0.014 (0.067)	−0.118, 0.147	0.8302
	Nintedanib 150mg bid	55	54	-0.083 (0.050)	0.129 (0.068)	−0.004, 0.262	0.0570
Yes	Placebo	33	31	−0.160 (0.058)			

	Treatment	N patients in RS	N analysed patients	Adjusted rates (SE)	Adjusted rates of difference (SE)	95% CI	p-value
	Nintedanib 50mg qd	27	27	−0.141 (0.062)	0.019 (0.085)	−0.147, 0.185	0.8235
	Nintedanib 50mg bid	30	30	−0.101 (0.058)	0.058 (0.081)	−0.102, 0.218	0.4751
	Nintedanib 100mg bid	39	39	−0.128 (0.049)	0.031 (0.076)	−0.117, 0.180	0.6788
	Nintedanib 150mg bid	31	30	−0.027 (0.060)	0.132 (0.083)	−0.031, 0.295	0.1119
FVC ≥70% predicted							
No	Placebo	24	22	−0.203 (0.075)			
	Nintedanib 50mg qd	25	25	−0.350 (0.074)	−0.146 (0.105)	(−.353, 0.060)	0.1647
	Nintedanib 50mg bid	23	23	−0.224 (0.071)	−0.021 (0.103)	(−.224, 0.181)	0.8363
	Nintedanib 100mg bid	16	16	−0.139 (0.087)	0.064 (0.115)	(−.162, 0.289)	0.5791
	Nintedanib 150mg bid	28	27	−0.176 (0.073)	0.027 (0.104)	(−.177, 0.231)	0.7942
Yes	Placebo	63	61	−0.186 (0.041)			
	Nintedanib 50mg qd	62	60	−0.109 (0.042)	0.077 (0.058)	(−.037, 0.191)	0.1874
	Nintedanib 50mg bid	63	63	−0.203 (0.040)	−0.017 (0.057)	(−.129, 0.094)	0.7589
	Nintedanib 100mg bid	70	69	−0.167 (0.037)	0.019 (0.055)	(−.089, 0.127)	0.7307
	Nintedanib 150mg bid	58	57	−0.010 (0.045)	0.176 (0.060)	(0.058, 0.294)	0.0036

Source: TOMORROW clinical trial report: Table 15.2.1.1.2.3: 8, page 598; Table 15.2.12.1.1: 9, page 851; Table 15.2.12.1.1: 10, page 852)

As a general comment, we welcome the opportunity to address NICE clarification questions specific to the FVC >80% predicted subgroup and provide the results for this subgroup, all confirming the cost-effectiveness of nintedanib in this subgroup. Nonetheless, we would like to highlight that we believe it is also reasonable and within the scope of this appraisal to rely on the analysis and results in the overall patient population, as we did in the submission dossier, for a number of reasons.

First of all, there is no evidence of the difference between the FVC>80% predicted subgroup and the overall population in terms of the primary endpoint, as demonstrated in the nintedanib study by Maher a et al., 2015 (2), and in the Australian registry study by Jo et al, 2018 (14). Moreover, we would like to draw the attention on the fact that there is no clinical rationale within the scope of this appraisal for the FVC ≤80% predicted restriction applied by NICE.

The restriction applied by NICE was only driven by a reliance of the restrictions in the comparator appraisal in other NICE TAs (TA504), and the focus was therefore on the cost-effectiveness versus a different set of relevant comparators in the conclusions of that appraisal. In other words, there is no clinical reason why patients with baseline FVC >80% predicted should be modelled differently with respect to patients with FVC ≤80%. Clinically, the FVC 80% predicted level is not a threshold representation of a change in the disease mechanism, it is instead helpful to segment patients who are in earlier stages of the disease (Jo et al, 2018). Not only is clinically meaningful to apply the overall population estimates to the FVC >80% predicted population, but it is also statistically appropriate as it yields the statistical power required to undertake robust analysis.

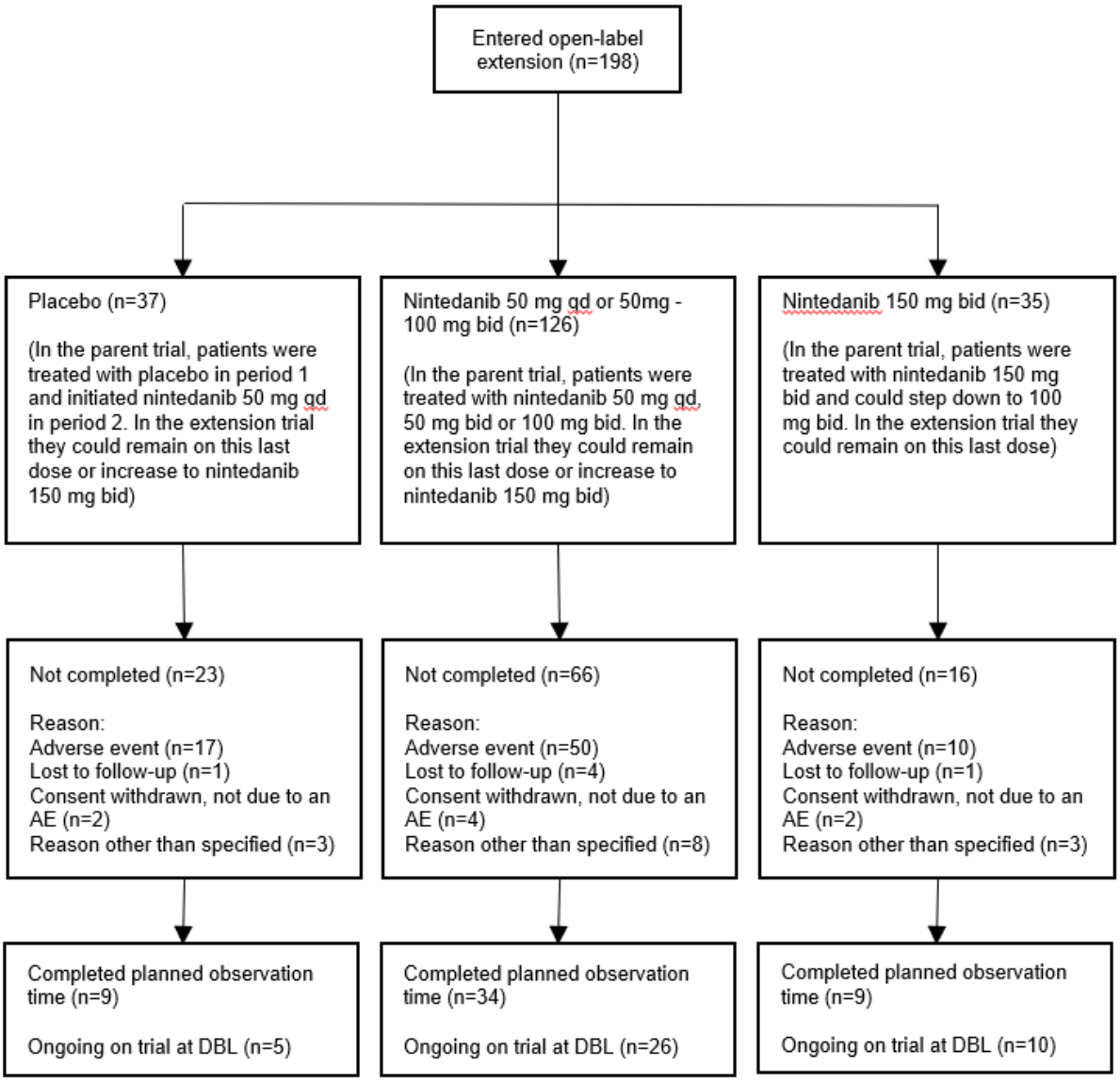
Data discrepancies

A10. CS Figure 1 and Table 13 suggests that 37 patients from the TOMORROW trial placebo group switched to Nintedanib 50mg od during period 2 with the option of increasing to 150mg bd in the open label extension phase. However, in CS Figure 44, 37 patients are described as continuing on placebo in the extension phase. Please clarify this apparent discrepancy.

We apologise that Figure 44 included in the submission is not correct. The corrected illustration of patients' disposition is provided below in Figure 1. We have also explained in the diagram how each arm has been defined. Please note that in the middle arm in the diagram we have grouped together the 3 arms exposed to the low-intermediate doses of nintedanib in the parent trial. Please also note that in TOMORROW study reports, the extension study arm which has enrolled patients from the placebo arm in TOMORROW period 1 has continued to be referred to as

'placebo' arm alongside the footnote 'Patients in this group actually received BIBF 50mg qd during period 2". In the published report, it is referred to as 'comparator arm': *"patients who received placebo in period 1, nintedanib 50mg once daily in period 2, and nintedanib at a range of doses between 50mg once daily and 150mg twice daily in the extension*" (Richeldi 2018, p. 1-2 (11).

Figure 1. Correction of Figure 44 included in the submission



Notes: Columns are displayed according to dose at randomisation in 1199.30. DBL: Database lock of 15OCT2015. Planned observation time is from first trial drug intake to follow−up visit

Source: Roll Over Study From 1199.30 BIBF 1120 in Idiopathic Pulmonary Fibrosis (IPF) - Study Results - ClinicalTrials.gov; Table 15.1.1: 2 Disposition of patients by treatment at randomisation in 1199.30, page 144. (15)

A11. Please check the data presented in Tables 37 and 38 and explain any discrepancies with data presented in the company submission for TA379. The total number of adverse events ('Any adverse event') reported across both INPULSIS trials in Table 93 of the company's submission for TA379 is 988 whereas in Table 37 of the current submission the number of adverse events reported is 977 and in Table 38 of the current submission it is 987. Furthermore, Table 37 reports 322/343 nintedanib group participants with baseline FVC ≤80% predicted had an adverse event, as a percentage, this would be 93.9% but Table 37 gives a value of 96.8% which suggests there is an error in reporting these data.

We apologise for the typing error in Table 37, which should read 332/343 nintedanib group participants with baseline FVC ≤80% predicted had an adverse event. The inconsistency in Table 38 is due to an inconsistency in the number of adverse events reported in the two publications Richeldi 2014 (16)and Kolb 2017 (17) .

Clinical study reports / data on file

A12. Priority question. Please supply the clinical study reports for INPULSIS-ON and the TOMORROW open-label extension studies. These do not appear to have been included in the company submission reference pack.

Apologies for this omission. The INPULSIS-ON and TOMORROW open-label extension clinical study reports will be uploaded to NICE Docs alongside this response.

A13. Priority question. Please supply the following reports referenced in the company submission:

> **76. Boehringer Ingelheim. INPULSIS patient data. 2014.**
>
> **85. Ingelheim B. data on file - phase III trial (trial no. 1199.32 and 1199.34) post-hoc analysis. 2014**

Reference 76 (Boehringer Ingelheim, INPULSIS patient data. 2014) refers to the individual patient data used to derive the time to discontinuation extrapolation and the concomitant medications used per patient. Reference 85 (Ingelheim B. data on file – phase III trial (trial no. 1199.32 and 1199.34) post-hoc analysis. 2014) also refers to individual patient data which were used to derive utility values used,

healthcare resource utilisation, proportions of patients starting in each FVC % predicted category and loss of lung function calculations in the model. We did not supply these for data privacy reasons, as although the data are de-identified they are not fully anonymous.

Having discussed this with the External Assessment Group during the clarification meeting, we agreed that these references are no longer required, however concomitant medications used in INPULSIS-1 and INPULSIS-2 can be found in the clinical study reports for these trials, as listed below:

- Use of on-treatment concomitant medications in INPULSIS-1: Table 15.1.4.3.1.2:1 (All on-treatment concomitant therapies (including baseline therapies) with a frequency >2% in at least one treatment arm – treated set, pages 283 – 300

- Use of on treatment concomitant medications in INPULSIS-2: Table 15.1.4.3.1.2: 1 (All on-treatment concomitant therapies (including baseline therapies) with a frequency >2% in at least one treatment arm – treated set, pages 282 – 303

Section B: Clarification on cost-effectiveness data

Costs

B1. CS Section B.3.5, Table 108, presents the total exacerbation cost as £4,627.58. In the provided model, the total exacerbation cost is given as £4645.33 (CostInputs!S128). The discrepancy appears to originate from the total costs calculations for GP visits and Specialist visits in the model, which do not match the total item costs in the company submission. Please identify and justify which values are correct and update the model accordingly.

Apologies for the incorrect data entry in Table 108. The correct values are those included in the model, which are based on the unit costs: GP visit £36,21; Specialist visit £123. These unit costs have been correctly reported in Table 108, but the corresponding values reported in the '*Total item cost*' column of this table are not correct and should be replaced with the values reported in the model: GP visit £4.55 and Specialist visit £35.59. Therefore, the total exacerbation cost reported in Table 108 needs also to be updated to the value reported in the model, namely £4,645.33.

Extrapolation of overall survival

B2. Priority question. The EAG notes the publication by Lancaster 2019 ('Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials') in CS Table 137. This publication reports an extrapolation of long-term survival from parametric survival distributions fitted to pooled Kaplan-Meier survival data from 6 clinical trials of nintedanib.

a) **Please clarify the relationship between this publication and the extrapolation of overall survival reported in the CS (B.3.3).**

b) **One of the 6 clinical trials included in the publication is the trial by Lancaster et al 2020 ('Effects of Nintedanib on Quantitative Lung Fibrosis Score in Idiopathic Pulmonary Fibrosis' NCT01979952).(109).**

Please clarify why this study was not included in the current extrapolation of overall survival. (NB. see also question A1 above)

a) The analysis done by Lancaster et al (18)and reported in the publication in BMJ Open Respiratory Research in 2019 differs from the survival analysis in our current submission to NICE in two main ways:

- Lancaster et al included a phase IIIb trial for nintedanib (NCT01619085), whereas this was not included in the updated survival analysis submitted to NICE

- Lancaster et al also used slightly different censoring rules, whereby patients who switched from blinded placebo to open-label nintedanib in INPULSIS-ON and the phase IIIb trial were analysed as part of the pooled nintedanib population from their first dose of nintedanib. In the updated survival analysis submitted to NICE, placebo patients who entered the OLE study were censored on the date they switched to nintedanib and contributed no further data to the analysis after this point (i.e. they did not contribute to the nintedanib cohort)

Overall, there are more patients in the analysis by Lancaster et al (1,691) than the survival analysis we submitted to NICE (1,236).

b) The phase IIIb trial was not included in the survival analysis submitted to NICE as it is not a pivotal trial, and because of substantial protocol changes that took place. In this trial, patients with IPF, FVC ≥50% predicted and DL_{CO} 30-79% predicted were originally randomised to receive nintedanib 150 mg two times per day or placebo double-blind for 12 months, but this was amended to a placebo-controlled period of 6 months following regulatory approval of nintedanib in some participating countries. The double-blind period was ≥6 months for some patients due to the variable time required to implement the protocol amendment.(18) Overall, it was considered that the phase IIIb trial did not provide additional long-term survival data, and was not as robust as the INPULSIS-1 and -2 trials due to protocol amendment, and was therefore excluded from the survival analysis submitted to NICE.

B3. Please report the proportion of the 725 nintedanib patients and the 511 placebo patients pooled in the extrapolation of overall survival (section B.3.3) by their respective source study (i.e. TOMORROW phase II trial and OLE; INPULSIS 1 and 2 and INPULSIS-ON).

A total of 1,236 IPF patients were included in the extrapolation of overall survival analysis; 725 patients were treated with nintedanib and 511 with placebo. The IPF trials used in this analysis were:

- TOMORROW (phase II trial and open-label extension [OLE] (Richeldi 2018): 170 patients (13.75%), randomly assigned to receive nintedanib or placebo. This study included survival data up to under two years for both nintedanib (672 days) and placebo (699 days) patients. (11)
- INPULSIS-1 and -2 (phase III trials) (Richeldi 2014): 1,066 patients (86.25%), randomly assigned to receive nintedanib or placebo and followed throughout the 52-week randomised period. (16)
- INPULSIS-ON (OLE from INPULSIS trials) (Crestani 2019): 734 patients previously receiving nintedanib or placebo in the INPULSIS-1 and -2 trials. This study included survival data up to almost six years for nintedanib patients (2,155 days) and under two years for placebo patients (570 days).(10)

B4. In the pooled individual patient data analysis of overall survival (CS Section B3.3), please clarify whether patients who received placebo in the RCTs (and who were censored when they switched to nintedanib during the open label extension periods) also contributed to the nintedanib cohort from the point at which they switched or if they were excluded from the nintedanib cohort in this analysis.

The RCT and OLE trial data were pooled for this analysis using the following censor rules:

- Placebo patients who entered the OLE study were censored on the date they switched to nintedanib and contributed no further data to the analysis after this point (i.e. they did not contribute to the nintedanib cohort).

- Nintedanib and placebo patients who did not enter the OLE study were censored at the last contact date recorded in the RCTs or during follow-up after RCT completion.
- Nintedanib who entered the OLE study were censored at the last contact date recorded in the OLE.

B5. Priority question. Please provide a scenario analysis based on overall survival for a subgroup of patients with a baseline FVC >80%. Please provide full details of the fitting of the parametric curves for this analysis.

Parametric survival models were fitted independently to the nintedanib and placebo treatment arms for consistency with the base-case analysis and given signs of non-proportionality of hazards between treatment arms (Figure 9). The following six parametric models were explored in the analysis: exponential, Gompertz, lognormal, log-logistic, Weibull and generalised gamma. All analyses were conducted in R using the "flexsurv" package with the same methodology as per the original analysis.

Goodness of fit was assessed using visual inspection and the statistical criteria – Akaike/Bayesian Information Criterion (AIC/BIC). The AIC and BIC values for nintedanib and placebo are presented in Table 8 and Table 9, respectively.

Table 8: AIC and BIC of the parametric models: nintedanib (baseline FVC predicted >80%)

Model	Exponential	Weibull	Log-logistic	Lognormal	Gompertz	Generalised gamma
AIC	1169.691	1163.786	1163.456	1163.707	1166.640	1165.114
BIC	1173.505	1171.415	1171.084	1171.335	1174.268	1176.556

AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 9: AIC and BIC of the parametric models: placebo (baseline FVC predicted >80%)

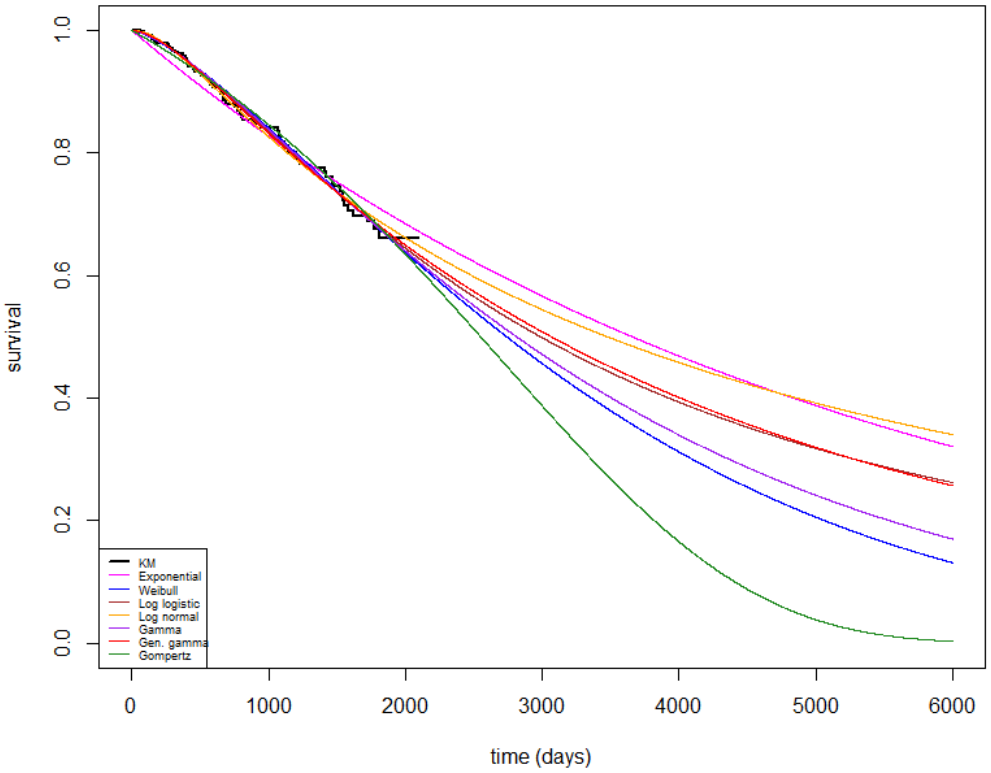
Model	Exponential	Weibull	Log-logistic	Lognormal	Gompertz	Generalised gamma
AIC	240.3215	234.0667	234.1453	234.2522	234.4183	235.9856
BIC	243.7683	240.9602	241.0387	241.1457	241.3118	246.3258

AIC: Akaike information criterion; BIC: Bayesian information criterion.

In the nintedanib arm, the three models with the lowest AIC and BIC were log-logistic, lognormal and Weibull, with the log-logistic model having the lowest AIC and BIC. In the placebo arm, the Weibull model had the lowest AIC and BIC, followed by the log-logistic, lognormal and Gompertz models, respectively. To ensure consistency in selecting the same survival model for each treatment arm, as recommended by NICE (19), the log-logistic model for placebo was selected for comparison, and it had similar AIC/BIC values to the Weibull model. When using the log-logistic model, the ICER (with PAS) was £[redacted]. When using the Weibull and lognormal models, the ICERs (with PAS) were £[redacted] and £[redacted], respectively.

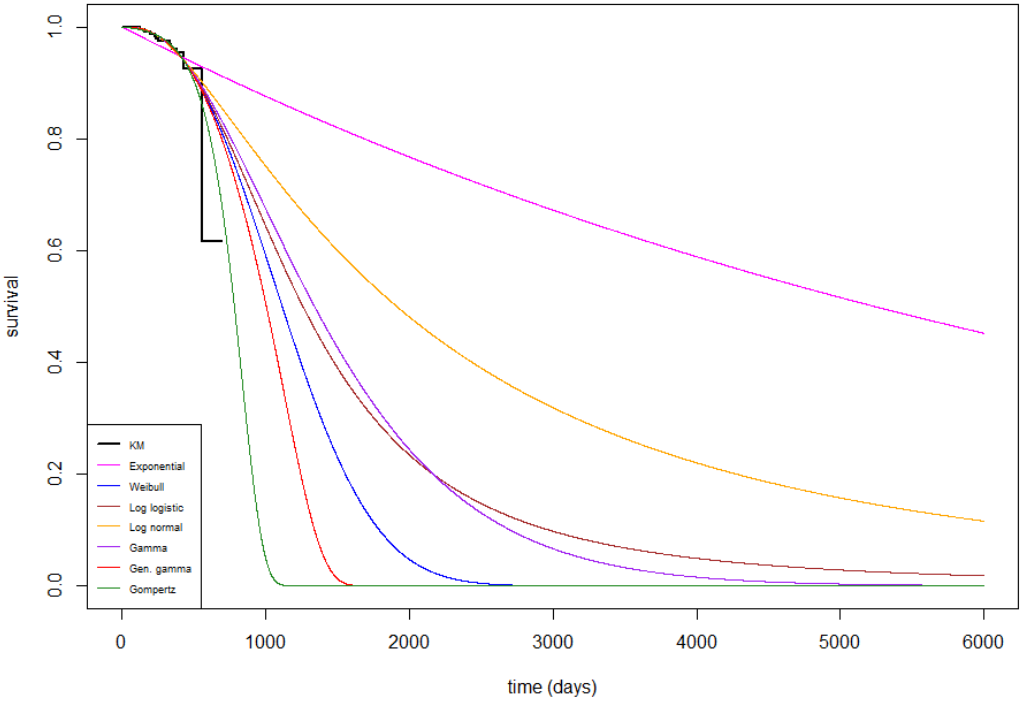
The survival extrapolations are presented in Figure 2 and Figure 3 and the coefficients are reported in Table 10 and Table 11.

Figure 2: Nintedanib extrapolation (baseline FVC predicted >80%)



KM, Kaplan-Meier.

Figure 3: Placebo extrapolation (baseline FVC predicted >80%)



KM, Kaplan-Meier.

Table 10: Coefficients of parametric models – nintedanib (baseline FVC >80% predicted)

Model	Variable	Coefficient	Standard error	95% confidence interval	
Exponential	**Rate**	-8.57124	0.128037	-8.82218	-8.32029
Weibull	**Scale**	0.315702	0.104946	0.110012	0.521392
	Shape	8.183058	0.13987	7.908918	8.457198
Log-logistic	**Shape**	0.394323	0.103821	0.190838	0.597807
	Scale	8.002241	0.138703	7.730387	8.274094
Lognormal	**Meanlog**	8.153893	0.16933	7.822012	8.485774
	Sdlog	0.282205	0.094797	0.096407	0.468003
Gompertz	**Shape**	5.42E-04	1.60E-04	2.29E-04	8.55E-04
	Rate	-8.97924	0.224957	-9.42015	-8.53833
Generalised gamma	**mu**	8.187184	0.15763	7.878235	8.496133
	sigma	0.049601	0.352795	-0.64186	0.741067
	q	0.444605	0.570304	-0.67317	1.562381

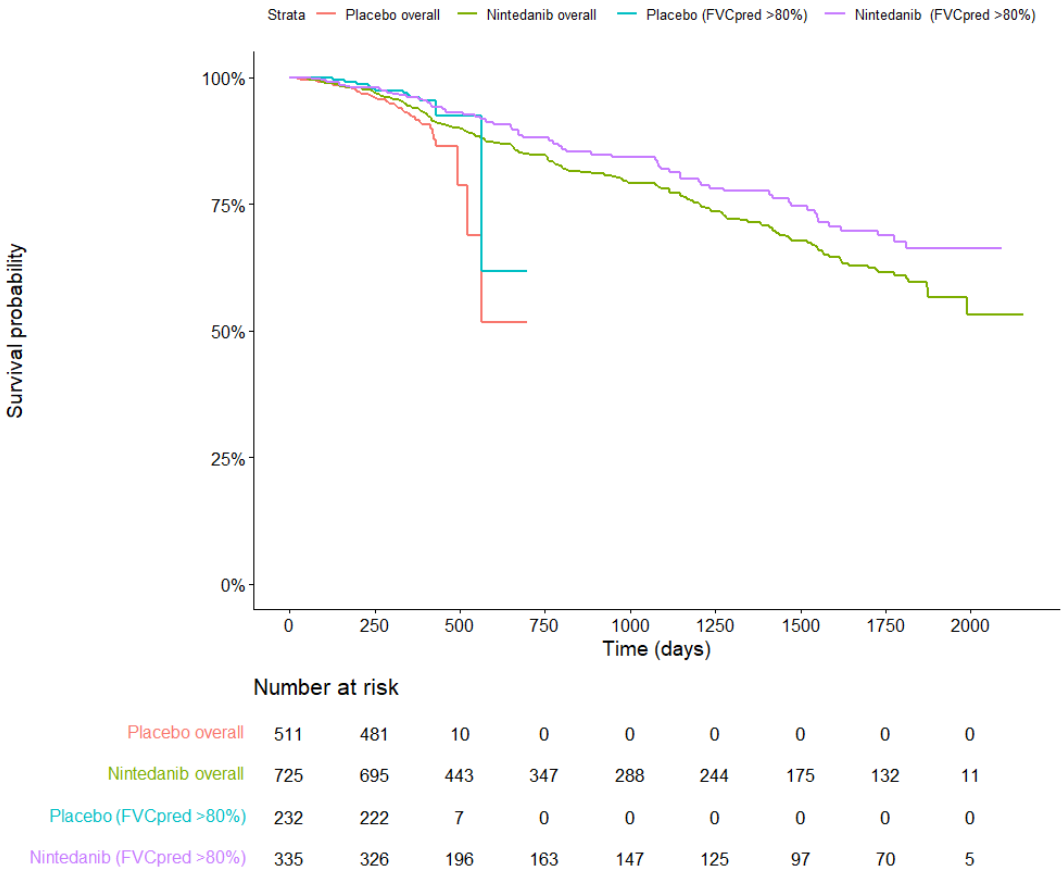
Table 11: Coefficients of parametric models – placebo (baseline FVC >80% predicted)

Model	Variable	Coefficient	Standard error	95% confidence interval	
Exponential	**Rate**	-8.93006	0.288675	-9.49586	-8.36427
Weibull	**Scale**	0.929779	0.274539	0.391692	1.467866
	Shape	7.160934	0.333214	6.507845	7.814022
Log-logistic	**Shape**	0.94053	0.273877	0.403741	1.477319
	Scale	7.138491	0.329321	6.493034	7.783948
Lognormal	**Meanlog**	7.555824	0.42684	6.719232	8.392415
	Sdlog	-0.04457	0.248831	-0.53227	0.443131
Gompertz	**Shape**	0.006731	0.002356	0.002113	0.011349
	Rate	-10.6258	0.772717	-12.1402	-9.11125
Generalised gamma	**mu**	7.084414	0.339306	6.419385	7.749442
	sigma	-1.58127	5.52701	-12.414	9.251468
	q	1.940197	10.71037	-19.0518	22.93214

B6. Priority question. Please report the pooled Kaplan-Meier data for overall survival for the subgroup of patients with a baseline FVC >80% predicted, overlaid with the Kaplan-Meier curves for overall survival currently presented in Figure 12. Please provide numbers of patients at risk at timepoints for all Kaplan-Meier curves (Figure 12 does not currently report these).

The pooled Kaplan-Meier curves for the overall population and the population with baseline FVC predicted >80%, along with the risk table, are presented in Figure 4.

Figure 4: Kaplan-Meier curves for the overall population and patients with baseline FVC predicted >80%



There is a reduced number of patients in the subgroup with FVC >80% predicted, and reduced power for the analysis. Therefore, we consider that it is difficult to draw conclusions on the long-term survival from the data for patients with a baseline FVC >80% predicted. In the Australian IPF registry, an exploratory analysis in patients with “mild FVC” (defined as >80% predicted) vs “moderate-severe FVC” (<80% predicted), showed that while patients with baseline FVC >80% predicted have improved survival outcomes compared with patients with baseline FVC <80% predicted, both Kaplan-Meier curves showed a similar rate of decline. The authors of the study concluded that patients with an FVC >80% predicted are likely to represent an earlier stage of the natural history of IPF, rather having a specific natural history.(14) Based on this, the company considers it appropriate to use the overall population estimates for the mortality analysis in the present cost-effectiveness model.

B7. Given the observation of apparent non-proportional hazards for overall survival (CS section B.3.3) please consider fitting one parametric model to the data and include treatment as a covariate. What impact would this have on the results?

The analysis we conducted included survival models fitted:

- independently to each treatment arm (nintedanib and placebo)
- and in all patients, using a treatment covariate to indicate the treatment effect of nintedanib (general model).

The following parametric models were used in the analysis:

- Exponential
- Weibull
- Log-logistic
- Log-normal
- Gompertz
- Generalised Gamma

The goodness of fit was assessed using visual inspection and the statistical criteria – Akaike/Bayesian Information Criterion (AIC/BIC). All analyses were conducted in R using the "flexsurv" package.

In the submission dossier we presented the results of survival models fitted independently to each arm; given the signs of non-proportionality displayed in the log-log survival plot, an assumption of non-proportional hazards and the use of independent survival models was deemed appropriate.

The AIC and BIC values of the general models with a treatment covariate are presented in Table 12.

Table 12. AIC and BIC of the general models

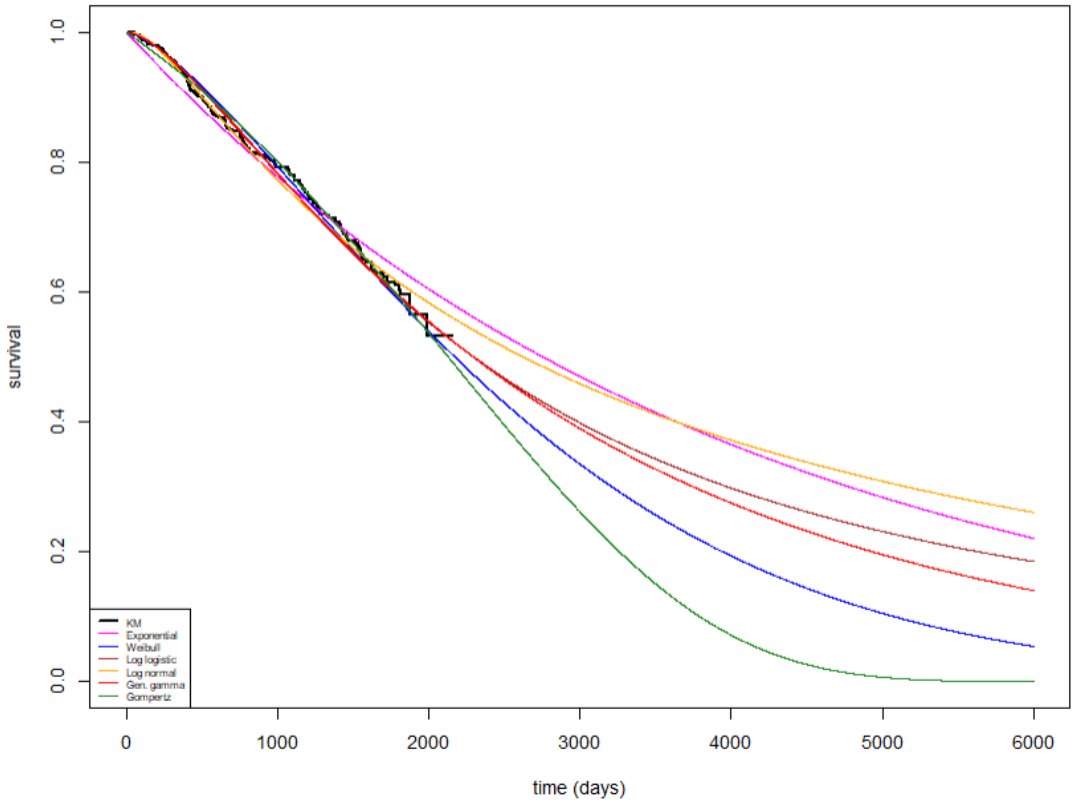
Model	Exponential	Weibull	Log-logistic	Log-normal	Gompertz	Generalised Gamma
AIC	4103.25	4073.33	4071.70	4076.59	4088.77	4073.14
BIC	4113.49	4088.69	4087.06	4091.95	4104.13	4093.62

AIC: Akaike information criterion; BIC: Bayesian information criterion.

The three models with the lowest AIC and BIC were log-logistic, generalised gamma and Weibull, with the log-logistic model having the lowest AIC and BIC and deemed the best fitting model.

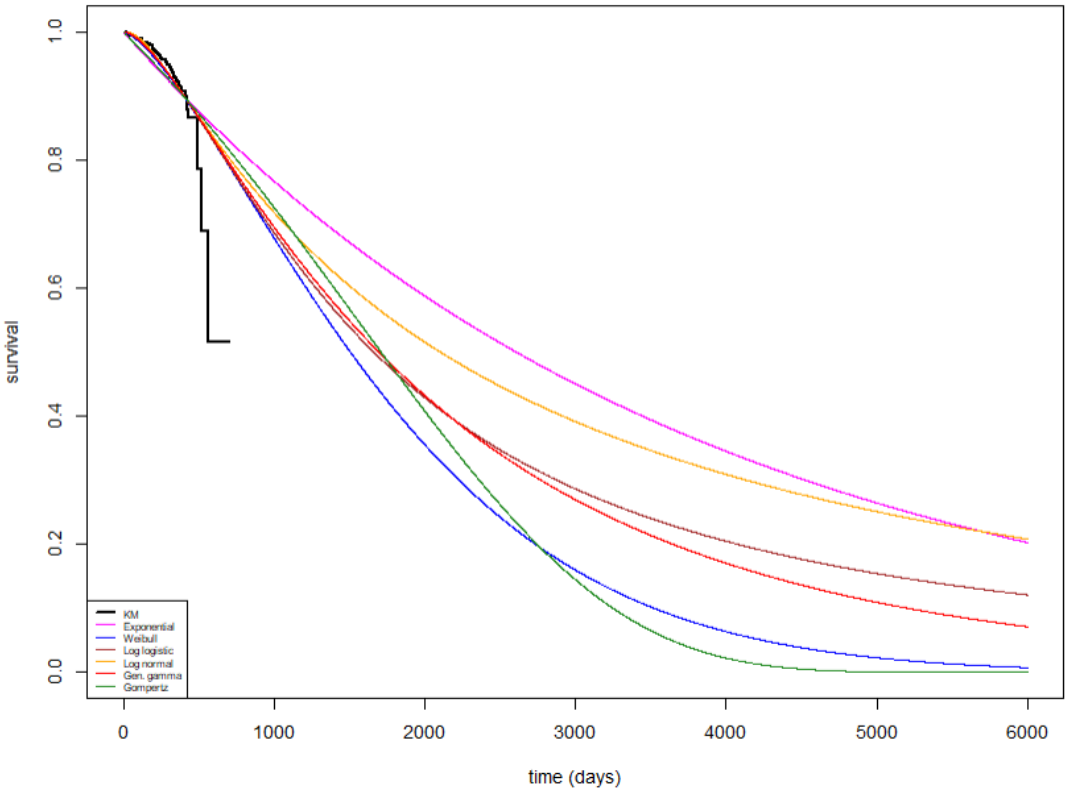
The parametric models generated using the general model for nintedanib and placebo are presented in Figure 5 and Figure 6.

Figure 5. General models: nintedanib extrapolation



KM, Kaplan-Meier.

Figure 6. General models: placebo extrapolation



KM, Kaplan-Meier.

The ICER with PAS for the three general models with the lowest AIC and BIC are presented in Table 13.

Table 13. Resulting ICERs in the cost-effectiveness model: General models

Model	ICER (with PAS)
General model: Weibull	£[redacted]
General model: Log-logistic	£[redacted]
General model: Generalised gamma	£[redacted]

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme.

Long-term validation of the general Log-logistic, Weibull and Generalised gamma curves against real-world data reported in the Australian and EMPIRE registries confirms that the general models do not perform as well as the independent curves when compared with the no-treatment cohort, as they considerably overestimate survival. This provides further rationale for use of the independent, rather than general models.

