NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nintedanib for treating progressive fibrosing interstitial lung disease [ID1599]

Contents:

The following documents are made available to consultees and commentators:

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

Nintedanib for treating progressive fibrosing interstitial lung diseases excluding idiopathic pulmonary fibrosis

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
NA	Consultee (company)	Boehringer Ingelheim	**Key points** **1. The committee have commented that nintedanib's treatment effect may decrease in the long term, but available data do not support this conclusion.** o The INBUILD trial was not designed to assess data beyond 52 weeks. The analysis of change in FVC (mL) up to database lock (DBL) 2 has important methodological limitations due to a healthy survivor bias observed in the placebo arm which underestimates the treatment effect of nintedanib. o Time-to-event analyses (absolute decline in FVC % predicted >5% and >10%) show consistent treatment effect over time up to DBL2.(1) o Data from INPULSIS-ON and a Greek registry in idiopathic pulmonary fibrosis (IPF) have shown that nintedanib has a sustained treatment effect over time.(2, 3) o Data from registries and meta-analyses have shown that nintedanib is associated with a significant long-term survival benefit compared with non-antifibrotic treatments.(4-6) o Overall, the conclusion that there is insufficient evidence of survival benefit, or that there is substantial likelihood of a treatment waning effect is not a reasonable interpretation of the evidence. It also does not take into account the full body of relevant evidence. **2. The committee have commented that they were not presented with the algorithm chosen by the company to estimate FVC % predicted and that they would like to see how this was done.** o FVC % predicted was reported as a secondary endpoint in the INBUILD trial. This was calculated according to the Global Lung Initiative (GLI) equation.(7) **3. The committee have commented that it is unclear whether the primary endpoint measured by FVC in millilitres per year over 52 weeks reflects a clinically meaningful change as measured by FVC % predicted.** o Published literature suggests that the change in FVC % predicted reported in INBUILD is clinically meaningful.(8) o Pre-specified analyses from INBUILD showed that treatment with nintedanib	Thank you for your comment. Please see responses to individual comments below.

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			reduced the proportion of patients with both a relative and absolute decline from baseline of >10% and >5% at week 52.(9) These declines are associated with mortality in ILD.(10) o Meta-analysis of nintedanib clinical trials in IPF, PF-ILD and systemic sclerosis-associated ILD show a strong association between annual rate of change in FVC % predicted and risk of death.(11) o The difference in FVC reported in INBUILD, measured in both mL and % predicted, was similar to that reported in INPULSIS.(9, 12) Clinical experts and patient groups agree that this difference has been meaningful for patients with IPF, as well as those receiving nintedanib for PF-ILD under named patient supply. **4. The committee have commented that the impact of restricted concurrent NHS treatments on the treatment effect of nintedanib is unclear.** o Post-hoc analyses of the INBUILD trial excluding all patients who took prohibited or restricted medications over 52 weeks were very similar to the primary analysis. This indicates that the treatment effect was not influenced by the use of restricted and prohibited medications.(13) o Post-hoc subgroup analyses from INBUILD have shown that the effect of nintedanib on reducing FVC decline was not influenced by the use of glucocorticoids, a type of immunomodulatory medication, at baseline.(13) o Clinical experts treating interstitial lung diseases at specialist tertiary centres in the UK also agree that restricted medications would not be expected to have any meaningful efficacy in the treatment of progressive fibrosing disease. **5. The committee have commented that there are uncertainties in the company's modelling and validation for overall survival in the placebo arm, and that this likely overpredicts deaths in the placebo arm.** o If plausible alternative survival curves with more optimistic survival for the placebo arm are selected, nintedanib remains cost-effective. o The ICER for nintedanib is only not cost-effective if clinically implausible curves are selected. **6. The committee have commented that there are uncertainties in fitting individual parametric distributions to the nintedanib and placebo arms, and that modelling resulted in ever-increasing survival benefits for nintedanib compared with placebo in the extrapolated periods.** o Independent survival models were used for consistency across outcomes, as the proportional hazards assumption was not met for the time to discontinuation outcome. o The original company base case is based on Bayesian analysis, the shape of which is informed by the long-term clinical trial data for nintedanib in IPF. However,	

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			we take the committee's point of view that there is uncertainty particularly for the placebo arm. ○ If reasonable alternative survival curves are selected that reduce the modelled difference in survival between nintedanib and BSC, the ICER remains cost-effective. **7. The committee have commented that there are uncertainties in the company's modelling of exacerbations and decline in lung function because of their lack of a link with mortality in the model.** ○ We acknowledge that this is a limitation of the current model, which was necessary to avoid double counting deaths. We did look into changing the structure of the model to include a link between mortality and exacerbations and decline in lung function, but this model generated unrealistically high life years for both BSC and nintedanib due to additional uncertainties generated by this approach. ○ Since the committee commented that the modelling of exacerbations and decline in lung function was acceptable, and since the main driver of the cost-effectiveness is the survival analysis, we do not believe that these limitations significantly impact the economic case for nintedanib. **8. The committee have commented that the modelling of stopping treatment was uncertain and may have underestimated the costs of nintedanib.** ○ Exploratory analyses have shown that selecting a different distribution for discontinuations still results in a plausibly cost-effective ICER for nintedanib. ○ The modelling of discontinuations was deemed to be acceptable by the Evidence Review Group. **9. The committee have commented that nintedanib does not meet NICE's criteria for an innovative treatment, due to shortcomings in the company's modelling.** ○ Clinical experts and patient groups unanimously agree that nintedanib is a step change in the treatment of PF-ILD, as there are no other evidence-based treatments available to slow disease progression. ○ The clinical relevance of nintedanib has been demonstrated in the INBUILD trial, and is independent of the economic modelling. ○ Therefore, the committee's view of uncertainties in the economic model should not impact on whether nintedanib is determined to be a step change in the treatment of PF-ILD.	
1	Consultee (Company)	Boehringer Ingelheim	**The committee have commented that nintedanib's treatment effect may decrease in the long term, but available data do not support this conclusion.** **The INBUILD trial was not designed to assess data beyond 52 weeks. The analysis of**	Thank you for your comment. The committee understood that there were methodological limitations

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			change in FVC (mL) up to DBL2 has important methodological limitations due to a healthy survivor bias observed in the placebo arm which underestimates the treatment effect of nintedanib. According to the clinical trial protocol, the objective of the INBUILD trial was "to investigate the efficacy and safety of 150 mg bid nintedanib in patients with PF-ILD compared to placebo over 52 weeks in Part A" and the primary objective was "to demonstrate a reduction in lung function decline, as measured by the annual rate of decline in FVC for nintedanib compared to placebo over 52 weeks". The objectives of part B were "to collect supportive, longer term efficacy (time to event endpoints) and safety data on the effect of nintedanib compared to placebo." Therefore, the study focussed on the primary endpoint of annual rate of decline in FVC (mL/year) over 52 weeks. The annual rate of decline in FVC (mL/year) including data collected after 52 weeks up to DBL2 was not pre-specified in the protocol or the trial statistical analysis plan (TSAP) and was added as a purely post-hoc exploratory analysis. In addition, the latter analysis has some methodological limitations which make interpretation of the results challenging. Due to the study design, the follow-up times of the patients differ for those in part B (i.e. beyond 52 weeks), and the number of patients attending the visits beyond 52 weeks decreases per visit. It should be noted that the mean change from baseline presented in response to clarification questions was based on DBL1. Figure 1 shows data up to DBL2. It can be seen that with further follow-up and additional patients reaching the week 84 timepoint (321 at DBL2 vs. 180 at DBL1), the treatment difference has increased, and the variability decreased, compared to the data from DBL1. This shows the uncertainty of the mean change from baseline beyond 52 weeks at timepoints when only few patients were observed in the trial. Figure 1: Mean of observed absolute change from baseline in FVC (mL) over time (overall population)	in the analysis of change in FVC in Part B of INBUILD, but this analysis informed the economic model. The committee concluded that there was uncertainty in nintedanib's long-term treatment effect and that it would take this into account of its decision-making. Please see the Final Appraisal Document (FAD) section 3.8.

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			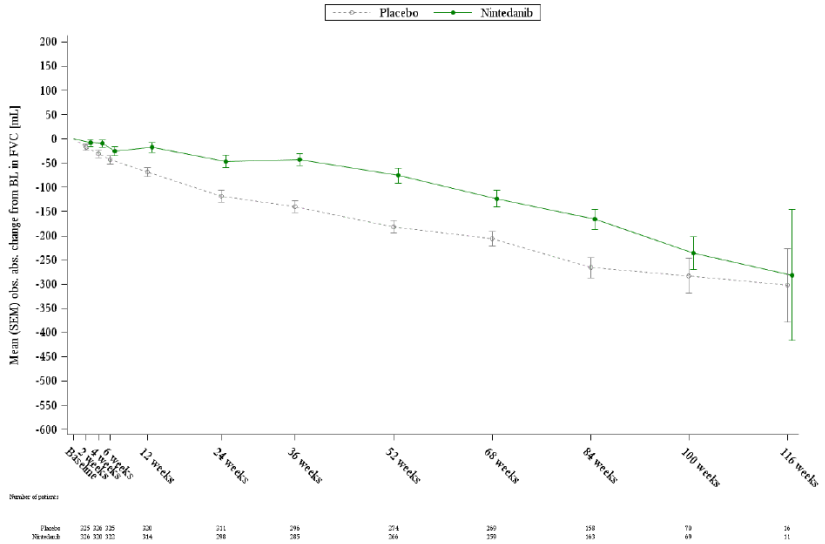 Variable follow-up leads to methodological limitations for the analysis of the annual rate of decline in FVC (mL/year) including data collected after 52 weeks. Data beyond 52 weeks seem to be associated with a healthy survivor bias, i.e. there seem to be healthier patients in the placebo arm compared to the nintedanib arm.(14) Table 1 (page 21, based on data up to DBL1) shows that initial mean baseline FVC actually increased in patients with longer follow-up in the placebo group, but not in the nintedanib group (mean difference placebo-nintedanib at 52 weeks = -8 mL vs. 60–74 mL at 68–100 weeks). This is consistent with the assumption that patients in the nintedanib arm drop out due to adverse events, whereas placebo patients drop out due to disease worsening. A healthy survivor bias might lead to biased differences for the FVC decline between the treatment groups beyond 52 weeks. This might decrease the advantage of nintedanib as the more severely affected patients (with stronger FVC decline) are underrepresented in the placebo arm (as for example more patients have died in the placebo group). In the Random slope & intercept (RS&I) model, patients with long term data and more available assessments are given a higher weight in the analysis compared to patients with shorter follow-up times. Thus, biased data beyond 52 weeks particularly affects the results of the RS&I model. Another methodological challenge for the analysis of annual rate of decline is the linearity	

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			assumption. The RS&I model assumes that FVC declines are linear and that treatment effect is captured by the difference in slopes. This fits well over 52 weeks but not necessarily over longer time periods. This can be illustrated when considering the intercept term for treatment in the RS&I models. For the annual rate of decline in FVC (mL/year) over 52 weeks (primary endpoint) the effect of nintedanib vs. placebo on the intercept is 13.7 mL and non-significant. This effect is not included in the slope (annual rate of decline in FVC) and could be interpreted as the "acute" effect of nintedanib. In contrast, the treatment intercept for annual rate of decline in FVC [mL/year] including data collected up to DBL2 is about 2 times higher (27.3 mL) as in the primary endpoint model and significant (p=0.0072). As this higher intercept value is also not included in the treatment effect this leads to a reduced estimate for the slope, i.e. a reduced annual rate of decline in FVC, compared to the annual rate of decline over 52 weeks. Therefore, the effect of nintedanib on the annual rate of decline in FVC (mL/year) is underestimated compared to the primary endpoint model. The higher intercept term for treatment is a hint that the linearity assumption, which is a requirement for the application of the RS&I models, might be violated for this analysis and reduces the effect size measured by the slope. All in all, the validity of the analysis of annual rate of decline in FVC (mL/year) including data collected up to DBL2 is limited and likely underestimates the treatment effect of nintedanib compared to placebo. To evaluate efficacy endpoints beyond 52 weeks, time to event endpoints should be considered instead. As by study design, the follow-up times of the patients differ in Part B (i.e. beyond 52 weeks). Time to event endpoints are a valid approach to evaluate longer term efficacy as they can deal with variable follow-up by censoring. Pre-specified time to event endpoints such as time to progression or death and time to first acute exacerbation or death became statistically significant at DBL2 (see below, data provided ahead of publication).(15) • Proportion of patients who had ILD progression (decline in FVC ≥10% predicted) or died up to DBL2: HR for nintedanib vs placebo 0.66 (95% CI: 0.53, 0.83; p=0.0003) • Proportion of patients who had an acute exacerbation or died: HR for nintedanib vs placebo 0.67 (95% CI: 0.46, 0.98; p=0.04) Absolute decline in FVC % predicted ≥5% and ≥10% was also consistent at 52 weeks and at DBL2 (see Table 2).(1) These analyses strengthen the evidence that nintedanib has a consistent effect over time, as the hazard ratios for 52 weeks and over the whole trial are similar and the 95% confidence intervals largely overlap.	

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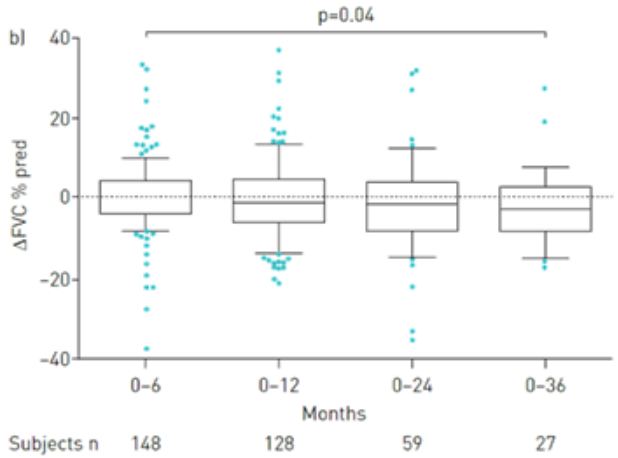
			Real-world data from a registry in IPF and longer term data from INPULSIS-ON have also shown that nintedanib has a consistent treatment effect over time. Data from INPULSIS-ON, a long-term extension of the INPULSIS trials in IPF, showed that the adjusted rate of decline in FVC over 192 weeks was comparable to that shown over 52 weeks in patients treated with nintedanib: • Adjusted annual rate of decline in FVC over 192 weeks (all patients treated with nintedanib): -135.1 mL.(2) • Adjusted annual rate of decline in FVC over 52 weeks (nintedanib) -113.6 mL.(2) This is a 22mL difference in the adjusted rate of decline at 192 weeks vs. 52 weeks for nintedanib (a period of 140 weeks) compared with an annual rate of decline in FVC over 52 weeks of 205.0 mL for placebo.(12) As noted below, the minimum clinically important difference in FVC % predicted is 2-6%, which equates to 75-80 mL in the patients in INPULSIS-ON.(2) This further suggests that the small difference seen between 52 and 192 weeks is not clinically meaningful. Data from a Greek registry of IPF patients across 7 hospitals has also shown that FVC % predicted was largely stable at 3 years for nintedanib patients, with no significant difference from baseline (see Figure 4 below). **Figure 4: Change from baseline in FVC% predicted at 0-6, 6-12, 12-24 and 24-36 months taken from the Greek INDULGE-IPF registry in IPF.(3)**  	

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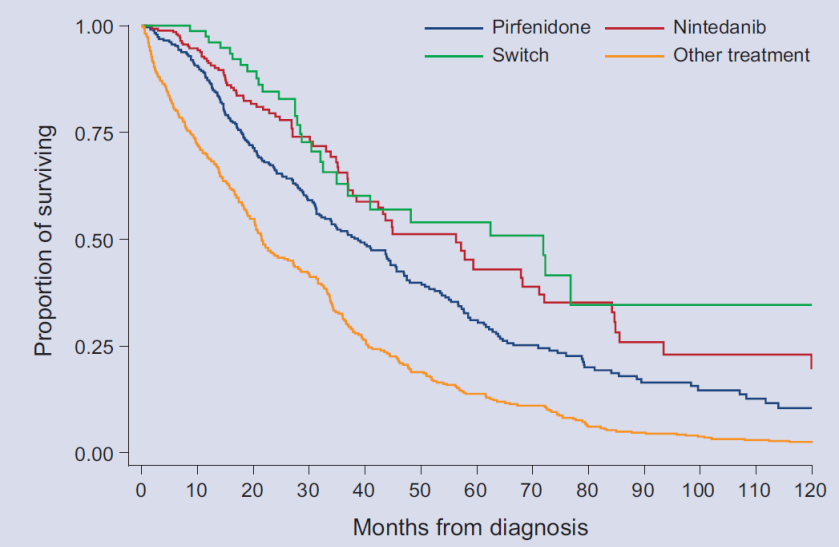
			Data from registries and meta-analyses have shown that nintedanib is associated with a long-term survival benefit compared with non-antifibrotic treatments. Long-term comparative data for IPF patients treated with nintedanib are available from the EMPIRE registry. This shows significantly longer median overall survival for the nintedanib group compared with those who received non-antifibrotic treatment (median survival 56.3 months for nintedanib vs. 21.4 months for other treatment, for a 34.9 month or 2.91 year difference in median survival; p<0.001).(4) This is comparable to the life years (LYs) gained in the company's base case in the economic model (LYs gained = 3.1 years for nintedanib vs. BSC). The median survival difference is also similar to that reported in the Greek INDULGE-IPF registry (54.7 months for nintedanib).(3) **Figure 5: Long-term survival reported in the EMPIRE IPF registry(4)**  Although the European IPF registry does not report survival data specifically for nintedanib, it does report long-term survival data on the use of antifibrotics, which included pirfenidone and nintedanib.(5) Previous meta-analysis and other real-world data have shown that nintedanib treated patients have similar or better survival compared with pirfenidone treated patients in IPF.(4, 16, 17) Similar efficacy of nintedanib and pirfenidone was also accepted by the	

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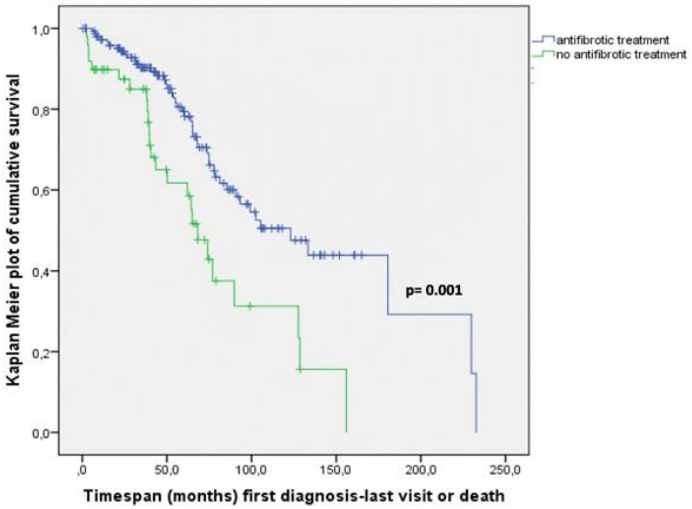
			committee in the appraisal of nintedanib for IPF (TA379).(18) Therefore, the antifibrotic treatment arm should provide an indication of the survival benefit of nintedanib in the European IPF registry population. This registry also reported a significant survival benefit for antifibrotic treatment compared with non-antifibrotic treatment (median survival on antifibrotics 123.1 months vs 68.3 months for prednisolone or other treatment, for a 54.8 month or 4.6 year difference in median survival, p=0.001).(5) This is a greater difference in overall survival than is modelled in the company base case. **Figure 6: Overall survival of IPF patients upon first diagnosis depending on treatment from the European IPF registry(5)**  Similarly, although the Australian registry does not report survival specifically for nintedanib, it does report long-term survival for patients treated with antifibrotics (including pirfenidone and nintedanib).(6) This registry also reported significantly improved survival for patients who received antifibrotic therapy compared with patients who did not (HR 0.56; 95% CI 0.34, 0.92; p=0.022). **Figure 7: Kaplan-Meier survival analysis of patients with IPF with or without antifibrotic treatment(6)**	

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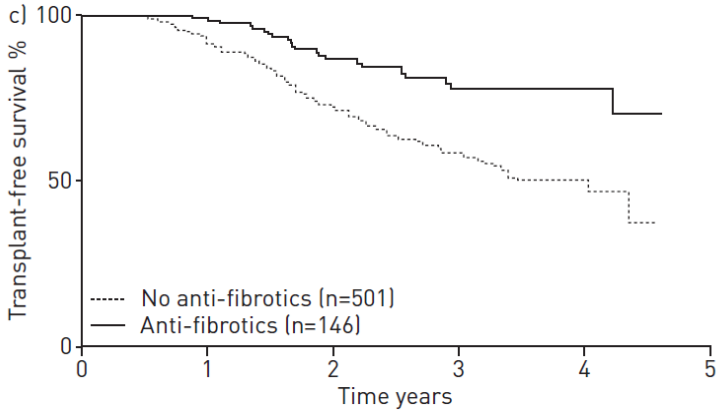
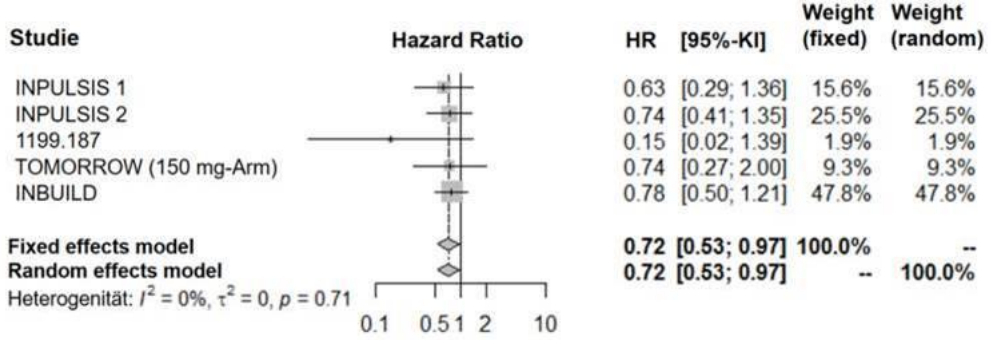
			 These registries all report a survival difference that is maintained, or could be said to increase, over time. Finally, a meta-analysis of randomised controlled trials in IPF (4 studies) and PF-ILD (1 study) has also shown that nintedanib treatment is associated with significantly improved survival compared with placebo (Figure 8).(19) This is confirmed by another meta-analysis of 8 randomised controlled trials and 18 cohort studies that found that antifibrotic treatment was associated with a significantly decreased risk of all-cause mortality (RR 0.55; 95% CI 0.45, 0.66).(20) **Figure 8: Meta-analysis of randomised controlled trials for nintedanib in IPF and PF-ILD** 	

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			Overall, the conclusion that there is insufficient evidence of survival benefit with nintedanib, or that there is a substantial likelihood of a treatment waning effect is not a reasonable interpretation of the evidence. It also does not take into account the full body of relevant evidence.	
2	Consultee (Company)	Boehringer Ingelheim	**The committee have commented that they were not presented with the algorithm chosen by the company to estimate FVC % predicted and that they would like to see how this was done.** FVC % predicted was reported as a secondary endpoint in the INBUILD trial. This was calculated according to the Global Lung Initiative (GLI) equation which takes the form of the equation below, and varies depending on individual patients' race, age, gender and height. This approach is described and validated in publications by Quanjer et al and Kubota et al.(7, 21) Predicted value = $e^{a}\times H^{b}\times A^{c}\times e^{d\times group}\times e^{spline}$ where a is the intercept, H is the height (cm), b is the exponent for the height, A is age (years), c is the exponent for age and spline is the contribution from the age spline. Group is Caucasian, African-American, South or North East Asian and takes a value of 1 or 0 depending on the group.	Thank you for your comment. The committee considered the algorithm provided. This is discussed in the section 3.3 of the FAD.
3	Consultee (Company)	Boehringer Ingelheim	**The committee have commented that it is unclear whether the primary endpoint measured by FVC in millilitres per year over 52 weeks reflects a clinically meaningful change as measured by FVC % predicted.** The committee accepted that nintedanib is associated with a slower decline in lung function (page 10 of the ACD). They state that a decline in FVC of at least 10% predicted defines disease progression and is associated with disease deterioration and mortality in PF-ILD (page 6 of the ACD). However, they question whether this is clinically meaningful as measured by FVC % predicted. **Published literature in IPF suggests that the change in FVC % predicted reported in the INBUILD trial is clinically meaningful.** In the overall population of the INBUILD trial, the adjusted mean absolute change from baseline to week 52 in FVC % predicted was a secondary endpoint, and reported change was -2.62% in the nintedanib group and -5.86% in the placebo group (see **Error! Reference source not found.** and section 11.1.3.1.2 of the Clinical Trial Report).(9) The adjusted mean difference showed that treatment with nintedanib reduced FVC % predicted decline by 3.24%	Thank you for your comment. The committee considered both the reference reported in the published literature (Bois et al. 2011) and the statement from the clinical experts and stakeholders – see comment numbers 13, 24 and 25. The committee agreed that the change in FVC (measured by millilitres over 52 weeks) reported in INUBILD reflects a clinically meaningful change. Please see the FAD sections 3.8.