Figure 7. General models: validation of parametric extrapolation against the Australian IPF registry data: no-treatment cohort

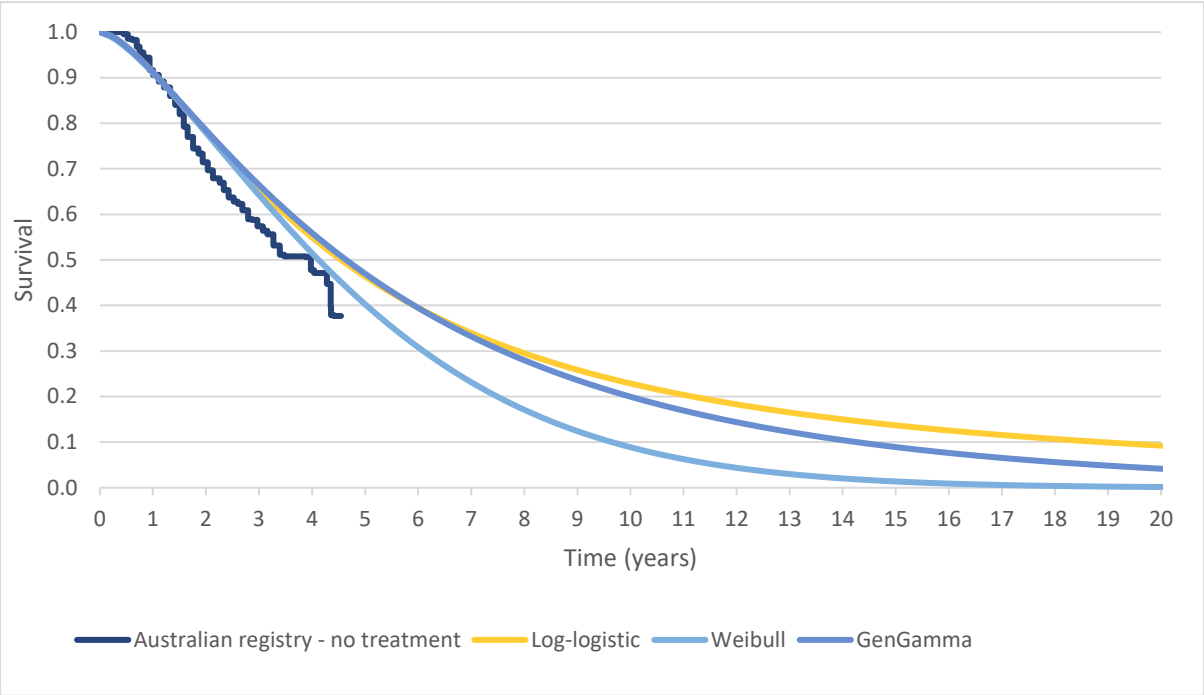
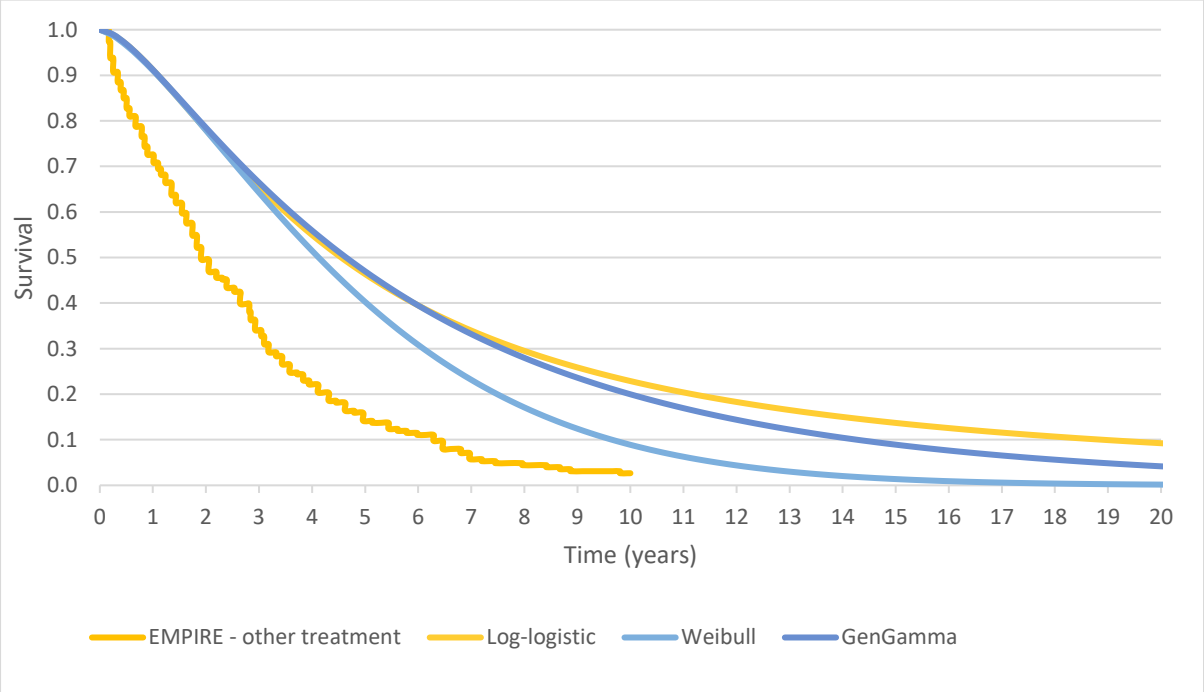


Figure 8. General models: validation of parametric extrapolation against the EMPIRE registry data: other-treatment cohort



B8. Please clarify whether the proportional hazards assumption for overall survival was assessed for the FVC >80% predicted subgroup?

The proportional hazards assumption was tested in the subgroup of patients with baseline FVC >80% predicted by assessing the log-log survival plots for nintedanib and placebo. The log-log survival plot is presented in Figure 9. It can be seen that the placebo and nintedanib curves cross at multiple time points, suggesting that the proportional hazards assumption does not hold.

Figure 10 displays the Schoenfeld residuals plot for the period in which there was observed data for both nintedanib and placebo patients. As shown in Table 14, the Schoenfeld residuals test showed a p-value of 0.079, indicating that there is no evidence against the null hypothesis of proportionality (assuming a p-value cut-off of 0.05). Nevertheless, given the signs of non-proportionality displayed in the log-log survival plot, an assumption of non-proportional hazards was considered to be appropriate.

Figure 9: Log-log survival plot (FVC >80% predicted)

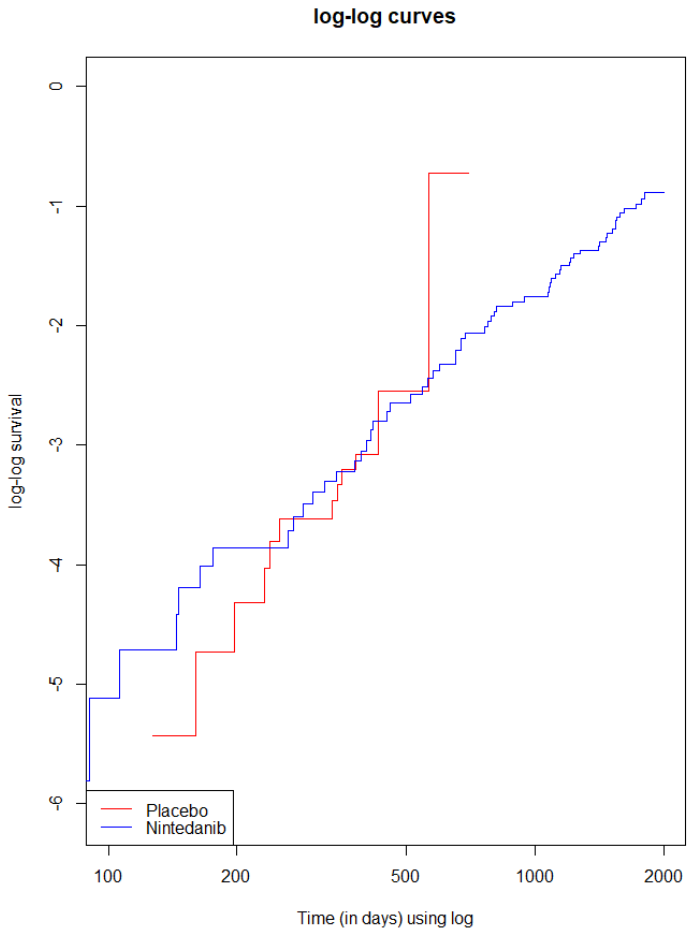
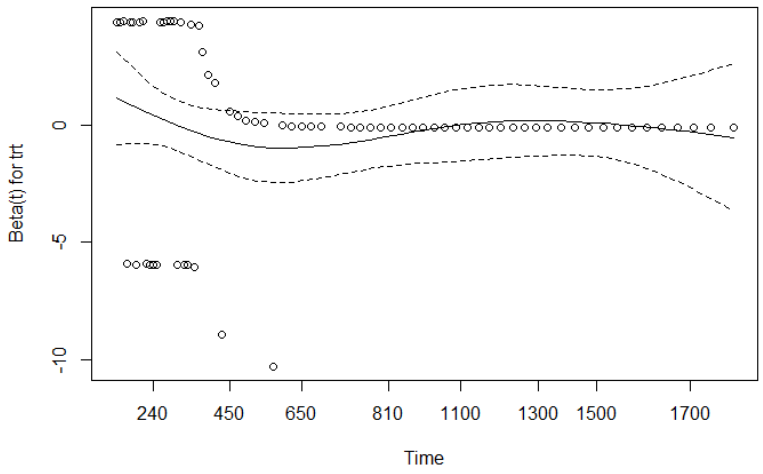


Table 14: Schoenfeld residuals test (FVC >80% predicted)

	chisq	df	p-value
Global test	3.09	1	0.079

Figure 10: Schoenfeld residuals plot (FVC >80% predicted)



Modelling other clinical outcomes

B9. Please comment on whether a scenario analysis was considered around the fitting of baseline transition probabilities for acute exacerbation, treatment discontinuation, and loss of lung function outcomes for the FVC >80% predicted subgroup?

Acute exacerbations were a rare event in the overall population in the INPULSIS trials, and even more so in the subgroup with FVC >80% predicted (Table 15).(2) As a result, it was not possible to run any scenarios based on acute exacerbations in the subgroup with FVC >80% predicted. We have therefore prepared a combined scenario for this subgroup only in relation to the probabilities for acute exacerbations and treatment discontinuation.

Table 15: Proportion of patients with an acute exacerbation and hazard ratio for time to first event in patients with FVC above and below 80% predicted (2)

	FVC >80% predicted		FVC ≤80% predicted	
	Nintedanib (n=295)	Placebo (n=190)	Nintedanib (n=343)	Placebo (n=233)
Patients with ≥1 acute exacerbation, n (%)	7 (2.4)	8 (4.2)	24 (7.0)	24 (10.3)
HR (95% CI)	0.49 (0.17, 1.35)		0.72 (0.41, 1.27)	
Treatment by subgroup interaction	p=0.6505			

Abbreviations: CI, confidence interval; FVC, forced vital capacity.

Similarly to the base case analysis, we have used an exponential model on phase II and phase III placebo clinical data (constant risk) to estimate the coefficient for deriving the treatment discontinuation baseline risk (Table 16) (analyses were conducted in R using the "surv" package. As in the base case, the probability of discontinuation for nintedanib has remained informed by the NMA Odds Ratio (1.42) applied to the baseline placebo risk.

Regarding nintedanib OR for loss of lung function, we have applied the base-case OR=0.54 based on the overall odds ratio for nintedanib vs. placebo reported in the NMA (combined scenario 1 in Table 17) and the OR=0.50 we applied in scenario 24 of the submission which was derived from the subgroup with FVC >80% predicted (combined scenario 2 in Table 17). Both combined scenarios produce an ICER well below £20,000 WTP threshold.

Table 16. 'R' output for risk of discontinuation (placebo arm)

Variable	Coefficient	SE	z	P>z	95% CI	
cons	7.777	0.1767	43.99	<0.001	7.430	8.123

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

Table 17. Combined scenario analyses: treatment discontinuation and loss of lung function derived from the FVC>80%pred subgroup

Combined scenarios	Coefficient for discontinuation hazard rate	ICER (with PAS)
1) Treatment discontinuation and loss of lung function with base-case OR=0.54 for loss of lung function applied to nintedanib	7.777	£[redacted]
2) Treatment discontinuation and loss of lung function with scenario 24 OR=0.50 for loss of lung function applied to nintedanib	7.777	£[redacted]

B10. Please provide the baseline exacerbation risk for the subgroup of patients with baseline FVC >80%. Please comment on whether you would expect the exacerbation risk to be greater for those patients with more severe lung disease.

In a post-hoc subgroup analysis of pooled data from patients with baseline FVC >80% versus ≤80% predicted in the INPULSIS® trials (Maher 2015) (2), the majority of exacerbations were reported in patients with baseline FVC ≤80% predicted. The effect of nintedanib on time to first acute exacerbation was consistent between the subgroups. In patients with baseline FVC >80% predicted, the hazard ratio (HR) for time to first acute exacerbation was 0.49 (95% CI 0.17–1.35) in favour of nintedanib. We have now conducted an additional scenario analysis using this HR for time to first acute exacerbation, resulting in an ICER of £[redacted]
(with PAS).

In patients with baseline FVC ≤80% predicted, the HR for time to first acute exacerbation was 0.72 (95% CI 0.41–1.27) in favour of nintedanib. The treatment-by-subgroup interaction p-value was not significant (p=0.6505). (Maher et al., 2015 (2)) (See also STA dossier page 63).

Network meta-analysis

B11. Priority question. Please provide the results of the NMA (CS table 21-26) for nintedanib vs placebo for the subgroup of patients with a baseline FVC >80%.

The NMA has not been rerun using only the subgroup of patients with a baseline FVC >80% as pirfenidone and n-acetyl cysteine are not relevant comparators in the decision problem for this review. No significant treatment by subgroup interactions for the primary or secondary endpoints were observed hence the cost-effectiveness model is based on the treatment effect obtained from the NMA results for the overall population for nintedanib versus placebo.

Section C: Textual clarification and additional points

C1. Please confirm that CS Tables 8 and 9 relate to the pooled INPULSIS trials only.

That is correct. Table 8 relates to the pooled INPULSIS-1 and -2 trials (Maher, 2015) (2). Table 9 also relates to pooled INPULSIS-1 and -2 trials (Kolb 2017 (17)).

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14. Jo HE, Glaspole I, Moodley Y, Chapman S, Ellis S, Goh N, et al. Disease progression in idiopathic pulmonary fibrosis with mild physiological impairment: analysis from the Australian IPF registry. Bmc Pulm Med. 2018;18(1):19.

15. Boehringer Ingelheim. TOMORROW roll-over study; Trial Number 1199.35. Clinical trial report (Follow-up report, Revision No. 1; date of revision 24 April 2017. 2017.

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17. Kolb M, Richeldi L, Behr J, Maher TM, Tang W, Stowasser S, et al. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. Thorax. 2017;72(4):340–6.

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QA2. The CS (Table 15) provides a risk of bias assessment for the TOMORROW and INPULSIS trials which the EAG assumes is based on the total trial populations (rather than baseline FVC % predicted subgroups). Please provide evidence to show that there were no unexpected differences in drop-out rates or missing data between respective trial arms for the FVC > 80% predicted subgroup.

NOTE: We have included below the TOMORROW trial data to complete the response we submitted on 26 July 2022.

Interpretation 1: Non-completers (drop-out rates) of planned observation period

In period 1 of TOMORROW trial, 219 patients were enrolled with an FVC>80% predicted into the trial: nintedanib 50mg qd: 43, 50mg bid: 45, 100mg bid: 50, 150 mg bid: 41; placebo: 40.

A total of 218 patients were treated in period 1 (these include patients with at least one treatment dose in the 12 months treatment period): nintedanib 50mg qd: 43, 50mg bid: 45, 100mg bid: 50, 150 mg bid: 40; placebo: 40.

Overall, 183 (83.9%) of patients completed the planned observation time of 52 weeks (after the last patient was randomised): 334 in the nintedanib arm (50mg qd: 76.7%, 50mg bid: 84.4%, 100mg bid: 94%, 150 mg bid: 82.5%); 32 in the placebo arm (80%).

The difference in treatment completers is not unexpected, because the main reason for patients prematurely discontinuing from trial medication was an adverse event: 50mg qd 9 (20.9%), 50mg bid 7 (15.6%), 100mg bid 2 (4%), 150 mg bid 7 (17.5%); placebo 6 (15%). The proportion of patients prematurely discontinuing due to adverse events other than worsening of IPF or worsening of pre-existing conditions, was higher in the nintedanib 150mg bid arm, as expected. Overall, 35 patients (16.1%) did not complete the observation time (Source: Table 1.5.13.1.1 Disposition of patients by FVC %pred at baseline (<=80%, >80%) − Study 1199.30 (period 1); Date:18JUL2022). (1)

Interpretation 2: Missing data for analysis purposes

NOTE: Please see table 1 below which has been updated with data for the FVC>80% subgroup. Please note that the proportion of missing data is very similar to the one in the overall sample in Table 3 in clarification question A4 submitted on 26 July 2022.

Updated Table 1. TOMORROW trial (NCT00514683). Missing data for the analysis of rate of decline in FVC (L/yr) at 12 months∞ – OC* – randomized and analysed sets by treatment arm; FVC>80% pred. subgroup

Subgroup with FVC>80% predicted at baseline	Placebo	Nintedanib 50mg qd	Nintedanib 50mg bid	Nintedanib 100mg bid	Nintedanib 150mg bid
Number of patients in randomised set	40	43	45	50	41
Number of analysed patients	38	43	45	50	40
Proportion with missing data	5%	0%	0%	0%	2.44%

∞ Based on visits up to visit 9.
*OC, observed cases
Source: Table 1.5.13.2.1.1 Rate of decline in FVC (L/yr) at 12 months* by FVC %pred at baseline (<=80%, >80%) OC − Randomised Set − Study 1199.30 (period 1); Clinical Trial Report Trial no. 1199.30; Date 28JUL2022. (1)

A4. Please report how many patients had missing data for the primary outcome in the TOMORROW trial, by treatment arm and by FVC % predicted subgroup.

NOTE: Please see table 4 below which has been updated with data for the FVC>80% subgroup.

Updated Table 4. TOMORROW trial (NCT00514683). Missing data for the analysis of rate of decline in FVC (L/yr) at 12 months∞ – OC* – randomized and analysed sets by baseline FVC ≤ or > 80% predicted subgroup

NCT00514683 (TOMORROW) Rate of decline in FVC (L/yr) at 12 months∞ – OC* – randomized and analysed sets by FVC 80% predicted subgroup										
	FVC>80% pred. at baseline					FVC≤80% pred. at baseline				
	Placebo	NDB 50mg qd	NDB 50mg bid	NDB 100mg bid	NDB 150mg bid	Placebo	NDB 50mg qd	NDB 50mg bid	NDB 100mg bid	NDB 150mg bid
Number of patients in randomised set	40	43	45	50	41	47	44	41	36	45
Number of analysed patients	38	43	45	50	40	45	42	41	35	44
Number of patients with missing data	2	0	0	0	1	2	2	0	1	1

∞ Based on visits up to visit 9.

*OC, observed cases; NDB, nintedanib
Source: Table 1.5.13.2.1.1 Rate of decline in FVC (L/yr) at 12 months* by FVC %pred at baseline (<=80%, >80%) OC − Randomised Set − Study 1199.30 (period 1). Clinical Trial Report Trial no. 1199.30; Date 28JUL2022. (1)

A8. CS Section B.2.6 describes how the rate of decline in FVC during the first 52-week period of the INPULSIS trials and the decline observed during the 192-week period during INPULSIS-ON did not differ by a clinically significant amount (22 ml). Please provide evidence to show whether this was similarly observed for the baseline >80/<80 FVC% predicted subgroups.

NOTE: The results in Table 6 have been validated and we confirm they are correct. We can therefore provide the Data on File reference.(2)

A9. Priority question. Please provide any available subgroup analyses of patients with baseline >80/<80 FVC % predicted for outcomes of the TOMORROW trial.

For TOMORROW trial, we present below in Table 7bis the subgroup analyses based on FVC % > or ≤80 predicted at baseline. In the subgroup with FVC > 80% predicted, the trend was consistent with the trend in the overall population, and the comparison of the nintedanib 150mg bid vs. placebo arm reached statistical significance (p=0.0182; 95%CI: 0.030, 0.323).

Table 7bis: Rate of decline in FVC (L/year) at 12 months* by FVC % predicted at baseline, observed cases, RS (TOMORROW trial)

	Treatment	N patients in RS	N analysed patients	Adjusted rates (SE)**	Adjusted rates of difference (SE)**	95% CI	p-value***
FVC >80% predicted							
No	Placebo	47	45	−0.188 (0.049)			
	Nintedanib 50mg qd	44	42	−0.219 (0.052)	−0.030 (0.071)	−0.170, 0.109	0.6718
	Nintedanib 50mg bid	41	41	−0.274 (0.050)	−0.086 (0.070)	−0.223, 0.051	0.2194
	Nintedanib 100mg bid	36	35	−0.221 (0.055)	-0.032 (0.074)	−0.177, 0.112	0.6607
	Nintedanib 150mg bid	45	44	−0.118 (0.055)	0.071 (0.074)	−0.074, 0.216	0.3384
Yes	Placebo	40	38	−0.185 (0.053)			
	Nintedanib 50mg qd	43	43	−0.133 (0.052)	0.053 (0.074)	−0.093, 0.199	0.4777
	Nintedanib 50mg bid	45	45	−0.154 (0.048)	0.031 (0.072)	−0.110, 0.172	0.6631

	Treatment	N patients in RS	N analysed patients	Adjusted rates (SE)**	Adjusted rates of difference (SE)**	95% CI	p-value***
	Nintedanib 100mg bid	50	50	−0.124 (0.045)	0.062 (0.069)	−0.074, 0.198)	0.3733
	Nintedanib 150mg bid	41	40	−0.009 (0.053)	0.177 (0.075)	0.030, 0.323	0.0182

RS, randomised set
The p−value for the interaction FVC %pred > 80% * treatment for the model including the subgroup and the interaction term FVC %pred > 80% * treatment is: 0.1408.
* Based on visits up to visit 9
** Based on a Mixed linear regression Model repeated measures with terms for treatment*time, gender*age, subject effect, subject*time, treatment, (subject effect and subject*time random, all other effects fixed) and a variance component variance−covariance matrix
*** Nominal p−value
Source: Table 1.5.13.2.1.1 Rate of decline in FVC (L/yr) at 12 months* by FVC %pred at baseline (<=80%, >80%) OC − Randomised Set − Study 1199.30 (period 1); Date 28JUL2022. (1)

References

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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
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 driven 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 over 60 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 company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	1. In the last 12 months, APF has received grants of £2,161 from Boehringer Ingelheim (BI) for our work in organising patient support groups in the UK and related activities. 2. We have also received £6,310 from NeRRe a company developing a treatment for cough (as yet, early stage). This was related to awareness raising and discussions with patients (survey and focus group). 3. As Chair of APF and a patient, I represent APF at BI's Patient Advisory Group meetings (generally every six months). Fees of c 700 euros per meeting paid to APF **4.** As President of the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation (EU-IPFF) I attend planning meetings for BI's planned Patient Partnership Summit in February 2021. Fees of c 1,000 euros were paid to EU-IPFF.
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	APF is in constant touch with patients and carers living with Idiopathic Pulmonary Fibrosis (IPF) and other forms of pulmonary fibrosis. Most of the over 60 support groups in our network across the UK include IPF patients with an FVC over 80%. For the specific purposes of this submission, we held in-depth interviews

experiences of patients and carers to include in your submission?	with 12 patients or carers and ran two focus groups involving another 13 people who were refused access to antifibrotics because their FVC (or that of their loved one) was over 80%. We also discussed the issue with a number of consultants and respiratory nurses working in specialist ILD centres and district general hospitals and with the staff running our telephone helpline.
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?	Idiopathic Pulmonary Fibrosis is a devastating disease. At diagnosis, you are told that your disease is incurable, is only going to get worse and that you have, on average, only 3-5 years to live. You are effectively given a death sentence. As the disease progresses you begin to feel more and more breathless. At first, you find it difficult to walk up slopes or 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 and become socially isolated. Eventually you find yourself stuck at home and need supplementary oxygen to move about and stay alive. You are seriously disabled and need help 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 to concentrate on getting through the day. The strain is taken by your carer, if you have one, who has to stay strong for you, manage the home and maintain links to the health care system. Many IPF patients and carers feel isolated and alone. Although there 32,500 with IPF living with the disease in UK (approximately 27,000 in England), this equates to an average of only four people per GP

	surgery. APF estimates that at least 10,000 IPF patients have an FVC over 80% and are currently not eligible to be given antifibrotic treatment (nintedanib or pirfenidone). Also, public awareness of the disease is low, which 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 IPF is worse than that of most cancer patients (only pancreatic and lung cancer, among the major cancers, will kill you quicker), people living with IPF do not receive the same level of support as cancer patients. There is no accelerated, timebound pathway to diagnosis, no agreed care pathway and only limited nursing and mental health support. 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 IPF patients with FVC over 80%, who are often treated in general hospitals until they are close to FVC 80%, when they are referred to specialist ILD centres. [redacted] ***from*** [redacted] *I went to the doctor just over 3 years ago because I had a tickly cough and was a bit breathless. I was shocked to be diagnosed with a disease I had never heard of (IPF) and told I had only 3-5 years to live. After that, I started to become more and more breathless, It became more and more difficult to move about – going up steps is a killer - and I had to give up work. Now I am stuck on my chair at home. My wife has to help me wash and get dressed in the morning and I cannot walk across the room without using supplementary oxygen. I am frightened about what the future holds and how my family will cope without me.*

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Standard NHS treatment of care for IPF patients (FVC over 80%) is to: • monitor the patient while waiting for their FVC to fall to 80% so they can be prescribed antifibrotic treatments. • Mange symptoms such as cough. It can take anything from a few months to over 2 years for a patient's FVC to drop to 80% so that they can be prescribed antifibrotics, such as nintedanib. The length of time an individual patient has to wait will depend on their FVC at diagnosis and how quickly their disease progresses. Another problem is that during the pandemic many patients had less contact with their health care professionals and could not access pulmonary function tests. HCPs were therefore often not aware that a patient's FVC had dropped to below 80% and as a result many patients were started on antifibrotics late. This situation is continuing, which is making patients and their carers anxious: ***ILD Consultant Specialist Nurse*** *I worried I'm not seeing my patients as often compared to before Covid. When I do see them, I'm noticing they are more deconditioned than they have let on over the phone. This is because many patients are still shielding and going out and about less.* Many IPF patients (FVC over 80%) are 'held' at district general hospitals (DGH) until their FVC falls to close to 80%, when they are referred to one of the 23 ILD centres in England, which can prescribe antifibrotics. While they are being treated in DGHs it is difficult for them to take part in clinical trials and other research. If nintedanib is approved for this group of patients, DGHs will refer them to ILD centres immediately on diagnosis thus increasingly their chances of participating in clinical trials.

A respiratory consultant at a DGH in SE England

At any one time, I have about 30 IPF patients in my care, who I see mostly in outpatient clinics. I ensure they have regular lung function tests and treat their symptoms. When their FVC falls to almost 80% I refer them to the ILD Centre so that they can be considered for antifibrotics. It's very hard explaining to patents why their health must deteriorate before they can be given the drug they need.

IPF patients (FVC over 80%) are extremely unhappy they cannot be prescribed antifibrotics and cannot understand why they are denied treatments which are known to work. They feel they are being treated unfairly since:

- In North America, Australia and Europe doctors are allowed to prescribe antifibrotics to IPF patients on diagnosis, whatever their FVC. The UK is the only country in the western world where this is the case and they do not understand why?
- Patients in England living with other forms of pulmonary fibrosis can be prescribed nintedanib, from the time of diagnosis and without any FVC limitations (following a NICE TA in 2021 [ID1599]).
- In Scotland many IPF patients with an FVC over 80% can be given antifibrotics, including nintedanib, if approved by an MDT (for example IPF patients who also have emphysema).

Since NICE has approved nintedanib for all other forms of pulmonary fibrosis and other IPF patients (FVC 80% to 50%) have been prescribed nintedanib in England for over six years, patients question why NICE needs to undertake a further TA, delaying by another year their access to nintedanib.

[redacted] ***– IPF patient from*** [redacted]

I was diagnosed with IPF just five months after my sister died from the disease. She had been on nintedanib so I was devastated when my consultant said I did not qualify for the treatment. I didn't

	understand. I could not believe that my health had to get worse before I could be given the drug. I was so angry! *My sister was prescribed nintedanib when she was already quite ill and found it difficult to tolerate the side effects. I did not want to be too frail before being given the drug and the chance to extend my life. My FVC is currently 86% but I will not have a lung function test for another 6 months. If that shows I am at 80% or below, I'll have to wait for them to process my case before I can receive the drugs. Who knows? I could be at 70% before I get it. I am already quite breathless and my family is worried that I will not be strong enough to tolerate the drug.* *It is discrimination that people with other forms of pulmonary fibrosis get the drug but I do not. I have to sit next to someone at our support group who has the same symptoms as me but they are on nintedanib and I am not. The psychological impact is terrible. I know my life will be shorter because I do not have access to the drug.* ***[redacted] – IPF Patient from [redacted]*** *I have been stable since my diagnosis, but to be told you have a terminal illness and that while there is a treatment you can't have it, feels so unfair. Can you imagine a cancer patient not being given a treatment in this way?* *We're all so unlucky to have this disease. But it's not just us the patient, is it? It's about our friends and family. They know there are drugs out there and they know I can't get access to them. My daughter is getting married. What am I supposed to do – ask her to bring the wedding forward on case I have an exacerbation and decline quickly?*

8. Is there an unmet need for patients with this condition?	Yes. IPF patients with an FVC over 80% are desperate to have access to nintedanib. Most of them would like to start taking the drug as soon as possible. They know that anti-fibrotic treatments have been 'game changers' for other IPF patients (FVC 80%-50%), slowing disease progression and increasing life expectancy. They also know that nintedanib works just as well for patients over FVC 80% as those under this threshold. IPF patients (FVC over 80%) look at patients on nintedanib, who they meet in support groups and on-line, and envy their access to antifibrotics. They feel it is unjust that they are denied these medications and ask: why them and not me? An indicator of the level of unmet need is that dozens of English patients, who can afford it, have chosen to buy generic versions of antifibrotics from India at a cost of about £4,000/year. A few patients even purchase the medicine from major UK hospital pharmacies (price over £30k/year) and others, with links in other countries, have managed to obtain the drug overseas while still living in the UK and being treated by the NHS. [redacted] ***– IPF patient from*** [redacted] *To be told you cannot have antifibriotics because you are too well is preposterous! Why can't I have my allocation now, so that I can maintain my quality of life for longer and extend my life? Surely, the earlier you start the greater the benefits? I spent 40 years working as a fireman and now I have to spend most of my state pension (about £4,000 a year) buying the drug I need from India. We are the only country in the western world which does not make the drug available on diagnosis. The way we are treated is unjust.*

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients consider the main advantage of nintedanib is that it directly targets the problem of lung fibrosis. They are aware from talks given by clinicians at support groups and on-line information (for example, the APF website) that nintedanib has been shown in clinical trials and other research to: • slow progression of the disease giving patients a better quality of life for longer and having a positive impact on family members and carers, who would keep their own independence for longer • increase life expectancy by up possibly to 2 years if the drug is taken consistently over a significant period of time. Another significant benefit of approving its use for this group of patients is that it would give patients and their families hope and reduce anxiety. [redacted] ***– a carer from*** [redacted] *My husband,* [redacted]*, died from IPF in 2019 – just 3 years and 5 months after being diagnosed with the disease. He was desperate to be given antifibrotics but was refused for the first 18 months because his FVC was over 80%. Eventually, he was given nintedanib but, by then, he had started to decline and he passed away in just two years. I cannot help thinking how things might have been different if he had been given nintedanib as soon as he was diagnosed. His quality of life could have been better and he would probably have lived longer.*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	IPF patients (FVC over 80%) know that taking nintedanib can have side-effects, especially diarrhoea and nausea. But they also know from conversations in support groups and on-line, that these are generally manageable and most IPF patients stay on the drug once prescribed. Almost all of the patients we consulted in preparing this submission consider the potential benefits of nintedanib out-weigh the possible side effects and are keen to be prescribed the drug.

	[redacted] – IPF Patient from [redacted] I was diagnosed three years ago and have been on nintedanib for over a year. The main side effect for me is diarrhoea but, following advice from my consultant, I have learnt how to manage it with travel diarrhoea pills. I know some IPF patients are apprehensive about taking nintedanib but for me the potential benefits of taking nintedanib far outweigh the side effects.
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 current rules discriminate against three specific groups of patients who will benefit if nintedanib becomes available to all patients with an FVC over 80%. They are: • **Patients whose FVC was high prior to being diagnosed** with IPF (people, say, with an FVC of 120% predicted) who must decline a disproportionately greater extent before becoming eligible for antifibrotic therapy. These patients generally have to wait longer before being prescribed antifibrotics. • **Patients who have an 'artificially' high FVC because co-existing IPF and emphysema** and are refused antifibrotic therapy even though their IPF-related FVC would be expected to be below 80% predicted. • **Patients diagnosed with Familial IPF,** who are treated as IPF patients and refused antifibrotics even though the genetic cause of their disease is known. Patients who are unlikely to benefit as much as others if nintedanib becomes available to all patients with an FVC over 80% are: • **The elderly and/or frail**. APF has learnt from patients that DGH clinicians do not always refer elderly and frail patients to specialist centres for antifibrotic drugs, because of concerns about the number of trips to distant ILD Centres they would need to make and potential side effects.

	In order to ensure that this group of patients can 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 to reduce the frequency of visits to ILD centres. This could be done, for example, by carrying out all tests at DGHs, use of virtual MDTs and by involving GPs in blood monitoring.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	If NICE does not approve nintedanib for IPF Patients (FVC over 80%) there are three implications for equality: 1. **People living in poverty will be the hardest hit.** People who are better off and well connected will find a way to obtain the drug but the majority of people will not, creating inequality in treatment. Those who can, will obtain nintedanib by buying a locally produced version of the drug from India, paying the full cost of the medicine in the UK or obtaining nintedanib in EU or other country, where they can claim residence. 2. **Patients will feel a heightened sense of injustice** compared to other IPF patients (FVC 80%-50%) and other pulmonary fibrosis patients, who can be given the drug. 3. **All IPF patients become disabled** in the last year or two of life and are heavily dependent on their carers and need help with showering and dressing and other simple tasks. Nintedanib delays progression of the disease and helps patients retain a reasonable quality of life for longer.

Other issues	
13. Are there any other issues that you would like the committee to consider?	**We have not included references to published scientific research because we assume the British Thoracic Society (BTS) and other parties will present this information. If you would like us to list our sources, we would be happy to do so.**

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- IPF is a devastating condition with an average life expectancy of 3-5 years, a prognosis worse than most cancers.
- IPF patients (FVC over 80%) urgently want access to nintedanib because it has been shown to slow progression and extend life and works just as well in patients above FVC 80% as below this threshold.
- IPF patients (FVC over 80%) strongly feel they are being treated unfairly. Patients like them in all other western countries are given access to nintedanib on diagnosis. UK pulmonary fibrosis patients with an FVC over 80% can also be prescribed the drug.
- All IPF patients should be given access to nintedanib.
- This would reduce current inequalities among patients mentioned in sections 11 and 12.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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

NICE National Institute for Health and Care Excellence

1.Your name	X
2. Name of organisation	Asthma + Lung UK on behalf of the Taskforce for Lung Health
3. Job title or position	X
4a. Brief description of the organisation (including who funds it). How many members does it have?	Asthma + Lung UK is a charity with a vision for a world where everyone has healthy lungs. We provide the secretariat to the Taskforce for Lung Health - a collaboration of the largest ever group of organisations and individuals who have come together, as a team, to improve lung health. The Taskforce has 44 members including patients, carers, health care professionals, the voluntary sector and professional associations.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies	No.

are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Taskforce is a collaboration of organisations and individuals who have come together as a coalition to improve lung health. We have gathered information about experiences from patients, carers, health care professionals, the voluntary sector and professional associations who work on our medicines optimisation working group, who have provided their insights on the topics included in the consultation.
Living with the condition	
6. What is it like to live with the condition? What do carers	It can be extremely difficult to live with Idiopathic Pulmonary Fibrosis (IPF.) As a progressive condition with no known cause or cure, people with IPF can find it both incredibly mentally and physically challenging.

experience when caring for someone with the condition?	One of our Taskforce members, X, a respiratory nurse consultant in Leicester, who supports peoplewith IPF described the overall impact on her patients: “Living with IPF is living each day with the knowledge that there is no cure, and that the pathway is downhill yet uncertain. A disease with the same prognosis as terminal cancer but without the infrastructure and understanding to support people along the pathway.” The physical impacts of IPF, including breathlessness, shortness of breath, fatigue, loss of appetite and weight loss, can be debilitating and make it difficult for people with IPF to undertake the daily tasks they were able to do before their diagnosis. Taskforce carer representative X explained the physical impacts of IPF on her husband: “My husband has had IPF for 8 years and is currently on the active lung transplant list. IPF is an extremely debilitating disease, it affects the whole family and their lives. You end up on oxygen with your life curtailed by the limitations of oxygen. The cough is extremely exhausting and causes social anxiety. The fatigue is overwhelming.” X, who lived with IPF and is sadly now deceased, explained how IPF had impacted him: “It affects you with shortness of breath, as if you had been running, but it's like that all the time, for any sort of effort.” IPF can also affect people’s ability to sleep, as X, who lives with IPF explained: “The IPF gets me out breath. The sleep apnoea causes my oxygen levels to be lower in the morning when I wake. I think it's simply because I keep waking up during the night, so I wake about 80 times an hour.” The mental toll of IPF is also significant. As a progressive condition with no known cure, people with IPF can find it difficult to cope with the uncertainty of what the future might hold, as Taskforce carer representative X explained:

	"You live with a disease that has no known cure and worry about any slight infection which may accelerate the disease. You fear how the end of your life will be, gasping for breath. This has a huge impact on mental health and wellbeing." This is a problem regularly reported to the nurses on the Asthma + Lung UK helpline, who explain that feelings of isolation can be a real challenge for people with IPF: "Isolation is caused by the severity of the condition and the feeling of loss of independence particularly if the patient is still working and has to stop, often quite suddenly. Mobility is also a factor as severe breathlessness would stop someone from getting out and about. Some older patients may live alone and find their social life comes to an end due to their mobility needs resulting in them feeing very alone." X, whose mother X had IPF for 11 years and passed away in 2020, explained how IPF can beisolating for people like her mother: "I think IPF can be a lonely disease, as people don't understand why you cough or why you're breathless. It's not a commonly recognised problem that others can relate to." IPF can also have a significant impact on those caring for someone affected by the disease. X, who has been caring for her husband, X, since he was diagnosed with IPF in 2018, highlighted the impact that IPF has had on her own mental health: "From that day I really struggled with my mental health. X is my whole life. It was a lot to process.The panic attacks lasted for about six to nine months." In addition to the mental and physical impacts of the condition, IPF also impacts patients and their families more broadly. Nurses on the Asthma + Lung UK helpline regularly speak with patients diagnosed with IPF and their carers who report the following additional impacts:

	• Financial: The financial impact of IPF can be significant for those who have to give up work following their diagnosis or the diagnosis of a loved one. • Travel: It can be particularly difficult for people living with IPF to travel, especially those who need oxygen for a flight or when abroad. People with IPF can also find it difficult to access affordable travel insurance to cover them for any problems while they're away. • Extreme weather conditions: people with IPF can find it difficult to manage very hot or very cold weather conditions. In the warmer weather there can be breathlessness issues[i] and in the cold weather there is the risk of infection. [ii] • Feeling isolated and alone: people with IPF can often find the condition very isolating as outlined above.
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 and carers believe improvements in the care and treatment of those living with IPF are needed. One challenge is that IPF can be difficult to diagnose because the symptoms are similar to other lung conditions, such as chronic obstructive pulmonary disease (COPD). [iii] This means that many patients don't get diagnosed as early as they could and may not receive the support they need to understand their diagnosis and prognosis. Many patients and carers also report that some medical professionals don't understand or haven't heard of their condition; that they didn't receive any clear information about the disease; that their diagnosis was delayed, and that treatments like nintedanib are not available to them. Taskforce patient rep X, who was diagnosed with IPF in 2015, highlighted the broad range of

	challenges of being diagnosed with a lung condition like IPF: “I've found that there are large gaps when it comes to IPF and other lung diseases: gaps in knowledge, gaps in research, gaps in funding, gaps in treatment and gaps in support for patients. “IPF has a worse outlook than many cancers, so why can't we learn from the successful approach to cancer and apply the lessons to lung disease?” In addition to the challenges faced at diagnosis, the availability of treatments for IPF is also limited. Where treatments like nintedanib do exist, patients tell us that they are in the agonising position of having to wait for their condition to deteriorate enough so that they can access potentially life-extending drugs. This is despite studies showing that patients with over 90% lung function receive the same benefit as patients with more impaired lung function. [iv]
8. Is there an unmet need for patients with this condition?	Given the lack of a known cure for IPF and the limited range of treatment options available to slow progression, it is vital that all patients can access existing treatments as early as possible to help manage their condition. Patients with IPF whose condition has not yet met the 80% forced vital capacity (FVC) level currently required to access nintedanib may experience significant impacts from IPF on their health and quality of life. However, despite the benefits that nintedanib might bring for these individuals, they are currently unable to access it until their condition deteriorates. Evidence shows that there are benefits to patients with a FVC above 80% taking nintedanib: • Case and Johnson (2017) on the clinical use of nintedanib in patients with IPF notes [v] that the effect of nintedanib was consistent across patient subgroups defined by baseline characteristics including FVC % predicted, diffusion capacity of the lung for carbon monoxide % predicted and the presence of emphysema. It additionally noted that the rate of decline in FVC and the treatment effect of nintedanib are the same in patients with preserved lung volume (FVC >90% predicted) as in patients with greater impairment in FVC, supporting the value of early treatment of IPF.

	• Case and Johnson (2017) also described the INPLUSIS trial which noted patients with well-preserved lung volume (FVC >90% predicted) (n=274) experienced the same rate of decline in FVC when treated with placebo, and received the same benefit from nintedanib, as patients with less well-preserved lung volume at baseline (n=787). This suggests that patients with 'mild' IPF are at risk of disease progression and a 'watch and wait' approach to the management of such patients is far from ideal. [vi] • Similar absolute changes in FVC from baseline to week 48 of INPULSIS-ON were observed in patients with FVC ≤50% and>50% predicted at baseline. This suggests that nintedanib may have a similar effect on FVC decline in patients with advanced disease as in patients with less advanced disease. [vii] This means that thousands of people with IPF may be able to benefit at earlier stages of their disease. Another study noted that in terms of the annual rate of decline in FVC, disease progression, acute exacerbations and SGRO total score the treatment effect of nintedanib was not different between different subgroups they tested.[viii] • Previous research has also shown that in terms of %FVC decline prior to the therapy and a slow rate of FVC decline, there was no significant difference between stable and worsened groups. It also found that the stable/improved group had significantly better prognosis than the worsened group and that an early disease progression with a %FVC decline despite antifibrotic therapy were significantly associated with a poor prognosis.[ix] • A further study noted that patients with untreated IPF characterised as ''mild'' in phenotype with a baseline FVC of 100% and DLCO 54% have a significantly reduced median survival post-diagnosis of 2.5 years. This is compared with a survival of 3.5, 3 and 3.75 years in a cohort of patients with IPF treated with pirfenidone, nintedanib and both treatments respectively. [x]

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As outlined above, evidence shows that patients should be able to access nintedanib when they are in the earlier stages of IPF. From what patients and carers have told us, earlier access to nintedanib could help extend their life, ease, and slow down symptoms, and improve their quality of life. Taskforce carer representative X told us that her husband believes the drug helped extend his life.He has had IPF for 8 years, has been on nintedanib for 3 years, and strongly believes the drugs are thereason he is here today. X who has been living with IPF for over 8 years, has only just been able to access nintedanib andbelieves that receiving it earlier would have helped slowed the disease: “Had Nintedanib been earlier my scarring could, potentially, have slowed down by as much as 50% which would have given me a better quality of life for much longer and bought me valuable time before having to consider more drastic options like lung transplantation. That’s where I’m at now...had it been available to me from the get-go, I wouldn’t be in the position I am in now at the age of just 37”.” X, whose mother, X, died in 2020 after living with IPF for 11 years, explains the difference thatnintedanib made to her mother’s symptoms and quality of life: “He later changed her medication to Nintedanib. I will never forget when we came out of the consultation. X sat down in the waiting area and cried. She said, “I never thought that anyone would offer anything else to help me, I thought he would just tell me there was nothing to try and to go home.” “The treatment helped relieve X cough for some time and she was able to start going for lunch or morning coffee with her friends and visit the local village church. She had stopped all this when the coughbecame disruptive.” It’s clear that drugs like nintedanib give hope to patients who otherwise have no other options for either treating or slowing the progression of their IPF.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There are side-effects of being treated with nintedanib, with up to 1 in 10 people experiencing these.[xi] The most common side-effect is diarrhoea and nausea, which were manageable in most patients. A clinical trial noted that diarrhoea had an incidence rate of 301.6 events/1000 PY and most events of diarrhoea were non-serious. Other notable side-effects are stomach pain, feeling sick and a decreased appetite. It is also recommended that potential users should have a pregnancy test as nintedanib may cause foetal harm during pregnancy. [xii]
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.	No.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is evidence that there is variation in the prescribing of antifibrotics with patients living nearer a specialist centre more likely to be approved for treatment. A study from 2017 that looked at patient levels in different postcode areas found that there is an inequality in respect to access for antifibrotic drugs depending on a patient's location.[xiii]
Other issues	
13. Are there any other issues that you would like the committee to consider?	No.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to	

be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- There is strong evidence to support extending access to nintedanib to people with an FVC above 80%.
- Evidence shows that nintedanib consistently slows the rate of scarring and helps extend life at the same rate for those with an FVC above 80% as those 80% and below.
- People with IPF with a FVC above 80% experience debilitating effects as a result of their condition. Accessing nintedanib earlier could help alleviate both physical and mental symptoms and slow disease progression.
- The lack of treatment options for people with IPF means improving access to existing treatments like nintedanib is vitally important, bringing hope to patients affected by this debilitating disease.

Thank you for your time.

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[i] Hot weather and pulmonary fibrosis | Action for Pulmonary Fibrosis (actionpf.org) accessed 21/06/2022

[ii] Coping with cold weather | Action for Pulmonary Fibrosis (actionpf.org) accessed 21/06/2022

[iii] NHS Choices, Idiopathic pulmonary fibrosis: Diagnosis, accessed 10.06.22

[iv] Kolb, M. et al (2016) *Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume*; Thorax 2017;**72:**340-346

[v] Case and Johnson, 2017, Clinical use of nintedanib in patients with idiopathic pulmonary fibrosis, BMJ Open Respiratory Research, 4(1): e000192

[vi] Kolb M, Richeldi L, Behr J, et al.. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax* 2017;72:340–346

[vii] Wuyts WA, Kolb M, Stowasser S, et al.. First data on efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis and forced vital capacity of ≤50 % of predicted value. *Lung* 2016;194:739–

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	**British Thoracic Society**
3. Job title or position	[redacted]
4. Are you (please tick all that apply):	x an employee or representative of a healthcare professional organisation that represents clinicians? **x** 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 professional society which represents health care professionals who care for those with respiratory disease.** The organisation is a charity and membership organisation which is funded through a combination of membership subscriptions, ownership of the journal Thorax and scientific conference and educational activities.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	**No – not applicable**

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.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No - none**
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,	The aims of any treatment for Idiopathic Pulmonary Fibrosis is to halt or reverse disease progression. The only licenced therapies for IPF, of which nintedanib is one, have been shown to statistically slow disease progression by approximately 50%. %. Pooled analysis from landmark nintedanib studies have also shown a reduction in the rate of acute exacerbations, mortality and improvements in quality of life scores (https://doi.org/10.1016/j.rmed.2016.02.001) A secondary aim of treatment is to improve symptoms particularly of cough and breathlessness with a view to improve quality of life.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Since IPF represents a progressive fibrotic lung disease with unrelenting progression, current therapies are aimed at slowing down disease progression as measured by FVC (ml). The change in FVC over 12 months is considered a surrogate marker for mortality and is therefore accepted by the US FDA and drug regulators as primary endpoints for clinical trials. In a recent meta-analysis of drug trials in IPF (Khan et al Am J Respir Crit Care Med 2022 https://doi.org/10.1164/rccm.202109-2091OC), a treatment effect could be observed as early as three-months with antifibrotics compared with placebo. For each 2.5% relative decline in FVC over three-months, there was a 15% increased risk of overall mortality, and a relative FVC decline > 5.7% over three-months more than doubled the risk of death. Thus even small reductions in FVC may be clinically significant and are likely to impact on patient mortality
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – of highest importance – there is a great unmet need. From the BTS ILD registry data, approximately one third of patients with clinically significant IPF, as shown by symptoms, reduction in measures of gas transfer (DLco, Kco) and the extent of disease on CT are not eligible for anti-fibrotic medication due to the presence of a FVC of greater than 80%. This group of patients receive a major dis-service in their clinical care due to the NICE reimbursement decision by not being able to offer any disease modifying treatment with anti-fibrotics in a disease that is ultimately and invariably progressive and terminal in its natural course, with a prognosis worse than most cancers if left untreated. Clinically it is unfair that a patient with a FVC of 81% should be treated any differently to a patient with a FVC of 79% in a disease that is ultimately progressive and life limiting. The utilization of FVC as a sole measure of severity is highly inaccurate and not substantiated in clinical practice. The value of FVC lies in identifying serial change in interstitial lung disease. However, as a means of quantifying severity at a single point in

	time, the FVC is grossly misleading. In the BTS ILD registry data, 38% of IPF patients had an FVC above 80% and IPF patients with a “normal” FVC above 80% have an average gas transfer factor of 55%, which is only 20% above the threshold of 35%, indicating end-stage disease and often used to trigger transplant evaluation. This DLco level denotes significant symptomatic fibrosis that warrants treatment with disease modifying therapies similar to patients with an FVC of less than 80%, which at present we must deny our patients. Furthermore, patients with associated emphysema are likely to have a spuriously high FVC and may never become eligible for anti-fibrotics despite having advanced disease and are at higher risk of mortality due to associated pulmonary hypertension. England is also an outlier with respect to access to antifibrotics as there are no FVC restrictions for IPF in European countries and Scotland. In the three key nintedanib studies (TOMORROW, INPULSIS1, INPULSIS2), participants with an FVC > 80% were included and a treatment benefit was clearly observed. Therefore the current 80% guideline is arbitrary and not based on clinical evidence.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients with an FVC above 80% are treated with observation (until FVC <80%), best supportive care which includes symptomatic management with referral to pulmonary rehabilitation and oxygen assessment.
• Are any clinical guidelines used in the	Yes guidelines include:

treatment of the condition, and if so, which?	[French practical guidelines for the diagnosis and management of IPF - 2021 update, short version]. Rev Mal Respir. 2022 Mar 14:S0761-8425(22)00026-2. German Guideline for Idiopathic Pulmonary Fibrosis - Update on Pharmacological Therapies 2017. Behr J, Günther A, Bonella F, Geißler K, Koschel D, Kreuter M, Prasse A, Schönfeld N, Sitter H, Müller-Quernheim J, Costabel U.Pneumologie. 2018 Feb;72(2):155-168. doi: 10.1055/s-0043-123035. Diagnosis of IPF. An ATS/ERS/JRS/ALAT Clinical Practise Guideline. Raghu et al. Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68. NICE Clinical Guideline CG163. Updated May 2017 .
• 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 is well defined by the NICE document CG 163 and guidelines as described above. There is universal consensus amongst ILD Clinicians that all patients with IPF no matter what their FVC should be offered antifibrotics as it is a life prolonging therapy in a disease with terminal outlook. Hence there are ethical issues in relation to restricting the use of anti-fibrotics until FVC drops to 80% or less.
• What impact would the technology have on the current pathway of care?	Access to nintedanib for patient with an FVC above 80% will have significant impact on patients in this cohort who currently feel they are at a disadvantage to other patients with IPF who have access to a therapy that can slow down their disease progression and prolong their survival as stipulated by trial and real-world studies. It will improve mortality and align England with the European and North American

	countries where it is a standard practice to offer these drugs with FVC of >80% predicted. Moreover, nintedanib is now approved in progressive pulmonary fibrosis (other than IPF) regardless of baseline FVC. Since IPF represents the prototypic progressive fibrotic lung disease, this also represents an unfair disadvantage to IPF sufferers.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes current care allows us to prescribe antifibrotics including nintedanib to patients with IPF who have an FVC below 80%. Nintedanib has also been approved to treat patients with progressive fibrotic Interstitial Lung Disease with no FVC restrictions.
• How does healthcare resource use differ between the technology and current care?	We cannot currently prescribe nintedanib for IPF patients with FVC above 80%
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist ILD centres should provide an MDT approach to diagnosis and management of this cohort of patients in line with current IPF care for those eligible for antifibrotics (FVC 50-80% predicted)
• What investment is needed to introduce the technology? (For	There are established ILD specialist centres who have the training and expertise to prescribe Nintedanib to this cohort. Local services will require investment in clinicians, specialist nurses and pharmacy services to take on this extra 30% of IPF patients. Furthermore, there would be a need to have more workforce

example, for facilities, equipment, or training.)	planning in non-specialist centres to be able to support with the use of anti-fibrotics and manage patients effectively closer to their homes.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. There are real world studies that have demonstrated survival benefits in patients with IPF who are on antifibrotic therapies. Nintedanib will benefit patients with IPF whose FVC is above 80% both psychologically and physically by prolonging their survival in line with these published studies. Survival and course of lung function in the presence or absence of antifibrotic treatment in patients with idiopathic pulmonary fibrosis: long-term results of the INSIGHTS-IPF registry. Eur Respir J 2020 Aug 13;56(2):1902279 Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis Chest 2021 Nov;160(5):1751-1763. Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS trials. Respiratory medicine April 2016; Volume 113, 74-79.
• Do you expect the technology to increase length of life more than current care?	Yes please see response above

• Do you expect the technology to increase health-related quality of life more than current care?	Yes please see above. There is evidence of improvement in quality-of-life questionnaire scores (SGRQ) from pooled analysis of nintedanib studies. There is a significant psychological burden of rapidly deteriorating FVC that cannot be measured in clinical studies and slowing FVC decline is likely to help alleviate some of this distress.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	We are not advocating treating patients with subclinical IPF. But those with significantly symptomatic disease as diagnosed by an expert and specialised MDT.
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	Easy to use as it is current care for IPF patients with FVC below 80%. Additional monitoring will be required once established on therapy in line with IPF patients currently. It will increase workload for specialist centres by approximately 30%.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	ILD specialists do not agree that a 10% decline in FVC is a failure of treatment in line with published studies as below. Effect of continued antifibrotic therapy after forced vital capacity decline in patients with idiopathic pulmonary fibrosis; a real world multicenter cohort study. Respir Med 2022 Jan;191:106722. However that is currently a NICE stopping rule for IPF patients below 80% FVC and we will abide by these current rules
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	Nintedanib therapy may have a positive impact on healthcare utilisation by reducing exacerbations of IPF. It may have a significant impact on the health related QOL and improve mortality.

quality-adjusted life year (QALY) calculation?	
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?	Currently this cohort of patients does not have access to life prolonging therapy in the form of antifibrotics yet patients with an FVC below 80% do. Other patients with progressive fibrotic ILDs (other than IPF) also have access to nintedanib regardless of baseline FVC. It will therefore provide equality of access to an antifibrotic therapy for this group of patients with similar prognosis.
• Is the technology a 'step-change' in the management of the condition?	Yes for the reasons stated above. From the BTS registry data approximately one third of patients with clinically significant IPF, as shown by symptoms, reduction in measures of gas transfer (DLco, Kco) and the extent of disease on CT are not eligible for anti-fibrotic medication due to the presence of a FVC of greater than 80%. This group of patients receive a major dis-service in their clinical care due to the NICE reimbursement decision by not being able

	to offer any disease modifying treatment with anti-fibrotics in a disease that is ultimately and invariably progressive and terminal in its natural course
• Does the use of the technology address any particular unmet need of the patient population?	Yes as stated in point 8
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?	In studies up to 20% of patients will stop therapy due to side effects and the impact on quality of life. In the majority of patients – 80% - side effects are manageable by prompt specialist nurse review and care advising on concomitant therapies or dose reductions and re-titrations.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No, Clinical trials do not exclude patients with an FVC above 80%. In fact the trials have demonstrated efficacy in patient populations with an FVC above 80% Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. Thorax . 2017 Apr;72(4):340-346.

	Real-World Study Analysing Progression and Survival of Patients with Idiopathic Pulmonary Fibrosis with Preserved Lung Function on Antifibrotic Treatment. Adv Ther . 2021 Jan;38(1):268-277
• If not, how could the results be extrapolated to the UK setting?	See above
• What, in your view, are the most important outcomes, and were they measured in the trials?	FVC decline - A clinically significant treatment response as stipulated by the US FDA is a statistically significant reduction in forced vital capacity (FVC) decline over time as specified by trial design. Moreover, it is a surrogate to mortality.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	No only FVC has been shown to be a validated surrogate for mortality in IPF trials
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No
21. How do data on real-world experience compare with the trial data?	Real world patients have a different cohort of patients compared to clinical trials. They tend to be older and with more comorbidities as well as patients with emphysema. Despite this, real world studies have shown continued benefit of antifibrotics on survival (multiple studies)

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes currently patients with an FVC above 80% are not treated equally to patients with an FVC below 80%. The current NICE ruling is actively discriminatory against: Former and current smokers. With IPF and moderate concurrent emphysema, FVC levels are misleadingly well preserved. Some patients progressing to end stage IPF with FVC levels >80% Those with premorbid values high in the normal range. Many subjects that are physically active in adolescent or early adulthood will have FVC values>140%. In such cases, a reduction in FVC to 80% represents a devastating reduction, usually associated with severe disease as judged by DLco levels, CT findings and symptoms. - The elderly. Percentage predictive values are notoriously unreliable in this age group. Based on the only system predicted normal system to be based on actual measurements in the elderly, it appears that ECCS overstates percent predicted values in this age group by up to 10%.
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Nintedanib is effective in reducing FVC decline in patients with IPF who have an FVC above 80%
- IPF Patients with an FVC above 80% have significant disease as seen by their symptoms, transfer factor and extent of fibrosis on their imaging, and make up 30% of patients currently not treated in the BTS registry
- IPF Patients with an FVC above 80% are at a major disadvantage compared to their counterparts with FVC below 80% as they are not eligible for antifibrotics and thus do not gain the survival advantage of antifibrotic therapy in a disease like IPF which is progressive and terminal.
- Former smokers or patients with concomitant emphysema are at great disadvantage with current restrictions of FVC predicted as they have spuriously high percent predicted FVC and should be able to have Nintedanib at the point of diagnosis as if we wait till FVC drop to 80% or less, the disease is too advanced, and they may not tolerate therapy.
- IPF patients are at a major disadvantage to other patients with fibrotic ILDs where once progression is confirmed, no baseline FVC threshold is stipulated.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

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Professional organisation submission

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

CONFIDENTIAL

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062] Post-factual accuracy check (FAC) version

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Declared competing interests of the authors and advisors

- The authors declare none.
- Dr Jones is a co-investigator and a principal investigator on preclinical studies of novel treatments for lung diseases, including idiopathic pulmonary fibrosis, funded under a collaborative framework agreement between the University of Southampton and Boehringer Ingelheim.

Rider on responsibility for report

The view 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.

This report should be referenced as follows:

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Contributions of authors

Keith Cooper critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Lorna Hazell critically appraised the clinical effectiveness systematic review, and drafted the report; Asyl L. Hawa, critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Jo Picot, critically appraised the clinical effectiveness systematic review, and drafted the report; Fay Chinnery critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Scott critically appraised the clinical effectiveness systematic review, and drafted the report; Jonathan Shepherd critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

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LIST OF ABBREVIATIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
ACD	Appraisal Consultation Document
AE	Adverse event
AIC	Akaike Information Criterion
ANCOVA	Analysis of covariance
BD	Twice daily
BSC	Best supportive care
CASA-Q	The Cough and Sputum Assessment Questionnaire
CG	Clinical Guideline
CI	Confidence interval
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
DIC	Deviance Information Criterion
DLco	Carbon monoxide Diffusing Capacity
DSA	Deterministic sensitivity analysis
EAG	Evidence Assessment Group
EMA	European Medicines Agency
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in the first second
FVC	Forced Vital Capacity
GI	Gastro-intestinal
HCRU	Health Care Research Unit
HRCT	High-resolution computerised tomography
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Unit

ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IPD	Individual patient level data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LOCF	Last observation carried forward
LYG	Life year gained
NAC	N-acetylcysteine
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	Network meta-analysis
OD	Once daily
OR	Odds ratio
PaO2	Partial pressure of oxygen in arterial blood
PAS	Patient Access Scheme
PFS	Progression-free survival
PGI-C	Patient's Global Impression of Change
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SGRQ	St. George's Hospital Respiratory Questionnaire
SGRQ-I	IPF-specific St. George's Hospital Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SpO2	Oxygen saturation by pulse oximetry
STA	Single Technology Appraisal
TA	Technology Appraisal
UCSD-SOBQ	University of California in San Diego Shortness of Breath Questionnaire
VC	Vital Capacity

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, health technology, evidence and information on the issues are in the main body of this EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of EAG's key issues

Issue number	Headline description	EAG report sections
1	Uncertainty in whether all relevant observational study evidence has been included in the systematic literature review	3.1.2
2	Exclusion of survival data from a published trial (Lancaster 2020 et al) which could inform the company's pooled survival analyses	3.1.2
3	The company's economic model base case uses overall survival estimates for the whole trial population, rather than the FVC > 80% predicted subgroup	4.2.6
4	Nintedanib-treated patients are followed up for much longer than placebo patients, which increases uncertainty in the longer-term comparison of clinical effectiveness	4.2.6

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves life expectancy (overall survival) and quality of life in quality-adjusted life years (QALYs). An ICER is the ratio of the additional costs to the QALYs gained.

The company report their base case cost-effectiveness results in company submission (CS) Table 115 and CS Table 116 using the list price and Patient Access Scheme (PAS) price for nintedanib respectively, reproduced in Table 2 and Table 3 below.

Table 2 Company base case results for nintedanib vs. best supportive care (using the list price for nintedanib)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£19,262	4.08	3.21				
Nintedanib	£89,177	7.40	5.69	£69,915	3.32	2.49	£28,094

Reproduced from CS Table 115.
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

Table 3 Company base case results for nintedanib vs. best supportive care (using PAS price for nintedanib)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£19,262	4.08	3.21				
Nintedanib	[redacted]	7.40	5.69	[redacted]	3.32	2.49	[redacted]

Reproduced from CS Table 116.

The base case results show that nintedanib offers a mean QALY gain of 2.49 for an additional mean cost of £69,915 (list price) and [redacted] (PAS price) versus best supportive care, producing ICERs of £28,094 and [redacted] per QALY gained respectively.

In reply to clarification question B5, the company provided additional results for the FVC>80% predicted subgroup using fitted OS curves for this subgroup. The FVC > 80% predicted subgroup results had an ICER, using the PAS price for nintedanib, of [redacted] per QALY (Table 4).

Table 4 Company results for nintedanib vs. best supportive care (PAS price for nintedanib) using OS curves for the FVC > 80% predicted subgroup

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£18,724	3.87	3.06				

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
Nintedanib	[redacted]	8.50	6.51	[redacted]	4.63	3.44	[redacted]
Produced by the EAG using OS parameter estimates provided in clarification response document Table 10 and 11							

1.3 The decision problem: summary of the EAG's key issues

No key issues were identified with respect to the decision problem, notwithstanding those issues listed below which stem from the company's use of whole trial population data instead of data from the decision problem population of people with FVC > 80% predicted.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Uncertainty in whether all relevant observational study evidence has been included in the systematic literature review

Report section	3.1 Critique of the methods of review(s)
Description of issue and why the EAG has identified it as important	The process for screening clinical effectiveness studies for inclusion in the systematic literature review (SLR) is not fully clear and at times appears unsystematic. The only observational evidence included in the SLR is from the INPULSIS-ON and TOMORROW open-label extension studies – both are follow-on studies from company sponsored nintedanib RCTs. However, it is not plausible that these are the only relevant available observational studies of nintedanib and best supportive care. For example, the CS cites a selection of IPF registries worldwide to validate model assumptions and outcomes or to asses trial generalisability. However, the inclusion/exclusion status of these registry studies is not clear. Any such studies that do meet the inclusion criteria should undergo the same systematic processes and reporting as the open-label extension studies.
What alternative approach has the EAG suggested?	A more explicit description of the inclusion/exclusion status of observational studies identified through the SLR literature searches.
What is the expected effect on the cost-effectiveness estimates?	Uncertain. It is possible that additional observational studies may provide data to inform clinical effectiveness estimates in the economic model.

What additional evidence or analyses might help to resolve this key issue?	The company should consider the potential impact on the model assumptions and results of all eligible observational studies.

Issue 2 Exclusion of survival data from a published trial (Lancaster 2020 et al) which could inform the company's pooled survival analyses.

Report section	3.1 Critique of the methods of review(s)
Description of issue and why the EAG has identified it as important	The CS excludes a published company-sponsored phase IIIb nintedanib RCT by Lancaster et al (2020) from their systematic literature review due to methodological limitations caused by protocol amendments (e.g. trial enrolment difficulties; lack of statistical power). The EAG notes that some of the trial outcomes are relevant to the decision problem and could also inform certain model assumptions (e.g. survival estimates). In our view not all of the methodological limitations cited would necessarily bias the trial's results to a significant degree. In response to an EAG clarification question, the company asserted that the results of the trial are supportive of (i.e. consistent with) the TOMORROW and INPULSIS trials and that inclusion of Lancaster et al (2020) would have a minimal impact on the overall results in their submission. Whilst this is reassuring, the company do not provide evidence to show the impact of this study on the model cost- effectiveness estimates.
What alternative approach has the EAG suggested?	A cost effectiveness scenario analysis including survival data from the Lancaster 2019 trial, in addition to the INPULSIS and TOMORROW trials, would illuminate the effect any apparent bias associated with Lancaster et al (2019).
What is the expected effect on the cost-effectiveness estimates?	This is uncertain at present.
What additional evidence or analyses might help to resolve this key issue?	As above, the company should provide a scenario analysis including survival data from the Lancaster 2019 trial, ideally using data for the subgroup of patients with FVC >80% if available. This would represent a more complete nintedanib evidence base than that of the current submission.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 3 The company's economic model base case uses overall survival estimates for the whole trial population, rather than the FVC > 80% predicted subgroup

Report section	4.2.6 Treatment effectiveness and extrapolation
Description of issue and why the EAG has identified it as important	The company's base case economic model uses OS data for the whole trial population, rather than the FVC > 80% predicted subgroup.
What alternative approach has the EAG suggested?	The EAG suggests that the base case economic model should use OS data for the FVC > 80% subgroup as this population is specified in the decision problem.
What is the expected effect on the cost-effectiveness estimates?	Using the EAG's corrected model, the ICER using the whole trial OS data is slightly higher at [redacted] per QALY compared to the ICER based on OS data for the FVC > 80% predicted subgroup, [redacted] per QALY.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommend using OS data for FVC > 80% predicted subgroup as the base case.

Issue 4 Nintedanib-treated patients are followed up for much longer than placebo patients, which increases uncertainty in the longer-term comparison of clinical effectiveness

Report section	4.2.6 Treatment effectiveness and extrapolation
Description of issue and why the EAG has identified it as important	The pivotal RCTs allowed placebo participants to receive nintedanib open-label at the end of the 52 week blinded trial. The open-label extension studies followed-up nintedanib patients for over five years, disproportionately longer than the follow-up period for placebo.
What alternative approach has the EAG suggested?	Based on the Kaplan Meier data submitted by the company in their clarification response (B5), the EAG considers there is no difference in survival between the nintedanib and placebo arms. We therefore assume that mortality is initially the same for both the trial arms for the FVC > 80% predicted subgroup. When the mean FVC % predicted of the FVC > 80% predicted subgroup has declined to that of the whole trial population, the placebo OS curve is assumed to follow the placebo parametric curve for the whole trial population. We estimate this happens after 5.5 years.
What is the expected effect on the cost-effectiveness estimates?	Using the EAG corrected model, the ICER using the OS data for the FVC > 80% predicted subgroup is [redacted] per QALY. Applying the EAG's assumptions for the extrapolation of the placebo arm, the ICER increases to [redacted] per QALY.
What additional evidence or analyses might help to resolve this key issue?	Longer term follow-up of people receiving best supportive care, eg. from real-world data sources, evidence would help to clarify this issue.

1.6 Secondary issues: summary of the EAG's view

The EAG has identified the following secondary issues for consideration. The common theme among them is uncertainties relating to the subgroup of people with IPF and an FVC > 80% predicted.

- **Network meta-analysis (NMA)**. The company use the odds ratios estimated from their NMA to inform clinical effectiveness parameters in their economic model, but these are not stratified by FVC % predicted subgroup. Historically, the NMA includes placebo arms from pirfenidone trials, but these arms do not include patients with FVC >80% predicted. Given that pirfenidone is no longer a comparator it is arguable whether the NMA is required in the current appraisal. Instead, these odds ratios could have been estimated from the INPULSIS and/or TOMORROW RCTs directly or from a pairwise meta-analysis of these trials. This would have allowed the odds ratios to be computed for the FVC >80% predicted subgroup. The EAG notes, however, that the odds ratios from the whole trial population(s) will likely be more precise due to the larger sample size.
- **Subgroup interaction tests.** The company base their assumption of similar treatment effects across FVC % predicted subgroups, at least in part, on the non-significant results of statistical interaction tests in the INPULSIS trials. However, as the company notes, these tests are likely to be underpowered to detect a significant difference between treatment and subgroups. There remains some uncertainty about the validity of assumptions of similarity or difference in treatment effects across patient subgroups. Further expert clinical advice would be beneficial.
- **Open-label extension studies.** The OLE studies from the INPULSIS and TOMORROW RCTs only include patients who have completed the respective parent trials and therefore may comprise a more skewed sample of patients (e.g. healthier, more motivated) than general IPF patient population seen in practice. Also, the results of the extension studies are not stratified by FVC % predicted subgroups and it is therefore uncertain whether the results are fully generalisable to the FVC > 80% predicted subgroup. Further expert clinical advice would be beneficial.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Based on the EAG critique of the company's model (discussed in section 5.3.5), we have identified four key aspects of the company's base case with which we disagree with the assumptions made. Our preferred model assumptions are the following:

- **Population modelled for OS**: FVC >80% predicted, rather than the whole trial population.

- **Extrapolation of OS:** For the first 5.5 years, we use the same survival curve for the BSC arm as for the nintedanib arm as the mortality rate for both arms is considered equal; thereafter we use the BSC survival curve from the whole trial population for the BSC arm.
- **OS hazard ratio for acute exacerbations:** we use a HR of 2.79, rather than 1.4.
- **Time horizon:** we use a time horizon of 35 years, rather than 50 years.

Table 5 below presents the results obtained from the model with the above preferred EAG model assumptions implemented. The results are most sensitive to the extrapolation of OS assumption.

Table 5 EAG deterministic base case results (using PAS price for nintedanib)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£23,264	5.71	4.49				
Nintedanib	[redacted]	7.20	5.62	[redacted]	1.49	1.14	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

Modelling errors identified and corrected by the EAG are described in section 5.3.4. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.2.2.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This EAG report is a critique of the company's submission (CS) from Boehringer Ingelheim which informs NICE's part-review of health technology guidance TA379 'Nintedanib for treating idiopathic pulmonary fibrosis (IPF)' published in 2016.

TA379 was informed by a company submission from Boehringer Ingelheim and critiqued by SHTAC in an EAG report, published in 2015.[1] (NB. At that time NICE referred to the EAG as the Evidence Review Group (ERG). To avoid potential confusion in this report arising from historical citing of the ERG (original 2015 appraisal) and the EAG (this current appraisal), from this point onward we only use the term EAG to describe this group in the past and the present). NICE's guidance recommends nintedanib as an option for adults with IPF but only in patients with a forced vital capacity (FVC) between 50% and 80% predicted. NICE have noted that this threshold for treatment was not supported by UK clinicians and recommended a part-review of TA379 [2].

The scope of this part-review is to assess the clinical and cost effectiveness of nintedanib in the subgroup of IPF patients with a FVC above 80% predicted. TA379 included evidence from two replicate phase III nintedanib randomised controlled trials (RCTs) (INPULSIS trials) and the phase II TOMORROW RCT. Our critique identifies the strengths and weakness of the current CS, focusing on new evidence submitted by the company for this subgroup of patients:

- post-hoc subgroup analyses of the INPULSIS and TOMORROW RCTs in patients with FVC >80% predicted, and
- longer-term clinical effectiveness and safety data from two open-labelled extension (OLE) studies (INPULSIS-ON and TOMORROW OLE).

One clinical expert was consulted to advise the EAG and inform this report. Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 8th July 2022. A response from the company via NICE was received by the EAG on 27th July 2022, and a further response was received on 4th August 2022; these can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on idiopathic pulmonary disease

CS section B.1.3.1 provides an overview of the effects of IPF on patients and their quality of life. IPF is a progressive, irreversible lung disease with no cure. The rate of disease progression is described as heterogenous and unpredictable with a median survival from diagnosis between 2 and 5 years. Forced vital capacity (FVC) is a lung function test that measures the amount of air that can be forcibly exhaled after a deep breath. The FVC % predicted expresses the FVC as a percentage of the predicted value based on population norms adjusted for age, gender and height. In the previous NICE nintedanib appraisal (TA379), the appraisal committee acknowledged that the FVC % predicted has some limitations but concluded this is the most widely used measure in clinical practice for monitoring lung function in IPF. Clinical expert advice to the EAG is that IPF is not described in terms of severity as this is not determined by lung function alone. Some patients with significant fibrosis/symptom burden, e.g., co-existent emphysema with IPF, have an FVC % predicted that is maintained above 80% despite advancing disease (as the emphysema prevents FVC decline). Typically, in clinical practice the preferred terminology is to describe IPF as early or advanced, but this does not directly relate to FVC thresholds.

2.2.2 Background information on nintedanib

Nintedanib (OFEV®) is a tyrosine kinase inhibitor which inhibits several steps in the process of lung fibrosis. It is licensed for use in IPF in adults, regardless of the patient's FVC % predicted value. The recommended dose is 150mg orally twice daily. CS Table 2 provides a comprehensive description of treatment with nintedanib including details of other conditions for which the product has a marketing authorisation.

2.2.3 The position of nintedanib in the current treatment pathway

CS section B.1.3.2 provides an accurate description of the current clinical pathway of care in IPF. Current management of IPF in the UK includes best supportive care and pulmonary rehabilitation. NICE clinical guideline 163 on IPF defines best supportive care as including non-pharmacological approaches aimed at symptom relief, management of co-morbidities, withdrawal of therapies suspected to be ineffective or causing harm and end of life care. The CS states that pulmonary rehabilitation includes educational and exercise components (CS section B.1.3.2) and should be tailored to the individual patient. Clinical expert advice to the EAG is that patients would also undergo regular assessments for oxygen requirements and

be given ambulatory oxygen as appropriate. Lung transplantation may improve survival and quality of life, but many patients are ineligible due to increasing age and comorbidities.

Pharmacological interventions aim to slow the rate of decline in lung function. Two antifibrotic drugs, nintedanib and pirfenidone, are licensed for the treatment of IPF. Pirfenidone is licensed for treatment of mild to moderate IPF only, while nintedanib is licensed for use in IPF regardless of severity[3,4]. Both drugs are currently recommended by NICE as options for adults with IPF but their use is restricted to patients with an FVC between 50% and 80% predicted. Our clinical expert advised that best supportive care and pulmonary rehabilitation usually continues alongside pharmacological treatments as appropriate, but as disease progresses the approach shifts to discontinuation of antifibrotics, symptom relief and palliative care. NICE guidance currently recommends that pirfenidone and nintedanib are stopped if disease progresses by a 10% or more decrease in FVC % predicted in any 12-month period [1,5]. A stopping rule has not been considered in the current CS (see section 4.2.6.5 of this report for our discussion of this).

2.2.4 Management of patients with IPF and a FVC >80% predicted

Patients with an FVC > 80% predicted are estimated to represent around a third of UK IPF patients.[6] These patients currently receive best supportive care but are not eligible to receive pharmacological treatment until their lung function (as measured by FVC) has declined below 80% predicted.

In NICE TA379, the clinical and cost-effectiveness of nintedanib was compared to both pirfenidone and best supportive care, however in this current appraisal the relevant comparator is best supportive care only. Pirfenidone is not an appropriate comparator because it is not recommended by NICE for treating IPF patients with FVC >80% predicted. In TA379, the NICE Committee concluded that the incremental cost effectiveness ratios (ICERs) for nintedanib compared to best supportive care were not in the range considered to be a cost-effective use of NHS resources. This recommendation was based on ICERs estimated by the company from their economic model (in patients with FVC % predicted over 50%) and an exploratory analysis provided by the EAG (including only patients with FVC >80% predicted).[1]

EAG comment on background

The company has provided an appropriate description of the disease burden for IPF, the intervention and the current treatment pathway. They have also presented

background information that is relevant to the patient population for whom nintedanib is not currently recommended.

2.3 Critique of the company's definition of the decision problem

The company's decision problem broadly matches the final scope issued by NICE (Table 6). The CS presents evidence for the majority of the outcomes listed in Table 6 for the subgroup of patients FVC >80% predicted in the INPULSIS RCTs. However, only selected clinical outcomes are presented for this subgroup for the TOMORROW RCT (further detail is given in section 3.2.3 of this report). The effect of nintedanib on overall survival is not presented in the CS for the subgroup of patients with FVC >80% predicted in the individual INPULSIS and TOMORROW RCTs. However, pooled Kaplan Meier survival curves from these RCTs and their OLE studies were provided for this subgroup on request (company's response to clarification question B6).

Table 6 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	EAG comments
Population	Adults with idiopathic pulmonary fibrosis with FVC >80% predicted	Same as final scope issued by NICE	No concerns
Intervention	Nintedanib	Same as final scope issued by NICE	No concerns
Comparators	Established clinical management without nintedanib	Same as final scope issued by NICE	No concerns
Outcomes	The outcome measures to be considered include: • pulmonary function parameters • physical function • exacerbation rate • mortality • adverse effects of treatment • health-related quality of life.	Same as final scope issued by NICE	The outcomes in the CS are appropriate and match the final scope with the following exception: • Physical function, e.g., 6-minute walk test (6MWT) was presented in the previous appraisal (TA379) but is not included in the current submission. • The 6MWT is not included in the company's economic model and therefore we do not consider this to be a major omission.