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			(95% CI 2.09, 4.40) compared with placebo at week 52. Published literature in patients with IPF suggest that the minimum clinically important difference for percent predicted FVC is between 2-6%.(8) This is therefore a clinically meaningful change in FVC % predicted. **Pre-specified analyses from INBUILD showed that treatment with nintedanib reduced the proportion of patients with both a relative and absolute decline from baseline in FVC of >10% and >5% at week 52.** In the overall population, fewer patients treated with nintedanib had an absolute decline from baseline in FVC % predicted of >10% (adjusted odds ratio 0.68; 95% CI 0.49, 0.95) or >5% (adjusted odds ratio 0.63; 95% CI 0.46, 0.85) at week 52.(9) Analyses of the proportions of patients with a relative decline from baseline in FVC % predicted of >10% (adjusted odds ratio 0.63; 95% CI 0.43, 0.94) or >5% (adjusted odds ratio 0.46; 95% CI 0.31, 0.69) at week 52 were also in favour of nintedanib vs. placebo.(9) In the overall population, treatment with nintedanib also reduced the risk of progression (defined as ≥10% absolute decline in FVC % predicted) or death by 35% vs. placebo (HR 0.65; 95% CI 0.49, 0.85).(9) Declines in FVC of both >10% and >5% have been associated with mortality.(10) In INBUILD a decline of >10% was associated with a more than three-fold increase in the risk of death over 52 weeks (hazard ratio 3.64; 95% CI 1.29, 10.28; p=0.015).(10) This is similar to the risk reported in the INPULSIS trials (HR 3.95; 95% CI: 1.87 to 8.33; P<0.001).(10) These differences vs. placebo are therefore clinically meaningful. **Meta-analysis of nintedanib clinical trials in IPF, PF-ILD and SSc-ILD show a strong association between annual rate of change in FVC % predicted and risk of death.** A meta-analysis was published at the 2021 American Thoracic Society Conference, assessing the strength of FVC as a surrogate marker for mortality. This analysis pooled data from patients who received nintedanib or placebo in the placebo-controlled periods of trials in IPF (TOMORROW, INPULSIS-1 and -2, Phase IIIb trial NCT01979952), PF-ILD (INBUILD) and systemic sclerosis-associated ILDs (SENSCIS). The authors then assessed the association between FVC % predicted and time to death over 52 weeks. This analysis showed a strong association between annual rate of change in FVC % predicted	

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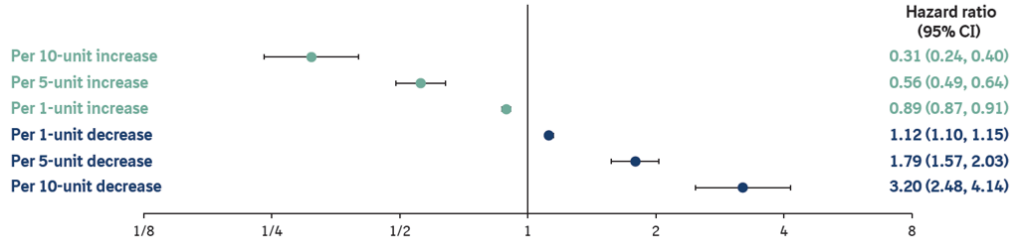
			and risk of death (see Figure 9 below). The p-value for association between rate of change in FVC % predicted as a continuous variable and death was <0.0001.(11) **Figure 9: Association between annual rate of change in FVC % and risk of death over 52 weeks(11)**  **The difference in FVC reported in INBUILD, measured both in mL and % predicted, was similar to that reported in INPULSIS. Clinical experts and patient groups agree that this difference has been meaningful for patients with IPF, as well as those receiving nintedanib for PF-ILD as part of a named patient supply programme.** The adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks reported in INBUILD was similar to that reported in INPULSIS: • INBUILD, nintedanib vs. placebo: 106.96 mL (95% CI 65.42, 148.50; p<0.0001)(9) • INPULSIS (pooled), nintedanib vs. placebo: 110.6 mL (95% CI, 83.2-137.9, p<0.001)(12) (information taken from the supplementary appendix) The difference in adjusted absolute mean change from baseline in FVC % predicted over 52 weeks was also similar in INBUILD and INPULSIS: • INBUILD, nintedanib vs. placebo: 3.24% (95% CI 2.09, 4.40)(9) • INPULSIS (pooled), nintedanib vs. placebo: 3.2% (95% CI 2.4, 4.0)(12) (information taken from the supplementary appendix) Clinical experts and patient groups unanimously agree that the effect of nintedanib in IPF has been highly meaningful for patients. This is highlighted in the previous submissions by the British Thoracic Society (BTS), Action for Pulmonary Fibrosis (APF) and clinical expert. In addition, BI have received requests for 'Named Patient Supply' (NPS) for nintedanib in PF-	

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			ILD from 19 out of 24 ILD specialist centres in the UK between 2018 and 2021. Named patient supply was considered in response to unsolicited requests from expert ILD physicians to access treatment with nintedanib in exceptional, life-threatening cases of PF-ILD. In total 258 patients have commenced NPS for nintedanib in PF-ILD, including patients from 19 different ILD specialist centres. This affirms that the ILD community, as stated in both clinician and patient submissions to NICE, view nintedanib as an innovation or 'step change' in the treatment of PF-ILD. This information also suggests that patients are receiving important benefit from nintedanib in PF-ILD in the UK. Previous submissions from Action for Pulmonary Fibrosis have also reinforced the benefit that patients have received from nintedanib in IPF: *"Anti-fibrotic treatments like nintedanib have been a 'game changer' for people living with IPF, slowing disease progression and increasing life expectancy."* "[redacted], *an RA-ILD patient, from Devon* *When I look around my support group, I see friends with IPF who have been diagnosed much longer than me and seem to be doing much better. They have all been on nintedanib or pirfenidone for a few years."* *"PF/ILD patients urgently want access to nintedanib because it directly targets their lung fibrosis and has been shown to slow progression, which a high priority for them."* **Overall, it is <u>not</u> a reasonable interpretation of the evidence to conclude that the treatment effect of nintedanib shown in INBUILD is not clinically relevant.**	
4	Consultee (Company)	Boehringer Ingelheim	**The committee have commented that the impact of restricted concurrent NHS treatments on the treatment effect of nintedanib is unclear.** **However, post-hoc analyses of the INBUILD trial excluding all patients who took prohibited or restricted medications over 52 weeks were very similar to the primary analysis. This indicates that the treatment effect was not influenced by the use of restricted and prohibited medications.** A post-hoc analysis was performed to assess the impact of restricted and prohibited medications on the primary endpoint (annual rate of decline in FVC).(13, 22) This was done by excluding all patients who took prohibited or restricted medications at baseline or on-treatment or post-study drug discontinuation over 52 weeks.	Thank you for your comment. The committee considered the evidence and concluded that the restricted use of concurrent treatments in INBUILD trial may reflect current NHS care for some but not all people with progressive fibrosing Interstitial lung disease (PF-ILD).

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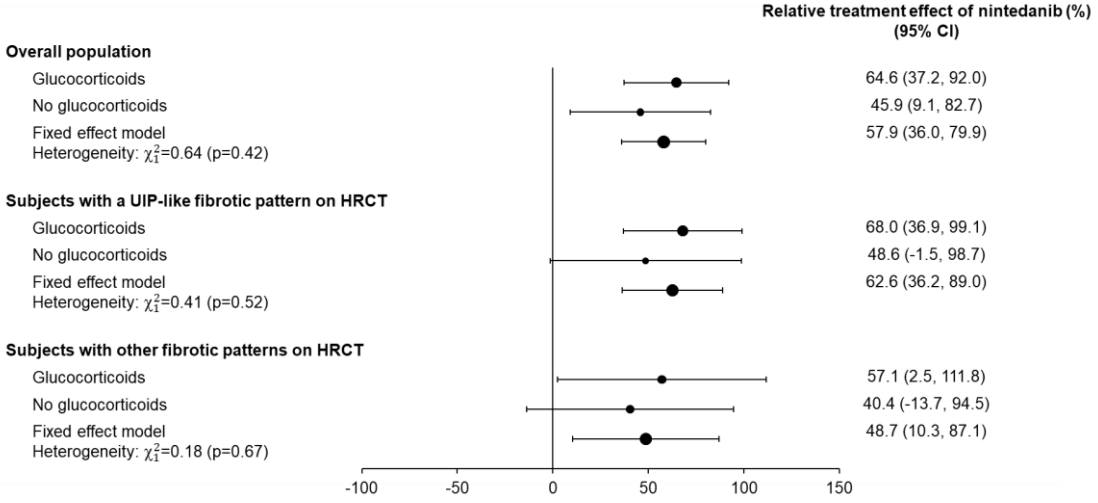
			As shown in **Error! Reference source not found.**, the results of the primary analysis and that of the analysis excluding all patients who took prohibited or restricted medications through the trial to 52 weeks are very similar (rate of decline in FVC [mL/year] over 52 weeks was 107.8 mL vs. 107.0 mL in the primary analysis, both p<0.001), indicating that the treatment effect was not influenced by the use of restricted and prohibited medications.(13, 22) **Post-hoc subgroup analyses from the INBUILD trial have shown that the effect of nintedanib on reducing FVC decline was not influenced by the use of glucocorticoids at baseline.** A post-hoc analysis of the rate of decline in FVC over 52 weeks in subgroups by glucocorticoid use at baseline has also been done.(13) This analysis found that there was no significant difference in the treatment effect of nintedanib between subjects taking glucocorticoids at baseline and those who were not (interaction p=0.18, see Figure 10). **Figure 10: Relative treatment effect of nintedanib vs placebo on rate of FVC decline over 52 weeks in subgroups by use of glucocorticoids at baseline(13)**  **Clinical experts treating interstitial lung diseases at specialist tertiary centres in the UK also agree that restricted medications would not be expected to have any meaningful efficacy in the treatment of progressive fibrosing disease.**	Please see the FAD section 3.6.

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			As stated in the British Thoracic Society's previous submission to NICE, the clinical consensus is that 'immunosuppressants are not given to treat the fibrotic component of an ILD, but the inflammatory component of the disease'. A consensus document agreed by the majority (21/24) of the clinical leads in ILD centres in England and Wales, plus 3 rheumatology experts, collated in short timelines has reaffirmed this statement. The consensus document also states the following: *'The patient population with chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD) often have a wide range of underlying clinical conditions that have led to their ILD. These extrapulmonary manifestations such as arthritis, glomerulonephritis, pericarditis and dermatological manifestations may require treatment with corticosteroids and/or immunosuppressants, but these are not to treat the ILD, and they do not have any meaningful impact on the ILD. By definition, patients with PF-ILD have progressed despite treatment with conventional therapies, including immunosuppressants and other restricted therapies.'* *'It is common clinical practice that when patients with predominantly fibrotic ILD present with lung function decline despite immunosuppression, clinical consideration would be to reduce or completely stop immunosuppressants due to a lack of efficacy. There are also significant safety concerns around the use of multiple immunosuppressants as evidenced in the IPF-focused PANTHER trial which clearly demonstrated an increased risk of mortality & hospitalisation in these patients.'* *'The ILD clinical community are concerned about using non evidence-based immunosuppressants that lack efficacy in PF-ILD patients who phenotypically behave like IPF and have similar radiological features. This is reflected in the very low levels of use of restricted immunosuppressants after 6 months in the INBUILD trial once these were allowed.'* *'From a clinical perspective, there are no treatments that are licensed for use, or really being consistently used in clinical practice for the management of UK patients with PF-ILD and therefore the placebo arm of the INBUILD trial is a true representation of UK clinical practice.'* Please see Appendix 2 (page **Error! Bookmark not defined.**) for the full consensus statement. **In summary, it is not a reasonable interpretation of the evidence to conclude that the**	

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			impact of restricted therapies on the treatment effect of nintedanib is unclear. It is clear that the restriction of these treatments in INBUILD has not biased the results of the trial, or reduced the relevance of the trial to UK clinical practice, when all relevant evidence is considered.	
5	Consultee (Company)	Boehringer Ingelheim	**The committee have commented that there are uncertainties in the company's modelling and validation for overall survival in the placebo arm, and that this likely overpredicts deaths in the placebo arm.** **If an alternative survival curve with more optimistic survival for the placebo arm is selected, nintedanib remains cost-effective.** The committee noted that the Bayesian survival curves dropped more quickly (had a higher death rate) than the registries survival, and that this meant that the company may be underestimating survival of patients who do not take nintedanib by using Weibull Bayesian curves. Whilst we accept that there is uncertainty in the placebo analysis, this is due to there being no long-term placebo clinical trial data available for patients with IPF or other PF-ILD. Nevertheless, the use of placebo clinical trial data from patients with IPF to generate an informative prior goes some way to reduce uncertainty in the survival estimates of control within the trial timeframe, which may in turn help produce more realistic long-term survival estimates. If an alternative curve that has a lower death rate over the long term is selected for placebo, namely the Bayesian gamma or log logistic curves, this results in an ICER that is <£25,000/QALY ([redacted] and [redacted] per QALY, respectively). These curves provide a good visual match to the Australian registry, which ILD expert clinicians believed to be the most appropriate registry to use in our Advisory Board in December 2020 due to similarities with UK clinical practice and how the registry is managed (see Figures 11 and 12). **Figure 11: BSC arm modelled using the Bayesian Gamma distribution, NDB modelled using Bayesian Weibull (company base case)**	Thank you for your comment. The committee considered the evidence and analyses and agreed that using the Australian registry to validate the survival curve for placebo arm is appropriate. It also agreed it is appropriate to use the log-logistic distribution based on the Bayesian analyses to model overall survival in the placebo arm. Please see the FAD sections 3.18 and 3.20-22.

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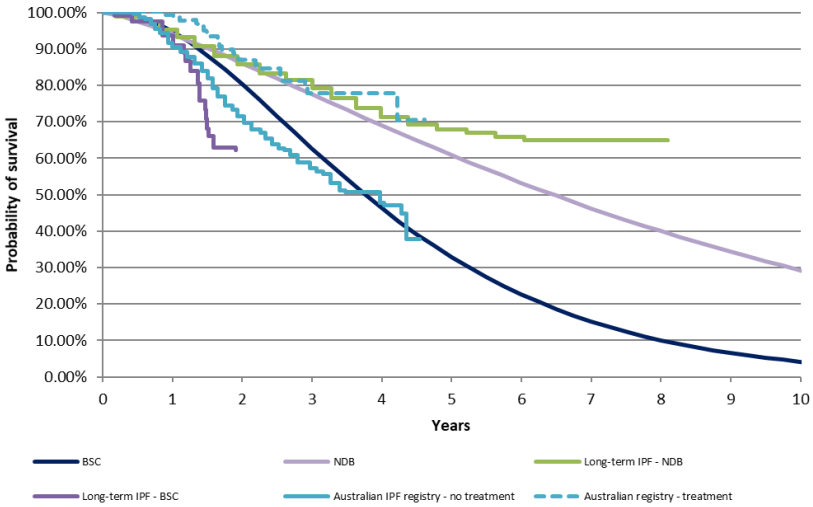
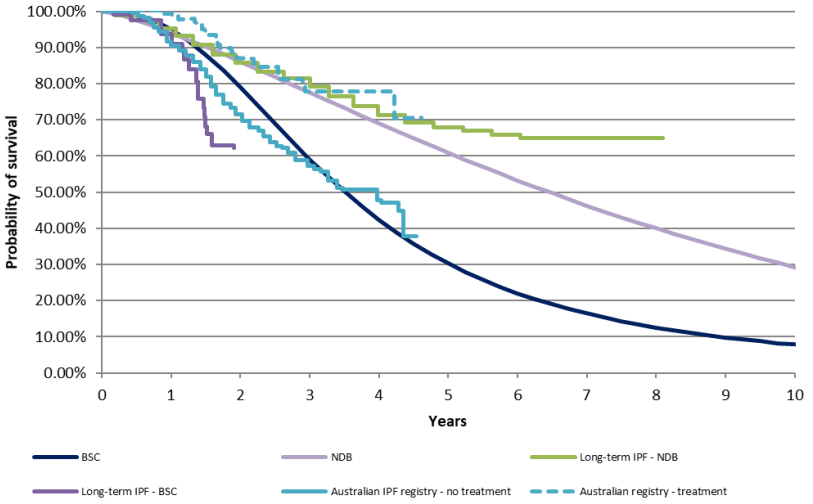
			 **Figure 12: BSC arm modelled using the Bayesian log-logistic distribution, NDB modelled using Bayesian Weibull (company base case)** 	

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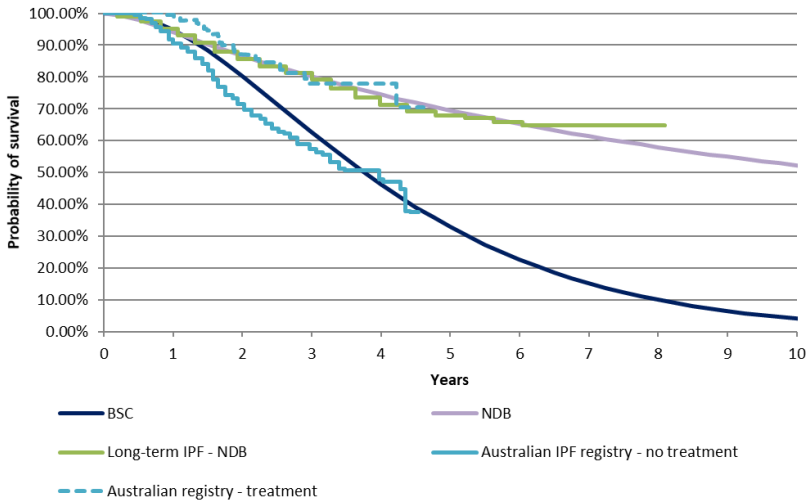
			It is also possible to select a survival curve for nintedanib that is a good visual match for the group receiving antifibrotic treatment in the Australian registry (the frequentist lognormal curve). If this is used together with the curves that provide the best visual match to the no treatment group in the Australian registry (Bayesian gamma or Bayesian log-logistic) this gives ICERs <£20,000/QALY ([redacted] and [redacted] respectively). **Figure 13: NDB arm modelling to match on-treatment group from the Australian registry (frequentist lognormal), BSC arm modelled using Bayesian gamma**  **Figure 14: NDB arm modelled to match on-treatment group from the Australian registry (frequentist lognormal), BSC arm modelled using Bayesian log-logistic**	

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			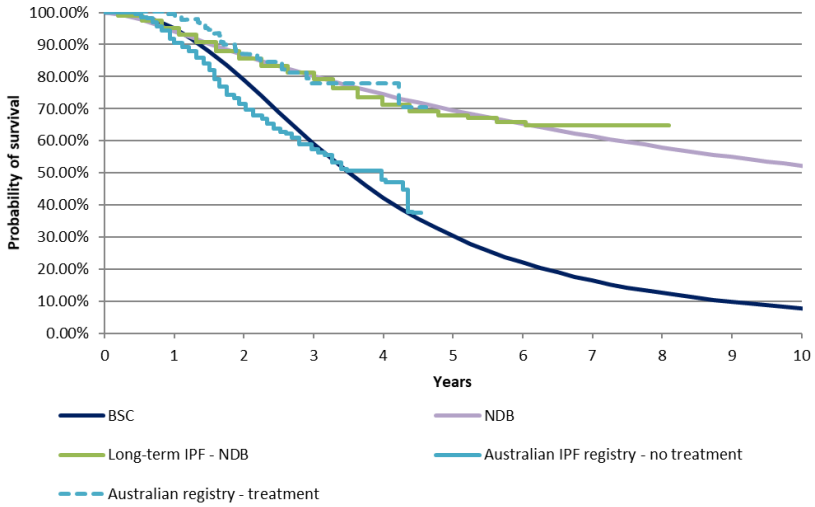 The committee commented that the European IPF registry may be the best source to validate the placebo arm survival estimates. Although data on nintedanib specifically are not reported in this registry, it does report long-term survival data on the use of antifibrotics, which included pirfenidone and nintedanib.(5) Previous meta-analysis and other real-world data have shown that nintedanib treated patients have similar or better survival compared with pirfenidone treated patients in IPF.(4, 16, 17) Similar efficacy of nintedanib and pirfenidone was also accepted by the committee in the appraisal of nintedanib for IPF (TA379).(18) Therefore, the antifibrotic treatment arm should provide an indication of the survival benefit of nintedanib in the European IPF registry population. The European IPF registry reported considerably higher survival estimates for both the no treatment and antifibrotic treated groups, compared with other registries and the long-term clinical trial data for IPF. This may be because no central HRCT scans or histology samples were performed to validate whether patients had IPF, which may have led to the inclusion of some patients without true IPF.(6) Therefore, if we select a survival curve for placebo that matches the data from the European registry, we must also select an alternative curve for nintedanib survival, otherwise nintedanib survival is underestimated by a considerable margin (see Figure 15). If alternative curves are selected that better match the European IPF registry data for both arms (frequentist lognormal for BSC and frequentist exponential for nintedanib, see Figure 16), the ICER is under £25,000/QALY ([redacted]).	