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 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 patient access schemes for the intervention or comparator technologies should be taken into account.	Same as final scope issued by NICE	No concerns
Subgroups	Not applicable	Not applicable	No concerns
Special considerations including issues related to equity or equality	Not applicable	Not applicable	No concerns

3 CLINICAL EFFECTIVENESS

In each of the following sub-sections we provide a brief re-cap on the evidence assessed in the previous NICE appraisal of nintedanib for IPF (NICE TA379) followed by a description and critique of the new evidence submitted by the company for this current part-review of TA379.

3.1 Critique of the methods of review(s)

3.1.1 Evidence submitted in TA379

The company conducted a systematic literature review (SLR) to identify RCTs on nintedanib and relevant comparators covering appropriate efficacy, safety and health related quality of life (HRQoL) outcomes. The EAG's critique of the review methods is described in section 3.1.1. of the 2015 EAG report [7]. No major concerns with respect to the review methods were noted.

3.1.2 New evidence submitted

An updated SLR was conducted to identify RCTs published from September 2014 up to 14th January 2022. The inclusion criteria for the company's updated SLR also include non-randomised trials and observational studies. The CS does not explain *a-priori* how observational studies would be used to inform the current appraisal. Appendix D.1.1 of the current CS provides details of the methods of this review. Appendix 9.1 of this report below presents the EAG's assessment of the methods of the company's updated SLR.

Following screening of titles and abstract records, a total of **150** records were selected for full text eligibility screening. CS Appendix D Table 137 lists the **89** records that were eligible for inclusion in the review but does not indicate how many unique studies these records describe. Of the remaining **61** full texts screened and excluded, reasons for exclusion by PICO criteria are summarised in CS Table 138 (see also company clarification response A1.b).) (NB. The EAG are unclear what is meant by the exclusion criterion 'timeframe out of scope' which was applied to 25 of these 61 studies).

CS Appendix D Table 136 provides an overview of **nine** "identified clinical trials". No details are given about criteria for selecting these nine trials from the 89 included records. Of these nine the CS presents evidence for a sub-set of five trials:

- phase III INPULSIS I and II RCTs,
- phase II TOMORROW RCT,

- INPULSIS-ON study and
- TOMORROW open label extension study.

In response to clarification question A1.a), the company justify why the other four studies were "not considered relevant to the decision problem" and thus excluded from the submission:

- The first excluded study ("**INMARK"; NCT02788474**) [8] had a much shorter duration (12 weeks) than the INPULSIS and TOMORROW trials (52 weeks). An open label extension to the INMARK trial (including nintedanib only; up to 40 weeks) provides relevant data for disease progression but no survival data are reported. The EAG acknowledges that due to the shorter duration of this study it is less informative for economic modelling than the INPULSIS and TOMORROW trials. Nonetheless, the INMARK study and its OLE appear to fulfil the company's PICO selection criteria and, as such, details of the study should have been reported in the CS to allow similarities or differences in characteristics and findings to be fully considered.
- The second excluded study was a company-sponsored phase IIIb trial of nintedanib by **Lancaster et al 2020 (NCT01979952**) [9] which reported relevant outcomes including deaths. The company reports that this was excluded because it is not a pivotal trial and due to substantial protocol changes (e.g. the primary analysis was conducted at six months instead of 52 weeks, thus compromising statistical power; possible bias due to premature treatment discontinuations which were greater in the placebo arm). Notwithstanding these issues, this study also appears to fulfil the company's PICO selection criteria and we would have expected the company to have provided details of this study, including its results, to allow an independent assessment of risk of bias and certainty of the findings.
- Furthermore, the EAG notes that the Lancaster et al 2020 trial was combined with the INPULSIS and TOMORROW trials and their open-label extensions in a published extrapolation of long-term survival in IPF patients (Lancaster et al 2019)[10]. The CS describes a similar method of extrapolation to inform the economic modelling for this appraisal, but without inclusion of the Lancaster trial. In response to EAG clarification questions A1b and B1 the company asserts that inclusion of this study would have minimal impact on the overall results for this submission. However, they do not provide any evidence to support this.
- The third excluded study was a safety and pharmacokinetic study in a Japanese population and not necessarily considered generalisable to the UK IPF population (**NCT01136174**).[11] We consider this a reasonable exclusion.

- The fourth excluded study had no results available (**UMIN0000020682**). [12] The EAG notes this study is likely out of scope as it compares nintedanib with pirfenidone (CS Table 136).

The company's reasons for exclusion of these four studies do not appear to fulfil the SLR exclusion criteria listed in CS Table 135. Rather, it appears that additional *ad-hoc* exclusion criteria have been applied relating to factors such as study generalisability, risk of bias and methodological quality. From the study information available to the EAG, it appears that none of the four excluded studies can be considered to provide findings with the same degree of certainty as those of the INPULSIS and TOMORROW RCTs and their extensions (we discuss study risk of bias in section 3.2.2 of this report). The company does not mention whether these four excluded studies were considered as providing supportive evidence, for example potentially informing cost effectiveness scenario analyses.

The EAG notes that the lack of consistency in the application of the PICO selection criteria to the full text articles raises the question of whether ad hoc exclusion criteria were also applied to records excluded at the title and abstract screening stage of the SLR. If so, then this suggests a bigger risk of bias in the selection of clinical effectiveness studies informing this appraisal.

INPULSIS-ON and TOMORROW OLE are the only non-randomised studies included. The EAG is unable to verify whether any other relevant non-randomised or observational studies may have been excluded from the company's SLR.

Finally, as the company's literature search was six months out of date, the EAG performed an updated search of the same databases used in the company searches. One EAG systematic reviewer screened the titles and abstracts from this search (n=311 records). No new RCTs, relevant to the decision problem, were identified.

ERG comment on the methods of review:

The EAG considers the SLR methods to be appropriate with the exception of:

- A lack of transparency in the process and criteria for study selection,
- Apparent *ad-hoc* reasons for exclusion applied to some studies,
- Lack of detail on the selection of observational studies

We are therefore unclear whether all the relevant evidence has been identified.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation

3.2.1 Included studies

3.2.1.1 Evidence submitted in TA379

The company included two replicate phase III double blind, placebo-controlled RCTs (INPULSIS I and II) and a phase II dose-escalation RCT (TOMORROW trial) on nintedanib in the original submission. In all studies, the primary endpoint was the rate of decline in FVC (ml/year) from baseline to 12 months of treatment. A summary of the methodology of the INPULSIS and TOMORROW trials is presented in section 4.3 of the original submission. [1] We assume that all patients in these trials continued to receive best supportive care as appropriate in addition to their allocated trial medication (nintedanib or placebo).

The company conducted subgroup analyses in the INPULSIS trials according to patients' baseline FVC:

- FVC predicted ≤70% vs. >70% (prespecified) (previous CS section 4.8)
- FVC predicted ≤90% vs. >90% (post-hoc) (previous CS section 4.8}.
- FVC predicted ≤80% vs. >80% (post-hoc, in response to clarification question A3).[13]

3.2.1.2 New evidence submitted

The CS provides the following new evidence:

- Further details of the post-hoc subgroup analysis from the INPULSIS RCTs for patients with baseline FVC predicted ≤80% vs. >80%,
- Post-hoc subgroup analysis from the TOMORROW RCT for patients with baseline FVC predicted ≤80% vs. >80% (provided in the company's response to clarification question A9),
- Open-label extension (OLE) studies for the INPULSIS (INPULSIS-ON) and TOMORROW (TOMORROW OLE) trials.

3.2.1.3 RCTs: Study characteristics

The methodology of the INPULSIS and TOMORROW RCTs are summarised in the current CS Tables 3 and 5 and CS section B.2.3 and key design features are summarised below in Table 7.

Table 7 Key design features of the INPULSIS and TOMORROW trials

Study	Key features
INPULSIS I and II	• Replicate 52-week, double-blind, randomised (3:2), placebo-controlled trials, evaluating the effect of oral nintedanib, 150 mg twice daily, on annual FVC decline, in patients with IPF • 487 patients with an FVC >80% predicted were randomised into the trial (295 nintedanib; 192 placebo) • Two randomised patients in the placebo arm were not treated
TOMORROW	• A 52-week, double-blind, randomised, placebo-controlled dose-escalation trial evaluating the effect of nintedanib administered at oral doses of 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid on FVC decline during one year, in patients with IPF (five trial arms in total) • 219 patients with an FVC >80% predicted were randomised into the trial: nintedanib 50mg qd (n=43), 50mg bd (n=45), 100mg bid (n=50), 150 mg bd (n=41); placebo (n=40) • One patient randomised to nintedanib 150mg was not treated

Source: CS Table 7 and responses to clarification question A2

3.2.1.4 RCTs: baseline characteristics of patients with FVC >80% predicted

Baseline characteristics for patients with FVC % predicted >80% in the TOMORROW trial are not provided in the CS as this was not a planned subgroup analysis in this study. Table 8 shows the baseline characteristics of patients in the pooled INPULSIS I and II trials stratified by FVC >80% and ≤80% predicted. CS Tables 9 and 10, respectively, present baseline characteristics for the FVC >90% and ≤90% predicted subgroups and the whole trial population. Baseline characteristics were broadly comparable between trial arms within each subgroup.

The age, sex and smoking history of the patients with FVC >80% predicted from UK sites in the INPULSIS trials were comparable with that of all patients in the British Thoracic Society (BTS) registry in 2021 (CS Table 18). This registry comprises demographic and clinical data for over 4000 patients with interstitial lung disease (including IPF and sarcoidosis) collected from 75 UK centres (largely specialist tertiary care hospitals) over an 8-year period. [14] UK trial participants with FVC >80% predicted had a similar smoking history to patients with FVC >80% predicted in the BTS registry but had a lower diffusing capacity for carbon monoxide (DLco). Clinical expert advice to the EAG is that the BTS Registry is a valuable resource, however a recognised limitation is it does not recruit consecutive patients, and only a limited number of centres contribute data.

The EAG notes that lung function parameters such as mean FVC and diffusing capacity of the lung for carbon monoxide (DLco) are higher in the group with FVC >80% predicted at baseline in the INPULSIS trials (Table 8). However, this group were slightly older on average, had a slightly higher proportion of smokers, a higher proportion of patients with centrilobular emphysema and a lower mean St George's Respiratory Questionnaire (SGRQ) score. Clinical expert advice to the ERG is that:

- FVC is not of use in patients with emphysema in determining the extent of disease in IPF or its progression over time. Radiological assessment of fibrosis and gas transfer testing are more useful. In patients with co-existent emphysema FVC may never decline below 80% despite significant radiological progression of fibrosis. Emphysema prevents FVC decline and is expected to be more frequent in patients with FVC >80% predicted.
- Our expert also commented that the higher prevalence of emphysema also explains the slightly lower FEV1/FVC ratio in these patients (as the emphysema lowers the FEV1 but not the FVC, whilst lung fibrosis alone will lower both FEV1 and FVC proportionally.)
- The lower SGRQ score indicates a better quality of life status in the FVC >80% predicted subgroup which is as expected.
- Our expert did not note any other meaningful differences in characteristics of patients between trial arms or subgroups.

Table 8 Baseline characteristics of participants in the INPULSIS trials stratified by baseline FVC >80% vs. FVC ≤80% predicted

Baseline characteristic	Baseline FVC >80% predicted		Baseline FVC ≤80% predicted	
	Nintedanib (n=295)	Placebo (n=190)	Nintedanib (n=343)	Placebo (n=233)
Male, n (%)	218 (73.9)	148 (77.9)	289 (84.3)	186 (79.8)
Age, yrs mean (SD)	68.0 (7.8)	67.6 (7.6)	65.4 (8.2)	66.5 (8.1)
Race, n (%)				
White	154 (52.5)	109 (57.4)	206 (60.1)	139 (59.7)
Asian	95 (32.2)	59 (31.1)	99 (28.9)	699 (29.6)
Black	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Missing†	22 (11.6)	46 (15.6)	25 (10.7)	36 (10.5)
Smoking status, n (%)				
Never smoked	77 (26.1)	50 (26.3)	97 (28.9)	72 (30.9)
Ex-smoker	199 (67.5)	126 (66.3)	236 (68.8)	157 (67.4)
Current smoker	19 (6.4)	14 (7.4)	10 (2.9)	4 (1.7)

Time since diagnosis, yrs mean (SD)	1.56 (1.34)	1.52 (1.35)	1.72 (1.37)	1.61 (1.27)
Centrilobular emphysema, n (%)	137 (46.4)	91 (47.9)	117 (34.1)	75 (32.2)
FVC, mean mL (SD)	3102 (783)	3241 (812)	2379 (546)	2309 (515)
FVC, % predicted mean (SD)	95.1 (12.5)	95.4 (13.7)	66.6 (8.0)	66.1 (8.1)
FEV_1/ FVC ratio, % mean (SD)	80.0 (5.8)	79.7 (5.7)	83.1 (5.4)	83.3 (5.7)
DL_{CO}, % predicted mean (SD)	51.4 (13.5)	51.2 (11.9)	44.0 (12.6)	43.5 (13.6)
SGRQ total score, mean (SD)	34.3 (18.5)	34.1 (17.1)	43.9 (18.6)	44.0 (18.5)

Abbreviations: DL_{CO}, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; FEV_1, forced expiratory volume; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

†In France, regulation did not permit the collection of data on race.

Source: Table reproduced from CS Table 8

3.2.1.5 Open label extension studies: study characteristics

The methodology of the INPULSIS-ON and TOMORROW OLE studies is summarised in the current CS Tables 4 and 6 and CS section B.2.3. The flow of participants between the parent trials and their respective OLE studies is depicted graphically in CS Figures 2 and 3. Key design features are summarised below in Table 9. The studies were conducted at sites in Europe, Asia, the Americas and Australasia with 173 participants enrolled in INPULSIS-ON study and 58 participants in the TOMORROW OLE.

Table 9 Key design features of the INPULSIS-ON and TOMORROW OLE studies

Study	Key features
INPULSIS-ON	• **Design.** A phase III open-label extension trial of the long-term safety of oral nintedanib in patients with IPF • **Eligibility.** Patients who completed the 52-week treatment period of the INPULSIS RCTs, and the 4-week follow-up visit. • **Treatment.** Patients received nintedanib up to a maximum dose of 150mg bd • **Follow up:** 68 months (CS Table 17)
TOMORROW OLE	• **Design.** A phase II open-label extension study of the long-term tolerability, safety and efficacy of oral nintedanib in patients with IPF • **Eligibility.** Patients who completed 52 weeks' treatment in the TOMORROW RCT (period 1) continued treatment in a blinded phase (period 2), until the last patient had completed 52 weeks' treatment in period 1.

	• **Treatment.** Patients in the placebo arm of the TOMORROW RCT switched to nintedanib 50mg qd during period 2. Patients received nintedanib at a range of doses between 50 mg qd and 150 mg bd in the extension • **Follow up**: Almost 8 years from start of period 1 to database lock (15th October 2015) (CS Table 17)

CS Figure 47 presents the participant flow from the INPULSIS trials to INPULSIS-ON. In summary:

- Of the 1061 patients treated in INPULSIS I and II, 807 (76.1%) completed the trials.
- Of the 807 completers, 734 (90.9%) continued in INPULSIS-ON.
- The proportions of patients continuing were similar between the parent trial arms: 430 (90.5% of the 475 randomised to nintedanib) continued on nintedanib and 304 (91.6% of patients randomised to placebo) switched to nintedanib.
- 457 (62.3%) of the 734 patients had an FVC ≤80% predicted and 277 (37.7%) had an FVC>80% predicted (company clarification response A7) at the start of the extension period.

CS Figures 43 and 44 show the participant flow from the TOMORROW trial to its OLE. Further details are provided in the company's response to clarification questions A2 and A10. In summary:

- 316 (73.1%) of the 432 randomised patients from the parent trial completed the planned observation time.
- 198 patients entered the OLE (45.8% of those originally randomised and 59.8% of those with complete observation time in the parent trial).
- 37 patients switched from placebo to nintedanib and 161 remained on nintedanib.
- The EAG notes that the company's economic model (and network meta-analysis) only uses data from the TOMORROW trial and/or its OLE from patients who were originally randomised to placebo (n=85) or the licensed dose of nintedanib 150mg bd (n=85). In these two groups, 71 patients entered the OLE: 37 patients switched from placebo to nintedanib and 34 patients continued on nintedanib 150mg bd in the OLE
- The proportion of patients with FVC >80% predicted entering the OLE was not reported in the CS.

3.2.1.6 Open label extension studies: Patients' baseline characteristics

Table 10 shows the baseline characteristics of the patients entering INPULSIS-ON. In response to clarification question A5.b), these represent characteristics at the point of

entering the OLE. These characteristics were similar to that reported for all patients at the start of the parent trials (CS Table 10) with the exception of mean baseline FVC % predicted which was, on average, slightly lower than the baseline in the parent trial (76.21% in INPULSIS-ON compared to 78.1 % to 80.5% in the parent trials). The baseline characteristics for the subgroup of patients with FVC >80% predicted (n=277) at the start of the INPULSIS-ON study were not provided in the CS. Table 10 Baseline characteristics of participants in INPULSIS-ON

Baseline characteristic	INPULSIS-ON (n=734)
Male, n (%)	587 (80.0)
Age, yrs mean (SD)	67.2 (7.8)
Race, n (%)	
White	431 (58.7)
Black	2 (0.3)
Asian	215 (29.3)
Missing†	86 (11.7)
Smoking status, n (%)	
Never smoked	204 (27.8)
Former smoker	503 (68.5)
Current smoker	27 (3.7)
BMI, Kg/ m^2 mean (SD)	27.5 (4.4)
Weight, Kg mean (SD)	78.22 (16.17)
FVC, % predicted mean (SD)	76.21 (19.06)
FVC, mL mean (SD)	2622.9 (811.1)

Abbreviations: BMI, body mass index; FVC, forced vital capacity; SD, standard deviation.
†Race was not collected in patients treated at French sites as this is prohibited by French law.
Source: Table reproduced from CS Table 11

The characteristics of the patients in the nintedanib 150mg bd and placebo arms of the parent TOMORROW trial at the start of the extension phase (Table 11) were broadly similar to the characteristics of patients in these two trial arms at the start of the parent study (CS Table 12). An exception was that the FVC and FVC % predicted were lower at the start of the extension study in those who switched from placebo. This is expected in patients who did not receive any active treatment in the parent trial. Baseline characteristics for patients with FVC >80% predicted were not presented for the TOMORROW open label trial.

Table 11 Characteristics of patients in the TOMORROW OLE

Baseline characteristic	Nintedanib 150 mg bid (N=35)	Comparator† (N=37)
Male, no. (%)	28 (80.0)	23 (62.2)
Age in years, mean (SD)	67.2 (7.0)	66.2 (7.3)
Time since IPF diagnosis, years, mean (SD)	2.9 (1.1)	3.5 (1.6)
FVC, L, mean (SD)	2.7 (0.9)	2.4 (0.7)
FVC, % predicted, mean (SD)	77.1 (21.4)	73.0 (17.9)
DL_{CO}, % predicted, mean (SD)	40.1 (14.4)	38.9 (10.5)
Smoking status		
Never smoked	12 (34.3)	14 (37.8)
Ex/ current smoker	23 (65.7)	23 (62.2)

Abbreviations: BMI, body mass index; DL_{CO}, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; SD, standard deviation
†Patients in the comparator group entered the extension trial on nintedanib 50 mg daily but had the option to increase dose to nintedanib 150 mg twice daily. Dose reduction from 150 mg twice daily to 100 mg twice daily and treatment interruption were permitted in both groups for the management of AEs
Source: Table reproduced from CS Table 13.

The EAG's clinical expert advised that patients in INPULSIS-ON and TOMORROW were generally representative of patients who would be treated with nintedanib in clinical practice. The exceptions are that the trial populations are slightly younger than the average UK population (early 70's), and the distribution of ethnicity is different from the UK in INPULSIS-ON (a lower proportion of white patients).

EAG comment on included studies

The baseline characteristics of patients in the subgroups with FVC >80% predicted and FVC ≤80% predicted in the INPULSIS and TOMORROW RCTs were similar between trial arms. Expert clinical advice to the EAG confirms no apparent unexpected differences in characteristics between subgroups.

A higher proportion of patients from INPULSIS RCTs entered the INPULSIS-ON study than was the case in the TOMORROW RCT and its open-label extension study. The baseline characteristics of patients entering the extension studies were similar to baseline characteristics of their respective parent RCTs. The exception was lung function (FVC) which had declined at entry to the extension studies, though this is to be expected over time. Our clinical expert noted that patients in the INPULSIS-ON and TOMORROW OLE were slightly younger and a lower proportion were white

compared to patients commonly seen in practice; this is in keeping with observations in the parent trials.

3.2.2 Risk of bias assessment

3.2.2.1 Evidence submitted in TA379

The company critically appraised the TOMORROW and INPULSIS RCTs using the NICE recommended criteria. Their judgements are repeated in Table 15 of the current CS. In the original appraisal we agreed with the company's judgments, with the following exceptions:

- Question 5 (Were there any unexpected imbalances in dropouts between groups?): we judged this 'uncertain' (unclear risk of bias) for TOMORROW.
- Question 6 (Is there any evidence to suggest that the authors measured more outcomes than they reported?): we judged 'yes' (increased risk of bias) for TOMORROW.
- Question 7 (Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?) We judged the last observation carried forward analysis in TOMORROW to be inappropriate for addressing missing data; for INPULSIS the lack of information available on analysis methods for missing data led us to judge the risk of bias as 'unclear'.

3.2.2.2 New evidence submitted

3.2.2.2.1 Risk of bias assessment for RCT subgroup analyses

The EAG assumes that the risk of bias judgements provided in the CS Table 16 were made in relation to the whole trial population in the INPULSIS and TOMORROW RCTs. We therefore requested from the company details of drop-out rates and missing data for the subgroup of patients with FVC >80% predicted (response to clarification question A2). These are the domains in which risk of bias may potentially vary between patient subgroups.

The company clarified that planned observation time was considered as complete if all visits until week 52 and the following follow-up visit were performed.

- In the pooled **INPULSIS** RCTs, a slightly higher proportion of patients did not complete the planned observation time in the nintedanib arm (43 patients; 14.6%) compared to the placebo arm (19 patients; 10.0%), however this was largely due to differences in adverse event rates which is not unexpected.

- Drop-out rates were more variable across the trial arms (ranging from 6% to 23.3%) in the **TOMORROW** RCT but were similar between the licensed dose, nintedanib 150mg bd, (7 patients; 17.5%) and placebo trial arms (8 patients, 20.0%).

Analyses of the primary outcome in the INPULSIS and TOMORROW trials required patients to have a minimum number of on-treatment measurements (we assume a baseline measurement was also required but this is not explicitly stated in the CS). This means that patients with partially complete data could still be included in the analysis and did not need to have completed the planned observation time.

- The reported proportions of patients with missing data for the analysis of the primary outcome (annual decline in FVC) in the subgroup of patients with FVC >80% predicted range from 1.1% to 2.4% in INPULSIS and 0% to 5% in TOMORROW.
- These proportions reflect the numbers of patients excluded from the analysis rather than the numbers of missing data points over the trial visits for those who were included.
- Appropriate regression methods were used to account for missing data under the 'missing at random' assumption but no sensitivity analyses were provided to test this assumption in this subgroup analysis due to lack of statistical power.
- The EAG notes, however, that the primary analyses were robust to other missing data assumptions in sensitivity analyses conducted for the whole trial population which is reassuring.

The company provides a narrative description of the potential issues associated with analysing INPULSIS trial patients in subgroups defined by different baseline FVC % predicted values (CS pages 54-54). In particular, such analysis may be subject to chance findings when multiple analyses are performed, and lack of statistically significant interactions may reflect underpowered tests and do not necessarily indicate a lack of true difference in treatment effect between subgroups. The EAG agrees with that these are valid considerations.

3.2.2.2.2 Risk of bias assessment for the open label extension studies

The company critically appraised the TOMORROW and INPULSIS-ON open-label extension studies using the STA User Guide 2022 criteria [15] and a checklist proposed by Bowers et al.[16] which assesses reporting quality, internal validity and external validity in OLE studies. The EAG is not aware of any other standardised tools for assessing OLE studies specifically, so this approach seems reasonable. Our own assessments of the studies using these

criteria differed in some places from those of the company and we summarise these in Appendix 9.2. In brief, we note that four countries which contributed data to the TOMORROW RCT are not represented in the TOMORROW OLE. The rate of sample slippage is a potential concern because less than 50% of randomised patients from the parent trial entered the OLE which appears lower than the average (74%) reported in a review of OLE studies by Bowers et al.[16] We also observe that potential confounders and effect modifiers are not clearly identified as such in either the CS or the published paper for the TOMORROW OLE or INPULSIS-ON.

EAG comment on risk of bias in included studies

We did not note any major risks of bias in the conduct of the subgroup analyses. However, as noted by the company, these analyses may be subject to limitations commonly associated with subgroup analyses in clinical trials such as multiplicity (type I error) and lack of statistical power for interaction tests (type II error). Results of the subgroup analyses should therefore be interpreted with caution.

Similarly, we have no significant concerns with the conduct of the OLE studies, with the caveat that less than half of the patients in the TOMORROW RCT entered its OLE study. The patients who entered the INPULSIS-ON and TOMORROW OLE studies, however, did appear to be similar to their respective parent trial populations, though only a limited set of baseline characteristics were available for the OLE studies.

3.2.3 Outcomes assessment

3.2.3.1 Evidence submitted in TA379

Table 2 of the previous CS details the clinical efficacy, safety and HRQoL outcomes measured in the INPULSIS and TOMRROW trials. The primary outcome for both trials was the annual rate of decline in FVC (ml/year) at 12 months for nintedanib compared to placebo. Following expert clinical advice, the EAG concluded that the company had included the most clinically meaningful outcomes with the exception of activities of daily living which were not measured in the trials or specified in the NICE final scope. The company's economic model derived the baseline risk of mortality, disease progression (defined by a 10-point drop in FVC% predicted) and time to first acute exacerbation using outcome data from the placebo arms of the INPULSIS and TOMORROW trials. The corresponding risks for nintedanib were derived by applying an odds ratio from the company's NMA to these respective baseline risks (see section 3.5 of this report).

3.2.3.2 New evidence submitted

No new outcome measures are presented in the current CS. Selected outcomes from the parent trials are included in the post-hoc analysis of the INPULSIS and TOMORROW RCTs for the subgroup of patients with FVC>80% predicted (Table 12). We describe the outcomes measured in the open-label extension studies in Table 13.

Table 12 Outcomes reported in the INPULSIS and TOMORROW RCTs for patients with FVC >80% predicted

Outcome	INPULSIS	TOMORROW
Efficacy	Annual rate of decline in FVC (mL/ year); Change from baseline in FVC (mL/ year); Time to first acute exacerbation	Annual rate of decline in FVC
Safety	Number of adverse events (overall, severe, serious, fatal, leading to discontinuation).	Adverse events reported for *whole trial population only*
HRQoL	Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at week 52	Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at week 52 reported for *whole trial population only*

Source: CS section B.2.6, company response to clarification question A9, CS Table 37

Although these data are mostly reported for the subgroup with FVC>80% predicted, data from the whole trial population are used to inform the baseline risks in the company's model, as done in TA379. The CS does not present overall survival for the subgroup of patients in the RCTs with FVC>80% predicted, either in the form of survival curves or as a hazard ratio. However, pooled Kaplan Meier survival curves from these RCTs and their open-label extension studies are provided for the subgroup with FVC >80% predicted in the company's response to clarification question B6.

A summary of the most frequently reported adverse events is shown in CS Table 38 stratified by baseline FVC >90% vs. FVC ≤90% predicted. The most frequently reported adverse events is shown in CS Table 38 stratified by baseline FVC >90% vs. FVC ≤90% predicted.

Additional HRQoL measures were recorded during the INPULSIS trials but are not presented in the CS for patients with FVC>80% predicted (e.g. UCSD-SOBQ, PGI-C and

CASA-Q cough score). NICE's preferred HRQoL tool, the EQ-5D, was measured in the INPULSIS trials but the CS does not present the change in EQ-5D over time for patients with FVC>80% predicted. Section 4.2.7.2 of this EAG report provides further details of how the trial-based EQ-5D data are used in the economic model.

A summary of the clinical outcomes in the INPULSIS-ON and TOMORROW open-label extension study is provided in Table 13.

Table 13 Outcomes reported in open label extension studies

Outcome	INPULSIS-ON	TOMORROW OLE
Efficacy	Annual rate of decline in FVC calculated over 192 weeks; absolute change in FVC (mL and % predicted) from baseline to week 192; number and rate of acute exacerbations; mortality over 5 years	Annual rate of decline in FVC from first drug administration until 15th October 2015;
		Overall survival; progression-free survival; incidence (and %) of patients with at least one acute IPF exacerbation; Annual rate of decline in DL_{CO}
Safety outcomes	Incidence of AEs (primary outcome)	Percentage of patients with at least one AE
HrQoL	Not reported	Not reported

Source: CS Tables 4, 6, 7, 19 & 20

EAG comment on outcomes assessment

Consistent with TA379, the company include efficacy, safety and HRQoL outcomes, appropriate to IPF. Presentation of survival data for the subgroup of patients with FVC >80% in the INPULSIS and TOMORROW RCTs would have been informative to assess the consistency between these trials.

3.2.4 Statistical methods of the included studies

3.2.4.1 Evidence submitted in TA379

The statistical approach used in INPULSIS and TOMORROW RCT was reported in the previous company submission (TA379).[1] The EAG considered the approach to be appropriate with the exception of the last observation carried forward imputation method for missing data for secondary outcomes in the TOMORROW trial. [7] We considered this method increased the risk of bias.

3.2.4.2 New evidence submitted

As described in section 3.2.3 of this report, the company has provided results of post-hoc subgroup analysis for selected outcomes in patients with FVC >80% predicted in the INPULSIS and TOMORROW RCTs. We assume that the same statistical approach has been applied to these analyses as was applied to analyses conducted in the whole trial population(s). However, we note that sensitivity analyses to account for missing data (e.g. using multiple imputation techniques) do not appear to have been provided for the post-hoc subgroup analyses. As often the case with subgroup analyses, results should be interpreted with caution due to smaller sample sizes. Similarly, tests of interaction between treatments and subgroups are likely to be underpowered to detect a difference in treatment effect between subgroups.

The statistical approach for the open-label extension studies is reported in CS Table 14 and in CS Appendix M. Sample size calculations and methods to account for multiplicity were not required for these studies due to their "descriptive" efficacy and safety analyses (CS page 306). No analysis for the subgroup of patients with FVC >80% predicted were conducted for the TOMORROW OLE study.

In **INPULSIS-ON** the outcomes were analysed as follows:

- The primary outcome was the incidence of adverse events during treatment period (up to 56.3 months in total). The CS reports that event rates per 100 patient exposure-years were calculated, however CS Table 39 appears to report simple percentages. Missing adverse event dates were imputed according to company conventions (not otherwise described).
- The annual rate of decline in FVC over the full 192 weeks of the extension was calculated using a similar approach to the analysis in the parent trial (random coefficient regression). This was compared numerically with the rate of decline during the parent trial. All patients with at least one post-baseline FVC measurement were included in the analysis. Missing data were not imputed for this outcome.
- Missing data on time to death and time to acute exacerbations were accounted for through censoring, however censoring rules are not presented in the CS.
- Analyses were based on patients who received at least one dose of nintedanib in INPULSIS-ON.

- Analyses were reportedly run separately for those patients who had received nintedanib in the parent trials and those who had received placebo, however CS Table 19 presents outcomes for the whole study population.
- Post-hoc subgroup analyses were conducted for patients with FVC ≤50% vs >50% predicted and for patients with an increase/no decline in FVC % predicted vs those with declines in FVC <10% and ≥10% predicted from baseline to week 24 (CS Appendix E).

In the **TOMORROW OLE** study:

- In keeping with the parent trial, a mixed model for repeated measures was used to estimate the annual rate of decline in FVC (primary outcome) using all available assessments from first drug administration in the extension study to trial database lock (15th October 2015), up to 61.8 months.
- Handling of missing data is not described in detail in the CS.
- Analyses were based on patients who received at least one dose of nintedanib in the blinded phase of the parent trial (period 1 of TOMORROW).
- Results are presented (CS Table 20) stratified by the parent trial treatment allocation and are given separately for the whole period from the start of parent trial to end of the OLE and for the OLE phase only.

EAG comment on study statistical methods:

The statistical methods used for the subgroup analyses mirrored that of the analysis of the whole trial population(s) in the parent RCTs and were generally appropriate. However, no sensitivity analyses were performed by the company to test the assumption that missing data on FVC was 'missing-at-random' (due to lack of power).

For the OLE studies, the analyses were largely descriptive and the statistical approach appeared to be appropriate to the outcomes measured.

3.3 Efficacy results of the intervention studies

3.3.1 Evidence submitted in TA379

The results from the INPULSIS and TOMORROW RCTs were discussed by the NICE appraisal committee and a summary of the evidence can be found in the ACD committee papers.[1] In the company's submission for TA379 three subgroup analyses from the INPULSIS trials were described:

- **FVC ≤70% versus >70% of predicted value** at baseline conducted for the primary and key secondary endpoints (prespecified; no numerical data were presented)
- **FVC >90% vs. ≤90% predicted value** at baseline (post hoc; numerical data presented for the primary outcome)
- **Emphysema vs no emphysema** at baseline (post hoc; no numerical data presented).

The overall conclusion from these analyses was no statistically significant differences in outcomes by subgroup.

The open label-extension studies were ongoing at the time of TA379 in 2016 and no evidence was available to inform decision making.

3.3.2 New evidence submitted

Subgroup analyses from the INPULSIS RCTs are reported in three places within the CS: section B.2.6, section B.2.7 and Appendix E. The company provided results from a post-hoc subgroup analysis in patients with FVC >80% predicted for the TOMORROW RCT in response to clarification question A9. The EAG's summary and critique of these subgroup analyses is presented in the next section (3.3.3) and additionally in Appendix 3 of this EAG report. We also summarise the results from the INPULSIS-ON and TOMORROW OLEs (section 3.3.4).

3.3.3 Post-hoc subgroup analyses from the RCTs: FVC ≤80% vs. >80%

Post-hoc subgroup analyses of the INPULSIS trials (reported in a conference abstract[17] and/or drawn from company unpublished data on file[13]) are presented for three outcomes: adjusted annual rate of decline in FVC, time to first acute exacerbation and adjusted mean change from baseline in SGRQ total score. These data are shown in Table 14. The company also shows the change from baseline in FVC over 52 weeks for these subgroups in CS Figure 5.

Table 14 Subgroup analyses by FVC% predicted ≤80% versus >80%

Outcome	baseline FVC >80% predicted			baseline FVC ≤80% predicted		
Adjusted annual rate of decline in FVC, mL/year	Nintedanib n=295	Placebo n=190	difference	Nintedanib n=343	Placebo n=233	difference
	-99.6	-228.0	128.4 mL (95% CI: 78.0, 178.8)	-125.7	-220.5	94.8 mL (95% CI: 48.3, 141.4)
	Treatment-by-time-by-subgroup interaction p=0.4959					
Time to first acute exacerbation	Hazard ratio: 0.49 (95% CI: 0.17, 1.35) in favour of nintedanib			Hazard ratio:0.72 (95% CI: 0.41, 1.27) in favour of nintedanib		
	Treatment-by-subgroup interaction p=0.6505					
Adjusted mean change from baseline in SGRQ total score at week 52	Nintedanib n=278	Placebo n=185	difference	Nintedanib n=331	Placebo n=228	difference
	2.99	4.05	−1.07 (95% CI: −3.45, 1.32)	4.04	5.71	−1.66 (95% CI: −3.97, 0.64)
	Treatment-by-subgroup interaction p=0.5814					
Source: CS text pages 62-64, CS Figure 4, CS Figure 6						

Post-hoc subgroup analyses of the TOMORROW trial were provided in response to clarification question A9 for the primary outcome only. The EAG notes that p-values here are nominal as this was not a prespecified analysis. Numerically, the greatest observed difference is for the nintedanib 150mg bd arm (-9mL decline in FVC/year) relative to placebo (-185mL decline in FVC/year) in patients with FVC >80% predicted (Table 15).

Table 15 Rate of decline in FVC (L/year) at 12 months* by FVC % predicted at baseline, observed cases (TOMORROW trial)

	Treatment	N patients in RS	N analysed patients	Adjusted rates (SE)**	Adjusted rates of difference (SE)**	95% CI	p-value***
FVC >80% predicted							
No	Placebo	47	45	−0.188 (0.049)			

	Treatment	N patients in RS	N analysed patients	Adjusted rates (SE)**	Adjusted rates of difference (SE)**	95% CI	p-value***
	Nintedanib 50mg qd	44	42	−0.219 (0.052)	−0.030 (0.071)	−0.170, 0.109	0.6718
	Nintedanib 50mg bid	41	41	−0.274 (0.050)	−0.086 (0.070)	−0.223, 0.051	0.2194
	Nintedanib 100mg bid	36	35	−0.221 (0.055)	-0.032 (0.074)	−0.177, 0.112	0.6607
	Nintedanib 150mg bid	45	44	−0.118 (0.055)	0.071 (0.074)	−0.074, 0.216	0.3384
Yes	Placebo	40	38	−0.185 (0.053)			
	Nintedanib 50mg qd	43	43	−0.133 (0.052)	0.053 (0.074)	−0.093, 0.199	0.4777
	Nintedanib 50mg bid	45	45	−0.154 (0.048)	0.031 (0.072)	−0.110, 0.172	0.6631
	Nintedanib 100mg bid	50	50	−0.124 (0.045)	0.062 (0.069)	−0.074, 0.198)	0.3733
	Nintedanib 150mg bid	41	40	−0.009 (0.053)	0.177 (0.075)	0.030, 0.323	0.0182

RS, randomised set (all randomised patients whether treated or not)
The p−value for the interaction FVC %pred > 80% * treatment for the model including the subgroup and the interaction term FVC %pred > 80% * treatment is: 0.1408.
* Based on visits up to visit 9
** Based on a Mixed linear regression Model repeated measures with terms for treatment*time, gender*age, subject effect, subject*time, treatment, (subject effect and subject*time random, all other effects fixed) and a variance component variance−covariance matrix
*** Nominal p−value
Source: Response to clarification question A9 received on 4th August 2022

3.3.4 Results from the open-label extension studies

3.3.4.1 Clinical outcomes from INPULSIS-ON

The company presents the clinical outcomes from the INPULSIS-ON study in CS Table 19:

- Participants treated with nintedanib for 52 weeks in the parent INPULSIS trials (not stratified by FVC % predicted) had an adjusted annual rate of decline in FVC of -113.6 mL.
- In comparison, over the 192 weeks of INPULSIS-ON, the adjusted rate of decline in FVC for all patients treated with nintedanib (i.e. also including placebo patients newly treated with nintedanib when they entered the open-label extension) was -135.1 mL.
- The company suggests that the 22 mL difference in the adjusted rate of decline at 192 weeks vs 52 weeks is not clinically meaningful because the minimum clinically important

difference in FVC% predicted of 2-6% would equate to 75-80 mL for patients in INPULSIS-ON. Our clinical expert agreed that this difference is not clinically meaningful.

In response to clarification question A8, the company provides further details of the rate of decline in FVC in INPULSIS-ON stratified by baseline FVC % predicted:

- This analysis showed a slightly higher rate of decline in the subgroup with FVC >80% predicted in INPULSIS-ON (-133.60mL) in the nintedanib group than observed for the same subgroup in the pooled INPULSIS trials (-99.57 mL) i.e., a difference of 34 mL.
- The company states that this is still a clinically insignificant difference (i.e. suggesting that the effect of nintedanib on slowing IPF progression persists over the longer-term), Again, our expert agreed this was not a clinically significant difference.

Additional outcomes are reported for INPULSIS-ON including post-hoc subgroup analyses of patients with FVC >50% predicted vs ≤50% predicted and patients with/without a decline in FVC ≥10% at the end of the INPULSIS parent trials. (CS text pages 73-74 and Appendix E).

3.3.4.2 Clinical outcomes from the TOMORROW open-label extension

The company presents the clinical outcomes from the TOMORROW OLE in CS Table 20.

- For participants who received nintedanib 150mg twice daily (licensed dose) in the 52-week TOMORROW RCT (period 1), continued to receive nintedanib during the blinded phase (period 2) and who then entered the open-label extension, the adjusted annual rate of decline in FVC was −125.4 mL/year (95% CI: −168.1 to −82.7).
- For participants who received placebo in the TOMORROW RCT (period 1), who were switched to nintedanib during the blinding phase (period 2) and who continued to receive nintedanib in the open-label extension, the adjusted annual rate of decline in FVC was −189.7 mL/year (95% CI: −229.8 to −149.6).

3.4 Safety results of the intervention studies

3.4.1.1 Safety outcomes from the RCTs

The safety results from the TOMORROW RCT and INPULSIS RCTs were provided for TA379 and can be found in the company's current submission in Appendix F. Diarrhoea was the most frequently reported adverse event in patients allocated to the nintedanib 150mg bd arm in the INPULSIS trials (398 patients; 62.4%) and the TOMORROW trial (47 patients; 55.3%).

The company presents two subgroup analyses of safety data (from the INPULSIS trials only) patients stratified by baseline FVC >80% vs. ≤80% predicted (Table) and by baseline FVC >90% vs. ≤90% predicted (see Appendix 9.3.4 of this report). A greater proportion of people receiving nintedanib in the baseline FVC >80% predicted subgroup experienced a severe or serious adverse event or an adverse event leading to treatment discontinuation. Adverse events rates were more comparable for the subgroup of patients with FVC ≤80% predicted. The EAG notes that a higher proportion of patients had one or more serious (or severe) adverse event in the subgroup with baseline FVC ≤80% predicted (nintedanib and placebo arms) compared to the FVC >80% predicted (nintedanib and placebo arms).

Table 16 Adverse events in INPULSIS trials by baseline FVC >80% vs. FVC ≤80% predicted

Event n (%)	Baseline FVC>80% predicted		Baseline FVC ≤80% predicted	
	Nintedanib (n=295)	Placebo (n=190)	Nintedanib (n=343)	Placebo (n=233)
AE(s)	277 (93.9)	167 (87.9)	332* (96.8)	211 (90.6)
Severe AE(s) [a]	76 (25.8)	30 (15.8)	98 (28.6)	69 (29.6)
Serious AE(s) [b]	80 (27.1)	44 (23.2)	114 (33.2)	83 (35.6)
Fatal AE(s)	11 (3.7)	6 (3.2)	26 (7.6)	25 (10.7)
AE(s) leading to treatment discontinuation [c]	66 (22.4)	14 (7.4)	57 (16.6)	40 (17.2)

Source: CS Table 37 edited by the EAG
Abbreviations: AE, adverse event.
[a] An event that was incapacitating or that caused an inability to work or to perform usual activities.
[b] An event that resulted in death, was immediately life threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonger hospitalisation, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.
[c] AEs leading to treatment discontinuation in >2% of patients in any treatment group.
* The EAG have corrected this value as per company response to clarification question A11.

3.4.1.2 Safety outcomes from the open-label extensions

The frequencies of adverse events in the INPULSIS-ON and TOMORROW OLE are summarised in Table 17. The proportions of patients experiencing severe or serious adverse events and events leading to discontinuation were higher in the OLE studies when compared to the parent trials. In keeping with the observations of the parent trials, diarrhoea was the most frequently reported adverse event in the INPULSIS-ON trial (519 patients; 70.7%) and

the TOMORROW-OLE (63 patients in nintedanib 150mg bd dose group; 74.1%). Again, event rates for diarrhoea were higher in the OLE studies compared to the parent trials. This could potentially be explained by patients switching from placebo to nintedanib begin to experience these adverse events in the extension.

Table 17 Adverse events in INPULSIS-ON and TOMORROW OLE

Event n (%)	INPUSIS-ON (n=734)	TOMORROW OLE	
		Nintedanib 150 mg Twice daily (n=85)	Comparator† (n=85)
≥1 AE(s)	723 (98.5)	84 (98.8)	83 (97.6)
≥1 Severe AE(s) [a]	412 (56.1)	41 (48.2)	50 (58.8)
≥1 Serious AE(s) [b]	506 (68.9)	47 (55.3)	55 (64.7)
Fatal AE(s)	Not reported	12 (14.1)	31 (36.5)
≥1 AE(s) leading to treatment discontinuation [c]	313 (42.6)	48 (56.5)	49 (57.6)

Source: CS Tables 39 & 40 edited by the EAG
Abbreviations: AE, adverse event.
[a] An event that was incapacitating or that caused an inability to work or to perform usual activities.
[b] An event that resulted in death, was immediately life threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonger hospitalisation, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.
[c] AEs leading to treatment discontinuation in >2% of patients in any treatment group.

3.5 Critique of the network meta-analysis (NMA)

3.5.1 Evidence submitted in TA379

In the absence of any head-to-head trials comparing nintedanib with pirfenidone, an NMA was constructed to allow an indirect comparison of these two treatments. The nintedanib outcome data used in the NMA were from the placebo-controlled INPULSIS I and II and TOMORROW trials. The pirfenidone comparator trials included in the NMA were also all placebo-controlled RCTs; therefore all comparisons were made via placebo. A total of nine outcomes were included in the NMA, of which six informed the economic model (mortality, acute exacerbations, loss of lung function, serious cardiac events, serious gastrointestinal events, overall discontinuations). For each outcome measure a series of scenario analyses examined the effect of removing specific studies from the analysis due to differences in potential effect modifiers (e.g. duration of disease).

3.5.2 Current NMA approach

The CS states that the NMA has not been updated from TA379 as no new relevant nintedanib RCTs were identified. Instead, "only results relevant to the scope of the decision problem are presented" (CS page 74). The EAG interprets this to mean that only results for the comparison of nintedanib vs placebo are given; results of the indirect comparison between nintedanib versus pirfenidone are not included as the latter is outside the current decision problem.

3.5.2.1 Outcome measures included

The economic model in the current submission uses the original (i.e. 2015) NMA effect estimates for the following outcomes: acute exacerbations, loss of lung function, serious cardiac events, serious gastrointestinal events and overall treatment discontinuation. Survival estimates in the model are no longer informed by the NMA – as we discuss below. The EAG cross-checked the NMA results presented in the current CS for the above outcomes with those reported in TA379 and found that they were consistent, as would be expected. (NB. We checked against the committee papers for TA379, noting that NMA results in the company submission for some outcomes were later superseded by corrected NMA results provided by the company in response to EAG clarification questions). The EAG assumes that given the absence of data from new trials, the company have retained the NMA estimates in order to maintain consistency with TA379.

In the current economic model a different approach is used to that of TA379 for extrapolating overall survival (OS). Individual parametric survival curves were fitted to both the nintedanib and placebo arms given some (inconsistent) evidence of an early proportional hazards violation (CS section B.3.3). Thus, the original NMA ORs for OS no longer inform the economic model (see section 4.2.6 of this report for further detail).

3.5.2.2 NMA patient population

The NMA patient population is people with IPF regardless of their baseline FVC % predicted value. We asked the company to rerun the NMA restricting the patient population to those with FVC >80% predicted, where feasible. The company declined, stating that "no significant treatment by subgroup interactions for the primary or secondary endpoints were observed hence the cost-effectiveness model is based on the treatment effect obtained from the NMA results for the overall population for nintedanib versus placebo" (clarification question response B11). However, in the CS the company also acknowledges that the INPULSIS trials were not designed to investigate the effects of nintedanib in subgroups and therefore

"the interaction tests were likely underpowered, and as such, lack of significance does not necessarily imply the absence of a true, underlying difference" (CS page 54). In the EAG's opinion it is plausible that the non-significant results of the interaction tests are due to lack of statistical power, a consequence of reduced numbers of patients in the subgroups. Therefore, we consider it equally justifiable to restrict the NMA to the FVC >80% predicted subgroup as it is not to restrict the NMA to this subgroup. In other words, both the EAG's and the company's preferred approaches to the NMA population should be considered.

3.5.2.3 Purpose of the NMA in the current appraisal

The above issues, however, are eclipsed by the conclusion we have reached which is that, given an indirect comparison between nintedanib against pirfenidone is no longer required, the NMA is effectively redundant. Instead, the EAG suggests that a pairwise meta-analysis of nintedanib versus placebo from the INPULSIS I and II and TOMORROW trials would be sufficient The company do not comment on the purpose of the NMA in the current appraisal, nor whether there are advantages or disadvantages from its inclusion. The EAG notes a potential benefit of the NMA is greater precision of effects from the increased number of placebo participants in the network (i.e. placebo participants from the INPULSIS and TOMORROW trials as well as the placebo participants from the pirfenidone trials). However, a potential disadvantage of the NMA is increased heterogeneity and consequent confounding of effects caused by differences between the nintedanib and pirfenidone trials in study characteristics. Moreover, the pirfenidone placebo trial arms do not include patients with FVC >80% predicted and thus could not be included in any NMA restricted to this subgroup. Hence, this is another reason why a pairwise nintedanib vs placebo comparison would be more appropriate to inform this appraisal.

EAG comment on the NMA

With the exception of survival, the company use the same NMA effect estimates from TA379 for the clinical effectiveness and safety outcomes in the base case economic model. The estimates are, therefore, based on the whole trial population rather than the FVC >80% predicted subgroup. Given that pirfenidone is no longer a relevant comparator treatment in the decision problem, the EAG suggests a more appropriate approach would be a pairwise meta-analysis of nintedanib versus placebo from the INPULSIS I and II and TOMORROW trials, stratified by FVC% predicted subgroups. The CS reports the results of the pooled analysis of the INPULSIS trials alongside the results of the NMA. The EAG notes that the results of these two sets of analyses (based on the whole trial population) are similar.

3.6 Additional work on clinical effectiveness undertaken by the EAG

None

4 `COST EFFECTIVENESS

4.1 EAG comment on the company's review of cost-effectiveness evidence

The company conducted a systematic literature review to identify cost-effectiveness studies and economic evaluations published since September 2014, which evaluated nintedanib and its comparators in adults with IPF. The company completed searches in relevant electronic databases, conference proceedings and Health Technology Assessment (HTA) databases (CS Appendix G 1.1). The electronic searches were supplemented by hand searching to identify other published or unpublished material (grey literature). The search strategy was not limited by country, language, study design or date, but the company limited their full text review of studies to those published in English (CS Appendix G1.1). Databases were searched on 14 January 2022. Eligibility criteria are described in CS Appendix G Table 145.

Six publications were included after full text screening; two were considered by the company as relevant to UK clinical practice: Rinciog et al. (2017)[18] and Loveman et al. (2014).[19]

Rinciog et al. conducted an NMA and developed a cost-effectiveness model assessing the cost-effectiveness of nintedanib vs. pirfenidone, N-acetylcysteine and placebo (best supportive care) for the treatment of IPF.[18] The evaluation used pooled patient-level data from three randomised RCTs of nintedanib: the phase II TOMORROW trial[20] and two phase III INPULSIS trials (INPULSIS-1 and INPULSIS-2[21]). In keeping with the decision problem, the CS discusses the results for the comparison of nintedanib versus best supportive care, but it includes patients with a starting FVC ≥50% predicted. Rinciog et al.[18] is the published version of the model submitted for the company's original submission for nintedanib (TA379).[1]

Loveman et al.[19] reports a systematic review and an economic evaluation of the clinical and cost effectiveness of IPF treatments, and this was discussed in the original CS in TA379. The current CS points out that the NMA and cost-effectiveness model did not include the INPULSIS[21] trials, and also that the estimated cost of nintedanib did not match the list price.

Consequently, the current economic evaluation follows the same approach used in TA379 as detailed in Rinciog et al.[18] with addition of evidence from the nintedanib OLE studies. The Rinciog et al.[18] publication does not include the stopping rule for patients treated with nintedanib whose predicted FVC falls by more than 10% in a year (as specified by the NICE recommendations in TA379 for nintedanib). The CS presents details of the study, and base-case results (Appendix G Table 148).

EAG conclusion

The company's review of the economic evaluation evidence was thorough and appropriate and the EAG is not aware of any additional relevant economic evaluations.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 18 shows the EAG's assessment of the concordance between the company's economic evaluation and the NICE reference case. We consider that the company's model is consistent with the reference case.

Table 18 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes
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.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other	Yes

	characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS: Personal Social Services		

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company proposes using the same Markov model in the current appraisal as previously developed for NICE TA379[1], in which a three-month cycle length is employed in line with observation periods in the clinical trials. Half-cycle correction was applied in the model. The company maintained that the original structure used in the TA379 economic model was appropriate for the current submission with the justification that survival evidence from long-term follow-up studies can be included without the need to alter the original model structure. The model, implemented using Microsoft Excel, represents IPF lung function decline using an established clinical measure, FVC% predicted, for the health states. FVC% predicted was selected to represent health states due to its consistent use in clinical trials in IPF patients and the ability to reflect the absolute state of patient condition in the model. Figure 1 depicts the company's model structure (CS Figure 10).

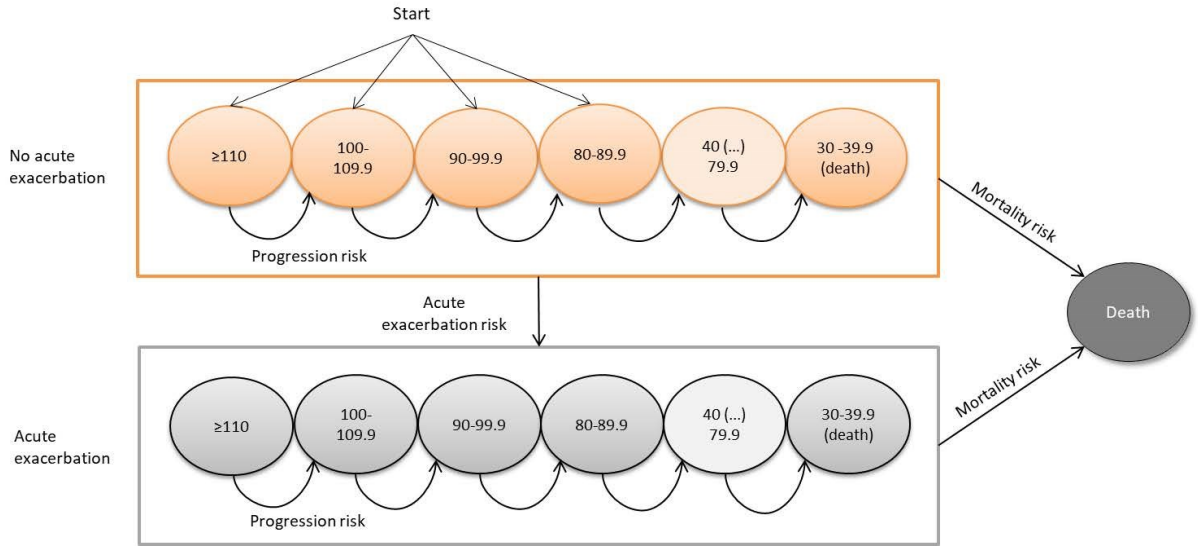

Figure 1 Model structure
Reproduced from CS Figure 10.

Health states are defined by 10-point percentage intervals in FVC% predicted from 30-39.9 to ≥110, with the lower FVC% predicted category representing death due to insufficient lung function. There are health states for patients who have not yet experienced an exacerbation event, and for patients who have experienced at least once exacerbation event. Patients who have exacerbations possess different health outcomes and costs compared with those who have not had an exacerbation. The final health states, death, is an absorbing state. Patients can move from their current health state to the death state at any point during the model.

At the start of the model, all patients begin in one of the non-exacerbation health states with FVC >80%. The distribution of patients among the initial four health states at the start of the model is based on the distribution of patients in the INPULSIS-1 and INPULSIS-2 trials,[21] detailed in Section 4.2.3. The starting age of all patients is stated as 66.75 years.

Patients can progress to different health states in the following ways: (1) loss of lung function; (2) exacerbation; (3) loss of lung function and exacerbation; and (4) death. Loss of lung function is a 10% decrease in FVC% predicted within 3 months (constant risk). Once a patient has progressed to a lower health state, i.e., a health state corresponding to a lower FVC% predicted category, the patient is unable to move back to a higher health state. Furthermore, once a patient experiences an exacerbation event and moves from a non-exacerbation health state to an exacerbation health state, the patient is unable to move back to a non-exacerbation health state. There is also an additional mortality hazard rate associated with patients in exacerbation health states; this parameter was not included in TA379. The model also allows for further adverse events including serious cardiac and gastrointestinal (GI) events, GI perforations, and mild-moderate diarrhoea.

The primary outcome measure of the economic model is incremental cost per QALY (ICER), although cost per life years (LYs) gained and exacerbation events avoided are also considered. In accordance with NICE IPF guidelines[22], the company did not explicitly model patients who transitioned from the FVC 40-49.9% predicted to the FVC 30-39.9% predicted health states, as the latter health state is assumed to be an unsustainable level of lung function; thus, the 30-39.9 health state is considered as representing death. The company assumes independence between mortality and loss of lung function in order to avoid double counting as the overall survival data includes all deaths. The EAG considers this to be a reasonable approach.

EAG comment on model structure

The economic model structure in the current appraisal is based on the model previously accepted by the NICE appraisal committee in TA379.[1] The EAG has no concerns regarding the model structure currently presented.

4.2.3 Population

The modelled population is adults with IPF. The analysis uses pooled data from the phase III INPULSIS 1 and 2 RCTs, the INPULSIS-ON OLE study, the phase II TOMORROW RCT and the TOMORROW OLE study. The baseline characteristics of the nintedanib and placebo patients are shown in CS Table 45. The baseline age in the model was 66.76 years. In accordance with the NICE scope for this appraisal, patients entering the model had an FVC >80% predicted. The distribution of FVC% predicted thresholds at baseline is shown in Table 19 (CS Table 60).

Table 19 Distribution of FVC % predicted in patients at the start of the model

Health state (FVC% predicted)	Distribution (%)
≥110	13.14%
100-109.9	16.43%
90-99.9	27.10%
80-89.9	43.33%
40-79.9	0.00%

Reproduced from CS Table 60.

EAG comment on model population

The EAG agrees that the economic model uses a population consistent with the NICE scope for this appraisal.

4.2.4 Interventions and comparators

The economic model compares the incremental cost effectiveness of nintedanib 150 mg twice daily to best supportive care. The intervention and comparator are consistent with the NICE scope.

4.2.5 Perspective, time horizon and discounting

The company analyses take the perspective of the NHS and Personal Social Services (PSS) in England, which aligns with the NICE manual for health technology assessments.[23] Costs and outcomes (life years and QALYs) are discounted at 3.5%. The company uses a lifetime horizon to reflect the chronic nature of IPF, where lifetime is assumed to be 50 years from the start of the model. Given that the starting age of the patient population is approximately

67 years, a shorter time horizon of 35 years is deemed more appropriate and used in the EAG base case analyses in section 6.1.

4.2.6 Treatment effectiveness and extrapolation

The clinical effectiveness parameters used in the model consist of OS, acute exacerbation, loss of lung function, treatment discontinuation and adverse events. Data from these studies have been taken from the TOMORROW trial and extension study, INPULSIS 1 and 2 trials, and the INPULSIS-ON extension study. More details on the extension studies are given in section 3.2 of this report. All the data used for the clinical effectiveness parameters were from the full trial populations, rather than for the FVC >80% predicted subgroup. The EAG considers that OS estimates for this subgroup should be included in the analysis to reflect the lower mortality rate for these patients.

4.2.6.1 Mortality (overall survival)

The company checked whether the proportional hazards (PH) assumption is supported by visual inspection of the log-cumulative hazard plot (CS Figure 13) and assessment of the Schoenfeld residuals. They concluded that the PH assumption does not hold as the lines in the figure are non-parallel and therefore the ratio of the hazard rates between arms does not remain constant over the follow-up period. As the PH assumption does not hold, independent parametric models were fitted for each treatment arm for OS.

The pooled Kaplan-Meier (KM) survival curves for nintedanib and placebo are shown in Figure 2 (CS Figure 12). The duration of follow-up for nintedanib is approximately 5.5 years which is longer than it was in the original appraisal in 2016 (NICE TA379). Further, nintedanib has markedly better survival probability than was predicted in the previous appraisal at 5 years (60% vs 40%).

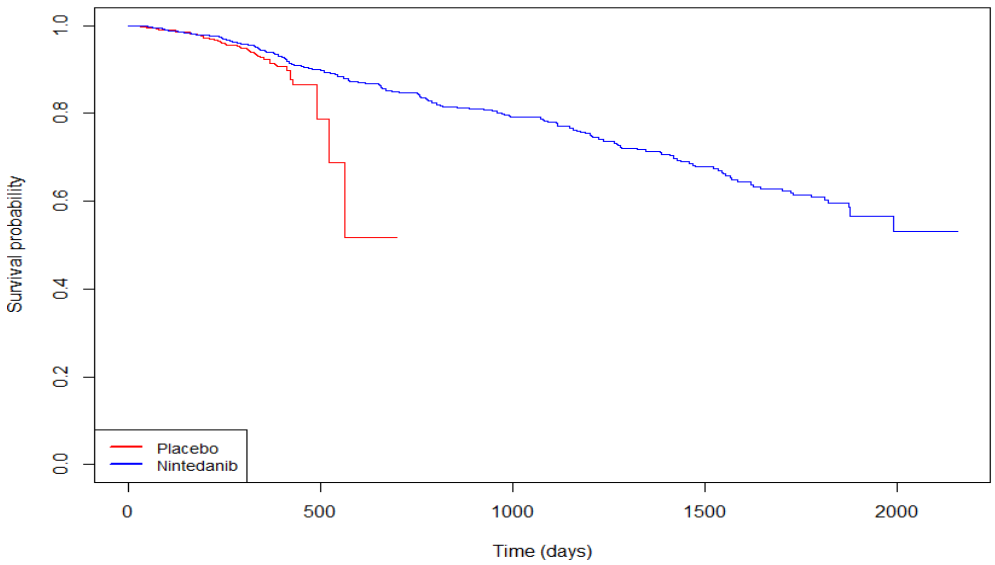

Figure 2 Kaplan-Meier curves of overall survival for nintedanib vs placebo

Reproduced from CS Figure 12

The parametric models, fitted using R software, were: exponential, Weibull, log-logistic, Gompertz, lognormal and generalised gamma. Goodness of fit was assessed using visual inspection and statistical fit using Akake/Bayesian Information Criterion (AIC/BIC). The AIC/BIC values are shown for both treatment arms in CS Tables 47 and 48.

In the nintedanib arm, the models with the best fit by AIC/BIC are the log-logistic, Weibull and generalised gamma. For the placebo arm, the models with the best fit are the Gompertz, Weibull and log-logistic. As the trial data available for the placebo is only 52 weeks, the company also compares the model fit with external data from a study of risk factors for acute exacerbations in IPF by Kondoh et al[24] (CS Figures 15 and 16) and an Australian IPF registry[25] (CS Figure 22). The CS states that in TA747, clinical experts and the NICE committee agreed that the Australian registry was most representative of UK clinical practice. The company concludes that the log-logistic model is the most suitable and used this in their base case. The parameter values for the parametric models are shown in CS Table 49 and 51. The CS also compares data from other international registries and these are discussed in more detail in section 5.3.3.

The EAG agrees with the log-logistic parametric model chosen for OS based on the statistical fit and visual fit to the Australian IPF registry and the Kondoh et al.[24] study. The extension studies report follow-up data for nintedanib in excess of five years, which provides more certainty in this treatment arm. The EAG also notes that the trial results are consistent with those from the Australian IPF registry for the nintedanib arm. The duration of follow-up

data for the placebo arm, however, remains relatively short at under two years. The EAG agrees that survival for placebo patients is likely to be similar to that reported in the Australian IPF registry.

In addition, the company has included a hazard ratio (HR) for the risk of mortality for patients who have had an exacerbation (not previously included in TA379). A HR of 1.395 was applied to these patients, based on the study by Kondoh et al.[24] which reported a HR of 2.79 for a six-month period; the company halved this value to account for the 3-month cycle length. The EAG considers it is appropriate to include a HR for these patients, however it is inappropriate to divide the hazard ratio by two as the HR is independent of time. The EAG notes that the HR from Kondoh et al[24] is consistent with a study by Kakugawa et al.,[26] which investigated risk factors for acute exacerbations in patients with IPF.

4.2.6.1.1 Mortality for the FVC >80% predicted subgroup

The EAG requested further information on the OS estimation of patients with a baseline FVC >80% predicted (clarification questions B5 and B6). The company provided a Kaplan-Meier plot for the overall population and patients with baseline FVC >80% predicted, reproduced in Figure 3 (clarification response document Figure 4). As with the full dataset, there are only 52 weeks follow-up for the placebo arm and more than five years follow-up for the nintedanib arm.

The company fitted parametric survival curves independently to the nintedanib and placebo (best supportive care) treatment arms using the methods described above. The log-logistic model was selected based on AIC/BIC statistical criteria and visual inspection. The parameters for the parametric models are shown in Tables 10 and 11 in the clarification response document. The company conducted a scenario analysis using the log-logistic, Weibull and lognormal parametric models. The resulting ICERs ranged from [redacted] to [redacted] per QALY.

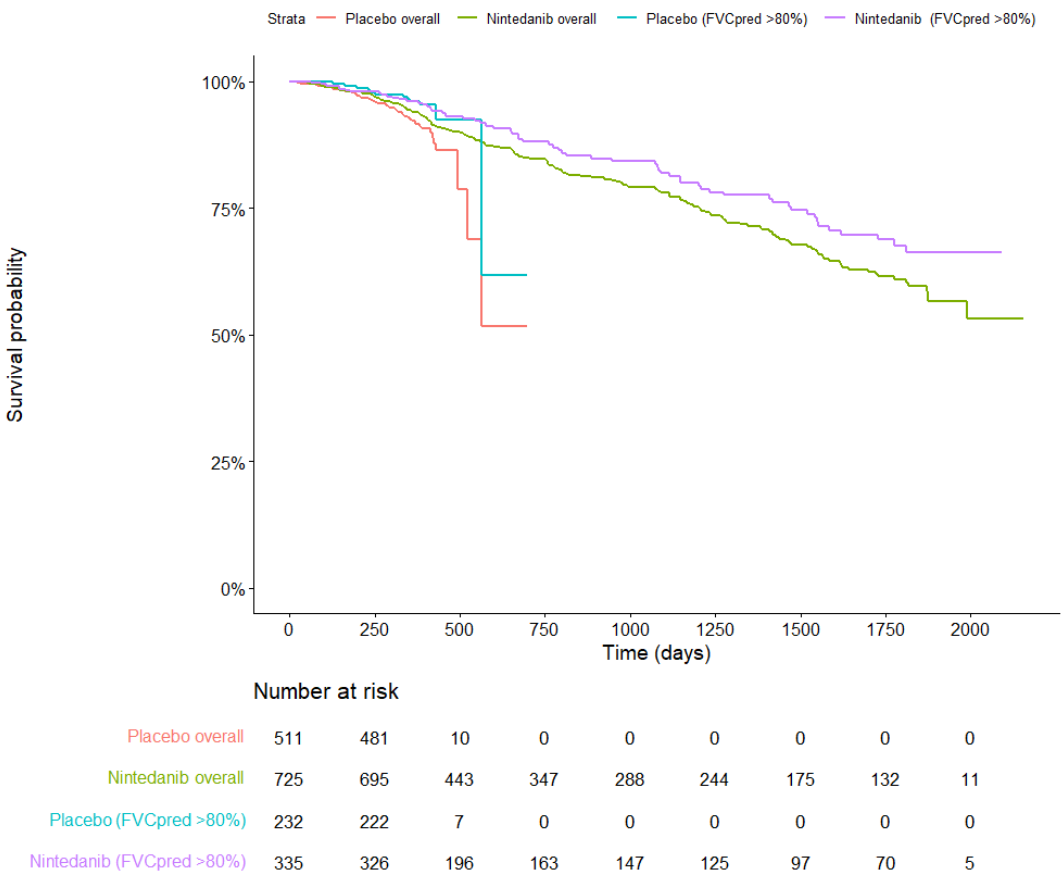

Figure 3 Kaplan-Meier curves for the overall population and patients with baseline FVC >80% predicted

Reproduced from Figure 4 of company clarification response document.

The clarification response document specifies how the OS curve for the placebo arm was fitted. However, the long-term extrapolation is uncertain due to the fact there is only one year follow-up data. The EAG notes that there is no difference between the OS curves for the nintedanib and placebo arms in the FVC >80% predicted subgroup for the first 52 weeks.

For the nintedanib arm, the EAG agrees with the company's fitted curve. Based on no difference between the OS curves in the KM data (Figure 3), the EAG assumes that mortality is initially the same for the best supportive care arm and the nintedanib arm in the FVC >80% predicted cohort. The initial mean FVC % predicted of the cohort is 95% and declines over time. When the modelled cohort reaches the same FVC % predicted as the whole trial population (FVC = 79%), we assume the best supportive care OS curve has the same survival as the whole trial population. Therefore, from this point the best supportive care arm uses the whole trial parametric curve. We estimate it to be 5.5 years before the mean FVC for the cohort is the same as the whole trial FVC.

A study by Jo et al.[25] reports the OS of a cohort with mild impairment (FVC>80%) in the Australian IPF registry (median follow-up 2.1 years). Of this cohort, 25% were receiving anti-fibrotic therapy. We compare the modelled survival for best supportive care using the company and EAG assumptions against this study (Table 20). The company's estimate for survival over four years is notably lower than the survival data from the Australian registry.[25]

Table 20 Company and EAG OS estimates for FVC>80% subgroup vs Australian IPF registry (mild[a] patients)

Year	Australian IPF registry (mild FVC)[25] OS	Company base case for BSC OS	EAG base case for BSC OS
0	100	100	100
1	99	96	96
2	89	80	88
3	73	58	79
4	71	39	70

[a] Patients were classified as 'mild' if FVC ≥80%

BSC, best supportive care; OS, overall survival

4.2.6.2 Acute exacerbations

The risk of first acute exacerbation was estimated from the INPULSIS trials. The company considered the risk was best represented as a constant risk. The exacerbation risk was 1.47% per 3-month cycle for the placebo arm for the adjudication committee estimate and 1.97% for the investigator-reported estimate. In the base case analysis, the adjudication committee-reported exacerbation risk was used, while the investigator-reported value was used in sensitivity analyses. The EAG notes that the investigator-reported value was used in the base case in the previous appraisal TA379.

The risk of exacerbation for nintedanib was informed by the NMA ORs applied to the baseline placebo risk. The OR value for nintedanib vs placebo is 0.56 (95% CI 0.35 - 0.89). (CS Table 59).

4.2.6.2.1 Acute exacerbations for the FVC >80% predicted subgroup

In response to clarification question B9, the proportion of patients with an acute exacerbation and the hazard ratio for time to first exacerbation event in patients with FVC above and below 80% predicted is shown in Table 15 of the company clarification response document.

The company comments that acute exacerbations were a rare event in the overall population in the INPULSIS trial and even more so in the subgroup with the FVC >80% predicted. For this reason, they did not consider it possible to run a scenario based on acute exacerbations in the subgroup with FVC >80% predicted. The subgroup analyses for FVC% predicted ≤80% versus >80% are shown in section 3.3 of this report.

The EAG agrees with the company that there is uncertainty in the results of the subgroup analyses due to the low number of events in the trials. Further, we note some unexplained inconsistencies in HRs between the FVC% predicted subgroups. For example, the HR for time to first acute exacerbation for the comparison of nintedanib versus placebo varies from 0.46 in the FVC >90% predicted subgroup, to 0.49 in the FVC >80% predicted subgroup and to 1.00 in the FVC >70% predicted subgroup. Clinical advice to the EAG is that although lower FVC (more severe IPF) is a recognised risk factor for acute exacerbation at any disease stage the actual HR benefit is most likely comparable. Hence, the HRs for the >90% and <80% FVC subgroups seem, in his opinion, more realistic. We therefore base the risk of exacerbation for nintedanib versus placebo on the whole trial population and the risks estimated for the subgroups in the EAG base case scenarios. The acute exacerbation probability per 3-month cycle for the best supportive care arm is 1.05% for the FVC >80% predicted subgroup and 2.58% for the FVC ≤80% predicted subgroup.

4.2.6.3 Loss of lung function

The company defines loss of lung function as a 10-point drop in FVC% predicted. Patients entered the model at different FVC% predicted health states to reflect the INPULSIS clinical trial as shown in CS Table 60. Lung function decline, with and without exacerbation, was incorporated using a logistic model derived from a logistic regression of the phase III clinical trial data. In both cases (i.e., with and without exacerbation), there was a diminishing effect in progression with loss of lung function; that is, the probability of progression was lower for patients with lower FVC% predicted. However, the absolute risk of progression was significantly higher when there was an exacerbation. This is graphically presented in CS Figure 29.

The risks associated with loss of lung function for nintedanib were obtained by applying ORs from a NMA to the baseline risk from the INPULSIS trials, assuming a constant hazard over time. The OR estimate for nintedanib vs placebo was 0.54 (95% CI: 0.42 to 0.69). The company investigated whether the rate of decline of lung function would be similar for the >80% predicted group. The CS states that the probabilities of progression were similar,

though slightly lower, in the >80% predicted group (CS Figure 30). The progression probabilities for the >80% predicted group were examined in a sensitivity analysis. The EAG agrees that the probabilities of progression are similar for the FVC >80% predicted group and it is reasonable to use the lung function decline from the whole population.

4.2.6.4 Treatment discontinuation

The company estimates overall discontinuation risk for the baseline best supportive care arm to be 5.5% per cycle. The associated risk for nintedanib (OR 1.42; 95% CI: 1.08 - 1.87) was calculated by applying ORs obtained from all trial evidence from the NMA to the baseline risk. The company assumes that patients would not discontinue from best supportive care, but they used this discontinuation risk to estimate the relative discontinuation risk in patients receiving nintedanib.

The company estimated the discontinuation rate for the FVC >80% predicted subgroup in response to clarification question B9. The discontinuation rate for this population is 3.8% per cycle for best supportive care. The EAG have included this discontinuation rate in our scenario analyses in section 6.2.2.

4.2.6.5 Treatment stopping rule

In TA379 the NICE committee recommended that nintedanib should be subject to a stopping rule for those patients whose FVC % predicted declines by 10% in a year. In the current CS the company dispenses with this stopping rule on the basis that:

- It was implemented to be consistent with the stopping rule for pirfenidone. However, pirfenidone is not a comparator in the current appraisal.
- Expert clinical advice to the company was that a stopping rule according to the above criteria would be difficult to impose.
- In NICE TA747 the appraisal committee noted that clinicians would stop treatment in patients with rapid disease progression, hence a stopping rule was not required.

Clinical advice to the EAG agrees that this stopping rule, based on a decline of FVC alone, is not used in routine clinical practice. The EAG notes that in TA379 the base case ICERs were not considered cost effective without the stopping rule. As discussed above in section 4.2.6.1, the OS data for nintedanib shows better survival than predicted in the previous appraisal at 5 years (60% vs 40%). Given the improvement in OS since that appraisal, the stopping rule may not be necessary, [redacted], due

to the improvement in cost effectiveness. The EAG has included scenarios using the company corrected model and the EAG base case in sections 5.3.4.1 and 6.2.2 respectively.

4.2.6.6 Adverse events

The CS model included AEs which had a substantial impact on costs and QALYs, had an incidence of more than 5%, or an incidence 1.5 times greater than the comparator arm. Serious cardiac events and serious GI events were included in the analysis. Gastrointestinal perforations were also included, based on their clinical importance.

The incidence of each of the serious AEs were estimated from the best supportive care arm and their associated risks for nintedanib were measured using OR values from the NMA presented in CS Table 71. Following recommendation from the NICE committee in TA379, mild-moderate diarrhoea was also included (CS Table 72).

EAG comment on treatment effectiveness and extrapolation

The company uses clinical effectiveness data for the whole trial population in their base case analysis, rather than using data for the FVC >80% predicted subgroup. The EAG considers that overall survival for this subgroup should be included in the analysis to reflect the lower mortality rate for these patients. The extrapolation of the best supportive care curve is uncertain, because patients receiving placebo were only followed up for 52 weeks in the trial. The EAG suggests an alternative assumption for modelling best supportive care whereby the initial mortality is equal for both treatment arms. Clinical effectiveness data for acute exacerbations and discontinuation are more uncertain and the EAG suggests the whole trial population effectiveness data may be appropriate for these parameters.

4.2.7 Health related quality of life (HRQoL)

4.2.7.1 Systematic literature review for utilities

The company conducted a systematic literature review in January 2022 to identify studies published since August 2014 that evaluated HRQoL in patients with IPF (CS Appendix H). The search strategy and database searches were in line with those for the cost-effectiveness review (CS Appendix G1.1). In addition, clinical trial databases were searched to identify ongoing and recently completed studies that met the inclusion criteria for the review. Eligibility criteria are given in CS Appendix H Tables 153 and 154.

Nine publications were identified after full text screening. Three studies reported HRQoL outcomes and health state utility values for relevant health states (including FVC% predicted status and adverse events of interest).[18,27,28] All three studies derived utility values from analysis of patient-level EQ-5D-3L data from the INPULSIS trials.[21] Two studies used UK preference weights to derive utilities: one was a cost-effectiveness analysis developed from the Belgian healthcare payer perspective,[28] and Rinciog et al. was a cost-effectiveness analysis from the UK NHS and Personal Social Services perspective.[18] The utility values reported were the same in both studies, so the company focusses on the analysis conducted from the UK perspective. Rinciog et al. presented utilities by FVC % predicted status, acute exacerbation-related disutility and adverse event-related disutility.[18] These values are used in the model in the current submission.

4.2.7.2 Study-based health related quality of life

The utility values applied in the model are utilities by FVC % predicted status, acute exacerbation-related disutility and adverse event-related disutility. FVC % predicted health state utility values were taken from EQ-5D 3L data from the INPULSIS trials[21] (CS B.3.4 table). These utility values were previously used in TA379.[1] They are described in CS section B.3.4 and were discussed in section 4.2.5 of the EAG report on the company's original nintedanib submission in 2015.