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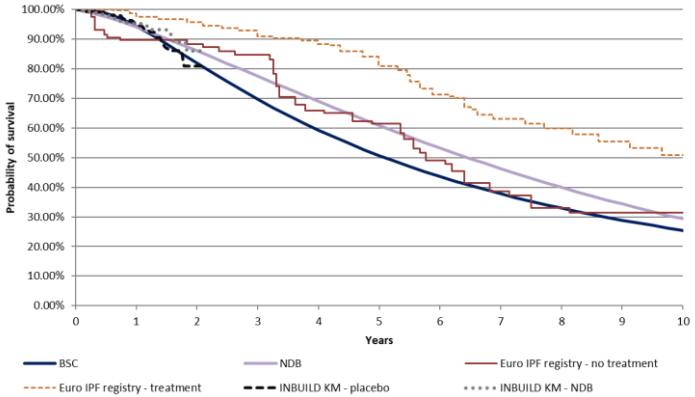
			These alternative scenarios are summarised in **Error! Reference source not found.** in Appendix 1 (page **Error! Bookmark not defined.**). **Figure 15: Modelled survival curves (BSC = frequentist lognormal; NDC = Bayesian Weibull) compared with data from the European IPF registry**  **Figure 16: Alternative survival curves that better match the European registry data for no treatment and antifibrotic treated patients (BSC = frequentist lognormal; NDB = frequentist exponential)**	

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			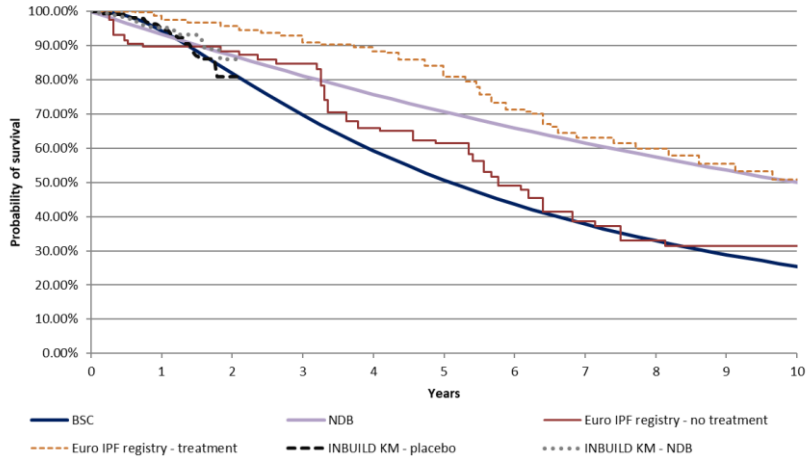 It is possible to select alternative curves for BSC where the ICER is >£30,000, for example the frequentist or Bayesian exponential and frequentist or Bayesian lognormal). However, these are implausible and unrealistic compared with survival data reported in IPF registries. **In summary, the survival modelling of BSC can be validated by comparison with real-world registries. If extrapolated curves are selected that provide a good visual match for data reported in these registries, nintedanib is still cost-effective. Therefore, the conclusion that modelling and validation of overall survival for the placebo arm is uncertain and its impact on the model results is not clear does not take account of all the relevant evidence.**	
6	Consultee (Company)	Boehringer Ingelheim	**The committee have commented that there are uncertainties in fitting individual parametric distributions to the nintedanib and placebo arms, and that the modelling resulted in ever-increasing survival benefits for nintedanib compared with placebo in the extrapolated periods.** **The ACD also states that the committee was not provided with evidence that the company had explored the proportionality of treatment effects in the observed data and had not been presented with information on the treatment effect over time implied by the company's chosen curves. It concluded that the company should explore the proportionality of hazards assumptions observed in the data and provide information on the treatment effect implied by the alternative survival modelling approaches considered.**	Thank you for your comment. The committee agreed that fitting independent parametric survival distributions to both placebo and nintedanib arms is reasonable although there are uncertainties. Please see FAD section 3.23.

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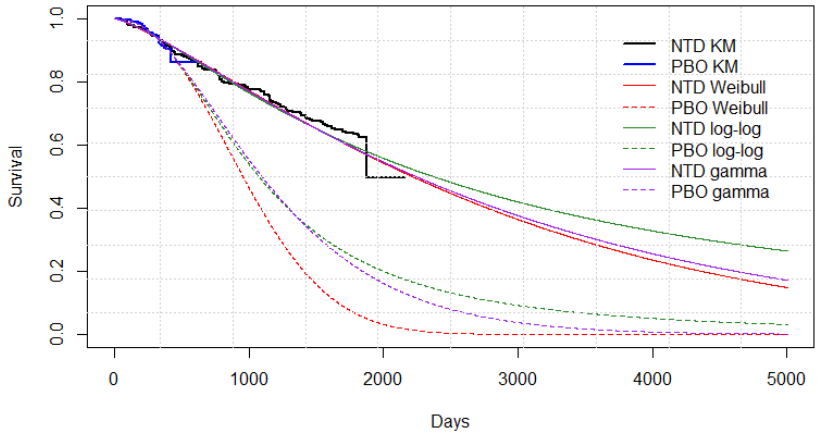
			The proportional hazards assumption was tested for all survival analysis outcomes in the economic model (overall survival, time to discontinuation, and time to first acute exacerbation) and these analyses were provided in response to clarification questions. Independent survival models were used for consistency across outcomes, as the proportional hazards assumption was not met for the time to discontinuation outcome. The general model (using treatment as a covariate) is unlikely to have been an appropriate approach for the Bayesian survival analysis. In the Bayesian survival analysis, the best-fit models were informed by the matched IPF data, where the Kaplan-Meier curves crossed. This suggests that the proportional hazards assumption is unlikely to have been met (see Figure 17 below). Additionally, due to the difference in the duration of observed events between nintedanib (5.9 years) and placebo (1.8 years) arms, any analysis of a general model with treatment as a covariate is unlikely to reach any meaningful results. **Figure 17: Modelled survival curves and Kaplan-Meier data from INBUILD**  The original company base case is based on Bayesian analysis, the shape of which is informed by the long-term clinical trial data for nintedanib in IPF. However, we take the committee's point of view that there is uncertainty in these long-term survival estimates based on clinical trial data, particularly for the placebo arm. It is possible to select a different survival distribution for placebo that more closely matches the Australian registry. This could be justified, as the ILD clinical experts (Leads at ILD Specialist Centres) consulted in our Advisory Board in 2020 considered this to be the best registry to	

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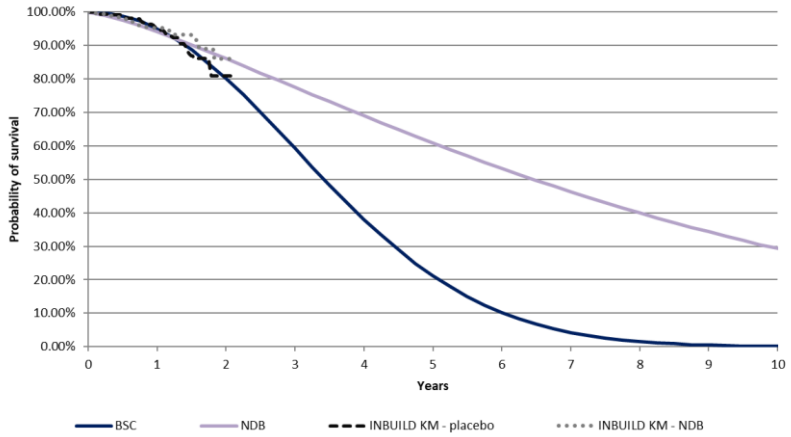
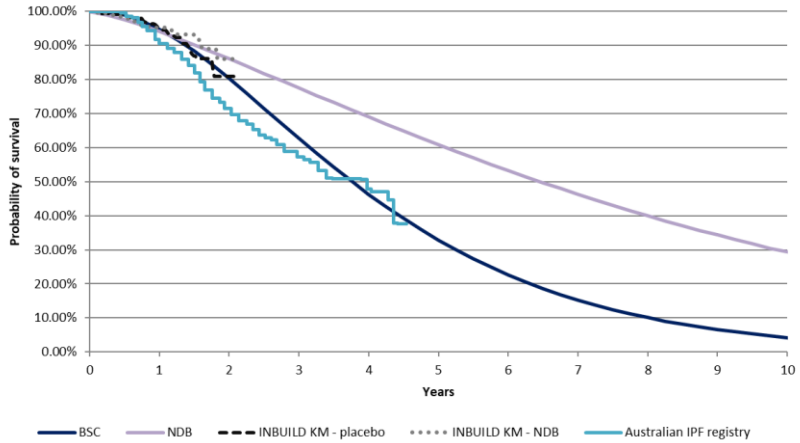
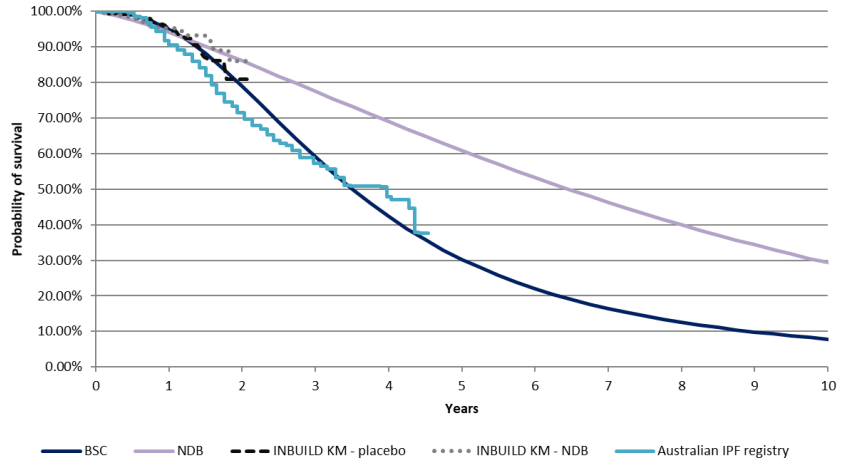
			validate the long term survival for placebo due to similarities in clinical practice and the way the registry is managed compared with the UK. As stated above, this results in an ICER that is <£25,000/QALY. Selecting these alternative curves for placebo also reduces the modelled difference in survival between nintedanib and BSC compared with the company base case (Figures 18-20). If alternative survival curves are selected that give the best visual match to the European IPF registry, the modelled difference in survival between nintedanib and BSC is also reduced compared with the company base case (see Figure 16 above), with an ICER <£25,000/QALY ([redacted]). **Figure 18: Company base case survival modelling (Bayesian Weibull for NDB and BSC)**  **Figure 19: Alternative modelling using a Bayesian Gamma distribution for BSC (Bayesian Weibull for NDB)**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Figure 20: Alternative modelling using a Bayesian loglogistic distribution for BSC (Bayesian Weibull for NDB)**  Although survival data from the INBUILD trial were immature, long-term survival data are available from registries of IPF patients. As stated in row 1 above, three registries report long-term comparative data and all show a statistically significant survival benefit for nintedanib/antifibrotic treatment compared with non-antifibrotic treatment that is maintained	

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			over time.(4-6) These report similar survival difference for nintedanib vs non-antifibrotic treatment as reported in the company modelling (base case) and greater survival difference compared with the modelling when the alternative survival curves for placebo are used (see **Error! Reference source not found.**). **Overall, evidence from registries in IPF suggest that the modelled difference in survival for nintedanib vs. placebo is reasonable. If a plausibly reduced difference in survival is modelled, nintedanib is still cost-effective.** In our view, taking all relevant evidence into account substantially addresses the uncertainties highlighted by the committee. However, BI is open to exploring approaches to address any remaining material uncertainty, if the committee believes this still exists.	
7	Consultee (Company)	Boehringer Ingelheim	**The committee have commented that there are uncertainties in the company's modelling of exacerbations and decline in lung function because of their lack of a link with mortality in the model.** We acknowledge that this is a limitation of the current model, which as noted in the ACD was necessary to avoid double counting deaths. In general, the committee accepted this model structure as relevant for decision making. We did look into changing the structure of the model to include a link between mortality and exacerbations and decline in lung function. However, the adapted model produced increased and unrealistic life years for both placebo and nintedanib, compared with the current model. This is likely because there is additional uncertainty generated by this approach, as a separate risk of death is needed for each health state in the model, and this is in itself uncertain. Although an important event for individual patients, exacerbations are relatively rare in patients with ILD. The ACD also states that the committee was aware that both the company and the ERG's varying risk of exacerbation in scenario analyses had little impact on the cost effectiveness. Since the committee commented that the modelling of exacerbations and decline in lung function was acceptable, and since the main driver of the cost-effectiveness is the survival analysis, we do not believe that these limitations significantly impact the economic case for nintedanib.	Thank you for your comment. The committee agreed that there are important uncertainties in the model structure and limitations when implementing it. Please see the FAD section 3.12-14.
8	Consultee (Company)	Boehringer Ingelheim	**The committee have commented that nintedanib does not meet NICE's criteria for an innovative treatment, due to shortcomings in the company's modelling. However,**	Thank you for your comment. Discussions

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			clinical experts and patient groups agree that nintedanib is a step change in the treatment of PF-ILD, as there are no other treatments available that slow disease progression in PF-ILD. These factors are independent of the economic modelling as they have been demonstrated in the INBUILD trial. As discussed in point 3 above, the change in FVC reported in INBUILD, both in mL and % predicted, has been demonstrated to be clinically relevant. FVC has been shown to be a strong indicator of mortality in patients with ILD.(11) There is also evidence from registries that nintedanib treatment results in longer median survival compared with other non-antifibrotic treatments.(4-6) This benefit is in the treatment of a disease which, if left untreated, has a median post-diagnosis survival that is worse than several types of cancer.(23-25) Clinicians and patient groups unanimously agree that nintedanib is a step change in treatment for patients with PF-ILD, based on the benefit demonstrated in the pivotal clinical trial and their experience of using nintedanib in IPF. As stated above, BI have also received requests for 'Named Patient Supply' (NPS) for nintedanib in PF-ILD from 19 out of 24 ILD specialist centres in the UK between 2018 and 2021. In total 258 patients have commenced NPS for nintedanib in PF-ILD, including patients from 19 different ILD specialist centres. This affirms that the ILD community, as stated in both clinician and patient submissions to NICE, view nintedanib as an innovation or 'step change' in the treatment of PF-ILD. These factors are separate from the economic modelling. Therefore, the committee's view of uncertainties in the economic model should not impact on whether nintedanib is determined to be a step change in the treatment of patients with PF-ILD. Evidence and feedback from clinical and patient groups is clear that nintedanib is a step change, and should be considered to be innovative. **Therefore, it is not a reasonable interpretation of the evidence to say that nintedanib is not innovative.**	about the innovative nature of a treatment include whether the technology offers demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case quality adjusted life year (QALY). The committee concluded that nintedanib was not innovative for PF-ILD. Please see the FAD section 3.32.
9	Consultee	Clinical expert	**Page 3 of ACD states "Why the committee made these recommendations Current treatment for fibrosing interstitial lung disease starts with immunosuppressants. If recommended, nintedanib would be given at the same time."** This statement is not quite accurate in my view. Some PF-ILD subtypes would be offered immunosuppressants (IS) but not all. Only in one sub type (scleroderma CTD ILD) is there any evidence for IS). In many sub types of PF-ILD, nintedanib would not be 'added in'. IS would be	Thank you for your comment. The wording was amended to "Current treatment for fibrosing interstitial lung disease often starts with immunosuppressants".

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			stopped and nintedanib given instead particularly where disease progression had occurred despite being on IS.	Please see the following section of the FAD: "Why the committee made these recommendations"
10	Consultee	Clinical expert	**Page 3 of ACD states: "It is also uncertain what its effects would be in clinical practice because the trial restricted use of some immunosuppressants in the first 6 months."** I do not feel this statement is quite correct. Almost 70% of patients were actually on a drug suppressing their immune system i.e. prednisolone. Prednisolone is considered equivalent broadly to other immunosuppressant drugs used e.g. mycophenolate, methotrexate. We use these types of drugs interchangeably broadly to try and treat lung diseases. The 30% not on prednisolone was likely either because IS drugs had been tried and were not helpful or the underlying ILD sub type did not merit use of IS type drugs e.g IS not advised in rheumatoid arthritis fibrotic ILD or asbestosis for example. So I believe the INBUILD trial and its results does absolutely reflect real clinical practice. One of the main reasons we do no just use prednisolone in everyone, where we wish to try and IS, is because of its side effect profile over longer time periods. We employ a "steroid sparring strategy" and switch prednisolone to other drugs such as methotrexate or mycophenolate for example. The effect of these different types of IS drugs however is thought to be similar.	Thank you for your comment. The committee considered the evidence and concluded that the restricted use of concurrent treatments in INBUILD trial may reflect current NHS care for some but not all people with PF-ILD. Please see the FAD section 3.6.
11	Consultee	Clinical expert	**Point 3.4, page 7: this paragraph mentions that nintedanib would be an "add on therapy"** As above in 1). Sometimes it might be – mainly in CTD or autoimmune ILD but in many other forms of PF-ILD IS would be stopped and nintedanib alone would be used if progression had occurred on IS.	Thank you for your comment. The committee noted that if recommended, nintedanib would be an add-on therapy rather than a direct comparator to conventional treatments in all patients. The conventional treatments for the underlying diseases may or may not be continued when adding nintedanib. Please see section 3.4 of the FAD.
12	Consultee	Clinical expert	**Point 3.6 page 9: states "Concurrent treatments in the INBUILD trial do not reflect current NHS care"** I do not agree with this conclusion above by NICE. The INBUILD study does reflect current	Thank you for your comment. The committee considered the evidence and concluded that the

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			NHS care as outlined above in my point 2. **"Patients could not have IS other than systemic corticosteroids for first 6 months of study".** Corticosteroids are a perfectly good IS to give and comparable to other IS drugs as outlined above. The main reason why they are not given longer term is due to their side effect profile not because they are not as effective. The only exception to this is in scleroderma ILD where the scleroderma lung study I showed that mycophenolate was an effective treatment to slow progressive ILD over the shorter term. Scleroderma patients were a small number overall in cohort. **Point 3.6 page 9: ACD states"Approximately 16% of patients started immunosuppressants during the second 6 months of the initial 52-week period (21% in the placebo arm and 11% in the nintedanib arm). The committee interpreted this to show that fewer patients randomised to nintedanib than placebo needed immunosuppressants, but that a substantial proportion of participants needed the treatments that the protocol restricted earlier in the trial."** Starting IS after first 6 months of study may also have been needed to treat joint disease or other features of the systemic disease components that these patients have rather than to treat their ILD. Do the company know what the indications were for addition of IS to these patients? It would be useful to know this. This paragraph 3.6 goes on to state again the trial design does not reflect clinical practice but I believe strongly it does. I do not support that conclusion by the ERG.	restricted use of concurrent treatments in INBUILD trial may reflect current NHS care for some but not all people with PF-ILD. Sentence on patients needing immunosuppressants has now been erased. Please see the FAD section 3.6.
13	Consultee	Clinical expert	Paragraph 3.7 page 10 of ACD states: **The committee noted it was unclear whether a between-group difference of 107 ml/year in adjusted rate of decline in FVC over 52 weeks equals a 10% difference (relative or absolute) in FVC% predicted, which would indicate a clinically meaningful change in FVC (see section 3.3).** The reduction in FVC seen in the nintedanib group in trial is definitely clinically significant. Patients on nintedanib on average had 107mls more of lung left at end of study. Falling FVC ultimately leads to death in this patient group so preventing that fall is significant and important to outcome. The drug does not need to hit a 10% reduction in FVC to prolong life. A healthy person without lung disease loses only 30mls of lung volume per year. These ILD patients are losing lung at a significantly accelerated rate and this leads to premature death in the end.	Thank you for your comment. The committee agreed that the decline in FVC measured by millilitres per year over 52 weeks, as reported in INBUILD, reflects a clinically meaningful change. Please see section 3.8 of the FAD.
14	Consultee	Clinical expert	Overall all I would request that NICE reconsider its first decision here. Hopefully the company can provide NICE with relevant modelling information which will help further assessments. I am not statistically trained and cannot comment much on modelling queries. I do not support ERG's conclusion that the INBUILD trial does not reflect UK clinical practice.	Thank you for your comment. The committee agreed that restricted use of concurrent treatments in INBUILD trial may reflect

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			The changes in FVC seen with nintedanib are clinically important and relevant to prognosis and outcome. Nintedanib would be an add on therapy only in some sub types of PF-ILD (not all). In a similar disease Idiopathic pulmonary fibrosis these anti fibrotic drugs have been proven to have a sustained effect on disease progression over time. I note that NICE would usually review any negative decision 3 years later and if a negative decision is final decision here I request that NICE mark this proposal for an earlier review than this as more data re the effectiveness of this drug is likely to be available well before 3 years have passed.	NHS clinical practice in some people with PF-ILD but not all. It agreed the decline in FVC (measured by millilitres per year over 52 weeks) as reported by INBUILD trial reflects a clinically meaningful change. The committee also noted that if recommended, nintedanib would be an add-on therapy rather than a direct comparator to conventional treatments in all people with PF-ILD, as the conventional treatments for the underlying diseases may or may not be continued when adding nintedanib. The committee have now recommended nintedanib as an option for treating PF-ILD, and a review is planned in 3 years. Please see the FAD sections 3.4, 3.6, 3.8 and 5.
15	Consultee	Association of Respiratory Nurse Specialists	Having read the document, it is clear how the conclusion has been reached. The study could and should have been more robust. However, it is disappointing that Nintedanib has not been approved for patients with Progressive Pulmonary Fibrosis and the resulting inequity with those living in Scotland who can already access this essential treatment. This decision will significantly limit treatment options for this cohort of patients and affect quality of life. More research is needed as a priority to provide a larger and superior evidence base enabling the company to resubmit with as little delay as possible.	Thank you for your comment. Following consultation responses, the committee have now recommended nintedanib as an option for treating PF-ILD.