The economic model includes adverse events that had a substantial impact on costs and QALYs, had an incidence of more than 5% or an incidence 1.5 times greater than the comparator arm. These are: serious gastrointestinal events; serious cardiac events, gastrointestinal perforation and, at the request of the NICE Committee in TA379, mild-moderate diarrhoea.

Acute exacerbations were associated with disutility, estimated from the INPULSIS trials[29] (CS section B.3.4, CS Table 86). The model uses the investigator reported exacerbation rate in the base case and explores the effect of the adjudicated committee exacerbation disutilities in a sensitivity analysis. These disutility values were previously used in TA379 and are shown in CS Table 84.

Utility decrements for serious cardiac events, and gastrointestinal perforation were obtained from a retrospective analysis of a UK database (CS section B.3.4, CS Table 87).[30] The company's search strategy did not identify any utility values for skin disorders, dizziness or anorexia. The EAG repeated the search and concludes that there are no missing sources.

Disutility values for the adverse events are given in Table 21 (CS section B.3.4, Table 87). Disutilities associated with adverse events were based on TA379 (shown in column 2), but the duration was reduced from one year to one month (column 3) following EAG and NICE Committee feedback during the TA379 appraisal. Disutility due to diarrhoea used the same assumptions as those in TA747 (nintedanib for progressive fibrosing interstitial lung diseases[22]) and was applied for one month.

TA379 reported disutility values for skin disorders, based on the study by Ara and Brazier.[30] These utility decrements are not reported in the current CS as rashes were an adverse event associated only with pirfenidone, not nintedanib. The EAG agrees this approach is appropriate.

Table 21 Adverse events-related disutility

Event	Mean value (2015)	Mean value (2022)	Source
Serious cardiac events	-0.198	-0.0165	Ara and Brazier[30]
Serious GI	-0.068	-0.0057	INPULSIS 1 and 2[29]
GI perforation	-0.118	-0.0098	Ara and Brazier[30]
Mild-moderate diarrhoea	N/A	-0.0028	Assumption: 50% of serious GI events[22]

Reproduced from CS Table 158 and adapted by the EAG
GI: gastrointestinal; N/A: not applicable.

EAG comment on HRQoL

The company's utility values used for FVC% predicted health states and disutilities for acute exacerbations have not been changed from the previous nintedanib submission (TA379) and were previously accepted by the NICE Committee.

The utility decrements for acute exacerbations presented in the CS were taken from the INPULSIS trials. The EAG were unable to find any alternative sources of disutility for acute exacerbations.

The disutilities calculated for adverse events are appropriate, following the changes to the duration for which they are applied, reflecting committee recommendations in TA379. Disutilities for mild-moderate diarrhoea have also been included following NICE committee comments in TA379 and use the same values as were used for TA747.

4.2.8 Resources and costs

4.2.8.1 Resource use review

The company completed a systematic literature review in January 2022 to identify costs and healthcare resource use (published since September 2014) evaluating nintedanib and its comparators in adults with IPF. The search strategy and database searches are described in CS Appendix G1.1; these were supplemented by hand-searching published and unpublished material and searching appropriate registries and clinical trial databases. Eligibility criteria are given in CS Appendix I Table 164.

Following full text screening, 16 articles were included in the review, of which three were relevant to UK clinical practice.[31] Two studies reported costs associated with the treatment of IPF as part of an economic analysis, [18,31] previously discussed in section 4.1. Cost inputs (values, sources, and assumptions) used by Rinciog et al.[18] are presented in CS Appendix I Tables 168. Diamantopoulos et al.[32] conducted a retrospective analysis of 1,014 patients from the INPULSIS trials to evaluate how many hospitalisations and physician visits patients experienced over three months, and the results are presented in CS Appendix I Table 169.

4.2.8.2 Drug acquisition costs

The list price of nintedanib is £2151.10 for a 30-day supply of 60 capsules (150mg each). Dosage is two capsules a day (150mg bd), giving a cost of £71.70 per day. Nintedanib is available with a patient access scheme (PAS) price discount of [redacted], lowering the cost to [redacted] per day. The company does not associate a cost with best supportive care, because this was the placebo (control) arm of the trial. Nintedanib is taken orally and there are no associated administration costs.

4.2.8.3 Health state unit costs and resource use

The company's economic model includes the following components:

- Drug acquisition costs
- Liver function test costs
- Patient monitoring (background follow-up) costs (hospitalisation, emergency department visits, GP visits, specialist visits, physiotherapist visits, chest HRCT [high-resolution computerised tomography], chest X-ray, oxygen requirement assessment, bronchoalveolar lavage, CT [computerised tomography] pulmonary angiogram, right heart catheterization procedure, and general diagnostic procedures (e.g. bronchoscopy)
- Oxygen use costs

- Treatment-related adverse event costs
- Acute exacerbation costs (hospitalisations, emergency department visits, GP visits and specialist visits)
- End-of-life palliative care cost

Costs were calculated using UK unit cost data from the National Schedule of Reference Costs (2019-20)[33] and the PSSRU Unit Costs of Health and Social Care[34] inflated to 2020/21 values using appropriate inflation indices.[34]

The economic model uses resource data obtained from a post-hoc analysis of patient-level data from the INPULSIS trials.[29] The company analysed and adjusted health care resource use data for the model health states (FVC % predicted groups) and calculated the probability of the resource usage within a 3-month cycle. The number of resource use observations for each FVC % predicted group is shown in CS section B.3.5, Table 89.

The costs for patient monitoring for each health state were calculated as a 3-month probability of using each resource (hospitalisation, emergency department visits, GP visits, etc), weighted by the number of patients in each FVC % predicted group. Total per-cycle and annual monitoring costs for each FVC % predicted group are given in CS section B.3.5, Table 104.

The NICE draft clinical guideline for the diagnosis and management of suspected IPF states patients with IPF should receive long-term oxygen therapy to prevent resting hypoxemia.[35] The CS highlights those patients with FVC >80% predicted would not require oxygen supplementation.

The model uses the safety data set from the INPULSIS trials[29] to determine the probability of patients visiting the hospital, the emergency department, a GP, and a specialist following an acute exacerbation within a 3-month cycle. The total exacerbation cost and breakdown by health care resource are shown in CS section B.3.5, Table 108. The model uses a total exacerbation cost (£4,628) for patients in both trial arms (placebo and nintedanib) who experience a new exacerbation.

The model assumes that all patients receive palliative care (in addition to ongoing monitoring) for the last year of their lives. The cost for end-of-life care consists of hospice and home care (excluding hospital) and was estimated to be £3,037.50 per 3-month cycle (the average cost of hospital and social care for the final year of life is £12,150).[34]

Evidence from the TOMORROW[20] and INPULSIS trials[21] shows that patients taking nintedanib can experience elevated liver enzyme levels. Consequently, the company model assumes all patients on active treatment would have routine liver function tests every three months.

EAG comment on resources and costs

Costs for each FVC % predicted group were calculated in the same manner as in TA379 and TA474, which had been accepted by the NICE appraisal committee. Costs have been inflated to 2020/21 values appropriately. Resource use data given in the CS were obtained from individual patient level data from the INPULSIS trials (this is the same approach used for TA379) and are relevant to the clinical pathway of patients with IPF. The EAG are not aware of any other source of resource use data for this patient group.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company reports their base case cost-effectiveness results in CS Tables 115 and 116 using the list price and Patient Access Scheme (PAS) price respectively. Table 22 and Table 23 below present the base case results using the list price and PAS price for nintedanib, respectively.

Table 22 Base case results for nintedanib vs. best supportive care (using list price for nintedanib)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£19,262	4.08	3.21				
Nintedanib	£89,177	7.40	5.69	£69,915	3.32	2.49	£28,094

Reproduced from CS Table 115.
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

Table 23 Base case results for nintedanib vs. best supportive care (using PAS price for nintedanib)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£19,262	4.08	3.21				
Nintedanib	[redacted]	7.40	5.69	[redacted]	3.32	2.49	[redacted]

Reproduced from CS Table 116.
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

The base case results show that nintedanib offers a mean QALY gain of 2.49 for an additional mean cost of £69,915 (list price) and [redacted] (PAS price) versus best supportive care, producing ICERs of £28,094 and [redacted] per QALY gained respectively.

5.2 Company's sensitivity analyses

5.2.1 Deterministic sensitivity analyses

The company reports results from their deterministic sensitivity analyses with the PAS discount applied, in CS Table 129, CS Figure 40, and CS Figure 41. Fourteen scenarios were considered for the one-way sensitivity analysis across four main parameters: probabilities, costs, utilities and adverse events, listed in CS Table 121. The variations in input parameters were based on the 95% confidence intervals. The company's results indicate that the discontinuation probabilities and mortality probabilities due to exacerbation are the main drivers of the model results, increasing the ICER to [redacted] and [redacted] per QALY respectively. The maximum range of the ICER in the one-way sensitivity analysis results ranges from [redacted] to [redacted] per QALY (using the PAS price for nintedanib).

[redacted]

5.2.2 Scenario analyses

The company considers 19 distinct scenarios for their scenario analyses, described in CS Tables 122 to 128, numbered from 15 to 33. The scenarios cover seven parameter groups: overall survival, exacerbations, loss of lung function, adverse events, costs, discontinuation, and FVC% predicted categories. Many of the scenarios explored involve implementing alternative odds ratios obtained from published literature.

Changing the choice of parametric distribution from the log-logistic model to the generalised gamma distribution for both nintedanib and best supportive care (scenario 16) had the largest effect on the ICER, reducing the ICER to [redacted] per QALY. All other scenarios did not have a substantial impact on the ICER. In these scenarios, the ICERs ranged from [redacted] per QALY when transition probabilities for FVC >80% predicted and an alternative odds ratio for nintedanib were used (scenario 24) to [redacted] per QALY when the exacerbation coefficient was included (scenario 21).

5.2.3 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) with input parameter distributions as presented in CS Table 117. The results from 1,000 iterations are reported in CS Table 120, whilst CS Figures 38 and 39 depict the scatterplot and cost-effectiveness acceptability curve (CEAC), respectively. The company assigns a multivariate normal distribution to overall survival and loss of lung function baseline transition, a beta distribution to exacerbation and discontinuation baseline transitions, adverse event risks, health state utilities and disutilities, and resource use proportions, and a lognormal distribution to costs and resource use. The EAG confirms that the probabilistic results are similar to the deterministic results.

5.2.4 Company base case results for FVC >80% predicted subgroup

In reply to clarification question B5, the company provided results for the FVC >80% predicted subgroup. The analysis used the log-logistic model for OS using the parameter values in Tables 10 and 11 of the clarification response document.

Table 24 Company results for nintedanib vs. best supportive care with OS for FVC >80% predicted subgroup (using PAS price for nintedanib)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£18,724	3.87	3.06				
Nintedanib	[redacted]	8.50	6.51	[redacted]	4.63	3.44	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

The FVC >80% predicted subgroup results have an ICER (with PAS) of [redacted] per QALY (Table 24Table 24). The company provides scenario analyses using the Weibull and

lognormal model. The ICERs using the Weibull and lognormal models were [redacted] and [redacted] per QALY respectively.

The company were asked to consider scenario analyses using baseline transition probabilities for acute exacerbation, treatment discontinuation, and loss of lung function outcomes for the FVC >80% predicted subgroup. The company did not run any scenarios based on acute exacerbations in the subgroup with FVC >80% predicted, because acute exacerbations were a rare event in the trials, especially in the FVC >80% predicted population (seven (2.4%) patients in nintedanib group and eight (4.2%) patients in the best supportive care group).

However, the company conducted a combined scenario concerning the probabilities of treatment discontinuation and loss of lung function for this subgroup. As in their base case analysis they assumed a constant risk of discontinuation. The company estimates the coefficient for the risk of discontinuation in the best supportive care group to be 7.777, corresponding to a discontinuation rate of 3.75% per 3-month cycle. The probability of discontinuation for patients taking nintedanib was informed by the odds ratio (OR) from the NMA (1.42), which was applied to the baseline best supportive care risk.

For loss of lung function, the company uses the overall trial OR for nintedanib vs placebo (OR = 0.54) and an OR of 0.50 which was derived from the subgroup with FVC >80% predicted (combined scenario 2 in Table 25). Both combined scenarios produce an ICER below [redacted] per QALY.

Table 25 Combined scenario analyses for nintedanib vs best supportive care: treatment discontinuation and loss of lung function derived from the FVC >80% predicted subgroup

Combined scenarios	Coefficient for discontinuation hazard rate	ICER (with PAS)
1) Treatment discontinuation and loss of lung function with base-case OR=0.54 for loss of lung function applied to nintedanib	7.777	[redacted]
2) Treatment discontinuation and loss of lung function with scenario 24 OR=0.50 for loss of lung function applied to nintedanib	7.777	[redacted]
Reproduced from Table 16 in the company clarification response document		

5.3 Model validation and face validity check

5.3.1 Company's model validation

The company states their approach to model validation in CS Section B.3.14. They report that the model structure, approaches, inputs and assumptions were validated as follows:

- Clinical expert advisory board[36] (April 2014), which included two clinical experts to validate the assumptions within the model and the model structure, to ensure that the model adheres to the clinical course of the disease and reflects current clinical practice.
- Validation by model developers: a senior modeller within the model developer's organisation (with no involvement in the development of the model for nintedanib) performed a detailed QA check on the model.
- Validation by the company: involved increasing and decreasing various parameters or changing assumptions in the model and then monitoring the impact on outputs. If the outputs were unexpected, further checks were made to determine whether this was the result of an error in the model.

5.3.2 EAG model validation

The EAG conducted a series of quality checks on the company model, assessing its transparency and validity. A range of tests were performed to verify model inputs, calculations, and outputs:

- Cross-checking all parameter inputs against values reported in the CS, model, and cite sources.
- Checking all model outputs against results stated in the CS, including the base case, PSA, DSA, and company's scenarios.
- Checking the individual formulae within the model.
- Manually running scenarios and checking model outputs against results reported in the CS for the DSA and scenario analyses.
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks).
- Checking Visual Basic (VBA) code for errors and re-running the code to ensure expected outputs were produced.

No errors were identified in the model.

5.3.3 External validation

The company compares their fitted survival curves with data from external clinical studies and international IPF registries. IN the CS, the extrapolated survival curves for nintedanib and best supportive care, using log-logistic, Weibull, and generalised gamma distributions,

were compared with the Australian IPF registry data,[25] and the Greek IPF registry[37,38] and the EMPIRE registry.[38]. The cost-effectiveness model also enables the comparison against the Finnish and the European IPF registries. The company has compared their model results to the European IPF registry[39] and the Finnish IPF registry[40] in the model. Table 26 shows the patient characteristics for these sources.

Table 26 Characteristics of patients in the IPF clinical trials and registries

Data source	Mean age (years)	FVC % pred	Male	Smoking history[a]
INPULSIS I and II trials[41]	66.8	79.51%	79.3%	72.2%
European IPF registry[39]	68.1	68.40%	73.3%	64.7%
EMPIRE registry[38]	67.3	77.08%	68.0%	ND
Long-term NDB IPF data[29]	66.8	79%	78.0%	67.5%
Australian registry[25]	70.9	81.00%	67.7%	71.1%
Greek IPF registry[37]	71.8	73.30%	79.1%	78.2%
Finnish IPF registry[40]	73.0	80.20%	65.1%	55.0%
Kondoh et al.[24]	64.1	77.0%	61.0%	54.0%
Reproduced from the company's model and adapted by the EAG [a] Ex-smokers and current smokers ND, No data; Pred, predicted				

The company opts to use the Australian registry as the primary source of validation based on NICE TA747,[22] where clinical experts and the NICE committee considered the registry to be a close representation of UK clinical practice. The company further notes that the baseline characteristics of the Australian IPF registry are comparable to those of patients in the TOMORROW and INPULSIS clinical trials, which are reported in CS Table 54. CS Figure 21 and Figure 22 depict the three parametric survival models versus Australian IPF registry data for nintedanib and best supportive care, respectively. For the first three years, all the three best fitting parametric curves (log-logistic, Weibull and generalized gamma) for nintedanib closely match the Australian IPF registry survival data. After year three, the closest fit is provided by the log-logistic curve. The pattern is similar for best supportive care, except the parametric curves start to deviate from the registry data after two years.

A Greek IPF registry,[37] reporting 5-year survival for patients on nintedanib, was compared with extrapolated survival for nintedanib. The company's models consistently predict higher overall survival than that seen in the registry data, as shown in CS Figure 23. The mean age of patients in the Greek IPF registry is 71.8 years, which is higher than that of patients in the TOMORROW and INPULSIS trials (66.5 years). Furthermore, the Greek registry comprised

more patients who were current or former smokers (78.2%) in comparison with clinical trials (72.6%).

The company also compares the extrapolated survival for nintedanib against the EMPIRE study,[38] a long-term real world study reporting 10-year survival rates. For the first two years the model predictions match the registry data, after which the survival rates with nintedanib in the model are higher than the Kaplan-Meier data, as can be seen in CS Figure 24. The extrapolated survival for best supportive care was also assessed against the EMPIRE study data for best supportive care; the modelled survival rates were higher than in EMPIRE (CS Figure 25). Although the mean age of patients in the EMPIRE study is the same as in the clinical trials (66.5 years), this is taken at the point of diagnosis rather than the start of treatment.

The company's OS extrapolation for best supportive care using the Weibull and log-logistic models are also compared to a retrospective study of 110 patients with IPF in Japan by Kondoh et al.[24] (CS Figure 15 and 16). The KM data from Kondoh et al are presented for patients with / without an acute exacerbation.

5.3.4 EAG corrections to the company model

The company model does not include general population mortality. Including general population mortality, where it is higher than IPF mortality (when patients are about 85 years old), increases the ICER to [redacted] per QALY (Table 27).

Table 27 Corrected company base case results using general population mortality for lifetime horizon (PAS price)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£19,247	4.05	3.18				
Nintedanib	[redacted]	7.00	5.44	[redacted]	2.96	2.26	[redacted]

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.

The company uses a lifetime (50-year) horizon in their model results. The EAG considers this too long as the starting age of the patient population is approximately 67 years old and so includes patients until age 117 years. We believe a 35-year time horizon is more appropriate. This change does not affect the ICER (Table 28).

Table 28 Scenario analysis using general population mortality for time horizon of 35 years (PAS price)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£19,246	4.05	3.18				
Nintedanib	[redacted]	7.00	5.44	[redacted]	2.95	2.25	[redacted]
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.							

5.3.4.1 Stopping rule for nintedanib

A stopping rule was recommended for nintedanib in TA379,[1] whereby patients experiencing an absolute decline of 10% or more in predicted FVC within any 12-month period discontinue treatment. This rule is not modelled in the current CS as clinicians consider the stopping rule difficult to impose. However, we have included the stopping rule in an EAG scenario analysis (Table 29; section 6.2.2). Using the stopping rule decreases the ICER to [redacted] per QALY.

Table 29 Scenario analysis using the EAG corrections model with nintedanib treatment discontinuation for patients experiencing a decline of ≥FVC 10% predicted

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£19,246	4.05	3.18				
Nintedanib	[redacted]	6.99	5.41	[redacted]	2.94	2.23	[redacted]
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.							

5.3.4.2 Analysis using OS parameters for the FVC >80% predicted subgroup

The company's model uses clinical effectiveness data for the whole trial population, rather than being restricted to the FVC >80% predicted subgroup. The company provides OS parameter values for this population as part of their clarification response (question B5). Table 30 shows the cumulative effect of including general population mortality, and using OS for the FVC >80% predicted subgroup with a time horizon of 35 years. The ICER for this analysis is [redacted] per QALY.

Table 30 Subgroup analysis with OS from for FVC >80% predicted subgroup using general population mortality with time horizon of 35 years (PAS price)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£18,712	3.85	3.05				
Nintedanib	[redacted]	7.95	6.15	[redacted]	4.09	3.10	[redacted]
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.							

5.3.5 EAG summary of key issues and additional analyses

A full summary of EAG observations on key aspects of the company's economic model is presented in Table 31.

Table 31 EAG observations of the key aspects of the company's economic model

Parameter	Company base case	EAG comment	EAG base case
Population	Uses FVC >80% predicted subgroup.	We agree	No change
Lung disease progression	CS Table 66;	Similar pattern of decline in lung function observed in patients with baseline FVC >80% predicted to whole trial population (CS Figure 30).	No change
Overall survival (OS)	Uses mortality for whole trial population.	Mortality for FVC >80% predicted population should be used.	No difference in mortality for placebo vs nintedanib for FVC >80% predicted population. Mortality from whole trial population used after 5.5 years.
Risk of mortality after exacerbation	HR of 1.4 for those with exacerbation, based on a study by Kondoh et al.[24] who reported HR of 2.79. The company divided this by two, to account for the cycle length.	It is inappropriate to divide the HR by two, as it is independent of time.	HR of 2.79.
Acute exacerbation	Uses OR for acute exacerbation for	Results are contradictory for FVC	No change but tested in scenario analyses.

	whole trial population.	>70% predicted and FVC >80% predicted analyses.	
Acute exacerbation rate	Uses acute exacerbation rate for whole trial population	Use acute exacerbation rate for FVC >80% predicted population in scenario analysis (1.05% per 3 month cycle for FVC >80% predicted and 2.58% for FVC ≤80% predicted)	No change but tested in scenario analyses.
Treatment discontinuation	Uses discontinuation rate for whole trial population.	We agree	No change but tested in scenario analyses.
Time horizon	50 years	Patient age is 117 years at end of time horizon.	35 years.
Utilities			
Health state utilities	CS Table 88	We agree. Uses values from TA379.	No change
AE disutility	CS Table 88	We agree.	No change
Resource use and costs			
Unit costs	CS Table 112	We agree. Uses updated values from TA379.	No change
Resource use	CS Table 112	We agree. Uses values from TA379.	No change

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 Deterministic sensitivity analyses

Figure 4 below shows the results of deterministic sensitivity analyses for the FVC >80% predicted subgroup using the EAG's corrected model and applying the PAS discount for nintedanib. We explored the same 14 scenarios as provided in the CS (CS Table 121) with one-way sensitivity analysis across four parameters: probabilities (of mortality, exacerbation, progression and discontinuation), costs, utilities and adverse events. Input parameter modifications were based on 95% confidence intervals.

The ICERs from the one-way sensitivity analysis range from [redacted] to [redacted] per QALY. The cost-effectiveness of nintedanib is most influenced by mortality probabilities due to exacerbation (scenario 1) and discontinuation probabilities (scenario 4), increasing the ICER to [redacted] and [redacted] per QALY, respectively.

[redacted]

Figure 4 Tornado diagram of nintedanib vs best supportive care (FVC >80% predicted subgroup)

As noted in section 5.2.2, the CS scenario analyses describe 19 separate assumption-testing scenarios in the model (CS Tables 122-128, numbered 15-33), covering seven parameters: overall survival, exacerbations, loss of lung function, adverse events, costs, discontinuation, and FVC% predicted categories. The company uses clinical effectiveness data from the whole trial population in their base case analyses. Table 32 shows the cost-effectiveness results for the 19 scenarios, using the EAG's corrected model and the PAS price for nintedanib for the FVC >80% predicted subgroup.

Table 32 Scenario analyses results using EAG corrected model for FVC >80% subgroup (using PAS price for nintedanib)

Scenario	Parameter	Description of parameter varied	ICER (per QALY)
EAG corrected model			[redacted]
15	Overall survival	Parametric distribution: Weibull model (NDB and BSC)	[redacted]
16		Parametric distribution: Generalised gamma model (NDB and BSC)	[redacted]

17		Baseline risk: allow progression from FVC40-49.9% pred to FVC30-39.9% pred (death)	[redacted]
18	Exacerbation	Baseline risk: use investigator estimates	[redacted]
19		Baseline risk: exclude recurrent exacerbation risk	[redacted]
20		Relative risk: NMA results, scenario 4 excluding Richeldi 2011 (OR=0.62)	[redacted]
21	Loss of lung function	Baseline risk: include exacerbation coefficient	[redacted]
22		Relative risk: NMA results, scenario 3 excluding Richeldi 2011 (OR=0.53)	[redacted]
23		Transition probabilities for FVC >80% predicted	[redacted]
24		Transition probabilities for FVC >80% predicted and OR for NDB patients with FVC >80% predicted (OR=0.50)	[redacted]
25	Safety	Relative risk: serious cardiac events, NMA results, scenario 2 excluding Richeldi 2011 (OR=0.92)	[redacted]
26		Relative risk: serious GI events, NMA results, scenario 2 excluding Richeldi 2011 (OR=1.88)	[redacted]
27		Serious AE disutility value: use alternative value for serious cardiac events (-0.00825)	[redacted]
28		Serious AE disutility value: use alternative value for GI perforation (-0.0021)	[redacted]
29		Serious AE disutility value: use extreme value for all serious AEs: maximum disutility – serious cardiac events value	[redacted]
30	Costs	Cost of right heart catheterisation. Cost for respiratory physiology used (£96.68)	[redacted]
31	Discontinuation	Relative risk: NMA results, scenario 3 excluding Richeldi 2011 (OR=1.39)	[redacted]
32	FVC% predicted values	Use the lowest value of each FVC% pred category (e.g. 80 for the 80-89.9 FVC% pred category) as starting point	[redacted]
33		Use the highest value of each FVC% pred category (e.g. 89.9 for the 80-89.9 FVC% pred category) as starting point	[redacted]
BSC: best supportive care; NDB: nintedanib; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; NMA: network meta-analyses; GI: gastrointestinal; AE: adverse event; OR: odds ratio.			

Using the generalised gamma distribution for both nintedanib and best supportive care (scenario 16), rather than the log-logistic model, had the most significant effect on the cost-effectiveness results, reducing the ICER to [redacted] per QALY. The remaining scenarios caused no significant changes to the ICER, which ranges from [redacted] (scenario 24) to [redacted] (scenario 21) per QALY.

6.1.2 Probabilistic analyses

The company conducted a probabilistic sensitivity analysis (PSA) to explore uncertainty in the model. The parameters are described in CS Table 117 and the results from 1,000 iterations are reported in CS Table 18. We repeated this PSA using the EAG corrected model and restricted the analysis to data from the FVC >80% predicted subgroup. The EAG

confirms that the deterministic and probabilistic results for nintedanib versus best supportive care are comparable (Table 33).

Table 33 Deterministic results vs probabilistic results using EAG corrected model for the FVC >80% predicted subgroup (using PAS price for nintedanib)

Intervention/comparator	Total costs	LYs	QALYs	ICER (per QALY)
Deterministic analysis				
Nintedanib	[redacted]	7.95	6.15	[redacted]
BSC	[redacted]	3.85	3.05	-
Probabilistic analysis				
Nintedanib	[redacted]	7.95	6.14	[redacted]
BSC	[redacted]	3.92	3.10	-
LYs: life years; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; BSC: best supportive care.				

6.2 EAG's preferred assumptions

Based on the EAG critique of the company's model, we have identified the following aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

- **Population used for overall survival**: FVC >80% predicted, rather than whole trial population.
- **Extrapolation of OS:** For the first 5.5 years, we use the same survival curve for the best supportive care arm as for the nintedanib arm as the mortality rate for both arms is considered equal; thereafter we use the best supportive care survival curve from the whole trial population for the best supportive care arm.
- **OS Hazard ratio for acute exacerbations:** we implement a HR of 2.79, rather than 1.4.
- **Time horizon:** we opted for a time horizon of 35 years, rather than 50 years.

6.2.1 Results from the EAG preferred model assumptions

Table 34 below presents the results obtained from the model with the above preferred model assumptions implemented.

Table 34 EAG base case model results (using PAS price for nintedanib) for the FVC >80% predicted subgroup

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£23,264	5.71	4.49				
Nintedanib	[redacted]	7.20	5.62	[redacted]	1.49	1.14	[redacted]
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year.							

Table 35 shows the cumulative cost-effectiveness results of applying the EAG preferred model assumptions to the corrected company's base case. Incorporating the EAG assumptions leads to an increase in the ICER from [redacted] to [redacted] per QALY. The change that has the most significant impact on the cost-effectiveness results is the OS extrapolation. The other suggested changes have a small impact on the ICER.

Table 35 Cumulative change from the EAG corrected model with the EAG preferred model assumptions (using PAS price for nintedanib)

Assumption	Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG corrected model	BSC	£19,247	3.18			[redacted]
	NDB	[redacted]	5.44	[redacted]	2.26	
+ Time horizon of 35 years	BSC	£19,246	3.18			[redacted]
	NDB	[redacted]	5.44	[redacted]	2.25	
+ FVC >80% pred population for OS	BSC	£18,712	3.05			[redacted]
	NDB	[redacted]	6.15	[redacted]	3.10	
+ HR = 2.79 for OS for acute exacerbations	BSC	£18,252	2.90			[redacted]
	NDB	[redacted]	5.62	[redacted]	2.72	
+ Equal OS for both arms for 5.5 years (EAG base case)	BSC	£23,264	4.49			[redacted]
	NDB	[redacted]	5.62	[redacted]	1.14	
BSC: best supportive care; NDB: nintedanib; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; OS: overall survival; HR: hazard ratio.						

6.2.2 Scenario analyses conducted on the EAG base case model

We performed scenario analyses using the EAG base case model to analyse the impact of changing some model assumptions on the overall cost-effectiveness results. In addition to replicating some of the company's scenarios, we also conducted further scenarios regarding acute exacerbation rates as follows:

- Acute exacerbation rate per 3-month cycle of 1.05% for FVC >80% predicted and 2.58% for FVC ≤80% predicted (rather than 1.47% - adjudicator-committee reported).
- Acute exacerbation (time to first acute exacerbation) HRs: for subgroups split by FVC 90% predicted, FVC 80% predicted, and FVC 70% predicted, as shown in Table 36.

Table 36 Scenario analysis: hazard ratios for time to first acute exacerbation for varying subgroups of patients

Outcome	**Baseline FVC >90% predicted**	**Baseline FVC ≤90% predicted**
Time to first acute exacerbation	0.46 (95% CI 0.09–2.48) in favour of nintedanib	0.66 (95% CI 0.39–1.11) in favour of nintedanib
	Baseline FVC >80% predicted	**Baseline FVC ≤80% predicted**
	HR: 0.49; 95% CI 0.17, 1.35	HR; 0.72; 95% CI 0.41, 1.27
	Baseline FVC >70% predicted	**Baseline FVC ≤70% predicted**
	HR: 1.00; 95% CI 0.44, 2.30	HR; 0.52; 95% CI 0.28, 0.99
Source: CS Figure 49 and CS text p.63, 65		

Table 37 presents the results from the scenarios conducted on the EAG base case model. Using the Weibull and lognormal distributions in the model results in the highest ICERs, [redacted] and [redacted] per QALY, respectively. Using the hazard ratio for the time to first acute exacerbation in the FVC 70% predicted subgroup also increases the ICER to just over the willingness-to-pay threshold of [redacted] per QALY.

Assuming overall survival was the same in both treatment groups for one year reduced the ICER to [redacted] per QALY, and to [redacted] per QALY if overall survival was assumed to be the same for three years. Including the stopping rule, whereby patients who experience a decline of ≥FVC 10% predicted within a year discontinue and the treatment effect is lost, reduced the ICER to [redacted] per QALY. Using a generalised gamma distribution in the model also notably affected the ICER, reducing it to [redacted] per QALY. The remaining scenarios did not change the ICER significantly, which ranged from [redacted] to [redacted] per QALY.

Table 37 Scenario analyses results using the EAG base case model (using PAS price for nintedanib) for the FVC >80% predicted subgroup

Scenario	Treatment	Total costs	Total QALYs	ICER (£/QALY)
EAG base case	BSC	£23,264	4.49	[redacted]
	NDB	[redacted]	5.62	
From Company Submission				
OS: Parametric distribution - Weibull (NDB and BSC) (CS scenario 15)	BSC	£22,161	4.20	[redacted]
	NDB	[redacted]	5.07	
OS: Parametric distribution – Generalised Gamma (NDB and BSC) (scenario 16)	BSC	£21,642	4.06	[redacted]
	NDB	[redacted]	5.64	
OS: Allow progression from FVC 40-49.9% pred to FVC 30-39.9% pred (scenario 17)	BSC	£23,111	4.46	[redacted]
	NDB	[redacted]	5.54	
Loss of lung function: Transition probabilities for FVC >80% pred (scenario 23)	BSC	£22,737	4.50	[redacted]
	NDB	[redacted]	5.65	
Loss of lung function: Transition probabilities for FVC >80% pred and OR for NDB in patients with FVC >80% pred (OR=0.5) (scenario 24)	BSC	£22,737	4.50	[redacted]
	NDB	[redacted]	5.65	
EAG scenarios				
OS: Parametric distribution - Lognormal (NDB and BSC)	BSC	£25,833	5.09	[redacted]
	NDB	[redacted]	6.03	
Acute exacerbation rate: 1.05% for FVC >80% pred and 2.58% for FVC ≤80% pred	BSC	£22,650	4.50	[redacted]
	NDB	[redacted]	5.61	
Acute exacerbation HR for FVC >90% pred and FVC ≤90% pred	BSC	£23,264	4.49	[redacted]
	NDB	[redacted]	5.63	
Acute exacerbation HR for FVC >80% pred and FVC ≤80% pred	BSC	£23,264	4.49	[redacted]
	NDB	[redacted]	5.64	
Acute exacerbation HR for FVC >70% pred and FVC ≤70% pred	BSC	£23,264	4.49	[redacted]
	NDB	[redacted]	5.47	
Equal OS for both arms for 1 year	BSC	£19,590	3.34	[redacted]
	NDB	[redacted]	5.62	
Equal OS for both arms for 3 years	BSC	£21,557	3.99	[redacted]
	NDB	[redacted]	5.62	
20-year time horizon	BSC	£23,099	4.47	[redacted]
	NDB	[redacted]	5.49	

50-year time horizon (lifetime)	BSC	£23,264	4.49	[redacted]
	NDB	[redacted]	5.62	
NDB: Discontinue treatment and lose treatment effect for patients that experience a decline of ≥FVC 10% predicted	BSC	£23,264	4.49	[redacted]
	NDB	[redacted]	5.57	
BSC: best supportive care; NDB: nintedanib; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; OS: overall survival; HR: hazard ratio; OR: odds ratio.				

6.3 Conclusions on the cost effectiveness evidence

The company's model generated a base case ICER of [redacted] per QALY for nintedanib vs best supportive care (using the PAS price for nintedanib). The model used clinical effectiveness estimates from the whole trial populations. In response to clarification question B5, the company produced a scenario analysis using the OS for the FVC >80% predicted subgroup, which had an ICER of [redacted] per QALY.

Our preferred model assumptions are the following:

- **Population used for the overall survival**: FVC >80% predicted, rather than the whole trial population.
- **Extrapolation of OS:** For the first 5.5 years, we use the same survival curve for the best supportive care arm as for the nintedanib arm as the mortality rate for both arms is considered equal; thereafter we use the best supportive care survival curve from the whole trial population for the best supportive care arm.
- **OS Hazard ratio for OS for acute exacerbations:** we use a HR of 2.79, rather than 1.4.
- **Time horizon:** we use a time horizon of 35 years, rather than 50 years.

The EAG's corrections and preferred assumptions increase the ICER for nintedanib vs best supportive care to [redacted] per QALY. These estimates are most sensitive to changes in the assumptions related to the OS extrapolation.

7 SEVERITY

The company calculates the QALY shortfall using the SCHARR QALY shortfall calculator,[42] and:

- General population QALYs calculated from EQ-5D health state profiles[43]
- HRQoL, measured using the EQ-5D-5L and mapped to the EQ-5D-3L[44]

- National life table data for age and sex-specific survival times[45]

The sex distribution (78% male) and starting age (68 years) were based on the baseline characteristics of people with FVC >80% predicted (CS Section B.2.3, Table 8). The company does not consider nintedanib suitable for a QALY weighting, because the absolute QALY shortfall compared with best supportive care in IPF is lower than 12 years; and the proportional shortfall is less than 85%.

EAG comment on severity

The EAG checked the company's calculations and we agree with the company's evaluation. We do not believe that there is a high degree of severity, as the absolute QALY shortfall is less than 12 years and the proportional shortfall is below 85%.

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9 Appendices

9.1 Appendix 1 EAG appraisal of systematic review methods

Table 38 EAG appraisal of systematic review methods

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The PICOD components are detailed in CS Appendix D Table 135.
Were appropriate sources of literature searched?	Yes	Included Medline, Embase, Cochrane Central Register of Controlled Trials, relevant clinical trial registries and conference abstracts, reference lists of key papers and systematic reviews. The CDSR was not searched however the EAG notes

		this would have yielded 11 additional references of which none were relevant.
What time period did the searches span and was this appropriate?	Yes	September 2014 to January 2022. The EAG performed an updated search. No new RCTs were identified.
Were appropriate search terms used and combined correctly?	Yes	CS Appendix D 1.1 Tables 131-133
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	The company do specify their selection criteria (CS Appendix D Table 135). We note that these are wider than the decision problem as they are based on those used for TA379 which has a wider scope in terms of population and comparators. However, it appears the company have applied additional ad-hoc exclusions to studies identified at full text review.
Were study selection criteria applied by two or more reviewers independently?	Yes	CS Appendix D.1.1
Was data extraction performed by two or more reviewers independently?	No.	One reviewer extracted the study data and a second reviewer validated the extracted data (CS Appendix D.1.1.) The EAG considers this approach adequate.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	The company assessed the risk of bias using the following tools/guides: • CRD criteria recommended by NICE for the nintedanib RCTs (CS Table 15) • STA User Guide (2022) and a publication by Bowers et al. for the open label extension studies (CS Tables 16 and 17)[15,16] • Cochrane Risk of Bias tool for other trials in the company's NMA.[1]
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	The CS does not state who performed the risk of bias assessments.

Is sufficient detail on the individual studies presented?	Yes	Further details of the trial characteristics are presented in CS sections B.2.2 and B.2.3.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	Pairwise and network meta-analysis were used to combine study results from the INPULSIS and TOMORROW RCTs. A full critique is provided in section 3.5 of this EAG report.