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			If the trials can include as many patients accessing the treatment as feasible then the benefits and cost effectiveness can be established. For patients we believe, the addition of Nintedanib in their treatment plan has made a significant difference to their progression and symptom burden.	
16	Consultee	British Society for Rheumatology	Lung fibrosis is an important contributing cause for mortality in autoimmune related ILD in particular scleroderma and this being a fibrotic disease, the clinical significance of INBUILD and another important trial SENSCIS are consistent with significant effect of nintedanib on lung function decay.	Thank you for your comment.
17	Consultee	British Society for Rheumatology	The relationship of lung function decline to long term mortality (15 years follow up) has been confirmed in scleroderma related mortality. Accepting INBUILD is too short to show this, translating the behaviour of lung function trajectory linking to mortality, any significant impact of nintedanib on halting of lung function decline will likely to manifest in decline in mortality in scleroderma-lung fibrosis.	Thank you for your comment. INBUILD included people with systemic sclerosis-interstitial lung disease, but only the progressing fibrosing phenotype whereas SENSCIS included all types of people with systemic sclerosis-interstitial lung disease. Data from SENSCIS were therefore not transferrable to the population covered in this appraisal, that is, people with PF-ILD. Please see FAD section 3.1
18	Consultee	British Society for Rheumatology	In SENSCIS study, half of patients recruited were on mycophenolate and within this group there was numerical improvement in rate of decline in FVC (-40 mls) with combination nintedanib and mycophenolate, compared to no-mycophenolate (-63.9 mls). This provides additional evidence that nintedanib with or without mycophenolate is beneficial in prevention of decline of FVC – an important surrogate for long term mortality.	Thank you for your comment. INBUILD included people with systemic sclerosis-interstitial lung disease, but only the progressing fibrosing phenotype whereas SENSCIS included all types of people with systemic sclerosis-interstitial lung disease. Data from

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				SENSCIS were therefore not transferrable to the population covered in this appraisal, that is, people with PF-ILD. Please see FAD section 3.1
19	Consultee	British Society for Rheumatology	The utility of an anti-fibrotic without additional risk of immunosuppression from immunosuppressants/biologics with associated increased risks of infection in autoimmune diseases is a step up novel agent in our armamentarium in treatment of this complication – and this is an increasing important consideration with the risk of COVID pandemic.	Thank you for your comment. Discussions about the innovative nature of a treatment include whether the technology offers demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case quality adjusted life year (QALY). The committee concluded that nintedanib was not innovative for PF-ILD. Please see the FAD section 3.32.
20	Consultee	British Thoracic Society	The appraisal consultation document states that “Current treatment for fibrosing interstitial lung disease (ILD) starts with immunosuppressants.” This is an incorrect interpretation of the evidence. There is currently no evidence based therapy for the treatment of fibrotic interstitial lung disease, other than antifibrotics for Idiopathic Pulmonary Fibrosis and mycophenolate for systemic sclerosis ILD. Fibrosing ILDs comprise a number of diseases including chronic hypersensitivity pneumonitis, non-specific interstitial pneumonia, asbestosis, unclassifiable ILDs and other connective tissue diseases eg Rheumatoid arthritis ILD for which there are no evidence based therapies. Immunosuppression is not an established treatment for all causes of fibrosing ILD. Many ILD clinicians would only recommend use when diseases have an inflammatory onset or an extra thoracic systemic component eg for extra pulmonary manifestations of Connective tissue diseases or where there is evidence of co-existent inflammatory hypersensitivity pneumonitis (as evidenced by ground glass shadowing on CT or cytological support from a BAL).	Thank you for your comment. The wording was amended to “Current treatment for fibrosing interstitial lung disease often starts with immunosuppressants”. Please see the following section: “Why the committee made these recommendations”
21	Consultee	British Thoracic	The appraisal consultation document states that “if recommended, nintedanib would be given	Thank you for your

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		Society	at the same time" – This comment is not evidence based as only those with systemic extra pulmonary manifestations of CTD or inflammatory hypersensitivity pneumonitis would have received immunosuppression. All other patients would not receive immunosuppression in clinical practice if they have fibrotic ILD eg asbestosis, RA-ILD, chronic HSP as there is no evidence base for giving it. In deed in line with the PANTHER study for IPF where immunosuppression was deemed to be harmful, there is growing evidence from studies in chronic HSP that immunosuppression may be harmful (especially in the context of specific genetic phenotypes) References: (https://www.atsjournals.org/doi/10.1164/rccm.201809-1646OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed) and in more recent CHP data (https://www.atsjournals.org/doi/full/10.1164/rccm.201902-0360OC). If patients are on immunosuppression and develop progressive fibrotic ILD then this is seen as a treatment failure and often immunosuppression is withdrawn due to the concerns about infection risk. Nintednaib would NOT be introduced at the same time as immunosuppressive therapy but only when immunosuppressive therapy had failed. As a result, in clinical practice a significant proportion of patients would not be on immunosuppression which reflects the trial design where immunosuppression was restricted for 6 months. However, in the trial 68% of patients remained on prednisolone doses less than 20mg which is reflective of clinical practise. The document also comments it is uncertain what the effect would be in clinical practice because the trial restricted use of immunosuppressants for 6 months. It is clear from the clinical trial that patients with progressive fibrotic ILD would benefit from nintedanib in that there is a reduction of FVC decline – these patients are reflective of clinical practice. There is evidence that in SSc-ILD, RA-ILD, HP and idiopathic NSIP, decline in FVC despite management is associated with a much higher mortality. Once treatment has failed, mortality increases strikingly, whatever subsequent additional treatments are used. Clinicians continue immunosuppression despite disease progression because until now, no better treatment has been available. NHS practice exists as it currently does and will continue to do so precisely because nintedanib is not approved.	comment. The committee noted that if recommended, nintedanib would be an add-on therapy rather than a direct comparator to conventional treatments, and that the conventional treatments for the underlying diseases may or may not be continued when adding nintedanib. Please see section 3.4 of the FAD.
22	Consultee	British Thoracic Society	Section 3.4. Steroids, azathioprine, rituximab and infliximab are not evidence based treatments for fibrosing ILD as per this statement and thus this is not evidence based.	Thank you for your comment. These treatments, although unlicensed and not evidence-based for PF-ILD, are used is clinical practice and are, therefore, appropriate comparators for nintedanib in this

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				appraisal. This is as per NICE's guide to the methods of technology appraisal (2013)
23	Consultee	British Thoracic Society	Section 3.6. The statement that "the committee interpreted this to show that fewer patients randomised to nintedanib than placebo needed immunosuppressants" is an incorrect conclusion and not statistically valid. The study was not powered to look at this and this finding could have occurred by chance. Also that "a substantial proportion of participants needed the treatment that was restricted earlier in the trial" again is factually incorrect as only 16% of patients were prescribed immunosuppressants after 6 months which means a significant greater proportion 84% DID NOT require immunosuppression after 6 months. "ERG noted that immunosuppressants are not restricted in clinical practise" – this is clinically inaccurate. There are a number of patients with progressive fibrotic ILD in whom immunosuppressants would not be given in clinical practise, notably Rheumatoid arthritis ILD, asbestosis and those with concerns about infection with immunosuppression. "Placebo without conventional standard treatments does not reflect NHS clinical practise. Therefore it is not an appropriate comparator" – again this is factually incorrect for all the reasons described in 1,2,4 and 5 above. "The clinical experts explained that nintedanib would be offered to reduce the dosage and use of corticosteroids" – This is factually incorrect as nintedanib would not be added to reduce dosage of prednisolone – this is the role of second line immunosuppressants. Nintedanib is not used as a steroid sparing agent. "The committee concluded that the INBUILD trial does not represent NHS clinical practice'; again factually incorrect for all the reasons stated in previous comments.	Thank you for your comment. Sentence on patients needing immunosuppressants has now been erased. The committee agreed that placebo is an appropriate comparator for NHS clinical practice. The committee further noted that the restriction of concurrent treatment in INBUILD trial may reflect current NHS care for some but not all people with PF-ILD. Please see FAD sections 3.6 and 3.7.
24	Consultee	British Thoracic Society	Section 3.7. A 107ml difference in FVC is significant in clinical practise whether it reaches the 10% threshold or not. The document noted the committee felt it was unclear whether this 107ml difference is clinically meaningful as it was uncertain the 10% threshold was achieved. The clinical experts at the meeting felt 107ml is clinically significant in line with other ILD colleagues. This difference is identical to the IPF treatment effect in the larger UIP sub-group in the IPF Clinical trials and nintedanib is an approved therapy in IPF. So questioning the significance of this effect for PF-ILD is not valid as its established already in IPF as a significant difference. Normal ageing experiences a 20-30ml decline per year so this 107ml difference is 5 x the normal ageing process especially cumulatively year on year. "The committee noted that the decrease of treatment effect suggested either a waning effect of nintedanib in the long term or a treatment effect of immunosuppressants, which more people had in the placebo arm than in the nintedanib arm" – this statement has no evidence base at	Thank you for your comment. The committee took into account the explanation that a difference of 107ml in decline of FVC is significant in clinical practice, as well as the range of value reported in the published literature (in company comment number 3) and agree that the difference in decline of

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			all and is not corroborated with the evidence that has been given for the 84 week data of the study. The effects seen are not statistically robust and MUST be taken with caution. Also, only 16% of the whole population was given immunosuppression and such a statement that this is an effect of immunosuppression is unsubstantiated and not evidence based and based on speculation rather than evidence that has been presented.	FVC (measured by millilitres per year over 52 weeks) as reported by INBUILD reflects a clinically meaningful change. Please see the FAD sections 3.8.
25	Consultee	British Thoracic Society	Section 3.8 “The committee concluded that there is uncertainty about whether nintedanib was associated with a ‘clinically meaningful change’ in FVC% predicted, compared with placebo” The experts and ILD clinicians defend the premise that 107ml difference is clinically meaningful irrespective of the FVC % change. Normal ageing experiences a 20-30ml decline per year so this 107ml difference is 5 x the normal ageing process especially cumulatively year on year.	Thank you for your comment. The committee took into account the explanation that a difference of 107ml in decline of FVC is meaningful in clinical practice, as well as the range of value reported in the published literature (in company comment number 3). The committee agreed that the decline in FVC (measured by millilitres per year over 52 weeks) as reported by INBUILD reflects a clinically meaningful change. Please see the FAD sections 3.8.
26	Consultee	British Thoracic Society	Section 3.29: There would be unlawful discrimination of all English patients with progressive fibrotic ILD as this therapy has been approved in Scotland for Scottish patients.	Thank you for your comment. The committee’s remit is to assess whether a drug can be recommended in England and Wales.
27	Consultee	Action for Pulmonary Fibrosis	**Overview** **Patients living with progressive fibrosing ILD (PF/ILD) are desperate to have access to nintedanib** for the reasons we explained in our earlier submission.	Thank you for your comment.

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			There is clearly a gap between the views of the NICE and Boehringer-Ingelheim but, **on behalf of people living with PF/ILD, Action for Pulmonary Fibrosis calls on NICE and the company to put the interests of patients and their families first and do all they can to find a flexible and pragmatic way to bridge the gap between their two positions**. The up-coming Innovative Medicines Fund may provide a means to do this, as might approval of the drug with an independent 'registry' study by NICE to evaluate efficacy of the treatment as part of a risk-sharing agreement between the company and NICE. Whatever it takes, please find a way to ensure access for patients to this treatment. Action for Pulmonary Fibrosis will continue to raise awareness of the inequality in access to treatments until everyone with PF/ILD has the access the treatments they deserve.	
28	Consultee	Action for Pulmonary Fibrosis	**Impact on people living with PF/ILD** At Action for Pulmonary Fibrosis, we are deeply concerned that the NICE appraisal did not take sufficient account of the impact that its preliminary recommendation would have on people living with progressive fibrosing ILD (excluding IPF) and their families. Action for Pulmonary Fibrosis has discussed the NICE decision with a focus group of PF/ILD patients and had individual conversations with other patients and carers living with the disease in England and in Netherlands, where the drug is available to patients with PF/ILD. In total we have spoken to 17 patients over the last 3 weeks. All the English patients interviewed are extremely upset and disappointed by the NICE decision. The strength of their feelings can be gauged in the following quotes, which are typical of those we received: Man living with Rheumatoid Arthritis-ILD (RA-ILD) Rejecting access to nintedanib for PF/ILD patients is devastating to patients and their families. Imagine that you are drowning in a lake, knowing that on the shore somebody has a lifeline to help you, but they will not throw that lifeline for you to catch. That is what this rejection feels like. Woman living with Pleuro-parenchymal fibroelastosis (PPFE) I feel very angry. I am in my 40s and have a young child and I work in the NHS. I have fibrosis at the top of my lungs but not at the bottom. My life expectancy is the same as	Thank you for your comment.

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			someone with IPF. It seems unfair that I'm not given a chance. I tried to get the drug, but I was denied. Now I'm too ill and so it's too late. I think I will fade away before I get this drug. I have no hope. Steroids have caused me to have osteoporosis and have worn away my stomach lining, so I'm now fed through a tube. It's been awful. There are only 40 other people like me living with PPFE in England. Without this drug, we have no hope. <u>Woman living with RA-ILD</u> I was on steroids for a few years and had put on a huge amount of weight. Since being given nintedanib, in 2020, on compassionate grounds, I have been able to reduce my steroid intake and I have lost a lot of weight. I'm able to move around again. It's made a great improvement to my quality of life. This will also have saved money for the NHS because I am no longer diabetic and hopefully will not be susceptible to some of the comorbidities of obesity. I knew about the drug and was aware that it wasn't available to me. I felt so sad, that I wasn't even considered for it. But now I am furious that people living with PF/ILD in Scotland have it, but we will not. It's simply unfair. <u>Woman in Netherlands living with desquamative interstitial pneumonia (DIP)</u> I was taking steroids but the side effects were becoming difficult and eventually it became clear the drug was not working. I was offered the chance to go on the INBUILD clinical trial in Belgium. I have now been on nintedanib for nearly 2 years. I feel very much better using this medication. My situation is stable and my cough is very much less. There are side effects, but I have managed these with my doctor's help. <u>Woman living with RA-ILD</u> I was diagnosed with RA-ILD in 2012. It started with a funny little cough. I'm a former nurse, but I was unable to work in a way that was reliable, so I had to stop work. I was on methotrexate but it was stopped after a bronchoscopy. I was denied access to nintedanib on compassionate grounds, but I don't why. We are all lumped together and that means none of us get the drug. I appreciate the aims of NICE, but SMC looked at the bigger picture and gave greater weight to the benefits nintedanib will bring to people living with this rare disease. In view of the recently announced £680 million Innovative Medicines Fund, I am hopeful that NICE will change its mind, but in the meantime, I am having to spend my hard-earned pension buying the drug from India. I can just about afford it, but what about all those people who cannot?	

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			Man living with chronic hypersensitivity pneumonitis (CHP) I was diagnosed with CHP in 2020 but was told that I would not be able to get nintedanib from the NHS for at least a year, if at all. Knowing that it is available in some European countries, we decided, with the support of relatives from abroad, to move to another country, where we could get the drug. At a time when Covid-19 was playing havoc with international travel, we managed to leave the UK and have moved abroad. The stress that this has caused and the heartache of leaving beloved relations, friends and our house is something which is difficult to accept or convey in words, it has been a monumental change to our lives. I cannot understand why other nations, having seen the same evidence and rationale as NICE have decided to authorise the drugs but NICE has not. It smacks of heartless cost saving. For me, this is unacceptable.	
29	Consultee	Action for Pulmonary Fibrosis	**Impact on inequality and disability** APF is also concerned about the implications NICE's decision will have on inequality and on the wellbeing of PF/ILD patients all of whom become disabled for the last 1-2 years of their lives. There are three aspects of this: 1. **People living in poverty will be the hardest hit** as 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 nintedanib from India – an increasing number of people with PF/ILD are already doing this, or • moving to Scotland or an EU or other country which has approved the drug for reimbursement, such as Netherlands. 2. **PF/ILD patients will feel a heightened sense of injustice compared to IPF patients** if NICE denies them access to nintedanib. The experience of people living with all types of progressive pulmonary fibrosis – PF/ILD and IPF is similar. Over time they become increasingly breathless, come to depend on supplementary and then home oxygen, and eventually die from respiratory failure or a related cause. Given these similarities of experience, PF/ILD patients feel discriminated against because NICE has approved antifibrotic medications, such as nintedanib, for IPF patients but not for	Thank you for your comment. The committee's remit is to assess whether a drug can be recommended in England and Wales, and within the population covered by the technology's marketing authorisation.

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			PF/ILD. While the majority of IPF patients are white men over 70 years of age, the PF/ILD community is more diverse with slightly more women than men and a higher proportion of people of Asian and Afro-Caribbean heritage. The NICE decision could be seen, by some, as having a differential impact on groups protected by equality legislation. 3. **All PF/ILD patients become disabled.** The NICE instructions for this consultation ask whether NICE's preliminary recommendation could have an adverse impact on people living with disability? They certainly will because all PF/ILD patients become disabled as the disease progresses and are generally disabled for periods between one and three years. Initially they find it difficult to walk up hills or flights of stairs but by the time they need supplementary oxygen they will be 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.	
30	Consultee	Sarcoidosis UK	Sarcoidosis is a 'rare' multi system disease of unknown origin with no known cure and it is one of the most common types of interstitial lung disease (ILD). End stage (i.e. Stage 4) sarcoidosis includes the presence of pulmonary fibrosis. About 20% of sarcoidosis patients develop pulmonary fibrosis.	Thank you for your comment.
31	Consultee	Sarcoidosis UK	Our members report that many aspects of their lives have been compromised due to sarcoidosis induced pulmonary fibrosis, for example being housebound or unable to work. One of our members has commented, "I have been unable to follow my vocation, I am very ill most of the time and even with conventional treatment (Azathioprine and Hydroxychloroquine) have largely been housebound throughout the last decade. We desperately need better medication so fibrosis won't halt our lives in the way it does now." When pulmonary fibrosis progresses, our members find their activities are limited and their quality of life suffers. Another patient commented, "I had considered myself 'comparatively lucky' until recently. I had a reasonably active quality of life with 22 years sarcoidosis, given that I have pulmonary sarcoidosis and subsequent pulmonary fibrosis. I have now been told the fibrosis has progressed, and find my activities are limited and I pass my responsibilities to others, hence having a lesser quality future to look forward to with my family."	Thank you for your comment.
32	Consultee	Sarcoidosis UK	Nintedanib has been shown to slow progress of pulmonary fibrosis in patients with ILD however it is currently not available to these patients in England. Our members consider this to be an equality issue, especially considering that the drug is available in Scotland. Our members comment that there are not currently enough treatment options for sarcoidosis patients with pulmonary fibrosis. Sarcoidosis patients tend to have a very individual experience of the condition, and one patient can experience completely different symptoms and responses to medications to another. Sarcoidosis-induced fibrosis can also manifest differently from patient to patient. Some of our members report adverse reactions to the currently	Thank you for your comment. The committee's remit is to assess whether a drug can be recommended in England and Wales.

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			available medications but there are often no other options. Our members believe that there need to be more choice for patients in order to have better outcomes. The more treatments available to patients, the better the outcomes will be for patients.	
33	Consultee	Sarcoidosis UK	Sarcoidosis is a rare disease which does not get the funding that is required. Whilst Nintedanib may be expensive in the short term, in the medium to long term it is far more expensive to have those with chronic sarcoidosis and fibrosis being unable to work or live a normal life. The impact of sarcoidosis-induced pulmonary fibrosis is not only financial but also emotional. One of our members has commented, “it hits not just the patient but also the family of the patient, their friends, relatives and work colleagues. With Nintedanib we have a chance to make a real difference to so many sarcoidosis patients’ lives. Please give us back more of our life.”	Thank you for your comment.
34	Consultee	Scleroderma and Raynaud’s UK	We are concerned that the action taken to suspend consultation ID1420 which considered the use of nintedanib within systemic sclerosis ILD (SSc-ILD) and its replacement with this current and broader consultation has overlooked the needs of patients with systemic sclerosis. Systemic sclerosis is a rare autoimmune disease characterised by fibrosis which affects multiple organs including the lungs which may be affected through progressive fibrosing interstitial lung disease which is a major contributory factor to death from the condition. There are limited effective treatments options for systemic sclerosis in general and even less for SSc-ILD, immunosuppressants for SSc-ILD are prescribed off-label and in most cases are unsuccessful in slowing progression. Patients may be offered lung transplantation in severe cases, but the grim reality is that few patients will be deemed ‘fit’ to undergo transplantation. The current outcomes of this consultation will contribute to the treatment inequalities experienced by rare disease patients in the UK, denying them an effective treatment option (as evidenced by the SENSCIS study, where SSc-ILD patients treated with nintedanib in combination with Mycophenolate mofetil had much slower lung progression than those taking MMF alone).	Thank you for your comment. INBUILD included people with systemic sclerosis-interstitial lung disease, but only the progressing fibrosing phenotype whereas SENSCIS included all types of people with systemic sclerosis-interstitial lung disease. Data from SENSCIS were therefore not transferrable to the population covered in this appraisal, that is, people with PF-ILD. Please see FAD section 3.1
35	Consultee	Scleroderma and Raynaud’s UK	Nintedanib has been FDA approved for use in SSc-ILD since 2019 and has EMA approval for SSc-ILD and other chronic fibrosing lung conditions. The decision to deny patients with SSc-ILD and other chronic fibrosing conditions access to this effective treatment will contribute to global health inequalities where UK-based patients with fibrosing lung conditions will have poorer outcomes and reduced quality of life than those from other western economies.	Thank you for your comment. INBUILD included people with systemic sclerosis-interstitial lung disease, but only the progressing fibrosing phenotype whereas SENSCIS included all types of people with systemic

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				sclerosis-interstitial lung disease. Data from SENSCIS were therefore not transferrable to the population covered in this appraisal, that is, people with PF-ILD. Please see FAD section 3.1
36	Consultee	Scleroderma and Raynaud's UK	Drug development and clinical trials are extremely challenging in the rare disease area; commercial interest is limited due to the relatively small number of patients affected. Whilst this drug is licenced and approved for other uses, we are concerned that lack of support from NICE may mean that companies may be discouraged from venturing into drug discovery in the rare disease arena or may not seek approval for treatments to be used in the UK market.	Thank you for your comment. The committee have now recommended nintedanib as an option for treating PF-ILD.
38	Consultee	Scleroderma and Raynaud's UK	We take on board the point made by the committee that there is a lack of long-term data to show long term effectiveness of nintedanib against progression of lung fibrosis and its effects on survival. This 'gap' would be best met through 'real world evidence'. By blocking the use of nintedanib in a comprehensive data-rich health care setting such as the NHS we may never gain insights into the full benefits of nintedanib for this group of patients.	Thank you for your comment. The committee have now recommended nintedanib as an option for treating PF-ILD.
39	Consultee	UK Clinical Pharmacy Association	We note that NICE appraisal documentation states that "It is also uncertain what its effects would be in clinical practice because the trial restricted use of some immunosuppressants in the first 6 months" Patients in the trial were being treated with immunosuppresants in the form of prednisolone tablets (only patients with >20mg prednisolone daily were excluded). 68.6% of patients (70.1% in the placebo arm and 67.2% in the nintedanib arm) used corticosteroids over the 52-week period in INBUIILD. Corticosteroids are the current first line immunosuppressant treatment for PF-ILD. Long-term use of corticosteroids has become the backbone of immunosuppressive therapy in PF-ILD but it is evident that such an approach is associated with significant morbidity to the patient. For this reason, other immunosuppressant agents, such as methotrexate, azathioprine and mycophenolate, are often prescribed to act as steroid sparing agents to enable the clinician to reduce the overall burden of oral corticosteroids. There is limited evidence for the role of second line immunosuppressants in PF-ILD with insufficient high-quality studies available to confirm their place in therapy. However, the national guideline advise that such treatments should be considered if corticosteroids do not control the disease or if the person experiences intolerable adverse effects. In practice many patients will be initially treated with 6 months oral corticosteroid therapy before second line immunosuppressant agents are added in. Such agents are unlicensed, have significant risk of	Thank you for your comment. The committee concluded that the use of restricted concurrent treatments in INBUILD trial may reflect current NHS care for some but not all people with PF-ILD. Please see the FAD section 3.6.

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			adverse side effects and require intensive monitoring during therapy, adding increased resources and cost to the prescription cost. We believe the INBUILD trial design to not be dis-similar to the treatment approach to a patient in practice and the background therapy should be regarded as standard practice.	
40	Consultee	UK Clinical Pharmacy Association	"The clinical experts explained that nintedanib would be offered to reduce the dosage and use of corticosteroids, but the committee was not presented with any evidence for this." We believe this statement was misinterpreted as it is the second line immunosuppressant therapy (such as mycophenolate, methotrexate) prescribed as an adjuvant has the aim to reduce oral corticosteroid dose.	Thank you for your comment. This sentence has now been amended. Please see the FAD section 3.6.
41	Consultee	UK Clinical Pharmacy Association	The post hoc analysis of SENSCIS study supports a synergistic benefit of both approaches immunosuppressant and nintedanib together in SSc-ILD. https://www.nejm.org/doi/full/10.1056/NEJMoa1903076	Thank you for your comment. INBUILD included people with systemic sclerosis-interstitial lung disease, but only the progressing fibrosing phenotype whereas SENSCIS included all types of people with systemic sclerosis-interstitial lung disease. Data from SENSCIS were therefore not transferrable to the population covered in this appraisal, that is, people with PF-ILD. Please see FAD section 3.1
42	Web comment	Not reported	***Has all of the relevant evidence been taken into account?*** The large INBUILD RCT has been the main focus for this submission. It includes a very heterogeneous group of conditions with different aetiologies and different pathogeneses but has interstitial lung disease as the common denominator. It includes a subgroup of patients with autoimmune-related interstitial lung disease (25.6%). Approximately 13% of patients recruited had rheumatoid arthritis-ILD and approximately 5-6% of the total study population had systemic sclerosis-ILD. Progressive ILD is a significant problem in patients with systemic sclerosis and I suspect only	Thank you for your comment. The committee have now recommended nintedanib as an option for treating PF-ILD.

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			a small number of patients were recruited to the INBUILD study as immunosuppressants that are frequently used to treat interstitial lung disease such as cyclophosphamide and mycophenolate were not allowed during the first 6 months of the study. However, very importantly there is a very relevant large multicentre randomised controlled trial which compares nintedanib with placebo in patients with systemic sclerosis who have associated interstitial lung disease (the SENCIS trial, NEJM 2019; 380:2518-28). The entry criteria for the SENSCIS study were slightly different to the INBUILD study. Patients had relatively early disease; they were allowed to enter the study if they were within 7 years of their first non Raynaud's symptom and the median disease duration was 3.4 years for study participants. An HRCT chest scan had to show fibrosis affecting at least 10% of the lungs but to enter the SENSCIS study they did not have to demonstrate progression of ILD prior to entry, in contrast to the INBUILD study. This study also had the primary end point as the annual rate of decline of FVC assessed over a 52 week period. Five hundred and seventy-six patients received at least one dose of nintedanib or placebo. 51.9% had diffuse cutaneous systemic sclerosis, approximately 60% participants were Scl-70 positive and 48.4% were receiving mycophenolate mofetil at baseline. The adjusted annual rate of change in FVC was -52.4 mils per year in the nintedanib group and -93.3 mils per year in the placebo group (P = 0.04). As mentioned previously, approximately 50% of patients were on mycophenolate mofetil at baseline and this had an additional positive effect on progression of inflammatory lung disease in both arms of the study. The patients on mycophenolate mofetil deteriorated more slowly than patients who were not on mycophenolate mofetil. These results suggest that nintedanib should be add on therapy where clinically indicated. Systemic sclerosis-ILD has its own marketing authorisation for nintedanib but I note from the public slides that no NICE submission is currently planned by the company. However, I hope that patients with systemic sclerosis-ILD will have access to nintedanib through some appropriate route. Systemic sclerosis associated pulmonary disease is the leading cause of systemic sclerosis related death. Pulmonary fibrosis accounts for 35% of these deaths. Pulmonary fibrosis can occur in both diffuse cutaneous and limited cutaneous systemic sclerosis. Up to 80% of patients with diffuse cutaneous systemic sclerosis develop interstitial lung disease. A third of these will develop clinically significant interstitial lung disease. Evidence has accumulated through small studies and the larger Scleroderma Lung Studies (I and II) and shown cyclophosphamide and mycophenolate mofetil to have a positive effect on the progression of SSc-ILD. Other immunosuppressants, including rituximab and tocilizumab, have been evaluated in RCTs and shown promising results. However, approximately 15% of this cohort with clinically significant ILD will develop progressive disease that does not respond to the	

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			currently available immunosuppressants in England, namely IV cyclophosphamide and mycophenolate mofetil. A deterioration in lung function occurs early in disease i.e. less than 5 years from disease onset. From early studies, we know that a forced vital capacity less than 50% of predicted at baseline is highly predictive of mortality in a patient with systemic sclerosis. Prior to using immunosuppressants in these patients, systemic sclerosis-ILD patients with a DLCO less than 40% had a 5 year survival of only 9%. We know that with the early use of immunosuppression such as cyclophosphamide and mycophenolate mofetil that we can slow the deterioration in forced vital capacity and so improve outcome and life expectancy. However unfortunately not all patients will respond to immunosuppression and thus there is an unmet need for other treatment options in these patients with severe rapidly progressive pulmonary fibrosis. ***Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?*** It is usual for RCTs in ILD to be of 12 months duration. I note that in the recommendations under section 1 it states that follow up was short so it was unclear if these people live longer. By extrapolation of the currently available treatments for patients with ILD, it would seem logical that any treatment that slows the rate of lung progression will lead to people living longer; this is what has happened in patients with systemic sclerosis associated ILD who have received and responded to IV methylprednisolone and IV cylopshosphamide and/or mycophenolate mofetil. Such long-term data for nintedanib could be collected via a managed access scheme/registry/ commissioning through evaluation process. It appears that the data are being collected by the company in the extension study but data are only available for a couple of years currently and there needs to be longer follow up to establish this but it does not seem appropriate to wait for these data. SSc-ILD patients were eligible for recruitment into the INBUILD study. We know from the SENSCIS trial that SSc-ILD patients who were also taking mycophenolate, whether they were in the nintedanib or placebo arms experienced a slower rate of annual fall in FVC. Such immunosuppressive drugs were not permitted in the first 6 months of the INBUILD study, which has been the main focus of this application and only 16% started these drugs during the second 6 months of the study. The results and modelling may therefore not reflect usual practice in managing patients with autoimmune-related ILD in England as stated in section 3.6. However, the earlier mentioned SENSCIS trial in SSc-ILD permitted the use of mycophenolate mofetil so does more accurately represent NHS clinical practice in the management of SSc-ILD. Perhaps more data from the SENSCIS trial should be included in this application.	

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			It was disappointing to learn that it was not possible to estimate nintedanib's cost effectiveness. I think the models could be reviewed so that it is possible. I agree with the statement in section 3.11 that there will be higher mortality rates with lower levels of lung function and so another reason to review the economic model. These patients experience significant morbidity and mortality without treatment. The aim of treatment in patients with autoimmune-related ILDs is to supress disease activity to prevent damage and maintain quality of life. The use of immunosuppression has improved outcomes in some patients with autoimmune-related ILDs but unfortunately not all patients respond so there remains an unmet need. Nintedanib, together with pirfenidone, are novel treatments that have slowed the rate of deterioration in lung function. I think these drugs do reflect a 'step change' in treatment and should be included in the final steps of a treatment algorithm for these patients living with ILD in England (section 3.28). I would anticipate that nintedanib would be taken for several years if it is tolerated and effective. Some patients are unable to tolerate it primarily due to gastro-intestinal side effects. Although, for clinical and cost-effectiveness reasons it should be discontinued if it is ineffective in a patient. A robust definition and assessment of response should be incorporated in a treatment algorithm. ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** Nintedanib has a marketing authorisation for the treatment of chronic fibrosing ILD with a progressive phenotype. We all recognise that finance in the NHS is finite and drugs have to be proven to be cost-effective. Hopefully a subgroup of patients with progressive ILD can be identified and be eligible to receive this drug via a NICE TA. For example, in the autoimmune patients with progressive ILD it may be most beneficial for nintedanib to be approved for use in patients who are progressing (FVC declined by 10% in 12 months with an increase in extent of fibrotic changes on HR chest imaging), despite maximal tolerated immunosuppression and/or who have the UIP pattern of fibrosis. Nintedanib should be stopped if there is no improvement/stabilisation of FVC decline. Stabilisation of FVC can be a good outcome in this cohort of patients with progressive disease.	
43	Web comment	UK Scleroderma Study Group	I am commenting on behalf of the clinical members of the UK Scleroderma Study Group (UKSSG) that includes medical specialists and NHS consultant rheumatologists from all of the major centres across UK that manage systemic sclerosis patients. Lung fibrosis (ILD) is the commonest cause of death related to systemic sclerosis that is the most lethal of the rhematic diseases. It is ta great disappointment that patients in England will not have access to the first drug approved in most countries for systemic sclerosis associated ILD (SSc-ILD).	Thank you for your comment. INBUILD included people with systemic sclerosis-interstitial lung disease, but only the progressing

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			In recognition of the importance of SSc-ILD for our patients, and consequent high unmet medical need, UKSSG members would like to make the following points. • SSc-ILD is a major cause of death and poor quality of life in SSc, affecting up to half of patients during the course of disease. Impact is due to symptoms and also the absence of approved therapies that has a very detrimental effect on mental wellbeing for patients. • SSc-ILD can be progressive over a short period of time, and so some cases were included in the INBUILD trial, but more often is a slowly progressive complication that leads to death after years of progression. This means that even modest slowing of progression is likely to improve survival, but this will not emerge from short term clinical trial results. • Link between lung function decline and survival in SSc-ILD has been shown in several high quality published academic studies that decline of lung function over 12 or 24 months is associated with significantly worse survival and so slowing this lung function decline is likely to improve outcome. • The positive SENSCIS clinical trial in SSc-ILD showed that nintedanib is effective in slowing decline in lung function in SSc-ILD compared with placebo. The trial results also suggest that benefit was numerically greater for cases receiving mycophenolate mofetil (MMF), an immunosuppressive drug that is recommended in SSc-ILD. These data suggest that for SSc-ILD there is a strong justification for using nintedanib in cases that progress on standard treatment with MMF. • In addition, infected digital ulceration occurs in SSc and may preclude use of immunosuppression such as MMF. In these cases, a non-immunosuppressant treatment for SSc-ILD would address an important unmet medical need. • From analysis of UK SSc patient cohorts, it has been shown that approximately 1 in 5 patients with SSc-ILD that are already treated with immunosuppression show significant decline in lung function to levels that predict poor survival within 5 years of onset of SSc. This equates to approximately 1 in 10 of the overall SSc population and these patients deserve access to approved drug therapy for SSc-ILD. The total UK SSc population is estimated as fewer than 12,000, and so inability to access nintedanib would directly impact around 1200 patients.	fibrosing phenotype whereas SENSCIS included all types of people with systemic sclerosis-interstitial lung disease. Data from SENSCIS were therefore not translatable to the population covered in this appraisal, that is, people with PF-ILD. Please see FAD section 3.1
44	Web comment	UK Scleroderma Study Group	***Has all of the relevant evidence been taken into account?*** The committee has focused on progressive ILD in several diseases but not on systemic sclerosis associated ILD (SSc-ILD) that is the main cause of death in this rheumatic disease with high mortality. The SENSCIS trial examined nintedanib in SSc-ILD and provides robust evidence of benefit and suggests added benefit to that obtained by MMF treatment. ***Are the summaries of clinical and and cost effectiveness reasonable interpretations of***	Thank you for your comment. INBUILD included people with systemic sclerosis-interstitial lung disease, but only the progressing fibrosing phenotype

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			the evidence? Impact of treatment that slows progression of ILD in SSc-ILD and prevents decline of lung function would be expected to reduce mortality from SSc-ILD based on robust observational cohort data from multiple large datasets and publications. Alternative treatments such as stem cell transplantation are expensive and have high treatment related mortality. Nintedanib may be more cost-effective if this comparator treatment was considered. ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** The recommendations are not a suitable basis for guidance to the NHS. The recommendations would deny patients with SSc-ILD that could not receive immunosuppression or those that had progressive disease despite immunosuppression of a licensed treatment when no alternative therapy is available. This is outside best practice in other similar countries in Europe and elsewhere with comparable healthcare systems. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** Women are much more likely to be affected by SSc than me. Black patients have a much worse outcome and survival form SSc and SSc-ILD than white patients.	whereas SENSCIS included all types of people with systemic sclerosis-interstitial lung disease. Data from SENSCIS were therefore not translatable to the population covered in this appraisal, that is, people with PF-ILD. Please see FAD section 3.1
45	Web comment	Not reported	***Has all of the relevant evidence been taken into account?*** See below ***Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?*** See below ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** The drug is approved for Idiopathic pulmonary fibrosis but not for sarcoidosis fibrosis for which it potentially has better outcomes. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and***	Thank you for your comment. The committee's remit is to assess whether a drug can be recommended in England and Wales and within the population covered by the marketing authorisation of the technology. .

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			maternity? The treatment is available in Wales and Scotland which discriminates on country of residence. The drug is approved for Idiopathic pulmonary fibrosis but not for sarcoidosis fibrosis for which it potentially has better outcomes.	
46	Web comment		***Has all of the relevant evidence been taken into account?*** No it hasn't. There is a substantial body of evidence that individuals who have fibrosis as a result of sarcoidosis would also benefit from this treatment and indeed have longer life and better prospects ***Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?*** The cost of treatment is only just over the quality of life year limit and with an NHS discount would be below it. Clinical research suggests that lung transplant prognosis is improving all the time. ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** No they are not. They are based solely on cost and not the ability of this treatment, which is approved in many other countries, to improve the lives of those who have sarcoidosis related pulmonary fibrosis. This treatment is already available in Scotland and Wales to people with Sarcoidosis. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** Yes. The recommendations discriminate between groups of individuals who suffer from pulmonary fibrosis from different causes. This seems to be based on how well known such causes are rather than the effectiveness of the treatment on pulmonary fibrosis regardless of cause. The actual number of individuals with Sarcoidosis fibrosis requiring this treatment on an annual basis would be small and therefore the overall cost to the NHS would be relatively low. It is discriminating against an underrepresented group whose prognosis is actually better than for those with IPF who are able to access this treatment.	Thank you for your comment.
47	Web comment	Not reported	***Has all of the relevant evidence been taken into account?*** I firmly believe that pulmonary fibrosis is generally terminal and there should be no discrimination between its various types. or even United Kingdom boarders. in general terms this disease is not self inflicted, effecting many people who still have much to offer society, and should be available to all who qualify.	Thank you for your comment. The committee's remit is to assess whether a drug can be recommended in England

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			Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? I believe there is a substantial imbalance when a 90 year old person whose life remains valuable following a lifetime of contributing to society is rightly given all the most expensive resources of the NHS following exposure to Covid. A pulmonary fibrosis sufferer may not qualify for a drug that can prolong there lives. ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** The recommendations should be based on the same criteria that allowed the drug to be approved in Scotland, consequently the Nintendanib drug should be given the same approval in England. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** I thought it would assist my case if I supplied a few bullet points about myself . In light of my current condition I believe that my only hope for a prolonged life is to be prescribed with Nintendanib. 1. MY AGE. I have always felt that I carry my age better than most and apart from my lung condition am in excellent health and feel very confident that I can well endure any side effects. 2. FITNESS. I have good musculature and continue to exercise on a daily basis. 3. MY WEIGHT. Despite being on a high dose of steroids I have managed to lose over a stone and a half in weight and continue to do so. I would of course ensure that I will be match fit if offered this Medication. 4. ACHIEVEMENTS I AM PROUD OF. A. 12 years as a medic and Physiotherapist in the RAF. B. Selection for the RAF and Olympic Gymnastic team, C. Helicopter winch man on mountain desert rescue. D. 40 years as volunteer Managing Director, Chairman and Trustee of a MENCAP charity. E. 8 years as swimming coach and lifeguard for a disabled swimming club. F. 30 Years as co-Founder, Owner and CEO with my wife of the largest Envelope Print and Mail-house businesses in the south west	and Wales and within the population covered by the marketing authorisation of the technology.

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			In conclusion I have been married for 54 years with a loving family unit. Our two daughters are sadly handicapped, one severely Autistic and the other with Crohns Disease and congenital deafness. Also my employees and their families rely on me to continue running a very successful Print & Mail House business, so I therefore request that you present my case and put me forward for consideration or trial. Thank you.	
48	Web comment	Not reported	***Has all of the relevant evidence been taken into account?*** I have been advised that Nintedanib has been approved for use in the US and Europe since 2014 and that it is also used in Scotland and Wales. I am wondering if there is evidence from these experiences which could/should be considered? ***Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?*** I am not an expert (or a patient) but am not wholly convinced they are. See comments below. ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** No, I do not believe so. The committee notes a number of uncertainties and on that basis I would argue that it is premature to make a decision about the use of Nintedanib. The clinical trial suggests decline of lung function is slowed and I would think this provides encouragement to undertake further research or trials if a decision to approve use of the drug can not be made at this juncture. I would prefer that this treatment be made available as it is elsewhere. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** I don't think there is discrimination in relation to the above protected characteristics per se but I do think there is in relation to medical conditions. My lay persons view is that expensive treatments are approved for high profile or well-known conditions such as most forms of cancer but not for those lesser known/rarer conditions. This can not be right, particularly when life expectancy for those with interstitial lung disease is shorter than for those with many cancers	Thank you for your comment. The committee have now recommended nintedanib as an option for treating PF-ILD.
49	Web comment		***Has all of the relevant evidence been taken into account?*** There have been many studies demonstrating the effectiveness of this drug with non IPF fibrosing lung disease as well as IPF. It has been approved in the US and many countries worldwide since 2014 with great success, the average life extension being 7 more years. Effectively tripling life expectancy in many people.	Thank you for your comment. The committee have now recommended nintedanib as an option for treating PF-ILD.