CDSR: Cochrane Database of systematic reviews; CRD: Centre for Reviews and Dissemination; STA: Single technology appraisal

9.2 Appendix 2 Comparison of company and EAG critical appraisal of open label extension studies

Table 39 Comparison of company and EAG quality assessment (STA User Guide criteria) for the INPULSIS-ON open-label extension study

Trial name	Company assessment	EAG assessment
Was the cohort recruited in an acceptable way?	Yes, patients who completed INPULSIS trials were eligible.	Yes, but with the caveat that only participants who completed INPULSIS RCT could enter the OLE.
Was the exposure accurately measured to minimise bias?	Yes, median (range) exposure for patients continuing and initiating treatment recorded.	Yes, exposure to actual treatment received was recorded during the RCT and the OLE.
Was the outcome accurately measured to minimise bias?	Yes.	Yes
Have the authors identified all important confounding factors?	Yes, decreasing patient numbers over time, potential for selection bias in patients who continued the extension.	Probably yes, with the caveat that there may be unknown confounding factors.
Have the authors taken account of the confounding factors in the design and/ or analysis?	Yes, subgroup analysis conducted by nintedanib dose, dose adjustment, and dose intensity.	Probably yes
Was the follow-up of patients complete?	Yes, data are based on the database lock for the final analysis.	Yes, but with the caveats that i) not all participants entered the open-label extension and ii) some participants dropped out of the OLE.
How precise (for example, in terms of confidence interval	Not applicable, due to small sample size.	Most results are presented with SE, SD or 95% CI. Sample size is larger than for the TOMORROW study which

and p values) are the results?		should mean results from this study are more precise than those of TOMORROW.
Source: CS Table 16 with addition of EAG quality assessment		

Table 40 Comparison of company and EAG quality assessment (STA User Guide criteria) for the TOMORROW open-label extension

Trial name	Company assessment	EAG assessment
Was the cohort recruited in an acceptable way?	Yes, patients who completed TOMORROW were eligible.	Yes, but with the caveat that only participants who completed both the RCT and subsequent blinded phase 2 section of TOMORROW could enter the OLE. CS Table 7 suggests four countries that contributed data to the TOMORROW RCT were not represented in the TOMORROW OLE.
Was the exposure accurately measured to minimise bias?	Yes, exposure by trial and treatment recorded.	Yes, exposure to actual treatment received was recorded across all the periods of study including the OLE.
Was the outcome accurately measured to minimise bias?	Yes.	Yes
Have the authors identified all important confounding factors?	Yes, decreasing patient numbers over time, switch in treatment and dose, potential for selection bias in patients who continued the extension.	Probably yes, with the caveat that there may be unknown confounding factors.
Have the authors taken account of the confounding factors in the design and/ or analysis?	Yes, analysis conducted separately for comparator arm which comprised patients who received placebo in period 1, nintedanib 50 mg once daily in period 2, and a range of nintedanib doses in the extension.	Yes, for changes in treatment and dose. The impact of missing patients (those who did not enter the OLE) on outcomes analysed is uncertain.
Was the follow-up of patients complete?	Yes, data are based on the database lock for the final analysis.	Yes, but with the caveats that i) not all participants entered the OLE and ii) not all patients completed the OLE
How precise (for example, in terms of confidence interval and p values) are the results?	Not applicable, due to small sample size.	Most results are presented with SE or 95% CI, but small sample sizes does mean the results are less certain than if the sample size had been larger.

Source: CS Table 16 with addition of EAG quality assessment

Table 41 Comparison of company and EAG quality assessment (Bowers et al. criteria) for the INPULSIS-ON open-label extension

Features indicative of high quality OLE studies (Bowers et al., 2012)[16]	Company assessment	EAG assessment
"Explicitly stated aims, to minimize the possibility of Type I Error"	☑ The objective was to assess the long-term efficacy and safety of nintedanib. The primary outcome was incidence of adverse events. The database was locked for final analysis on Sept 12, 2017 so all endpoints were recorded up to 192 weeks from baseline. Only descriptive statistics were used. No formal statistical inferences were used, but to aid the interpretation of the data, patients were divided into groups.	Yes. Aim stated as "to assess the long-term efficacy and safety of nintedanib" with the primary outcome to "characterise the long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis, and this was analysed in patients who received at least one dose of nintedanib in INPULSIS-ON"
"A well-characterized sample representative of the target population in whom the medication will be used"	☑ Patients who entered INPULSIS-ON were divided into two groups: those who had already received nintedanib (masked) in INPULSIS and continued nintedanib (open-label) in INPULSIS-ON, and those who had received placebo in INPULSIS and initiated nintedanib in INPULSIS-ON. Patients receiving nintedanib 150 mg twice daily or placebo at the end of an INPULSIS trial received nintedanib 150 mg twice daily in INPULSIS-ON. Patients receiving nintedanib 100 mg twice daily or	Partially. The sample is well characterised with baseline characteristics provided for the INPULSIS RCTs with a more limited range of characteristics reported for the participants who entered the INPULSIS-ON extension (CS Table 11).

Features indicative of high quality OLE studies (Bowers et al., 2012)[16]	Company assessment	EAG assessment
	placebo at the end of an INPULSIS trial could receive nintedanib 100 mg twice daily or 150 mg twice daily in INPULSIS-ON. Permanent or temporary dose reductions to 100 mg twice daily and treatment interruptions were allowed, to manage adverse events.	
"Outcome assessment is masked to treatment received where possible"	? Outcomes were assessed with clinical and laboratory evaluation and the recording of adverse events reported during and until 28 days after discontinuation of treatment. The published report does not state whether the outcomes assessors were blind to treatment allocation.	Unclear. As the OLE was not blinded and participants knew they were receiving nintedanib it is likely that outcome assessors were not blind to OLE treatment allocation, but they may have been blind to OLE participants' earlier RCT allocation.
"A low rate of sample slippage in relation to the numbers randomized in the preceding RCT, but the length of follow-up should be considered in making this assessment"	☑ The sample size decreased over time, but this is justified by the long 68-months follow-up duration (NOTE: long-term assessment per se' is an important objective in OLE studies; Bowers et al., 2012), and by the fact that this reduction was partly due to patients switching to prescribed nintedanib in clinical practice once it became available.[16] Sample size calculation was not required and the number of patients eligible depended on the number of patients completing the parent trials INPULSIS-1 and	The EAG considers that rate of sample slippage in relation to the numbers randomised in the preceding RCT is similar to what might be expected for studies of this type. After the 52-week RCT and 4-12 week treatment gap, 71.9% of those who had received placebo in the RCT and 67.4% of those who had received nintedanib entered the OLE (for the total RCT population 69.2% of participants entered the OLE). The proportion of RCT participants entering the OLE is not far below the mean of 74% (min-max 6-100%) calculated for a random sample of 40 OLEs.[16]

Features indicative of high quality OLE studies (Bowers et al., 2012)[16]	Company assessment	EAG assessment
	INPULSIS-2 and willing to participate in this extension trial. Of 807 patients who completed the INPULSIS trials, 734 were treated in INPULSIS-ON, of whom 430 were continuing nintedanib and 304 were initiating nintedanib. 295 of 430 patients continuing nintedanib and 219 of 304 patients who initiated nintedanib in INPULSIS-ON discontinued nintedanib during the trial. All analyses were evaluated using observed case analysis, i.e. using only the available data, without imputation for missing data. Missing or incomplete AE dates were imputed. Missing data for time-to-event endpoints were managed by censored data analyses.	
"The quality of a study can only be judged if objectives, design, conduct, analysis and results are adequately described and the STROBE guidelines for reporting observational studies in epidemiology should be followed"	☑ The published version of the report comply with STROBE guidelines.*	The published version of the INPULSIS-ON open-label extension does not explicitly identify potential confounders or effect modifiers and the statistical method of adjustment for the primary outcome is not described. In most other respects the published paper complies with STROBE guidelines.
"The limitations of the specific study design used and its execution should be discussed"	☑ The limitations are discussed in the published study and include: absence of a comparator group; decreasing patient numbers over time. There was also potential for selection bias due to patients in the	Yes, the published study includes a discussion of study limitations.

Features indicative of high quality OLE studies (Bowers et al., 2012)[16]	Company assessment	EAG assessment
	INPULSIS trials who had a more favourable course of disease or were better able to tolerate nintedanib. These patients would have been more likely to complete the trial and so be eligible for INPULSIS-ON. They might also have been more likely to remain on treatment in INPULSIS-ON, potentially reducing the observed decline in FVC and mortality in INPULSIS-ON.	
Source: CS Table 17 with addition of EAG quality assessment		

Table 42 Comparison of company and EAG study quality assessment (Bowers et al. criteria) for the TOMORROW open-label extension

Features indicative of high quality OLE studies Bowers et al., 2012)[16]	Company assessment	EAG assessment
"Explicitly stated aims, to minimize the possibility of Type I Error"	☑ The main objective was to present long-term efficacy and safety data. The primary efficacy endpoint was the annual rate of decline in FVC and was calculated using all FVC assessments from first drug administration in the extension study until database lock on 15th October 2015, up to 61.8 months.	Yes. The clinicaltrials.gov entry (where nintedanib is called BIBF 1120) for the TOMORROW OLE states "The aim of this trial is to offer continuation of BIBF 1120 treatment for patients with Idiopathic Pulmonary Fibrosis (IPF) who have completed a prior clinical trial with that drug. The primary objective will be to establish the long term tolerability and safety profile of BIBF 1120 in Idiopathic Pulmonary Fibrosis (IPF). As a secondary objective the

Features indicative of high quality OLE studies Bowers et al., 2012)[16]	Company assessment	EAG assessment
	All endpoints were exploratory and only descriptive statistics were performed.	effects of long-term treatment with BIBF 1120 on survival as well as safety and efficacy parameters will be investigated in an open-label, not randomized, un-controlled design".
"A well-characterized sample representative of the target population in whom the medication will be used"	☑ Patients who completed 52 week's treatment in TOMORROW period 1 continued treatment in a blinded phase (period 2), until the last patient had completed 52 weeks' treatment in period 1. In period 2, patients treated with nintedanib in period 1 continued their dose, and placebo-treated patients were switched to nintedanib 50 mg qd in a blinded manner. Patients who completed period 2 could continue/start nintedanib in the open-label extension trial. Patients entered the extension trial on the dose that they were receiving at the end of period 2, but had the option to increase dose to nintedanib 150 mg bid. Dose reduction from 150 mg bid to 100 mg bid and treatment interruption were permitted for the management of adverse events. In the extended period study, the comparator group received placebo in period 1 and nintedanib 50mg qd in period 2.	Partially. The sample is well characterised with baseline characteristics provided for the TOMORROW RCT and a more limited range of characteristics reported for those participants who entered the TOMORROW OLE (CS Table 13).

Features indicative of high quality OLE studies Bowers et al., 2012)[16]	Company assessment	EAG assessment
"Outcome assessment is masked to treatment received where possible"	? The published report does not state whether the outcomes assessors were blind to treatment allocation.	Unclear. As the OLE was not blinded and participants knew they were receiving nintedanib it is likely that outcome assessors were not blind to OLE treatment allocation, but they may have been blind to OLE participants' earlier RCT allocation.
"A low rate of sample slippage in relation to the numbers randomized in the preceding RCT, but the length of follow-up should be considered in making this assessment"	☑ The sample size decreased over time, but this is justified by the nearly 8-years follow-up duration from the start of period 1 (NOTE: long-term assessment per se' is an important objective in OLE studies; Bowers et al., 2012)[16] The number of patients eligible for the extension study depended on the number of patients completing the TOMORROW trial and willing to participate in this extension trial. Of 428 patients treated in period 1, a total of 286 entered period 2, and 198 entered the extension, including 35 in the nintedanib 150 mg twice daily group and 37 in the comparator group (35 of whom increased dose to nintedanib 150 mg twice daily). The full analysis set included all patients in the treated set who provided baseline data (for the first	The EAG considers that rate of sample slippage in relation to the numbers randomised in the preceding RCT is a potential concern. After the 52-week RCT and period 2 (length unclear, CS Figure 1 suggests a maximum of about 30 weeks) 46% of the RCT participants entered the OLE. A 2012 review of OLE studies found across a random sample of 40 OLEs a mean of 74% (min-max 6-100%) of the participants randomized in the preceding RCT(s) were enrolled in the OLE.[16] The rate of sample slippage in relation to the numbers randomized in the preceding RCT would therefore appear to be higher than average. This rate of sample slippage is not unexpected given the long duration of follow up, however, we are uncertain how this compares, on average, with that in studies of a similarly long duration.

Features indicative of high quality OLE studies Bowers et al., 2012)[16]	Company assessment	EAG assessment
	trial visit) for at least 1 endpoint in the open-label extension trial.	
"The quality of a study can only be judged if objectives, design, conduct, analysis and results are adequately described and the STROBE guidelines for reporting observational studies in epidemiology should be followed"	☑ The published version of the report comply with STROBE guidelines.	The published version of the TOMORROW trial extension lacks a clearly reported rationale for the study and does not state specific objectives. {Richeldi, 2018 #4} Confounder & effect modifier terminology are not used so the reader would need to identify potential confounders and effect modifiers themselves by interpreting/inferring from the text. In most other respects the published paper complies with STROBE guidelines.
"The limitations of the specific study design used and its execution should be discussed"	☑ The limitations are discussed in the published study and include: switches in treatments and doses; lack of a true placebo group; potential for selection bias in patients who continued into the extension. Patients who died or were unable to enter the extension due to disease progression were excluded from the analyses. The small patient numbers available for analyses beyond period 1 means these results may underestimate the rate of FVC decline, particularly in the comparator group, in which most patients received nintedanib 150 mg twice daily in the extension.	Yes, the published study includes a discussion of study limitations.
Source: CS Table 17 with addition of EAG quality assessment		

9.3 Appendix 3 Additional clinical effectiveness results

9.3.1 Post-hoc subgroup analyses from INPULSIS trials: FVC ≤90% vs. >90%

Evidence for the primary endpoint (adjusted annual rate of decline in FVC) was presented for TA379. In the current submission the company additionally provides the data as a figure (CS Figure 7). New for this submission are data presented for: time to first acute exacerbation, adjusted mean change from baseline in SGRQ total score and time to an absolute decline in FVC ≥10% predicted or death as shown in Table 43.

Table 43 Subgroup analyses by FVC% predicted ≤90% versus >90% (INPULSIS trials)

Outcome	baseline FVC >90% predicted			baseline FVC ≤90% predicted		
Time to first acute exacerbation	Hazard ratio: 0.46 (95% CI: 0.09, 2.48) in favour of nintedanib			Hazard ratio: 0.66 (95% CI: 0.39–1.11) in favour of nintedanib		
	Treatment-by- subgroup interaction p=0.956					
Adjusted mean change from baseline in SGRQ total score at week 52	Nintedanib n=NR	Placebo n=NR	difference	Nintedanib n=NR	Placebo n=NR	difference
	2.16	3.02	−0.87 (95% CI: −3.97, 2.24)	4.00	5.64	−1.65 (95% CI: −3.60, 0.31)
	Treatment-by-subgroup interaction p=0.3382					
Time to an absolute decline in FVC ≥10% predicted or death	Nintedanib n=166	Placebo n=108	difference	Nintedanib n=472	Placebo n=315	difference
	Hazard ratio: 0.59 (95% CI: 0.38, 0.89) in favour of nintedanib			Hazard ratio: 0.61 (95% CI: 0.48, 0.78) in favour of nintedanib		
	Treatment-by-subgroup interaction p=0.830					
Source: CS text pages.64-65, CS Figure 8						

9.3.2 Prespecified subgroup analysis from INPULSIS trials: FVC ≤70% vs. >70% predicted value

Evidence from the pooled INPULSIS studies for the primary endpoint (adjusted annual rate of decline in FVC) was described in the company submission for TA379 [1] stating that no statistically significant differences in outcomes by subgroup were found, but no numerical data were presented. New for this submission are some numerical data as shown in Table 44

Table 44 Subgroup analyses by FVC% predicted ≤70% versus >70% (INPULSIS trials)

Outcome	baseline FVC >70% predicted			baseline FVC ≤70% predicted		
Annual rate of decline in FVC	Nintedanib n=431	Placebo n=269	difference	Nintedanib n=207	Placebo n=154	difference
	NR	NR	109.0 (95% CI: 68.2, 149.9)	NR	NR	113.5 (95% CI: 51.3, 175.7)
	Treatment-by-time-by subgroup interaction p=0.9505					
Acute exacerbations	Nintedanib n=431	Placebo n=269		Nintedanib n=207	Placebo n=154	
	15 (3.5%)	9 (3.3%)		16 (7.7%)	23 (14.9%)	
Time to first acute exacerbation	Hazard ratio: 1.00 (95% CI: 0.44, 2.30)			Hazard ratio; 0.52 (95% CI: 0.28, 0.99)		
	Treatment-by-subgroup interaction p=0.1747					
Change from baseline in SGRQ total score over 52 weeks	Nintedanib n=410	Placebo n=263	difference	Nintedanib n=199	Placebo n=150	difference
			-0.34 (95% CI: -2.34, 1.65)			-3.34 (95% CI: -6.29, -0.38)
	Treatment-by-subgroup interaction p=0.0631					
Source: CS text page 70, CS Figures 48-50 NR : Not reported						

9.3.3 Subgroup analyses by baseline characteristics other than FVC % predicted

A narrative summary of post-hoc subgroup analyses conducted in the INPULSIS trials for patients with and without emphysema at baseline was presented in the company submission for TA379 and this is expanded on in the current submission with additional subgroup analyses reported for the first time in the current submission in CS section 2.7 and Appendix

E. No statistically significant differences between subgroups were observed for any of the subgroup analyses reported.

9.3.4 Adverse events in INPULSIS trials by baseline FVC >90% vs. FVC ≤90% predicted

In the baseline FVC >90% predicted subgroup receipt of nintedanib also led to a higher proportion of severe adverse events and adverse events that led to permanent drug discontinuation. Severe or serious adverse events occurred more frequently in the subgroup of patients with baseline FVC ≤90% predicted (nintedanib and placebo arms) than FVC >90% predicted (nintedanib and placebo arms).

Table 45 Adverse events in INPULSIS trials by baseline FVC >90% vs. FVC ≤90% predicted

Event n (%)	Baseline FVC >90% predicted		Baseline FVC ≤90% predicted	
	Nintedanib (n=166)	Placebo (n=108)	Nintedanib (n=472)	Placebo (n=315)
Any AE(s)	156 (94.0)	100 (92.6)	453 (96.0)	278 (88.3)
Severe AE(s) [a]	37 (22.3)	18 (16.7)	137 (29.0)	81 (25.7)
Serious AE(s) [b]	38 (22.9)	28 (25.9)	156 (33.1)	99 (31.4)
Fatal AE(s)	4 (2.4)	2 (1.9)	33 (7.0)	29 (9.2)
AE(s) leading to Permanent drug discontinuation [c]	36 (21.7)	8 (7.4)	87 (18.4)	46 (14.6)

Source: CS Table 38 edited by the EAG
Abbreviations: AE, adverse event.
[a] An event that was incapacitating or that caused an inability to work or to perform usual activities.
[b] An event that resulted in death, was immediately life threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonger hospitalisation, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.
[c] AEs leading to treatment discontinuation in >2% of patients in any treatment group.

CONFIDENTIAL

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

EAG probabilistic analyses of EAG and company base case

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1. Introduction

At the pre-meeting briefing meeting on 11th October 2022, NICE requested more details on the company and EAG base case probabilistic sensitivity analyses (PSA). In this document we provide this information, including the probability of nintedanib being cost effective at the £20,000 and £30,000 thresholds.

2. Company corrected base case

The PSA results for the company's corrected base case are shown in Table 1. The ICER is [redacted] per QALY for nintedanib vs BSC. The probability of nintedanib being cost effective at £20,000 and £30,000 thresholds are [redacted] and [redacted] respectively.

Table 1 EAG probabilistic base case results (using PAS price for nintedanib)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£19,789	4.12	3.23				
Nintedanib	[redacted]	7.00	5.43	[redacted]	2.89	2.20	[redacted]
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year. Deterministic results shown in EAG report table 27.							

3. EAG base case

The PSA results for the EAG's base case are shown in Table 2. The ICER is [redacted] per QALY for nintedanib vs BSC.The probability of nintedanib being cost effective at £20,000 and £30,000 thresholds are [redacted] and [redacted] respectively.

Table 2 EAG probabilistic base case results (using PAS price for nintedanib)

Technology	Total			Incremental			
	Costs	LYG	QALY	Costs	LYG	QALY	ICER (£/QALY)
BSC	£23,599	5.71	4.48				
Nintedanib	[redacted]	7.20	5.61	[redacted]	1.49	1.14	[redacted]
BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALY: quality-adjusted life year. Deterministic results shown in EAG report Table 34.							

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 7 September 2022** 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 '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Table 1 Summary of EAG's key issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Point 2 in Table 1 page 11 *'The company's economic model base case uses overall survival estimates for the whole trial population, rather than the FVC > 80% predicted subgroup.'*	*'The company's economic model base case uses overall survival estimates for the whole trial population, rather than the FVC > 80% predicted subgroup.* ***The Company produced the ICER for the OS FVC>80% predicted subgroup in response to the Clarification question B5'.***	This statement is incomplete and provides an inaccurate representation to the reader.	This is a headline description of the key issue and it needs to be concise. What the company did or did not *produce* is not the issue here, it is about what they *used* in their base case. Therefore, this is not a factual inaccuracy and no change necessary.

Issue 2 List of registries used by the Company to validate the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13 *'Indeed, the CS cites selected international IPF registries (e.g., Australian, British, Greek) to validate model assumptions and outcomes.'*	*'Indeed, the CS cites selected international IPF registries (e.g., Australian,* ***EMPIRE,*** *Greek) to validate model assumptions and outcomes.'*	This statement is inaccurate. The British registry was used to assess the generalisability of the trials' population and not to validate the model assumptions/outcomes. Moreover, it is not accurate to class the British registry as an international registry. To validate the model the following registries were used: EMPIRE, European IPF, Australian, Greek, and Finnish. The model contains	For simplicity we have removed this sentence.

		all these registry data as well as the respective validation analyses. In the CS the validation against the most relevant registries was presented, namely Australian, EMPIRE and Greek registries.	

Issue 3 Length of follow-up of placebo patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16 *'We therefore assume that mortality is initially the same for both the trial arms for the FVC > 80% predicted subgroup. When the mean FVC % predicted of the FVC > 80% predicted subgroup has declined to that of the whole trial population, the placebo OS curve is assumed to follow the placebo parametric curve for the whole trial population. We estimate this happens after 5.5 years.'*	*'[…trial population.] We estimate this happens after 5.5 years.* ***However, the assumption of equal OS during the first 5.5 years of treatment is not validated against the real-world OS for the mild FVC subgroup estimated in the Australian registry study by Jo et al., 2018 (Figure 1). Figure 1 shows that after the first 27 months of follow-up, the 5.5 years scenario produces levels of survival which are higher than the survival levels for the mild FVC population studied in Jo et al (2018). However, the issue is that the modelled OS curve for BSC in the FVC>80% population should not be higher than the OS curve for patients with mild FVC, because the latter includes a mixed population treated with BSC or antifibrotics. For the same reason, also the 2 years, 3 years, and 4 years scenarios are inappropriate.***	The Company challenges the accuracy of the EAG 5.5 years scenario, as well as the correctness of the logic of the underpinning assumption, for the following reasons: 1. The EAG scenario based on the assumption of no difference in OS until 5.5 years of follow-up in the FVC>80% indication, produces an OS curve for BSC which is not consistent with the real-world data presented in Jo et al. 2018. Indeed, the EAG 5.5 years scenario curve should not be higher than Jo et al 2018 OS curve,	Not a factual inaccuracy. No change necessary. The company has a difference of opinion about the extrapolation of the BSC curve and the assumption of equal OS during the first 5.5 years of treatment.

	The assumption of equal OS up to 1 year from nintedanib treatment initiation is the most suitable assumption for the base case. Indeed, it is validated against the Australian registry curve of Jo et al 2018. It is also more plausible than the 2 years scenario, as it yields an OS curve which is broadly parallel to the OS for the mild IPF subgroup in Jo 2018, with the difference between the two curves being justified by the fact that the higher OS curve for the mild subgroup reflect the benefits of the antifibrotics taken by 25% of this cohort. This difference visibly increases over time due to the modelled BSC OS declining survival curve, illustrating the steadier trajectory of the OS for the Australian 'mixed antifibrotics' cohort with respect to the modelled BSC cohort.'	because in Jo et al ~25% of patients are on antifibrotic. A mixed IPF population where 25% of patients are on antifibrotics are expected to have all the time higher or at least equal survival probabilities than a population not taking antifibrotics. Figure 1 shows that this occurs only in EAG scenario which assumes 1 year of equal OS. In Figure 1, one can see that at 27 months of follow-up, the EAG 5.5 years scenario curve becomes equal to the mild FVC curve produced by Jo et al., and then overtakes it. This is inconsistent with the literature on the benefits of antifibrotics. This issue is also evident in Table 20 of the EAG report, where in year 3 the OS for EAG BSC is 79%,	

		whilst it is 73% in Jo et al. 2018. 2. An additional pitfall of the EAG's argument is the assumption itself of equal survival between the nintedanib and BSC subgroups up to 5.5 years. Conceptually, this assumption implies that nintedanib is not effective for 5.5 years from treatment initiation. Because lung function decline is a key predictor of survival, this claim implicitly denies the evidence that nintedanib is effective in delaying lung function decline (evidence included in the CS and presented in Maher 2015). It also implicitly denies the new analysis on the rate of lung function decline at 12 months that we submitted in response to clarification question A9. This new analysis demonstrated that in	

		the FVC > 80% predicted subgroup, the trend was consistent with the trend in the overall population, and the comparison of nintedanib 150mg bid vs. placebo arm reached statistical significance (p=0.0182; 95%CI: 0.030, 0.323). The EAG's 5.5 years scenario as well as the 2-, 3-, and 4-years' scenarios and the underpinning logic are therefore inconsistent with real world and trial evidence and potentially misleading. It is also unsupported by the clinical experts we have consulted.	
Page 57 *'The clarification response document does not specify how the OS curve for the placebo arm was fitted, given there is only one year follow-up data. The EAG notes that there is no difference between the OS curves for the nintedanib and placebo*	*'The clarification response document* ***specifies*** *how the OS curve for the placebo arm was* ***fitted. However, the long-term extrapolation is uncertain, due to the fact that there is only one year follow-up data.*** *The EAG notes that there is no difference between the OS curves for the nintedanib and placebo*	The EAG statement is imprecise, because it is technically feasible to fit parametric curves using 12 months follow-up data, and we did explain in clarification question B5 how the parametric curves were fitted to placebo (and nintedanib), with the same	We have amended the text as suggested.

arms in the FVC ≥80% predicted subgroup for the first 52 weeks.'	*arms in the FVC **>80%** predicted subgroup for the first 52 weeks.'*	level of detail provided in the CS. If the EAG meant to comment on how it is possible to choose the best fitted curve, given the long-term uncertainty and no difference between arms for the first 52 weeks, we appreciate that this is a valid point. However, in our response to clarification question B6, we did caution against the use of the >80% subgroup to model survival because of the small sample, and we recommended to make use of the survival from the overall IPF population. It is more appropriate to use the overall population dataset analysis, because it offers a larger dataset, which to a certain extent can compensate for the short follow-up of placebo patients in the trials.	
Page 58 *'The initial mean FVC % predicted of the cohort is 95% and declines over time. When the modelled cohort reaches the same FVC % predicted as the whole trial*	*'The initial mean FVC % predicted of the cohort is 95% and declines over time. When the modelled cohort reaches the same FVC % predicted as the whole trial population (FVC = 79%), we assume the*	Providing a base case analysis which contains data or assumptions which are invalid when assessed against real world data is	As stated above, this is not a factual inaccuracy. No change necessary.

population (FVC = 79%), we assume the best supportive care OS curve has the same survival as the whole trial population. Therefore, from this point the best supportive care arm uses the whole trial parametric curve. We estimate it to be 5.5 years before the mean FVC for the cohort is the same as the whole trial FVC.'	*best supportive care OS curve has the same survival as the whole trial population. Therefore, from this point the best supportive care arm* ***could make use of*** *the whole trial parametric curve. We estimate it to be 5.5 years before the mean FVC for the cohort is the same as the whole trial FVC.* ***However, the scenario based on this assumption produces an OS curve which is not validated by real world data (see Figure 1 and Table 20), and therefore we do not recommend the use of the 5.5 years scenario as a base case.'***	methodologically inappropriate.	

<table>
<tr>
<td>Page 58,

“We compare the modelled survival for best supportive care using the company and EAG assumptions against this study (Table 20). The company’s estimate for survival over four years is notably lower than the survival data from the Australian registry”

Table 20 Company and EAG OS estimates for FVC>80% subgroup vs Australian IPF registry (mild patients)

<table>
<tr><th>Year</th><th>Australian IPF registry (mild FVC)[25] OS</th><th>Company base case for BSC OS</th><th>EAG base case for BSC OS</th></tr>
<tr><td>0</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>1</td><td>99</td><td>96</td><td>96</td></tr>
<tr><td>2</td><td>89</td><td>80</td><td>88</td></tr>
<tr><td>3</td><td>73</td><td>58</td><td>79</td></tr>
<tr><td>4</td><td>71</td><td>39</td><td>70</td></tr>
<tr><td colspan="4">[a] Patients were classified as ‘mild’ if FVC ≥80%
BSC, best supportive care; OS, overall survival</td></tr>
</table>
</td>
<td>“We compare the modelled survival for best supportive care using the company and EAG assumptions against this study (Table 20). The company’s estimate for survival over four years is lower than the survival data from the Australian registry and the difference increases over time. This is justified by the fact that the ~25% of the mild population studies in Jo et al 2018 are on antifibrotics.”

[Update of last column to include OS assuming equal OS between nintedanib and BSC for 1 year]
<table>
<tr><th>Year</th><th>Australian IPF registry (mild FVC)[25] OS</th><th>Company base case for BSC OS</th><th>EAG base case for BSC OS</th></tr>
<tr><td>0</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td>1</td><td>99</td><td>96</td><td>96</td></tr>
<tr><td>2</td><td>89</td><td>80</td><td>83</td></tr>
<tr><td>3</td><td>73</td><td>58</td><td>62</td></tr>
<tr><td>4</td><td>71</td><td>39</td><td>44</td></tr>
<tr><td colspan="4">[a] Patients were classified as ‘mild’ if FVC ≥80%
BSC, best supportive care; OS, overall survival</td></tr>
</table>
</td>
<td>The EAG statement is misleading because it implies the Australian registry cohort were all receiving BSC.

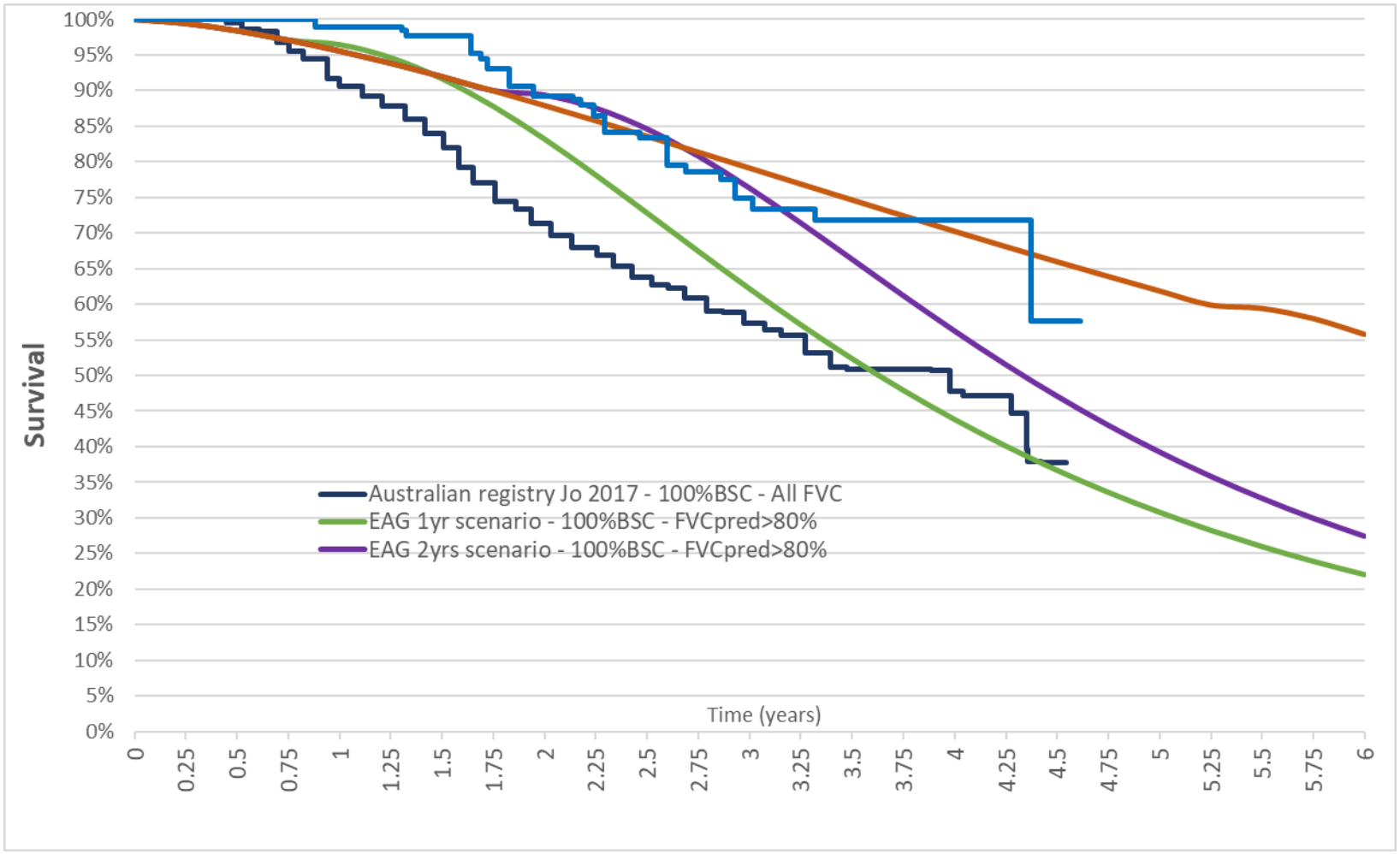
Moreover, the EAG OS estimates for the base case analysis based on the 5.5 years scenario are not reasonable because they are of the same magnitude and even higher than the survival probabilities of the Australian Registry, where ~25% of the mild IPF subgroup were taking antifibrotics.

See also the justification provided above in this table in relation to page 16.</td>
<td>Not a factual inaccuracy. No change necessary.

This paragraph in the EAG report already states that 25% of patients were receiving anti-fibrotic therapy.</td>
</tr>
</table>

Page 75 Table 32 EAG observations of the key aspects of the company's economic model Fourth row, fourth column *'No difference in mortality for placebo vs nintedanib for FVC ≥80% predicted population. Mortality from whole trial population used after 5.5 years.'*	*'No difference in mortality for placebo vs nintedanib for FVC **>80%** predicted population. Mortality from whole trial population used **after 12 months.'***	See the justification about the use of 1 year scenario that we provided above in this table in relation to page 16 of the EAG Technical report.	As stated above, this is not a factual inaccuracy. No change necessary.
Page 79 6.2 EAG's preferred assumptions • *'Extrapolation of OS: For the first 5.5 years, we use the same survival curve for the best supportive care arm as for the nintedanib arm as the mortality rate for both arms is considered equal; thereafter we use the best supportive care survival curve from the whole trial population for the best supportive care arm.* '	• *'Extrapolation of OS: For the first **12 months,** we use the same survival curve for the best supportive care arm as for the nintedanib arm as the mortality rate for both arms is considered equal; thereafter we use the best supportive care survival curve from the whole trial population for the best supportive care arm.* '	See the justification provided above in this table in relation to page 16.	As stated above, this is not a factual inaccuracy. No change necessary.
Page 16 and throughout the whole EAG Technical Report. For example: *'Applying the EAG's assumptions for the extrapolation of the placebo arm, the ICER increases to [redacted] per QALY'.* *'Table 5 EAG deterministic base case results'* *'Table 35 EAG base case model results'* *Etc.*	**Could the EAG replace throughout the Technical Report all the ICERs (and relevant text) based on the 5.5 years assumption with the 12 months assumption of equal OS between nintedanib and BSC.**	To ensure that the ICERs are aligned with the revised base case settings based on the 12 months assumption of equal OS between nintedanib and BSC.	As stated above, this is not a factual inaccuracy. No change necessary. Also, please note the correct term for our report is 'the EAG report' and not the 'the Technical report'

Figure 1: OS comparison of Australian IPF registries (Jo 2017 and Jo 2018) versus EAG scenarios



Issue 4 Management of patients with IPF and a FVC >80% predicted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21 (section 2.2.4) *'Pirfenidone is not a comparator because it is not licensed for treating IPF patients with FVC >80% predicted.'*	'*Pirfenidone is not **an appropriate** comparator for this appraisal because it is not **recommended by NICE** for treating IPF patients with FVC >80% predicted.'*	The EAG statement is inaccurate. Pirfenidone is licensed for treating patients with mild to moderate IPF. There is no mention in the SmPC that it is not indicated for patients with FVC >80% predicted. Rather, pirfenidone is not an appropriate comparator for this appraisal because it is not recommended by NICE for patients with FVC >80% predicted. This restriction is enforced, as it is currently for nintedanib, using the Blueteq system.	This text has been corrected.

Issue 5 3.2.2.2. New evidence submitted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 34, top of the page • *'Drop-out rates were more variable across the trial arms (ranging from 6% to 23.3%) in the TOMORROW RCT but were similar between the licensed dose, nintedanib 150mg bd, (7*	• *'Drop-out rates were more variable across the trial arms (ranging from 6% to 23.3%) in the TOMORROW RCT but were similar between the licensed dose, nintedanib 150mg bd, (7 patients; 17.5%) and placebo trial arms (**8 patients**, 20.0%).'*	'9 patients' is not correct. It should read '8 patients', to match the source.	This text has been corrected.

patients; 17.5%) and placebo trial arms (9 patients, 20.0%).'			

Issue 6 3.2.2.2. New evidence submitted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 35 *'Analyses of the primary outcome in the INPULSIS and TOMORROW trials required patients to have a minimum number of on-treatment measurements (it is unclear if a baseline measurement was also required).'*	*'Analyses of the primary outcome in the INPULSIS and TOMORROW trials required patients to have a minimum number of on-treatment measurements* ***(including baseline measurement).***	This statement is inaccurate. In relation to the primary outcome, Table 7 'Comparative summary of trial methodology' and Table 14 'Summary of statistical analyses' in the CS do specify that baseline measurement was required. (E.g., in Table 7: *'Rate of decline in FVC (expressed in mL/ year), evaluated from baseline until 12 months of treatment, compared to placebo'*.)	We have amended the text to say "we assume a baseline measurement was also required but this is not explicitly stated in the CS)"

Issue 7 3.2.4.2 New evidence submitted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 39 *'No analysis for the subgroup of patients with FVC >80% predicted were conducted for*	*'No analysis for the subgroup of patients with FVC >80% predicted were conducted for* ***the TOMORROW*** *OLE* ***study****.'*	The EAG statement is inaccurate. The analysis of the rate of decline in FVC for patients with	This text has been corrected.

the INPULSIS-ON or TOMORROW OLE studies.'		FVC>80% predicted in INPULSIS-ON was provided in response to clarification question QA8 and Table 6. This is also referred to on pages 43-44 (section 3.3.4.1) of the EAG report.	