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			Fibrotic lung disease carries a prognosis much worse than many cancers and should be afforded every practicable intervention. The Quality of Life year assessment of cost is under £20 pa. This drug falls into that category with bulk purchase. Only 170 extra people roughly each year will make use of the drug, but for that 170 people the drug is life changing. This is a very useful document supporting its use. https://err.ersjournals.com/content/26/145/170053 ***Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?*** No. The cost fits within the criteria of cost per QOLY when bulk purchase is considered. cost is c £21 k without NHS discount. With the discount it falls well below the £20 k pa threshhold ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** Whilst decisions need to be made, ignoring substantial research carried out on the global stage is counter productive. As we have seen with Covid, when health systems work together and build on each others research, treatments and research prospers. There is ample evidence globally that this is a life changing drug for many people. To deny this treatment is inhumane. ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** All fibrosing lung disease carries a dire prognosis without treatment. This drug is the best available treatment for substantially prolonging life. To differentiate different fibrosing lung diseases including IPF for treatment but not other fibrotic lung diseases is discriminatory.	
50	Web comment		A fundamental assumption in the appraisal process is that "Current treatment for fibrosing interstitial lung disease starts with immunosuppressants". This is incorrect. There is no evidence base for immunosuppressants in a range of progressive fibrosing interstitial lung diseases (PF-ILD), nor are they licensed, and in IPF (which has many clinical and molecular features in common with PF-ILD) immunosuppressant-based treatment caused major harm (more deaths and hospitalisations compared with placebo)(1). Confusion may have arisen because some patients with PF-ILD receive immunosuppressants for extrapulmonary manifestations, such as rheumatoid arthritis and connective tissue	Thank you for your comment. Section 3.6 now mentions that patients who started immunosuppressants during the second 6 months might have rheumatoid arthritis. The

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			diseases. Here, immunosuppressants are not used to treat the PF-ILD. Furthermore, the appraisal mixes up 'ILD' and 'PF-ILD', often apparently using these terms interchangeably (e.g. ERG comment on page 20 of the committee papers). Patients with a steroid-responsive inflammatory ILD (who likely represent most patients in the physician survey, Figure 1, page 17 of the committee papers) are not relevant to this appraisal since clearly, they do not fulfil the criteria for progression (by definition, patients with PF-ILD have progressive fibrosis). There are no treatments that are being consistently used for the management of patients with PF-ILD. Immunosuppressants are not a relevant comparator for novel therapies for PF-ILD, and that the placebo arm of the INBUILD trial is a good representation of UK clinical practice. "No treatment" is the correct comparator for a cost effectiveness analysis of nintedanib. 1. Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ, Network IPFCR. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968-77. ***Has all of the relevant evidence been taken into account?*** Yes ***Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?*** No ***Are the recommendations sound and a suitable basis for guidance to the NHS?*** No ***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** No	committee also noted that if recommended, nintedanib would be an add-on therapy rather than a direct comparator to conventional treatments in all people with PF-ILD, as the conventional treatments for the underlying diseases may or may not be continued when adding nintedanib. Please see section 3.4 of the FAD.
51	Web comment		I would like to add that I have a friend who is suffering from progressive lung sarcoidosis and would greatly benefit in regard to her life expectancy from this drug becoming available in the UK	Thank you for your comment.

NICE National Institute for Health and Care Excellence

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 August 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Boehringer Ingelheim
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Abby Tebboth

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NICE National Institute for Health and Care Excellence

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 August 2021. Please submit via NICE Docs.

Comment number	Comments
	Key points **1. The committee have commented that nintedanib's treatment effect may decrease in the long term, but available data do not support this conclusion.** o The INBUILD trial was not designed to assess data beyond 52 weeks. The analysis of change in FVC (mL) up to database lock (DBL) 2 has important methodological limitations due to a healthy survivor bias observed in the placebo arm which underestimates the treatment effect of nintedanib. o Time-to-event analyses (absolute decline in FVC % predicted >5% and >10%) show consistent treatment effect over time up to DBL2.(1) o Data from INPULSIS-ON and a Greek registry in idiopathic pulmonary fibrosis (IPF) have shown that nintedanib has a sustained treatment effect over time.(2, 3) o Data from registries and meta-analyses have shown that nintedanib is associated with a significant long-term survival benefit compared with non-antifibrotic treatments.(4-6) o Overall, the conclusion that there is insufficient evidence of survival benefit, or that there is substantial likelihood of a treatment waning effect is not a reasonable interpretation of the evidence. It also does not take into account the full body of relevant evidence. **2. The committee have commented that they were not presented with the algorithm chosen by the company to estimate FVC % predicted and that they would like to see how this was done.** o FVC % predicted was reported as a secondary endpoint in the INBUILD trial. This was calculated according to the Global Lung Initiative (GLI) equation.(7) **3. The committee have commented that it is unclear whether the primary endpoint measured by FVC in millilitres per year over 52 weeks reflects a clinically meaningful change as measured by FVC % predicted.** o Published literature suggests that the change in FVC % predicted reported in INBUILD is clinically meaningful.(8) o Pre-specified analyses from INBUILD showed that treatment with nintedanib reduced the proportion of patients with both a relative and absolute decline from baseline of >10% and >5% at week 52.(9) These declines are associated with mortality in ILD.(10) o Meta-analysis of nintedanib clinical trials in IPF, PF-ILD and systemic sclerosis-associated ILD show a strong association between annual rate of change in FVC % predicted and risk of death.(11) o The difference in FVC reported in INBUILD, measured in both mL and % predicted, was similar to that reported in INPULSIS.(9, 12) Clinical experts and patient groups agree that this difference has been meaningful for patients with IPF, as well as those receiving nintedanib for PF-ILD under named patient supply. **4. The committee have commented that the impact of restricted concurrent NHS treatments on the treatment effect of nintedanib is unclear.** o Post-hoc analyses of the INBUILD trial excluding all patients who took prohibited or restricted medications over 52 weeks were very similar to the primary analysis. This indicates that the treatment effect was not influenced by the use of restricted and prohibited medications.(13) o Post-hoc subgroup analyses from INBUILD have shown that the effect of nintedanib on reducing FVC decline was not influenced by the use of glucocorticoids, a type of immunomodulatory medication, at baseline.(13) o Clinical experts treating interstitial lung diseases at specialist tertiary centres in the UK also agree that restricted medications would not be expected to have any meaningful efficacy in the treatment of progressive fibrosing disease. **5. The committee have commented that there are uncertainties in the company's modelling**

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

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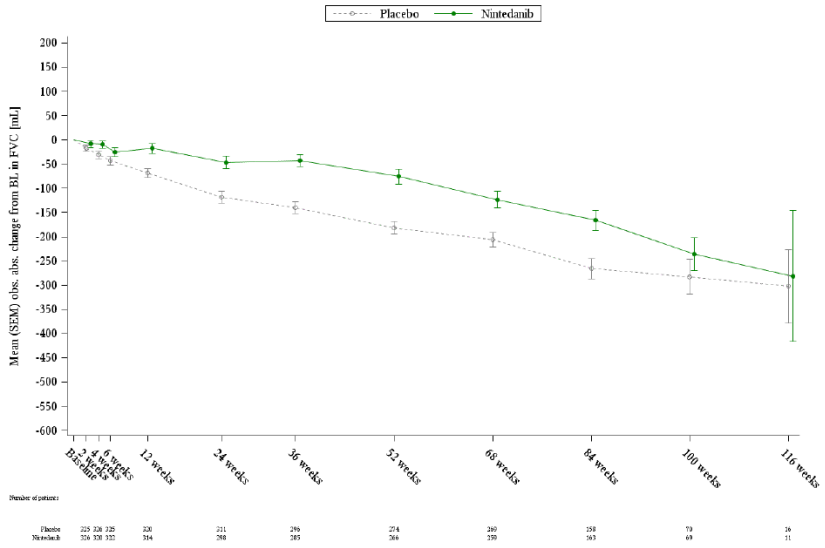
	and validation for overall survival in the placebo arm, and that this likely overpredicts deaths in the placebo arm. o If plausible alternative survival curves with more optimistic survival for the placebo arm are selected, nintedanib remains cost-effective. o The ICER for nintedanib is only not cost-effective if clinically implausible curves are selected. **6. The committee have commented that there are uncertainties in fitting individual parametric distributions to the nintedanib and placebo arms, and that modelling resulted in ever-increasing survival benefits for nintedanib compared with placebo in the extrapolated periods.** o Independent survival models were used for consistency across outcomes, as the proportional hazards assumption was not met for the time to discontinuation outcome. o The original company base case is based on Bayesian analysis, the shape of which is informed by the long-term clinical trial data for nintedanib in IPF. However, we take the committee's point of view that there is uncertainty particularly for the placebo arm. o If reasonable alternative survival curves are selected that reduce the modelled difference in survival between nintedanib and BSC, the ICER remains cost-effective. **7. The committee have commented that there are uncertainties in the company's modelling of exacerbations and decline in lung function because of their lack of a link with mortality in the model.** o We acknowledge that this is a limitation of the current model, which was necessary to avoid double counting deaths. We did look into changing the structure of the model to include a link between mortality and exacerbations and decline in lung function, but this model generated unrealistically high life years for both BSC and nintedanib due to additional uncertainties generated by this approach. o Since the committee commented that the modelling of exacerbations and decline in lung function was acceptable, and since the main driver of the cost-effectiveness is the survival analysis, we do not believe that these limitations significantly impact the economic case for nintedanib. **8. The committee have commented that the modelling of stopping treatment was uncertain and may have underestimated the costs of nintedanib.** o Exploratory analyses have shown that selecting a different distribution for discontinuations still results in a plausibly cost-effective ICER for nintedanib. o The modelling of discontinuations was deemed to be acceptable by the Evidence Review Group. **9. The committee have commented that nintedanib does not meet NICE's criteria for an innovative treatment, due to shortcomings in the company's modelling.** o Clinical experts and patient groups unanimously agree that nintedanib is a step change in the treatment of PF-ILD, as there are no other evidence-based treatments available to slow disease progression. o The clinical relevance of nintedanib has been demonstrated in the INBUILD trial, and is independent of the economic modelling. o Therefore, the committee's view of uncertainties in the economic model should not impact on whether nintedanib is determined to be a step change in the treatment of PF-ILD.
1	**The committee have commented that nintedanib's treatment effect may decrease in the long term, but available data do not support this conclusion.** **The INBUILD trial was not designed to assess data beyond 52 weeks. The analysis of change in FVC (mL) up to DBL2 has important methodological limitations due to a healthy survivor bias observed in the placebo arm which underestimates the treatment effect of nintedanib.** According to the clinical trial protocol, the objective of the INBUILD trial was "to investigate the efficacy and safety of 150 mg bid nintedanib in patients with PF-ILD compared to placebo over 52 weeks in Part A" and the primary objective was "to demonstrate a reduction in lung function decline, as measured by the annual rate of decline in FVC for nintedanib compared to placebo over 52

weeks". The objectives of part B were "to collect supportive, longer term efficacy (time to event endpoints) and safety data on the effect of nintedanib compared to placebo."

Therefore, the study focussed on the primary endpoint of annual rate of decline in FVC (mL/year) over 52 weeks. The annual rate of decline in FVC (mL/year) including data collected after 52 weeks up to DBL2 was not pre-specified in the protocol or the trial statistical analysis plan (TSAP) and was added as a purely post-hoc exploratory analysis. In addition, the latter analysis has some methodological limitations which make interpretation of the results challenging. Due to the study design, the follow-up times of the patients differ for those in part B (i.e. beyond 52 weeks), and the number of patients attending the visits beyond 52 weeks decreases per visit.

It should be noted that the mean change from baseline presented in response to clarification questions was based on DBL1. Figure 1 shows data up to DBL2. It can be seen that with further follow-up and additional patients reaching the week 84 timepoint (321 at DBL2 vs. 180 at DBL1), the treatment difference has increased, and the variability decreased, compared to the data from DBL1. This shows the uncertainty of the mean change from baseline beyond 52 weeks at timepoints when only few patients were observed in the trial.

Figure 1: Mean of observed absolute change from baseline in FVC (mL) over time (overall population)



Variable follow-up leads to methodological limitations for the analysis of the annual rate of decline in FVC (mL/year) including data collected after 52 weeks. Data beyond 52 weeks seem to be associated with a healthy survivor bias, i.e. there seem to be healthier patients in the placebo arm compared to the nintedanib arm.(14) Table 1 (page 21, based on data up to DBL1) shows that initial mean baseline FVC actually increased in patients with longer follow-up in the placebo group, but not in the nintedanib group (mean difference placebo-nintedanib at 52 weeks = -8 mL vs. 60–74 mL at 68–100 weeks). This is consistent with the assumption that patients in the nintedanib arm drop out due to adverse events, whereas placebo patients drop out due to disease worsening.

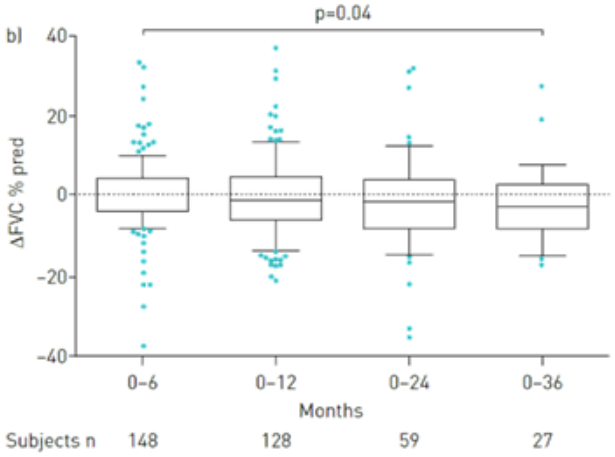
A healthy survivor bias might lead to biased differences for the FVC decline between the treatment groups beyond 52 weeks. This might decrease the advantage of nintedanib as the more severely affected patients (with stronger FVC decline) are underrepresented in the placebo arm (as for example more patients have died in the placebo group). In the Random slope & intercept (RS&I) model, patients with long term data and more available assessments are given a higher weight in the analysis compared to patients with shorter follow-up times. Thus, biased data beyond 52 weeks

	particularly affects the results of the RS&I model. Another methodological challenge for the analysis of annual rate of decline is the linearity assumption. The RS&I model assumes that FVC declines are linear and that treatment effect is captured by the difference in slopes. This fits well over 52 weeks but not necessarily over longer time periods. This can be illustrated when considering the intercept term for treatment in the RS&I models. For the annual rate of decline in FVC (mL/year) over 52 weeks (primary endpoint) the effect of nintedanib vs. placebo on the intercept is 13.7 mL and non-significant. This effect is not included in the slope (annual rate of decline in FVC) and could be interpreted as the "acute" effect of nintedanib. In contrast, the treatment intercept for annual rate of decline in FVC [mL/year] including data collected up to DBL2 is about 2 times higher (27.3 mL) as in the primary endpoint model and significant (p=0.0072). As this higher intercept value is also not included in the treatment effect this leads to a reduced estimate for the slope, i.e. a reduced annual rate of decline in FVC, compared to the annual rate of decline over 52 weeks. Therefore, the effect of nintedanib on the annual rate of decline in FVC (mL/year) is underestimated compared to the primary endpoint model. The higher intercept term for treatment is a hint that the linearity assumption, which is a requirement for the application of the RS&I models, might be violated for this analysis and reduces the effect size measured by the slope. All in all, the validity of the analysis of annual rate of decline in FVC (mL/year) including data collected up to DBL2 is limited and likely underestimates the treatment effect of nintedanib compared to placebo. To evaluate efficacy endpoints beyond 52 weeks, time to event endpoints should be considered instead. As by study design, the follow-up times of the patients differ in Part B (i.e. beyond 52 weeks). Time to event endpoints are a valid approach to evaluate longer term efficacy as they can deal with variable follow-up by censoring. Pre-specified time to event endpoints such as time to progression or death and time to first acute exacerbation or death became statistically significant at DBL2 (see below, data provided ahead of publication).(15) • Proportion of patients who had ILD progression (decline in FVC ≥10% predicted) or died up to DBL2: HR for nintedanib vs placebo 0.66 (95% CI: 0.53, 0.83; p=0.0003) • Proportion of patients who had an acute exacerbation or died: HR for nintedanib vs placebo 0.67 (95% CI: 0.46, 0.98; p=0.04) Absolute decline in FVC % predicted ≥5% and ≥10% was also consistent at 52 weeks and at DBL2 (see Table 2).(1) These analyses strengthen the evidence that nintedanib has a consistent effect over time, as the hazard ratios for 52 weeks and over the whole trial are similar and the 95% confidence intervals largely overlap. **Real-world data from a registry in IPF and longer term data from INPULSIS-ON have also shown that nintedanib has a consistent treatment effect over time.** Data from INPULSIS-ON, a long-term extension of the INPULSIS trials in IPF, showed that the adjusted rate of decline in FVC over 192 weeks was comparable to that shown over 52 weeks in patients treated with nintedanib: • Adjusted annual rate of decline in FVC over 192 weeks (all patients treated with nintedanib): -135.1 mL.(2) • Adjusted annual rate of decline in FVC over 52 weeks (nintedanib) -113.6 mL.(2) This is a 22mL difference in the adjusted rate of decline at 192 weeks vs. 52 weeks for nintedanib (a period of 140 weeks) compared with an annual rate of decline in FVC over 52 weeks of 205.0 mL for placebo.(12) As noted below, the minimum clinically important difference in FVC % predicted is 2-6%, which equates to 75-80 mL in the patients in INPULSIS-ON.(2) This further suggests that the small

difference seen between 52 and 192 weeks is not clinically meaningful.

Data from a Greek registry of IPF patients across 7 hospitals has also shown that FVC % predicted was largely stable at 3 years for nintedanib patients, with no significant difference from baseline (see Figure 4 below).

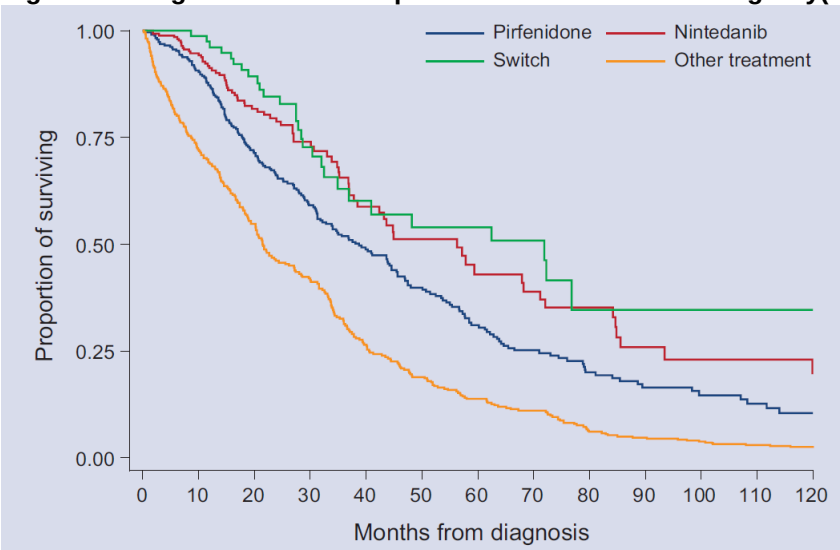
Figure 4: Change from baseline in FVC% predicted at 0-6, 6-12, 12-24 and 24-36 months taken from the Greek INDULGE-IPF registry in IPF.(3)



Data from registries and meta-analyses have shown that nintedanib is associated with a long-term survival benefit compared with non-antifibrotic treatments.

Long-term comparative data for IPF patients treated with nintedanib are available from the EMPIRE registry. This shows significantly longer median overall survival for the nintedanib group compared with those who received non-antifibrotic treatment (median survival 56.3 months for nintedanib vs. 21.4 months for other treatment, for a 34.9 month or 2.91 year difference in median survival; p<0.001).(4) This is comparable to the life years (LYs) gained in the company's base case in the economic model (LYs gained = 3.1 years for nintedanib vs. BSC). The median survival difference is also similar to that reported in the Greek INDULGE-IPF registry (54.7 months for nintedanib).(3)

Figure 5: Long-term survival reported in the EMPIRE IPF registry(4)



Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

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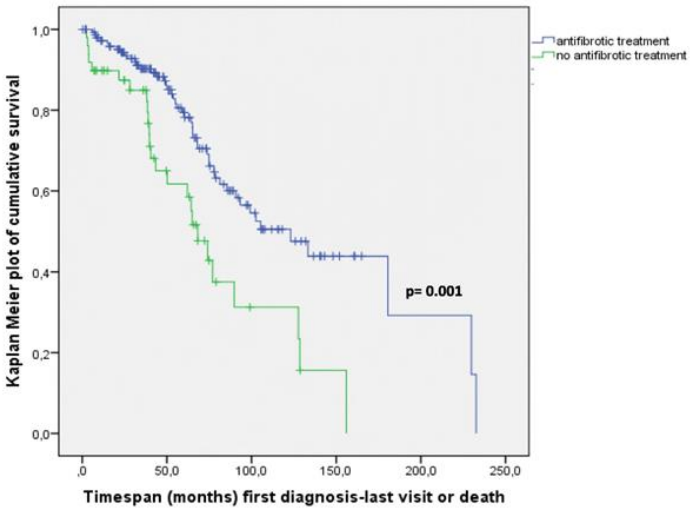
Although the European IPF registry does not report survival data specifically for nintedanib, it does report long-term survival data on the use of antifibrotics, which included pirfenidone and nintedanib.(5) Previous meta-analysis and other real-world data have shown that nintedanib treated patients have similar or better survival compared with pirfenidone treated patients in IPF.(4, 16, 17) Similar efficacy of nintedanib and pirfenidone was also accepted by the committee in the appraisal of nintedanib for IPF (TA379).(18) Therefore, the antifibrotic treatment arm should provide an indication of the survival benefit of nintedanib in the European IPF registry population.

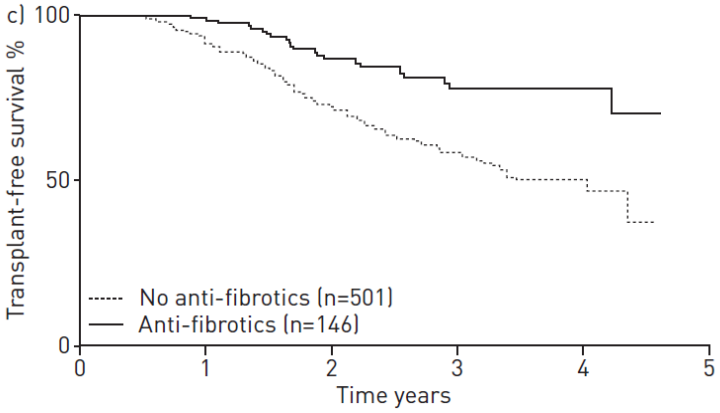
This registry also reported a significant survival benefit for antifibrotic treatment compared with non-antifibrotic treatment (median survival on antifibrotics 123.1 months vs 68.3 months for prednisolone or other treatment, for a 54.8 month or 4.6 year difference in median survival, p=0.001).(5) This is a greater difference in overall survival than is modelled in the company base case.

Figure 6: Overall survival of IPF patients upon first diagnosis depending on treatment from the European IPF registry(5)



Similarly, although the Australian registry does not report survival specifically for nintedanib, it does report long-term survival for patients treated with antifibrotics (including pirfenidone and nintedanib).(6) This registry also reported significantly improved survival for patients who received antifibrotic therapy compared with patients who did not (HR 0.56; 95% CI 0.34, 0.92; p=0.022).

Figure 7: Kaplan-Meier survival analysis of patients with IPF with or without antifibrotic treatment(6)



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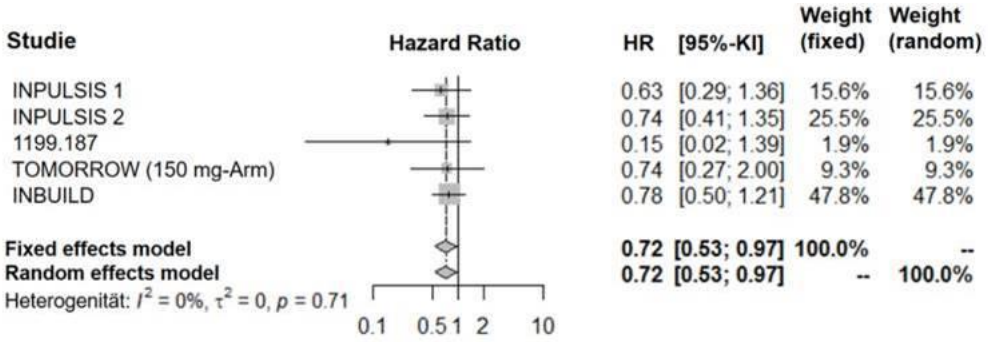
	These registries all report a survival difference that is maintained, or could be said to increase, over time. Finally, a meta-analysis of randomised controlled trials in IPF (4 studies) and PF-ILD (1 study) has also shown that nintedanib treatment is associated with significantly improved survival compared with placebo (Figure 8).(19) This is confirmed by another meta-analysis of 8 randomised controlled trials and 18 cohort studies that found that antifibrotic treatment was associated with a significantly decreased risk of all-cause mortality (RR 0.55; 95% CI 0.45, 0.66).(20) **Figure 8: Meta-analysis of randomised controlled trials for nintedanib in IPF and PF-ILD**  **Overall, the conclusion that there is insufficient evidence of survival benefit with nintedanib, or that there is a substantial likelihood of a treatment waning effect is not a reasonable interpretation of the evidence. It also does not take into account the full body of relevant evidence.**
2	**The committee have commented that they were not presented with the algorithm chosen by the company to estimate FVC % predicted and that they would like to see how this was done.** FVC % predicted was reported as a secondary endpoint in the INBUILD trial. This was calculated according to the Global Lung Initiative (GLI) equation which takes the form of the equation below, and varies depending on individual patients' race, age, gender and height. This approach is described and validated in publications by Quanjer et al and Kubota et al.(7, 21) Predicted value = $e^{a} \times H^{b} \times A^{c} \times e^{d \times group} \times e^{spline}$ where a is the intercept, H is the height (cm), b is the exponent for the height, A is age (years), c is the exponent for age and spline is the contribution from the age spline. Group is Caucasian, African-American, South or North East Asian and takes a value of 1 or 0 depending on the group.
3	**The committee have commented that it is unclear whether the primary endpoint measured by FVC in millilitres per year over 52 weeks reflects a clinically meaningful change as measured by FVC % predicted.** The committee accepted that nintedanib is associated with a slower decline in lung function (page 10 of the ACD). They state that a decline in FVC of at least 10% predicted defines disease progression and is associated with disease deterioration and mortality in PF-ILD (page 6 of the ACD). However, they question whether this is clinically meaningful as measured by FVC % predicted. **Published literature in IPF suggests that the change in FVC % predicted reported in the INBUILD trial is clinically meaningful.** In the overall population of the INBUILD trial, the adjusted mean absolute change from baseline to

week 52 in FVC % predicted was a secondary endpoint, and reported change was -2.62% in the nintedanib group and -5.86% in the placebo group (see Table 3 and section 11.1.3.1.2 of the Clinical Trial Report).(9) The adjusted mean difference showed that treatment with nintedanib reduced FVC % predicted decline by 3.24% (95% CI 2.09, 4.40) compared with placebo at week 52.

Published literature in patients with IPF suggest that the minimum clinically important difference for percent predicted FVC is between 2-6%.(8) This is therefore a clinically meaningful change in FVC % predicted.

Pre-specified analyses from INBUILD showed that treatment with nintedanib reduced the proportion of patients with both a relative and absolute decline from baseline in FVC of >10% and >5% at week 52.

In the overall population, fewer patients treated with nintedanib had an absolute decline from baseline in FVC % predicted of >10% (adjusted odds ratio 0.68; 95% CI 0.49, 0.95) or >5% (adjusted odds ratio 0.63; 95% CI 0.46, 0.85) at week 52.(9)

Analyses of the proportions of patients with a relative decline from baseline in FVC % predicted of >10% (adjusted odds ratio 0.63; 95% CI 0.43, 0.94) or >5% (adjusted odds ratio 0.46; 95% CI 0.31, 0.69) at week 52 were also in favour of nintedanib vs. placebo.(9) In the overall population, treatment with nintedanib also reduced the risk of progression (defined as ≥10% absolute decline in FVC % predicted) or death by 35% vs. placebo (HR 0.65; 95% CI 0.49, 0.85).(9)

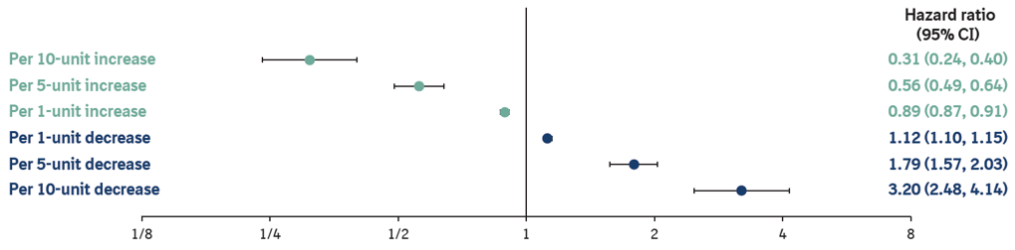
Declines in FVC of both >10% and >5% have been associated with mortality.(10) In INBUILD a decline of >10% was associated with a more than three-fold increase in the risk of death over 52 weeks (hazard ratio 3.64; 95% CI 1.29, 10.28; p=0.015).(10) This is similar to the risk reported in the INPULSIS trials (HR 3.95; 95% CI: 1.87 to 8.33; P<0.001).(10) These differences vs. placebo are therefore clinically meaningful.

Meta-analysis of nintedanib clinical trials in IPF, PF-ILD and SSc-ILD show a strong association between annual rate of change in FVC % predicted and risk of death.

A meta-analysis was published at the 2021 American Thoracic Society Conference, assessing the strength of FVC as a surrogate marker for mortality. This analysis pooled data from patients who received nintedanib or placebo in the placebo-controlled periods of trials in IPF (TOMORROW, INPULSIS-1 and -2, Phase IIIb trial NCT01979952), PF-ILD (INBUILD) and systemic sclerosis-associated ILDs (SENSCIS). The authors then assessed the association between FVC % predicted and time to death over 52 weeks.

This analysis showed a strong association between annual rate of change in FVC % predicted and risk of death (see Figure 9 below). The p-value for association between rate of change in FVC % predicted as a continuous variable and death was <0.0001.(11)

Figure 9: Association between annual rate of change in FVC % and risk of death over 52 weeks(11)



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	The difference in FVC reported in INBUILD, measured both in mL and % predicted, was similar to that reported in INPULSIS. Clinical experts and patient groups agree that this difference has been meaningful for patients with IPF, as well as those receiving nintedanib for PF-ILD as part of a named patient supply programme. The adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks reported in INBUILD was similar to that reported in INPULSIS: • INBUILD, nintedanib vs. placebo: 106.96 mL (95% CI 65.42, 148.50; p<0.0001)(9) • INPULSIS (pooled), nintedanib vs. placebo: 110.6 mL (95% CI, 83.2-137.9, p<0.001)(12) (information taken from the supplementary appendix) The difference in adjusted absolute mean change from baseline in FVC % predicted over 52 weeks was also similar in INBUILD and INPULSIS: • INBUILD, nintedanib vs. placebo: 3.24% (95% CI 2.09, 4.40)(9) • INPULSIS (pooled), nintedanib vs. placebo: 3.2% (95% CI 2.4, 4.0)(12) (information taken from the supplementary appendix) Clinical experts and patient groups unanimously agree that the effect of nintedanib in IPF has been highly meaningful for patients. This is highlighted in the previous submissions by the British Thoracic Society (BTS), Action for Pulmonary Fibrosis (APF) and clinical expert. In addition, BI have received requests for 'Named Patient Supply' (NPS) for nintedanib in PF-ILD from 19 out of 24 ILD specialist centres in the UK between 2018 and 2021. Named patient supply was considered in response to unsolicited requests from expert ILD physicians to access treatment with nintedanib in exceptional, life-threatening cases of PF-ILD. In total 258 patients have commenced NPS for nintedanib in PF-ILD, including patients from 19 different ILD specialist centres. This affirms that the ILD community, as stated in both clinician and patient submissions to NICE, view nintedanib as an innovation or 'step change' in the treatment of PF-ILD. This information also suggests that patients are receiving important benefit from nintedanib in PF-ILD in the UK. Previous submissions from Action for Pulmonary Fibrosis have also reinforced the benefit that patients have received from nintedanib in IPF: *"Anti-fibrotic treatments like nintedanib have been a 'game changer' for people living with IPF, slowing disease progression and increasing life expectancy."* "[redacted], *an RA-ILD patient, from Devon* *When I look around my support group, I see friends with IPF who have been diagnosed much longer than me and seem to be doing much better. They have all been on nintedanib or pirfenidone for a few years."* *"PF/ILD patients urgently want access to nintedanib because it directly targets their lung fibrosis and has been shown to slow progression, which a high priority for them."* **Overall, it is <u>not</u> a reasonable interpretation of the evidence to conclude that the treatment effect of nintedanib shown in INBUILD is not clinically relevant.**
4	**The committee have commented that the impact of restricted concurrent NHS treatments on the treatment effect of nintedanib is unclear.** **However, post-hoc analyses of the INBUILD trial excluding all patients who took prohibited or restricted medications over 52 weeks were very similar to the primary analysis. This indicates that the treatment effect was not influenced by the use of restricted and prohibited**

medications.

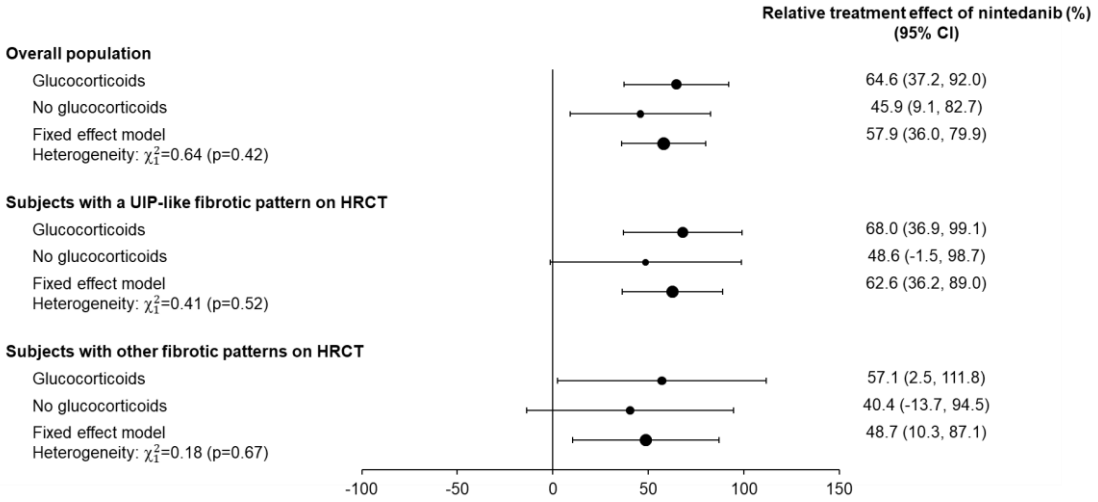
A post-hoc analysis was performed to assess the impact of restricted and prohibited medications on the primary endpoint (annual rate of decline in FVC).(13, 22) This was done by excluding all patients who took prohibited or restricted medications at baseline or on-treatment or post-study drug discontinuation over 52 weeks.

As shown in Table 4, the results of the primary analysis and that of the analysis excluding all patients who took prohibited or restricted medications through the trial to 52 weeks are very similar (rate of decline in FVC [mL/year] over 52 weeks was 107.8 mL vs. 107.0 mL in the primary analysis, both p<0.001), indicating that the treatment effect was not influenced by the use of restricted and prohibited medications.(13, 22)

Post-hoc subgroup analyses from the INBUILD trial have shown that the effect of nintedanib on reducing FVC decline was not influenced by the use of glucocorticoids at baseline.

A post-hoc analysis of the rate of decline in FVC over 52 weeks in subgroups by glucocorticoid use at baseline has also been done.(13) This analysis found that there was no significant difference in the treatment effect of nintedanib between subjects taking glucocorticoids at baseline and those who were not (interaction p=0.18, see Figure 10).

Figure 10: Relative treatment effect of nintedanib vs placebo on rate of FVC decline over 52 weeks in subgroups by use of glucocorticoids at baseline(13)



Clinical experts treating interstitial lung diseases at specialist tertiary centres in the UK also agree that restricted medications would not be expected to have any meaningful efficacy in the treatment of progressive fibrosing disease.

As stated in the British Thoracic Society's previous submission to NICE, the clinical consensus is that 'immunosuppressants are not given to treat the fibrotic component of an ILD, but the inflammatory component of the disease'. A consensus document agreed by the majority (21/24) of the clinical leads in ILD centres in England and Wales, plus 3 rheumatology experts, collated in short timelines has reaffirmed this statement.

The consensus document also states the following:

'The patient population with chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD) often have a wide range of underlying clinical conditions that have led to their ILD. These

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	extrapulmonary manifestations such as arthritis, glomerulonephritis, pericarditis and dermatological manifestations may require treatment with corticosteroids and/or immunosuppressants, but these are not to treat the ILD, and they do not have any meaningful impact on the ILD. By definition, patients with PF-ILD have progressed <u>despite treatment with conventional therapies, including immunosuppressants and other restricted therapies</u>.' *'It is common clinical practice that when patients with predominantly fibrotic ILD present with lung function decline despite immunosuppression, clinical consideration would be to reduce or completely stop immunosuppressants due to a lack of efficacy. There are also significant safety concerns around the use of multiple immunosuppressants as evidenced in the IPF-focused PANTHER trial which clearly demonstrated an increased risk of mortality & hospitalisation in these patients.'* *'The ILD clinical community are concerned about using non evidence-based immunosuppressants that lack efficacy in PF-ILD patients who phenotypically behave like IPF and have similar radiological features. This is reflected in the very low levels of use of restricted immunosuppressants after 6 months in the INBUILD trial once these were allowed.'* *'From a clinical perspective, there are no treatments that are licensed for use, or really being consistently used in clinical practice for the management of UK patients with PF-ILD and therefore the placebo arm of the INBUILD trial is a true representation of UK clinical practice.'* Please see Appendix 2 (page 24) for the full consensus statement. **In summary, it is not a reasonable interpretation of the evidence to conclude that the impact of restricted therapies on the treatment effect of nintedanib is unclear. It is clear that the restriction of these treatments in INBUILD has not biased the results of the trial, or reduced the relevance of the trial to UK clinical practice, when all relevant evidence is considered.**
5	**The committee have commented that there are uncertainties in the company's modelling and validation for overall survival in the placebo arm, and that this likely overpredicts deaths in the placebo arm.** **If an alternative survival curve with more optimistic survival for the placebo arm is selected, nintedanib remains cost-effective.** The committee noted that the Bayesian survival curves dropped more quickly (had a higher death rate) than the registries survival, and that this meant that the company may be underestimating survival of patients who do not take nintedanib by using Weibull Bayesian curves. Whilst we accept that there is uncertainty in the placebo analysis, this is due to there being no long-term placebo clinical trial data available for patients with IPF or other PF-ILD. Nevertheless, the use of placebo clinical trial data from patients with IPF to generate an informative prior goes some way to reduce uncertainty in the survival estimates of control within the trial timeframe, which may in turn help produce more realistic long-term survival estimates. If an alternative curve that has a lower death rate over the long term is selected for placebo, namely the Bayesian gamma or log logistic curves, this results in an ICER that is <£25,000/QALY ([commercial-in-confidence information removed] and [commercial-in-confidence information removed] per QALY, respectively). These curves provide a good visual match to the Australian registry, which ILD expert clinicians believed to be the most appropriate registry to use in our Advisory Board in December 2020 due to similarities with UK clinical practice and how the registry is managed (see Figures 11 and 12).

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Figure 11: BSC arm modelled using the Bayesian Gamma distribution, NDB modelled using Bayesian Weibull (company base case)

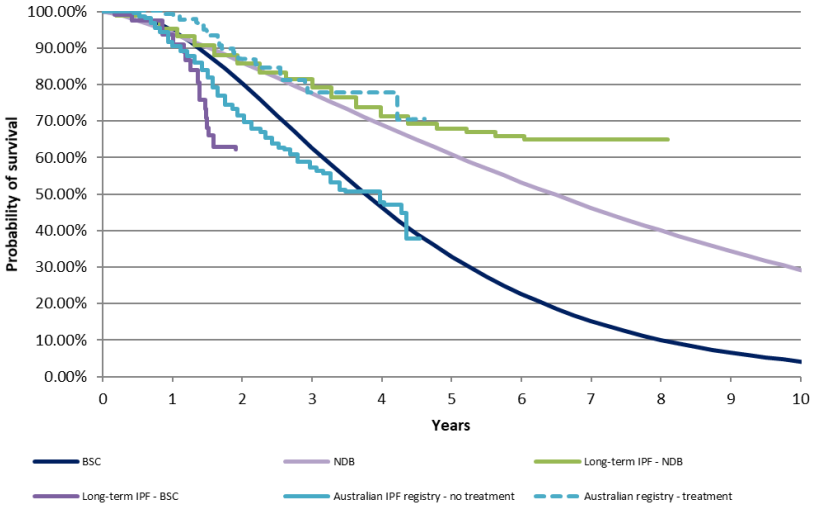
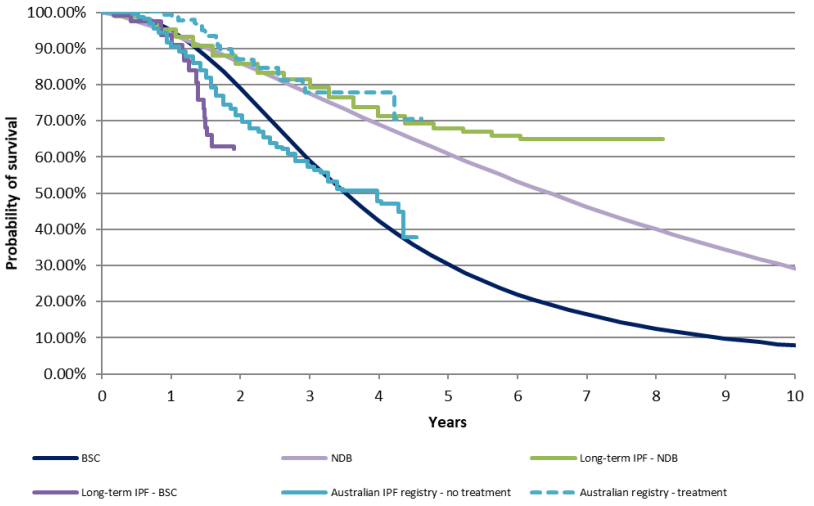


Figure 12: BSC arm modelled using the Bayesian log-logistic distribution, NDB modelled using Bayesian Weibull (company base case)



It is also possible to select a survival curve for nintedanib that is a good visual match for the group receiving antifibrotic treatment in the Australian registry (the frequentist lognormal curve). If this is used together with the curves that provide the best visual match to the no treatment group in the Australian registry (Bayesian gamma or Bayesian log-logistic) this gives ICERs <£20,000/QALY ([commercial-in-confidence information removed] and [commercial-in-confidence information removed] respectively).