Issue 8 Table 17 Adverse events in INPULSIS-ON and TOMORROW OLE

Description of problem

Page 46

Table 17 Adverse events in INPULSIS-ON and TOMORROW OLE

Event n (%)	INPUSIS-ON (n=734)	TOMORROW OLE	
		Nintedanib 150 mg Twice daily (n=85)	**Comparator† (n=85)**
≥1 AE(s)	723 (98.5)	83(97.6)	84(98.8)
≥1 Severe AE(s) [a]	412 (56.1)	41(48.2)	50(58.8)
≥1 Serious AE(s) [b]	506 (68.9)	47(55.3)	55(64.7)
Fatal AE(s)	Not reported	12(14.1)	12(14.1)

Description of proposed amendment

Event n (%)	INPUSIS-ON (n=734)	TOMORROW OLE	
		Nintedanib 150 mg Twice daily (n=85)	**Comparator† (n=85)**
≥1 AE(s)	723 (98.5)	**84(98.8)**	**83(97.6)**
≥1 Severe AE(s) [a]	412 (56.1)	41(48.2)	50(58.8)
≥1 Serious AE(s) [b]	506 (68.9)	47(55.3)	55(64.7)
Fatal AE(s)	Not reported	12(14.1)	**31(36.5)**
≥1 AE(s) leading to treatment discontinuation [c]	313 (42.6)	48(56.5)	49(57.6)

Justification for amendment

The data entered by the EAG in the second row *'≥1 AE(s)'* and in the fourth row *'Fatal AEs'* for the comparator are incorrect and do not match the data in the CS.

EAG response

This table has been corrected.

≥1 AE(s) leading to treatment discontinuation [c]	313 (42.6)	48(56.5)	49(57.6)			

Issue 9 Section 4 Cost Effectiveness

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
From page 51 onwards, in order to refer to the FVC% predicted subgroups, the EAG has made use of ≥80% (but it should be >80%) and has made use of <80% (but it should be ≤80%).	Amendment of all the references to the target population as **FVC>80%** versus the population with FVC predicted level **≤ 80%.**	The use of the FVC80% predicted thresholds '≥80%' and '<80%' is inaccurate, because the FVC predicted level equal to 80% has been already covered by the recommendation in TA379 (FVC≤80% predicted population) and it is outside the scope of the current appraisal. We appreciate that the adapted cost-effectiveness model has maintained the FVC% predicted labels used in the original model (TA379) to define the health states, and this may have created confusion. We appreciate that we should have clarified that the labels in the original model have not been updated in the adapted model.	The EAG confirm TA379 covers patients with forced vital capacity (FVC) between 50% and 80%. The target population thresholds in the EAG report have been corrected to match the current NICE scope.
Page 81 Table 37 Scenario: hazard ratios for time to first acute exacerbation	Correction as detailed in the row above, also in relation to the **FVC 70% and FVC 90%** predicted subgroups.	The use of '<' and '≥' is inaccurate and does not match the sources.	This text has been corrected in line with the sources.

Issue 10 4.2.7.2 Study-based health related quality of life

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62 *'The economic model includes adverse events that had a substantial impact on costs and QALYs, had an incidence of more than 5% or an incidence 1.5 times greater than the comparator arm. These are: IPF exacerbations, gastrointestinal events (including mild-moderate diarrhoea at the request of the NICE Committee in TA379, and gastrointestinal perforation events), skin disorders, dizziness, anorexia and cardiac events.'*	*'The economic model includes adverse events that had a substantial impact on costs and QALYs, had an incidence of more than 5% or an incidence 1.5 times greater than the comparator arm. These are**: serious gastrointestinal events; serious cardiac events, gastrointestinal perforation and, at the request of the NICE Committee in TA379, mild-moderate diarrhoea**.'*	The statement is inaccurate. IPF exacerbations have not been implemented in the model as adverse events, but as health states. The list of adverse events included in the CS and the model were: serious cardiac events, serious gastrointestinal events, gastrointestinal perforations, and mild-moderate diarrhoea.	This text has been corrected.
Page 62 *'The company's search strategy did not identify any utility values for skin disorders, dizziness or anorexia.*'	**Delete the sentence**	This statement is superfluous, because Skin disorders, dizziness and anorexia are not relevant to the current appraisal comparison of nintedanib to best supportive care.	Not a factual inaccuracy, no change necessary. Skin disorders, dizziness or anorexia are listed as relevant adverse events in CS Table 154 (Eligibility criteria for the HRQoL search).
Page 63 *'Disutility values for other important adverse events are*	*'Disutility values for **the** adverse events are given in Table 21.'*	The EAG statement is inaccurate. The adverse events are serious cardiac events, serious	This text has been amended.

given in Error! Reference s ource not found.Table 21.'		gastrointestinal events, gastrointestinal perforations, and mild-moderate diarrhoea. There are no other important adverse events.	

Issue 11 4.2.8.3 Health state unit cost and resource use

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
'The EAG notes that the costs the company uses to calculate the total exacerbation cost do not appear to match the cited sources. We have corrected these [...], '	**Delete the statement**	The unit costs that the company used in the model did match the cited source, which is: "National Schedule of Reference Costs Version 2 - Year 2019-20 - NHS trusts and NHS foundation trusts" available at 2_National_schedule_of_NHS_costs_FY19_20_V2.xlsx (live.com) If the EAG's statement refers to the fact that the exacerbation costs reported in Table 108 in the CS do not match the unit costs implemented in the model, they are correct. The Company has already addressed this discrepancy in clarification question B1. However, it should be noted that the ICERs in the CS are based on the correct values as these were included in the model.	Total exacerbation costs are given as £4,627.58 in CS Section B.3.5, Table 108. The total exacerbation cost in the company's model is given as £4645.33 (CostInputs!S128); this is the same figure used in the EAG corrected model. This statement has been deleted.

Issue 12 5.2.2 Scenario analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 68 *'All other scenarios did not have a substantial impact on*	*'All other scenarios did not have a substantial impact on the ICER. **In these scenarios**, the ICERs ranged from [redacted] per QALY when transition probabilities for*	The EAG statement is imprecise, because the ICER range mentioned by the EAG does not cover scenario 16,	This text has been amended

the ICER. The ICERs ranged from [redacted] per QALY when transition probabilities for FVC ≥80% predicted and an alternative odds ratio for nintedanib were used (scenario 24) to [redacted] per QALY when the exacerbation coefficient was included (scenario 21).'	*FVC ≥80% predicted and an alternative odds ratio for nintedanib were used (scenario 24) to [redacted] per QALY when the exacerbation coefficient was included (scenario 21).'*	which was mentioned in a previous sentence.	

Issue 13 5.2.4 Company base case results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 69 *'The company did not run any scenarios based on acute exacerbations in the subgroup with FVC ≥80% predicted, because acute exacerbations were a rare event in the trials, especially in the FVC ≥80% predicted population (nine (2.4%) patients in nintedanib group and eight (4.2%) patients in the best supportive care group)'.*	*'The company did not run any scenarios based on acute exacerbations in the subgroup with FVC **>80%** predicted, because acute exacerbations were a rare event in the trials, especially in the FVC **>80%** predicted population (**seven** (2.4%) patients in nintedanib group and eight (4.2%) patients in the best supportive care group)'.*	The data reported by the EAG are inaccurate. The acute exacerbations for nintedanib are 7, not 9. See Table 15 in clarification question QB9, which was informed by the data reported in Maher 2015.	The '≥' in the sentence have been corrected to '>'. The Maher reference (Maher TM, Flaherty KR, Noble PW, Vancheri C, Wuyts WA, Kimura T, et al. Effect of baseline FVC on lung function decline with nintedanib in patients with IPF. 1 5 Diffuse Parenchymal Lung Dis. 2015;OA4499) is an abstract and does not provide detail about patients experiencing an acute exacerbation.

			2.4% of 295 patients receiving nintedanib (reported by Maher 2015) is seven. This text has been amended.

Issue 14 5.3.3 External validation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 71 *'The extrapolated survival curves for nintedanib and best supportive care, using log-logistic, Weibull, and generalised gamma distributions, were compared with the Australian IPF registry data, and the Greek IPF registry.'*	*'**In the CS the** extrapolated survival curves for nintedanib and best supportive care, using log-logistic, Weibull, and generalised gamma distributions, were compared with the Australian IPF registry data, the Greek IPF registry, **and the EMPIRE registry**. **The cost-effectiveness model also enables the comparison against the Finnish and the European IPF registries.** '*	The EAG statement is imprecise. In the CS, the validation against the EMPIRE registry has also been presented.	This text has been amended
Page 71 *'The company does not compare their model results to the European IPF registry[39] or the Finnish IPF registry'*	*'The company **has compared** their model results to the European IPF registry[39] and the Finnish IPF registry **in the model'***	The EAG statement is inaccurate. The validation versus the European IPF and Finnish registry was presented in the model: the Validation worksheet contains the datasets and the relevant plots for selecting the comparison with: EMPIRE,	This text has been amended

		EuroIPF, Australian, Greek, and Finnish registries.	
Page 71 *'For the first three years, the model curves for best supportive care and nintedanib closely match the Australian IPF registry survival data for patients.'*	*'For the first three years,* ***all the 3 best fitting parametric curves log-logistic, Weibull and generalized gamma*** *for best supportive care and nintedanib closely match the Australian IPF registry survival* ***data. After year 3, the closest and most plausible fit is provided by the log-logistic curve.****'*	The EAG statement is imprecise.	We have amended the text to say: *For the first three years,* ***all the 3 best fitting parametric curves log-logistic, Weibull and generalized gamma*** *for* ~~***best supportive care and***~~ *nintedanib closely match the Australian IPF registry survival* ***data. After year 3, the closest*** ~~***and most plausible***~~ ***fit is provided by the log-logistic curve.****'* The pattern is similar for best supportive care, except the parametric curves start to deviate from the registry data after 2 years.

Issue 15 5.3.4 EAG corrections to the company model

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Page 72 Table 27 Model procedure and adverse events costs (after inflation)	**Removal of the cost corrections from the report and from the**	The Company is unable to retrieve the unit costs data used by the EAG in their model. The screenshot below provides an example that the unit costs used	The company appears to have supplied a different

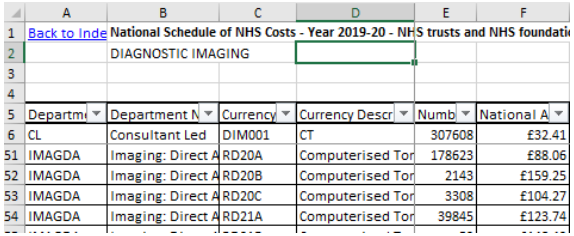
	Original costs in CS (£)	Corrected costs (£)
Procedure		
Chest HRCT	£97.48	£97.96
Chest X-ray	£33.65	£33.73
Adverse events		
Serious GI	£2967.90	£2945.14
Serious cardiac	£2759.99	£2687.84
GI perforation	£3005.92	£2974.34

Original costs taken from CS Table 112, corrected costs calculated by the EAG
Abbreviations: GI, gastro-intestinal; HRCT, high-resolution computed tomography
[a] Costs are from the National Schedule of NHS Costs (2019-20)

scenarios, and removal of Table 27.

by the Company do match the source used in the CS. Therefore, it seems that the EAG have used a different source. However we believe our source is appropriate, and therefore the EAG report should not state that the current costings required corrections. Could the EAG provide their source and justify the preference for using their source over the CS source.

Source used in the CS:
2_National_schedule_of_NHS_costs_FY19_20_V2.xlsx (live.com)



	A	B	C	D	E	F
1	Back to Inde	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundati				
2		DIAGNOSTIC IMAGING				
3						
4						
5	Departme	Department N	Currency	Currency Descr	Numb	National A
6	CL	Consultant Led	DIM001	CT	307608	£32.41
51	IMAGDA	Imaging: Direct A	RD20A	Computerised Tor	178623	£88.06
52	IMAGDA	Imaging: Direct A	RD20B	Computerised Tor	2143	£159.25
53	IMAGDA	Imaging: Direct A	RD20C	Computerised Tor	3308	£104.27
54	IMAGDA	Imaging: Direct A	RD21A	Computerised Tor	39845	£123.74

verion of the NHS costs for 2019/20 in their reference pack. The EAG agrees that the company costs are consistent with those from V2 of the NHS 2019/20 costs.

We have removed the cost corrections and Table 27 and updated all EAG results.

Issue 16 Appendix 9.2. Comparison of company and EAG critical appraisal of OLE studies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 97 Table 43 *'The rate of sample slippage in relation to the numbers randomized in the preceding RCT would therefore appear to be higher than average.'*	*'The rate of sample slippage in relation to the numbers randomized in the preceding RCT would therefore appear to be higher than average.* ***However, this should be weighted against the fact that the study follow-up was considerably long****'.*	The EAG statement is not balanced. Bowers recommended that '*the length of follow-up should be considered in making this assessment'.*	Not a factual inaccuracy. No change made
Page 98 Table 43 *'The published version of the TOMORROW trial extension lacks a clearly reported rationale for the study and does not state specific objectives'*.	*'The published version of the TOMORROW trial extension* ***has reported the rationale for the study in the Abstract. The specific objectives have been specified on page 581'***.	The statement is inaccurate. In the abstract of the publication, the authors stated: *"The study rationale was to ascertain the adverse events (AEs) profile and benefit of nintedanib beyond the 52 weeks TOMORROW trial duration".* The objectives were stated on p. 581: To *"[..] present efficacy and safety data from TOMORROW periods 1 and 2 and the open-label extension". "All endpoints were exploratory [….]. Analyses were descriptive with no formal statistical comparisons between group".*	Not a factual inaccuracy. No change made It is possible to infer the study objectives from the information reported in the journal article, however, there is no *clearly reported statement on the purpose* of the study e.g. we can find no mention of 'objectives' or 'rationale'

Issue 17 3.5.2.1 Outcome measures included

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 47 *'Individual parametric survival curves were fitted to both the nintedanib and placebo arms given some (inconclusive) evidence of an early proportional hazards violation'.*	*'Individual parametric survival curves were fitted to both the nintedanib and placebo arms given **some evidence** of an early proportional hazards violation'.*	The EAG statement is inaccurate and not balanced. Some evidence is conclusive (based on the log-cumulative hazard plot), and some evidence is inconclusive (P value > 0.05). The choice of the independent models was therefore based on 'some evidence' namely the part of the evidence which was conclusive.	Not a factual inaccuracy. However, we have replaced 'inconclusive' with 'inconsistent' as this better describes the uncertainty regarding proportional hazards.

Issue 18 Uncertainty in whether all relevant observational study evidence has been included in the systematic literature review

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 1 on page 11: *'Uncertainty in whether all relevant observational study evidence has been included in the systematic literature review'*	**Removal of this statement**	The PICO criteria were applied consistently and rigorously when making include/ exclude decisions at all the screening stages of the SLR process. Therefore, the expectation is that all relevant non-randomised or observational studies had been included. All studies which met the PICO criteria for the SLR were extracted in a data extraction workbook. The EAG's concern is therefore not justified.	Not a factual inaccuracy. No change necessary. The SLR inclusion criteria permit inclusion of a wide range of study designs, including observational studies. The SLR includes the (observational) open-label extension studies from the pivotal RCTs. However, the inclusion/exclusion status of other observational evidence in the SLR is not clear. For example, CS Table 137 (List of references included in the SLR) includes the Greek registry study by Antoniou et al 2020. This study cited in various sections of the CS for comparison/validation of clinical effectiveness estimates but there is no further mention of its inclusion/exclusion status beyond Table 137.

In the table on page 13, under "Description of issue and why the EAG has identified it as important", it states: *'The company has not explicitly described the rationale for including non-randomised and observational studies, or the criteria for their inclusion/exclusion.'*	**Removal of the final clause of this sentence ("or the criteria for their inclusion/exclusion.")**	The inclusion/ exclusion criteria are reported in Table 134 in Appendix D of the company submission and were the same regardless of the study design. Observational studies were not specified in the exclusion criteria and were therefore included in the SLR¥.	We have removed this sentence.
On page 26; line 15, it states that '*The EAG notes that the lack of consistency in the application of the PICO selection criteria to the full text articles raises the question of whether ad hoc exclusion criteria were also applied to records excluded at the title and abstract screening stage of the SLR. If so, then this suggests a bigger risk of bias in the selection of clinical effectiveness studies informing this appraisal'.*	**Removal of this statement**	At title/ abstract as well as full text review, the PICO criteria were applied consistently when making include/ exclude decisions. All studies which met the PICO criteria for the SLR were extracted in a data extraction workbook, including the observational studies described in Section 3.1.2 in the EAG report. The observational studies were included in Table 135 and 136 in the company submission. By this definition, these studies were included in the SLRs rather than being excluded ad hoc. These studies were however, not considered relevant to the decision problem for the reasons described in the clarification questions (A1a). Therefore,	The reporting of the results of inclusion/exclusion screening were sufficiently unclear that we asked for clarification. The company's response mentioned additional, not previously disclosed, exclusion criteria had applied to full texts, based on their relevance to the decision problem. These additional criteria are not listed in the PICO criteria, or anywhere else in the CS. We therefore maintain that it is not implausible to assume that other such undisclosed criteria may have been applied ad hoc at title/abstract stage.

		they were not included in the clinical section of the company submission or used to inform the cost-effectiveness analysis.	
On page 26; line 21, it states that "INPULSIS-ON and TOMORROW OLE are the only non-randomised studies included. The EAG is unable to verify whether any other relevant non-randomised or observational studies may have been excluded from the company's SLR"	**Removal of the final sentence.**	The PICO criteria were applied consistently and rigorously during screening; therefore, the expectation is that all relevant non-randomised or observational studies had been included. The EAG's concern is therefore not justified.	Please see our responses above
On page 26, it states that "We are therefore unclear whether all the relevant evidence has been identified"	**Removal of this statement**	As described above, the PICO criteria were applied consistently, and as a consequence the expectation is that all relevant evidence had been captured. The EAG's concern is therefore not justified.	Please see our responses above
Table 39 in Appendix 1 under *"Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?*", the EAG has put *"unclear"* as "*The CS does not state who performed the risk of bias assessments."*	**Change from "unclear" to "Yes"**	The company submission states that "CRD guidance was followed" during the quality assessment. In accordance with CRD guidance page 43, the quality assessment was undertaken by two researchers (in the data extraction workbook, a QC on the quality	Not a factual inaccuracy, no change necessary. In order to make an informed critical appraisal of the SLR methodology there needs to be clear reporting of all methodological

		assessment was conducted by an independent researcher).	procedures. It is insufficient to cite published methodological guidance with the expectation that the reader will infer all recommended procedures were followed. See PRISMA 2020 for current reporting standards for systematic reviews. Also, it should be noted that the workbook mentioned by the company has not been made available to the EAG and does not appear to be in the public domain.

[¥]With regards to issue 1, the rationale for including observational studies and non-randomised trials in the efficacy and safety SLR was to identify data relating to longer term survival beyond that of the relevant clinical trials, particularly in patient populations relevant to UK clinical practice. The inclusion and exclusion criteria were the same regardless of study design, as shown in Table 134 in Appendix D. The company acknowledges that this rationale may not have been clearly stated in the company submission and therefore it may have been unclear why some observational studies were not included in the clinical section as supporting evidence despite being included in the SLR.

Issue 19 EAG comment on the NMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 48, conclusive paragraph *'Given that pirfenidone is no longer a relevant comparator treatment in the decision problem, the EAG suggests a more appropriate approach would be a pairwise meta-analysis of nintedanib versus placebo from the INPULSIS I and II and TOMORROW trials, stratified by FVC% predicted subgroups.'*	To add at the end of the paragraph: ***'However, the EAG acknowledges that:*** ***1) The Company has conducted pairwise comparisons between nintedanib and placebo for the FVC>80% predicted subgroup in response to the clarification questions. This subgroup analysis came from pooled TOMORROW and INPULSIS trials data.*** ***2) The Company has provided the results from the pooled analysis in the CS in a table above each of the NMA results.*** 3) ***The results are exactly the same or very close. Therefore, the EAG support Company's conclusion that using the pooled data (from the whole population) would not have had a large impact on the CEA.***	We recommend that the EAG comment on page 48 of the Technical report is put into context in order to provide the reader with complete factual information. If the EAG consider that the NMA is effectively redundant then the pooled analysis the Company has undertaken is the most appropriate evidence. Furthermore, there is no evidence of a difference between the FVC >80% predicted subgroup and the overall population in terms of the primary endpoint, as demonstrated in the nintedanib study by Maher et al. 2015. The Australian registry study by Jo et al, 2018, is also supportive, as the study showed no difference in the annual decline in FVC% predicted between mild and moderate-severe groups.	Not a factual inaccuracy. However, for clarity we have added the following sentence to the end of the paragraph: "The CS reports the results of the pooled analysis of the INPULSIS trials alongside the results of the NMA. The EAG notes that the results of these two sets of analyses (based on the whole trial population) are similar."

Issue 20 3.2.1.5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 31 *'331 (76.6%) of the 432 randomised patients from the parent trial completed the planned observation time.'*	*'**316 (73.1%)** of the 432 randomised patients from the parent trial completed the planned observation time.'*	This statement is inaccurate (data reported are not correct).	We have corrected this figure

Issue 21 Summary of EAG's preferred assumptions and resulting ICER

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18 Table 1 EAG deterministic base case results (using PAS price for nintedanib) Technology / Total: Costs, LYG, QALY BSC: £23,240, 5.17, 4.49 Nintedanib: [redacted], 7.20, 5.62	Technology / Total: Costs, LYG, QALY BSC: £23,240, **5.71**, 4.49 Nintedanib: [redacted], 7.20, 5.62	This statement is inaccurate. The value reported reported for LYG does not match the EAG model results.	This typographical error has been corrected.

Issue 22 Summary of EAG's preferred assumptions and resulting ICER

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
'Using the hazard ratio for the time to first acute exacerbation in the FVC 70% predicted subgroup also increases the ICER over the willingness-to-pay threshold of [redacted] per QALY'.	*'Using the hazard ratio for the time to first acute exacerbation in the FVC 70% predicted subgroup increases the ICER to [redacted].'* OR *'Using the hazard ratio for the time to first acute exacerbation in the FVC 70% predicted subgroup increases the ICER **just** over the willingness-to-pay threshold of [redacted] per QALY.'*	This statement does not inform the reader accurately.	This sentence has been corrected using the second option.

Issue 23 EAG model spreadsheet Exacerbation worksheet

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Acute exacerbation rate EAG probabilities FVC > 70% 1.05% FVC < 70% 2.58%	EAG probabilities FVC **≥ 80%** 1.05% FVC < **80%** 2.58%	The labels used in the model in are not accurate.	The labels in the !Exacerbation sheet have been corrected.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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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 redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for your response is **5pm** on **21 October 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Felix Chua
2. Name of organisation	Royal Brompton Hospital, part of Guy's & St Thomas' Hospital NHS Foundation Trust, London
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? ☒ A specialist in the treatment of people with idiopathic pulmonary fibrosis? ☒ A specialist in the clinical evidence base for idiopathic pulmonary fibrosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The principal aim of treating IPF when the FVC is >80% predicted is to reduce the rate of disease progression and in some cases, halt it for a period. Forestalling fibrotic progression in this manner can have positive consequences including delaying the onset respiratory disability and possibly prolonging survival. It should be remembered that symptoms are related to multi-domain deterioration of lung physiology and that the gas transfer factor (TLco) is typically lower than the FVC at any point during the disease course. Thus, instigating potentially disease-modifying treatment of IPF when the person's FVC is still >80% predicted means potentially dampening the decline in other parameters when the disease is still amenable to intervention.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Stabilisation (i.e. non-changing) lung function or a decreased rate of lung function decline (e.g. loss of FVC of <10% in absolute terms per annum). In a very few cases, lung function may even increase slightly some months after initiating antifibrotic treatment but unravelling genuine improvement from improved performance at lung function testing is challenging.
10. In your view, is there an unmet need for patients and healthcare professionals in idiopathic pulmonary fibrosis?	There are two key unmet needs in IPF: (1) the ability to consistently achieve earlier diagnosis of those affected, and (2) the unmet need that directly results from the prevailing situation where patients with an FVC >80% are not able to access antifibrotic treatment that could positively alter the natural history of their disease and the consequential benefits that come with this.
11. How is idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Current management consists of symptom-based care – oral steroids, oxygen, pulmonary rehabilitation, psychological support, anti-reflux therapy, prophylactic antibiotics and treatment of secondary cardiac complications. It is inarguable that none of these inputs, alone or in combination, constitute 'best care'. The practice guidelines that are most widely used are the ATS/ERS/JRS/ALAT Clinical Practice Guideline for IPF, 2018 (and updated in 2022) as well as NICE TA379 (nintedanib for IPF) and TA504 (update of TA282; pirfenidone for IPF). At present, there is no clearly defined pathway of care for those with FVC >80% predicted; as a result, there is variation in practice/care relating to uneven

• What impact would the technology have on the current pathway of care?	availability and timing of specialist Respiratory input, oxygen assessment and provision as well as access to pulmonary rehabilitation. The current technology, by enabling access to nintedanib when FVC is >80% predicted, would grant these individuals access to a treatment proven to slow the progression of IPF and thus significantly and genuinely transform the care of people with this devastating disease.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology would represent a critical disease-targeting add-on therapy to conventional care in NHS practice. The main difference in healthcare resource utilisation would mainly be at the level of tertiary care (antifibrotic prescribing centres), to a lesser extent secondary care (co-sharing of clinical monitoring) and primary care (monthly blood test monitoring, for the majority this is for no more than 6 months). The technology should be used in tertiary care where dedicated multi-disciplinary specialist ILD teams work and are able to supervise the diagnosis, evaluation and commencement as well as dispensing of antifibrotic treatment. Any additional investment would be in the form of increased clinician, specialist nursing and pharmacist time at the tertiary or prescribing centre; an expansion of existing antifibrotic treatment set-up, in other words.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, as experience from treating people with FVC 50-80% predicted since 2014 has shown. I expect the technology to increase the length of life, based on its proven efficacy in delaying fibrotic disease progression. In closely-monitored cohorts including but not restricted to phase III trials, divergence in survival (as a grouped analysis) is evident between 3 – 6 months after initiating nintedanib. People with IPF who are able to adhere to treatment with manageable side effects are those with the greatest potential for therapeutic benefit, including the opportunity to lengthen their life. I think the technology might increase health-related quality of life more than current care in a small subgroup of patients, especially if it leads to preservation

	of FVC around the 70 – 90% predicted mark for a period longer than in the untreated state. However, I cannot quantify the size of this subgroup.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be more effective for people with IPF with FVC >80% predicted; anecdotally, such people might also tolerate the treatment better. Moreover, initiating treatment when the condition is so-called 'very mild' (but still potentially progressive) also means an opportunity for longer treatment, thereby maximising the drug's potential for slowing down the intrinsically progressive nature of IPF. In my view, the technology would not be effective for people whose primary disability and symptoms were caused by a disease other than IPF (e.g. severe heart failure) or if they have very severe IPF, i.e. nominally accepted as FVC <40% predicted.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology would involve monthly blood monthly for an initial period (3-6 months typically) but not necessarily more lung function or imaging tests compared to current care. Lung function monitoring at 9-12-month intervals is conventional for people on nintedanib treatment, as it is for the majority of those with IPF following current care. The technology is associated with potential but well-understood adverse effects – management of these require specialist nursing +/- pharmacist and clinician input. Development of gastrointestinal side effects may mandate the use of anti-emetic and anti-diarrhoeal treatment.
16. Treatment with nintedanib in the NHS is stopped if disease progresses in any 12-month period. **If a formal rule was not implemented for the technology, would informal rules be used to stop treatment with this technology? If yes, what specific measures would be used for this?** **If a formal rule was not implemented for the technology, on average, how long would you expect people to receive the technology before discontinuing?**	Informal and ad hoc rules are employed by all NHS treatment centres and include temporary or permanent cessation of nintedanib if adverse effects are severe, or if the treated individual requests cessation due to poor tolerability. Such informal rules are implemented after discussion between the patient and the specialist nurses and their physicians. The drug is also permanently ceased if there is clearly no therapeutic gain, i.e. the disease remains inexorably progressive and the individual's clinical situation is irrevocably declining. These scenarios are far less applicable/likely in those with FVC >80% predicted. In the absence of a formal 'stop' rule, I would envisage that there would be a substantial group of people tolerating and continuing the treatment for at least 2 -

	3 years. In my experience, those who have tolerated nintedanib for 5 years or more constitute less than 10% of the treated cohort at my institution.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The use of this technology will result in substantial health benefits for people with IPF who are currently not able to access treatment, namely those with FVC >80% predicted. In my view, the health-related benefits will extend beyond parameters included in the calculation of QALY. Data from phase III trials as well as extension and open-label studies have shown unequivocally that IPF with FVC in that range is associated with potential for progression, similar to disease characterised by FVC <80% predicted. The technology is home-based orally administered treatment, similar to other aspects of current care involving medications. Sadly, the instruments that are employed to assess quality of life do not sufficiently capture all the benefits of such treatment because of the difficulty in quantifying some benefits (while others are nuanced). It should also be remembered that patients on nintedanib 'self-select' for remaining on treatment, i.e. those with greater tolerability and generally taking fewer other drugs (typically when their FVC is higher) will remain on the antifibrotic for longer.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I consider this is to be the case; the technology would be clearly be a step change for many people with IPF; approximately 30 – 40% of incident and prevalent cases of IPF are people with FVC at or above 80% of predicted. Hitherto, they have not been able to receive treatment that could curtail the progression of their condition. Thus, the option for them to access this technology would represent a positive paradigmatic change. In this sense, the technology directly addresses a major current unmet need.

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?	Development of adverse effects of the technology, depending on their severity and impact on the patient, may require a dose reduction or temporary suspension of treatment to enable the side effects to abate or be actively managed. Quality of life may be affected by adverse effects to a varying extent but in all antifibrotic treatment centres, specialist nurses and doctors are available to advise and help affected patients and their families/carers. The impact on their quality of life may thus be temporary; however, like all other forms of medical therapy, the drug may need to be permanently ceased if side effects prove severe or intolerable.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The clinical trials of the technology broadly and mostly reflect UK clinical practice. Importantly, individuals with a range of FVC above 50% predicted were included with no upper FVC limit. The most important outcomes were a smaller annual rate of FVC decline and a higher proportion of patients, compared to placebo, who experienced a decline in FVC of 5% or greater. Additionally, patients treated with nintedanib experienced a longer time (interval) to their first acute exacerbation episode as a pooled analysis. Surrogate outcome measures may not reliably predict long-term clinical outcomes; in the trials, quality of life scores did not reach statistical significance. I am not aware of any new adverse effects that have emerged since the trials; in clinical practice, the frequency of all-severity diarrhoea is lower than in the trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No. All data pertaining to subgroup analyses (including preserved FVC, i.e. above either 70% or 80% predicted) have been captured by systematic review. In short, there is efficacy data for the range of FVC above 50% predicted, and no new adverse effect signals have been demonstrated since the trials.
22. How do data on real-world experience compare with the trial data?	In my experience, real-world experience has mirrored trial data.

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	The main inequalities concern a lack of equity to access treatment in people with IPF whose FVC is deemed 'too high' to qualify for nintedanib (or for that matter, pirfenidone, the other antifibrotic agent). At present, unintentional antifibrotic treatment discrimination affects the following groups: 1. Patients with **concomitant emphysema** in whom the %-predicted FVC is often >80% but for whom a disproportionate reduction in gas transfer factor is evident, 2. Patients with **large constitutional (pre-morbid) lungs** and who therefore need to experience more progressive IPF before their FVC falls below the 80% predicted boundary, 3. **Older patients** because %-predicted FVC reference values based on the European Community for Coal and Steel (ECCS), the most widely used system in England, were estimated by regression equations and not based on detailed measurements of lung function in specific age groups. Reference ranges for females have also been taken as 80% of the values for men. In my opinion, this technology evaluation should not exclude any group of persons, especially the three groups cited above. In my opinion, no other group of individuals who are protected by the equality legislation are excluded. I do not think that the technology appraisal will lead to an adverse impact on the disabled.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

1. People with IPF who have an FVC >80% predicted are currently inequitably prevented from accessing potentially disease-modifying antifibrotic treatment (the technology under partial review being nintedanib).
2. Inability to access treatment for this group of individuals, as predicated by existing NICE recommendations, represents a key unmet clinical need.
3. In evidential terms, subgroup analyses of the trials have demonstrated that the technology (nintedanib) has therapeutic efficacy when the FVC is >80% predicted.
4. Post-trial real-world experience mirrors the findings of the randomised controlled studies, including efficacy at curtailing the progression of IPF and the adverse effect profile of the drug (no new adverse effects or concerns have emerged).
5. Current inequalities surrounding the inability to access the technology (nintedanib) involve three subgroups of individuals whose FVC is >80% predicted by dint of: concurrent emphysema, the result of large premorbid lungs and the elderly, for whom certain reference equations for calculating %-predicted FVC may be disadvantageous.

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Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Clinical expert statement

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Part 1: Treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Simon Hart
2. Name of organisation	Hull University Teaching Hospitals NHS Trust/ Hull York Medical School
3. Job title or position	Consultant physician/ Reader in Respiratory Medicine
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 idiopathic pulmonary fibrosis? ☒ A specialist in the clinical evidence base for idiopathic pulmonary fibrosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

8. What is the main aim of treatment for idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Slow progression with the aim of improving 5-year survival Reduce exacerbations of IPF
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduce rate of lung function decline by 25-50%
10. In your view, is there an unmet need for patients and healthcare professionals in idiopathic pulmonary fibrosis?	Certainly. IPF remains a terrible disease with prognosis worse than most cancers.
11. How is idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are no approved treatments. We try to offer a clinical trial if available, but trial inclusion criteria are restrictive to most patients don't qualify. (https://erj.ersjournals.com/content/46/suppl_59/OA4501) Generally, for IPF we consider non-drug options such as pulmonary rehabilitation and supplemental oxygen, but patients with FVC>80% are typically not terribly breathless and not hypoxaemic, so these options are rarely used in this group. Guidelines: International IPF treatment guideline (https://www.thoracic.org/statements/resources/interstitial-lung-disease/IPF-Full-length.pdf) This guideline makes recommendations for and against treatments based on evidence. There is no mention of FVC cut-off criteria since this is a regulatory decision. Pathway: This is standard across ILD centres in the NHS. Impact: Offering nintedanib, an anti-fibrotic therapy, for IPF patients with FVC>80% would permit early treatment of IPF. Patients and clinicians want this

	because early intervention with a disease-modifying therapy makes perfect sense – to slow the disease down before it causes irreparable lung damage, disabling symptoms, and impaired quality of life. Combined evidence from clinical trials supports that nintedanib slows disease progression similarly regardless of FVC.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Patients would be treated in specialist ILD centres in secondary care as currently. The only difference is that patients with FVC>80% would be offered nintedanib, instead of current practice which is to monitor FVC every 6-12 months until lung damage progresses to such an extent that FVC drops to 80% or less. No immediate investment required, ILD centres would need to look at their workload and staffing since patients on antifibrotic drug therapy require close monitoring.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, I expect that slowing the rate of lung function decline by approximately 50% would translate into a doubling of life expectancy, on average. In terms of QoL, antifibrotic drug therapy with nintedanib has not been shown to improve QoL scores in clinical trials over 52 weeks, but trials have been underpowered for QoL. In real life, over longer periods of time, I expect that slowing lung function decline will translate into better QoL compared with current practice (no treatment).
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, analysis of trial data from patient subpopulations shows a consistent effect of nintedanib across all groups.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Current care is no treatment, whereas drug therapy with nintedanib requires frequent monitoring (including blood tests) and hospital visits.
16. Treatment with nintedanib in the NHS is stopped if disease progresses in any 12-month period. **If a formal rule was not implemented for the technology, would informal rules be used to stop treatment with this technology? If yes, what specific measures would be used for this?** **If a formal rule was not implemented for the technology, on average, how long would you expect people to receive the technology before discontinuing?**	IPF is always progressive, with or without antifibrotic drug therapy, so a formal stopping rule is nonsensical. In general, decisions about stopping therapy should be pragmatic and based on discussion and agreement between patient and clinician. For example, if side effects are intolerable, or if IPF progresses such that the patient is approaching end of life, then typically a mutual decision is made to stop therapy. Please note that this reflects current NHS practice for patients treated with nintedanib with FVC<80%. End of life issues don't apply to the technology under review here since patients with FVC>80% are those with milder, earlier disease.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	I am not a health economist so I do not feel qualified to respond to this question.

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, because current therapy is no treatment.
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?	ILD clinics are well versed in managing patients on nintedanib therapy since it was approved in 2016, including dealing with side effects.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No, the trials include patients with FVC >80%, and UK practice currently excludes these patients from being offered antifibrotic therapy. Discussions about the trial primary outcomes (FVC) have been well rehearsed by NICE and others over the last 8 years since the INPULSIS trials results were published. Lots of real life data have not revealed any new adverse effects.
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?	Lots of real world data have been published, some in abstract form, and are consistent with clinical trial data.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into	Patients with co-existing emphysema and IPF are currently disadvantaged because the emphysema pushes up the FVC, making it more likely that the FVC is >80% and therefore currently ineligible for therapy. Application of this

account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	technology would correct that injustice. A similar argument applies to patients who happen to have larger than average lungs to start with, whereby the FVC is often >80% despite CT scan evidence of severe lung damage. The proposed technology would not introduce any new EDI issues.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

IPF is always progressive, regardless of FVC, leading to a prognosis worse that most cancers.

The aim for patients with IPF and FVC>80% is to slow progression of lung damage.

There are no currently approved treatments on the NHS for IPF patients with FVC>80%.

Offering nintedanib to IPF patients with FVC>80% would start slowing progression of IPF before it causes irreparable lung damage

Application of this technology would correct the injustice of disease-modifying therapy being currently denied to patients with larger lungs, such as those with co-existing emphysema.

Thank you for your time.

Your privacy

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Single Technology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted (part-review of technology appraisal guidance 379) [ID4062]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted or caring for a patient with idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted .The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **21 October 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with idiopathic pulmonary fibrosis in people with a forced vital capacity above 80% predicted

Table 1 About you, idiopathic pulmonary fibrosis (IPF) with a forced vital capacity above 80% predicted, current treatments and equality

1. Your name	Bob Bray
2. Are you (please tick all that apply)	☐ A patient with IPF? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with IPF? ☒ 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 and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience

Patient expert statement

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with IPF? **If you are a carer (for someone with IPF) please share your experience of caring for them**	I agree with the APF statement submitted. My own situation was having been a firefighter in London for over 40 years and before the health & safety work act (1974) I was convinced that my diagnosed IPF in 2018 was due to my exposure to various smoke & chemicals. Unfortuately I lost my older brother to IPF in 2016 which indicates my condition is famile. My FVC was above 80% and so not entitled to antifribrotics. Which is very hard to understand especially knowing the outcome of IPF. I was advised to purchase them from India online and did so. All indications are that it is slowing the progression down. It was very hard to understand and to have to self fund my antifribrotics which basically was costing me my state pension which I had worked for. It all just seems so unjust and unfair . This is my patient impact statement.
7a. What do you think of the current treatments and care available for IPF with a forced vital capacity above 80% predicted on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for IPF with a forced vital capacity	

above 80% predicted (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of nintedanib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nintedanib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
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 effects you have heard about, please describe them and explain why	
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	
12. Are there any potential equality issues that should be taken into account when considering IPF in people	

with a forced vital capacity above 80% predicted and nintedanib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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