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Figure 13: NDB arm modelling to match on-treatment group from the Australian registry (frequentist lognormal), BSC arm modelled using Bayesian gamma

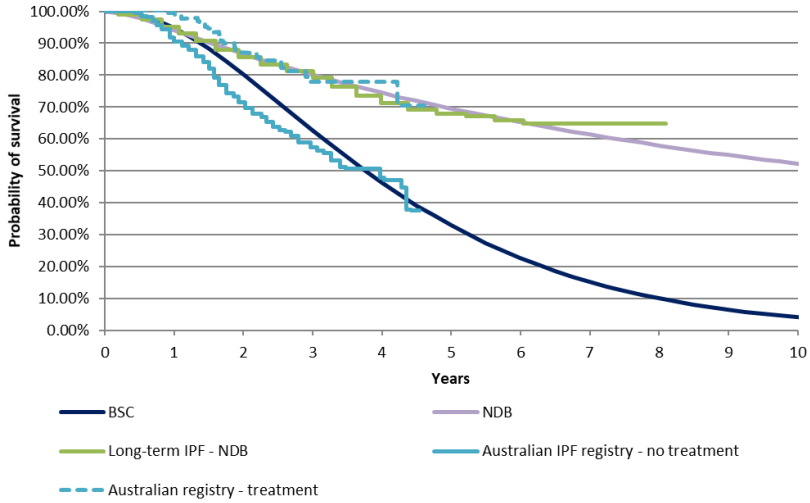
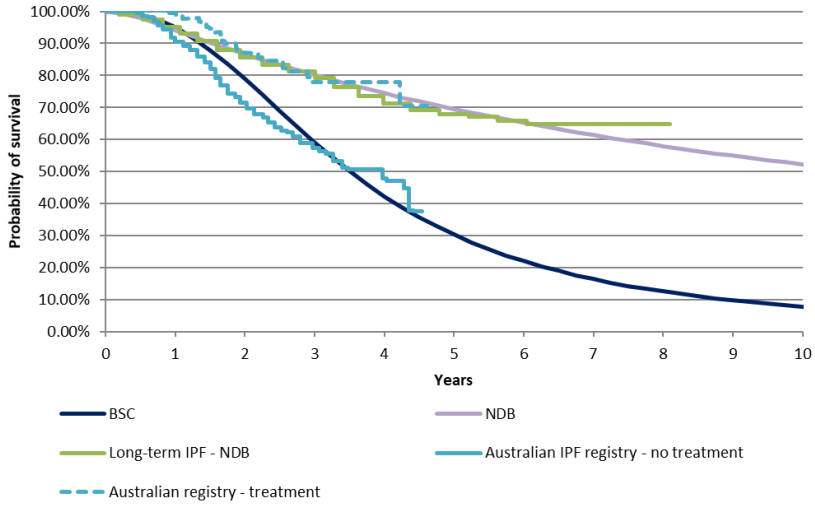
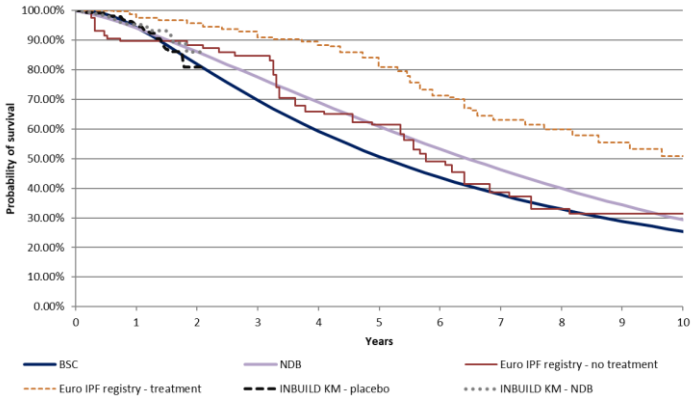
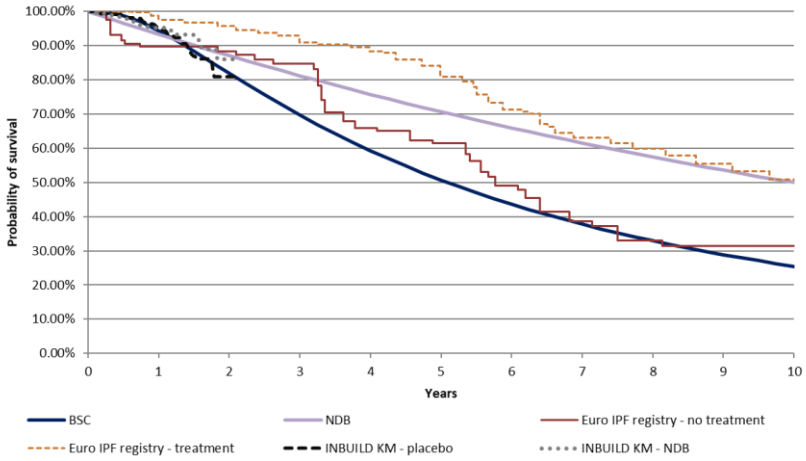


Figure 14: NDB arm modelled to match on-treatment group from the Australian registry (frequentist lognormal), BSC arm modelled using Bayesian log-logistic



The committee commented that the European IPF registry may be the best source to validate the placebo arm survival estimates. Although data on nintedanib specifically are not reported in this registry, it does report long-term survival data on the use of antifibrotics, which included pirfenidone and nintedanib.(5) Previous meta-analysis and other real-world data have shown that nintedanib treated patients have similar or better survival compared with pirfenidone treated patients in IPF.(4, 16, 17) Similar efficacy of nintedanib and pirfenidone was also accepted by the committee in the appraisal of nintedanib for IPF (TA379).(18) Therefore, the antifibrotic treatment arm should provide an indication of the survival benefit of nintedanib in the European IPF registry population.

The European IPF registry reported considerably higher survival estimates for both the no treatment and antifibrotic treated groups, compared with other registries and the long-term clinical trial data for IPF. This may be because no central HRCT scans or histology samples were performed to validate whether patients had IPF, which may have led to the inclusion of some patients without true IPF.(6) Therefore, if we select a survival curve for placebo that matches the data from the European registry,

	we must also select an alternative curve for nintedanib survival, otherwise nintedanib survival is underestimated by a considerable margin (see Figure 15). If alternative curves are selected that better match the European IPF registry data for both arms (frequentist lognormal for BSC and frequentist exponential for nintedanib, see Figure 16), the ICER is under £25,000/QALY ([commercial-in-confidence information removed]). These alternative scenarios are summarised in Table 6 in Appendix 1 (page 23). **Figure 15: Modelled survival curves (BSC = frequentist lognormal; NDC = Bayesian Weibull) compared with data from the European IPF registry**  **Figure 16: Alternative survival curves that better match the European registry data for no treatment and antifibrotic treated patients (BSC = frequentist lognormal; NDB = frequentist exponential)**  It is possible to select alternative curves for BSC where the ICER is >£30,000, for example the frequentist or Bayesian exponential and frequentist or Bayesian lognormal). However, these are implausible and unrealistic compared with survival data reported in IPF registries. **In summary, the survival modelling of BSC can be validated by comparison with real-world registries. If extrapolated curves are selected that provide a good visual match for data reported in these registries, nintedanib is still cost-effective. Therefore, the conclusion that modelling and validation of overall survival for the placebo arm is uncertain and its impact on the model results is not clear does not take account of all the relevant evidence.**
6	**The committee have commented that there are uncertainties in fitting individual parametric distributions to the nintedanib and placebo arms, and that the modelling resulted in ever-**

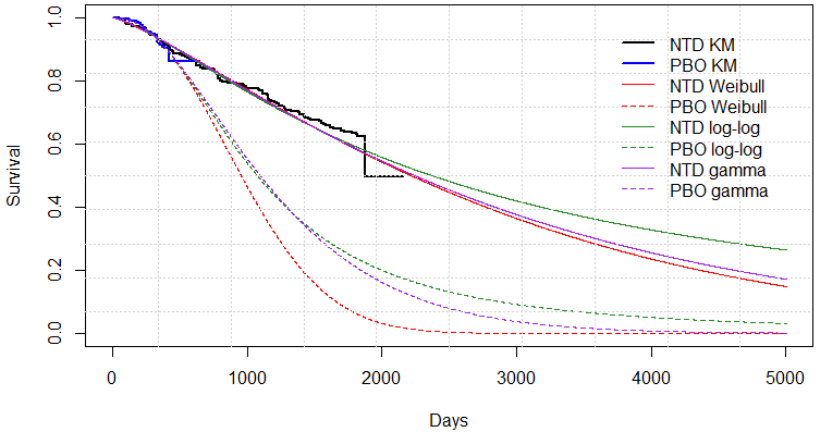
increasing survival benefits for nintedanib compared with placebo in the extrapolated periods.

The ACD also states that the committee was not provided with evidence that the company had explored the proportionality of treatment effects in the observed data and had not been presented with information on the treatment effect over time implied by the company's chosen curves. It concluded that the company should explore the proportionality of hazards assumptions observed in the data and provide information on the treatment effect implied by the alternative survival modelling approaches considered.

The proportional hazards assumption was tested for all survival analysis outcomes in the economic model (overall survival, time to discontinuation, and time to first acute exacerbation) and these analyses were provided in response to clarification questions. Independent survival models were used for consistency across outcomes, as the proportional hazards assumption was not met for the time to discontinuation outcome.

The general model (using treatment as a covariate) is unlikely to have been an appropriate approach for the Bayesian survival analysis. In the Bayesian survival analysis, the best-fit models were informed by the matched IPF data, where the Kaplan-Meier curves crossed. This suggests that the proportional hazards assumption is unlikely to have been met (see Figure 17 below). Additionally, due to the difference in the duration of observed events between nintedanib (5.9 years) and placebo (1.8 years) arms, any analysis of a general model with treatment as a covariate is unlikely to reach any meaningful results.

Figure 17: Modelled survival curves and Kaplan-Meier data from INBUILD



The original company base case is based on Bayesian analysis, the shape of which is informed by the long-term clinical trial data for nintedanib in IPF. However, we take the committee's point of view that there is uncertainty in these long-term survival estimates based on clinical trial data, particularly for the placebo arm.

It is possible to select a different survival distribution for placebo that more closely matches the Australian registry. This could be justified, as the ILD clinical experts (Leads at ILD Specialist Centres) consulted in our Advisory Board in 2020 considered this to be the best registry to validate the long term survival for placebo due to similarities in clinical practice and the way the registry is managed compared with the UK. As stated above, this results in an ICER that is <£25,000/QALY.

Selecting these alternative curves for placebo also reduces the modelled difference in survival between nintedanib and BSC compared with the company base case (Figures 18-20). If alternative survival curves are selected that give the best visual match to the European IPF registry, the modelled difference in survival between nintedanib and BSC is also reduced compared with the company base case (see Figure 16 above), with an ICER <£25,000/QALY ([commercial-in-

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confidence information removed]).

Figure 18: Company base case survival modelling (Bayesian Weibull for NDB and BSC)

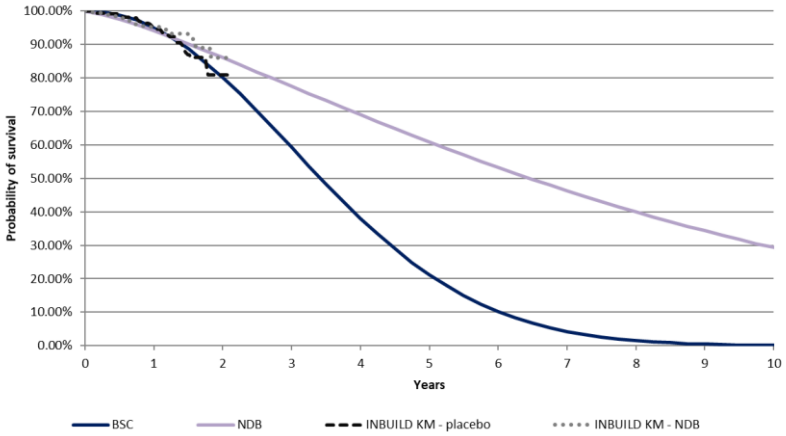


Figure 19: Alternative modelling using a Bayesian Gamma distribution for BSC (Bayesian Weibull for NDB)

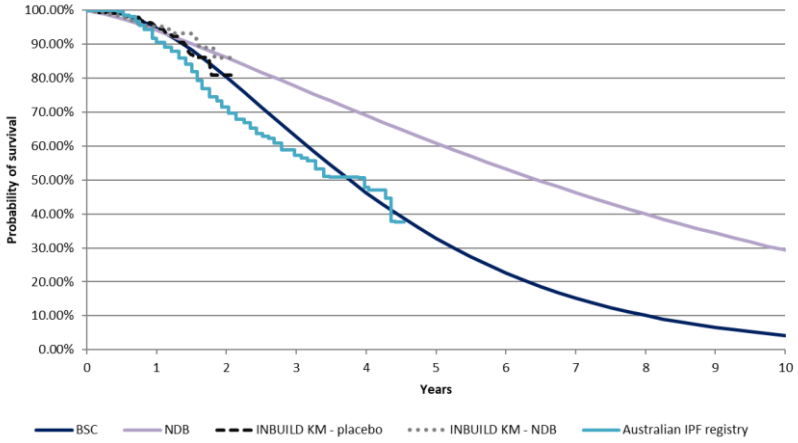
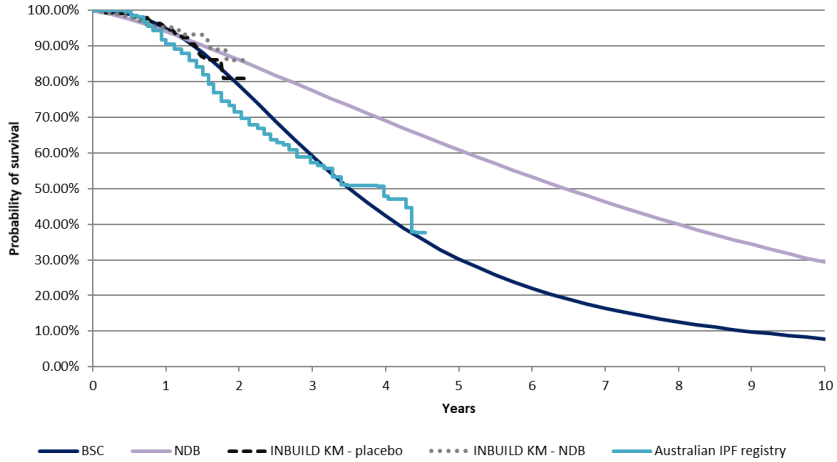


Figure 20: Alternative modelling using a Bayesian loglogistic distribution for BSC (Bayesian Weibull for NDB)



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	Although survival data from the INBUILD trial were immature, long-term survival data are available from registries of IPF patients. As stated in row 1 above, three registries report long-term comparative data and all show a statistically significant survival benefit for nintedanib/antifibrotic treatment compared with non-antifibrotic treatment that is maintained over time.(4-6) These report similar survival difference for nintedanib vs non-antifibrotic treatment as reported in the company modelling (base case) and greater survival difference compared with the modelling when the alternative survival curves for placebo are used (see Table 5). **Overall, evidence from registries in IPF suggest that the modelled difference in survival for nintedanib vs. placebo is reasonable. If a plausibly reduced difference in survival is modelled, nintedanib is still cost-effective.** In our view, taking all relevant evidence into account substantially addresses the uncertainties highlighted by the committee. However, BI is open to exploring approaches to address any remaining material uncertainty, if the committee believes this still exists.
7	**The committee have commented that there are uncertainties in the company's modelling of exacerbations and decline in lung function because of their lack of a link with mortality in the model.** We acknowledge that this is a limitation of the current model, which as noted in the ACD was necessary to avoid double counting deaths. In general, the committee accepted this model structure as relevant for decision making. We did look into changing the structure of the model to include a link between mortality and exacerbations and decline in lung function. However, the adapted model produced increased and unrealistic life years for both placebo and nintedanib, compared with the current model. This is likely because there is additional uncertainty generated by this approach, as a separate risk of death is needed for each health state in the model, and this is in itself uncertain. Although an important event for individual patients, exacerbations are relatively rare in patients with ILD. The ACD also states that the committee was aware that both the company and the ERG's varying risk of exacerbation in scenario analyses had little impact on the cost effectiveness. Since the committee commented that the modelling of exacerbations and decline in lung function was acceptable, and since the main driver of the cost-effectiveness is the survival analysis, we do not believe that these limitations significantly impact the economic case for nintedanib.
8	**The committee have commented that the modelling of stopping treatment was uncertain and may have underestimated the costs of nintedanib.** **Exploratory analyses have shown that selecting a different distribution for discontinuations still results in a plausibly cost-effective ICER for nintedanib.** Exploratory analyses provided at technical engagement and presented at the committee meeting showed alternative modelling of discontinuations. Using the Bayesian Weibull distribution for nintedanib and the ERG's preferred distribution for discontinuation (Weibull), the exploratory ICER was [commercial-in-confidence information removed]/QALY. Although the ERG state that this analysis "does not provide correct ICERs" they agreed that it does give an idea of the impact of changing the distribution for discontinuation and shows that alternative modelling still results in a plausibly cost-effective ICER for nintedanib. The Evidence Review Group noted at the technical engagement meeting that a different model structure or assumptions might not be possible or necessary, given the additional uncertainties this would introduce. The modelling of discontinuations was therefore deemed to be acceptable by the

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	ERG.
9	**The committee have commented that nintedanib does not meet NICE's criteria for an innovative treatment, due to shortcomings in the company's modelling. However, clinical experts and patient groups agree that nintedanib is a step change in the treatment of PF-ILD, as there are no other treatments available that slow disease progression in PF-ILD. These factors are independent of the economic modelling as they have been demonstrated in the INBUILD trial.** As discussed in point 3 above, the change in FVC reported in INBUILD, both in mL and % predicted, has been demonstrated to be clinically relevant. FVC has been shown to be a strong indicator of mortality in patients with ILD.(11) There is also evidence from registries that nintedanib treatment results in longer median survival compared with other non-antifibrotic treatments.(4-6) This benefit is in the treatment of a disease which, if left untreated, has a median post-diagnosis survival that is worse than several types of cancer.(23-25) Clinicians and patient groups unanimously agree that nintedanib is a step change in treatment for patients with PF-ILD, based on the benefit demonstrated in the pivotal clinical trial and their experience of using nintedanib in IPF. As stated above, BI have also received requests for 'Named Patient Supply' (NPS) for nintedanib in PF-ILD from 19 out of 24 ILD specialist centres in the UK between 2018 and 2021. In total 258 patients have commenced NPS for nintedanib in PF-ILD, including patients from 19 different ILD specialist centres. This affirms that the ILD community, as stated in both clinician and patient submissions to NICE, view nintedanib as an innovation or 'step change' in the treatment of PF-ILD. These factors are separate from the economic modelling. Therefore, the committee's view of uncertainties in the economic model should not impact on whether nintedanib is determined to be a step change in the treatment of patients with PF-ILD. Evidence and feedback from clinical and patient groups is clear that nintedanib is a step change, and should be considered to be innovative. **Therefore, it is not a reasonable interpretation of the evidence to say that nintedanib is not innovative.**

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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.

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Appendix 1: Additional data tables

Table 1: Initial mean baseline FVC values of patients attending visits beyond 52 weeks

	Placebo		Nintedanib		Placebo-Nintedanib
Visit at…	N	Mean (ml)	N	Mean (ml)	Mean difference (ml)
52 weeks	274	2,339	265	2,347	-8
68 weeks	204	2,380	205	2,320	60
84 weeks	91	2,454	89	2,380	74
100 weeks	19	2,370	16	2,298	72

Source: Boehringer Ingelheim. Descriptive statistics and absolute change from baseline in FVC over the whole trial (DBL1).
FVC, forced vital capacity

Table 2: Time to absolute decline in FVC % predicted ≥5% or ≥10% at 42 weeks and up to DBL2

	Nintedanib			Placebo				
	N	Patients with event (%)	Observation time (patient-years)	N	Patients with event (%)	Observation time (patient-years)	HR (95% CI)	P value
Time to absolute decline in FVC % predicted ≥5%								
52 weeks	332	170 (51.2)	217.4	331	222 (67.1)	185.7	0.68 (0.56, 0.83)	0.0001
DBL2	332	217 (65.4)	299.8	331	263 (79.5)	233.1	0.67 (0.56, 0.81)	<0.0001
Time to absolute decline in FVC % predicted ≥10%								
52 weeks	332	73 (22.0)	295.2	331	115 (34.7)	283.9	0.60 (0.45, 0.80)	0.0005
DBL2	332	114 (34.3)	432.0	331	160 (48.3)	393.5	0.64 (0.50, 0.81)	0.0002

Source: Boehringer Ingelheim. Analyses of time to absolute decline in FVC % predicted >=5% or >=10% over the whole trial.
CI, confidence interval; DBL2, database lock 2; FVC, forced vital capacity

Table 3: Absolute change from baseline in FVC (mL) and FVC % predicted at week 52 – treated set, overall population

		Baseline[1]		Change from baseline in FVC at week 52			Comparison vs. placebo		
Treatment	N	Mean	SD	Adjusted mean	SE	95% CI	Adjusted mean	SE	95% CI
Absolute change from baseline in FVC (mL)									
Placebo	331	2321.15	727.97	-192.20	13.83	(-219.37, -165.03)			
Nintedanib 150 mg bid	332	2340.07	740.19	-85.45	14.05	(-113.04, -57.86)	106.75	19.72	(68.03, 145.48)
Absolute change from baseline in FVC % predicted									
Placebo	331	69.27	15.21	-5.86	0.41	(-6.67, -5.05)			
Nintedanib 150 mg bid	332	68.70	16.04	-2.62	0.42	(-3.44, -1.80)	3.24	0.59	(2.09, 4.40)

Source: Table 11.1.3.1.2:1 of the Clinical Trial Report(9)
CI, confidence interval; FVC, forced vital capacity; SE, standard error; SD, standard deviation
1 Based on the number of patients that were included in the model and had baseline data available.
2 Based on MMRM, with fixed effects for baseline, HRCT pattern, visit, treatment-by-visit interaction, baseline-by-visit interaction and random effect for patient.
Within-patient error were modelled by unstructured variance-covariance structure

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Table 4: Annual rate of decline in FVC (mL/year) over 52 weeks – treated set, overall population

	Rate of FVC decline over 52 weeks				Comparison vs. placebo			
Treatment	**N**	**Adjusted rate**	**SE**	**95% CI**	**Adjusted difference**	**SE**	**95% CI**	**p-value**
Overall population (primary analysis)								
Placebo	331	-187.78	14.84	(216.92, -158.64)				
Nintedanib 150 mg bid	332	-80.82	15.07	(-110.42, -51.22)	106.96	21.15	(65.42, 148.50)	<0.0001
Overall population (excluding patients with restricted or prohibited medication use)								
Placebo	240	-157.17	15.31	(-187.26, -127.08)				
Nintedanib 150 mg bid	279	-49.41	14.47	(-77.84, -20.98)	107.75	21.07	(66.36, 149.15)	<0.0001

Source: Table 8:3 of the Response Document to 1st Request for Supplementary Information sent to the EMA(22)
CI, confidence interval; FVC, forced vital capacity; SE, standard error

Table 5: LYs gained in the economic model compared with difference in median survival reported in IPF registries

Source	Difference for nintedanib vs non-antifibrotic treatment	Unit
Company base case model	3.11 years	LYs gained
Company alternative model (Bayesian gamma for BSC, Bayesian Weibull for NDB)	2.53 years	LYs gained
Company alternative model (Bayesian loglogistic for BSC, Bayesian Weibull for NDB)	2.34 years	LYs gained
Company alternative model (frequentist lognormal for BSC, frequentist exponential for NDB)	3.21 years	LYs gained
EMPIRE registry	2.91 years (p<0.001)	Median survival
European IPF registry	4.6 years (p=0.001)	Median survival

BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; LYs, life years; NDB, nintedanib

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Table 6: Summary of alternative scenarios for survival analysis

BSC		NDB		ICER
Model selected	**Data source used to validate**	**Model selected**	**Data source used to validate**	
Bayesian gamma	Australian registry (no treatment)	Bayesian Weibull	Long-term IPF trial data (company base case)	<£25,000 ([commercial-in-confidence information removed])
Bayesian loglogistic	Australian registry (no treatment)	Bayesian Weibull	Long-term IPF trial data (company base case)	<£25,000 ([commercial-in-confidence information removed])
Bayesian gamma	Australian registry (no treatment)	Frequentist lognormal	Australian registry (AF treatment)	<£20,000 ([commercial-in-confidence information removed])
Bayesian loglogistic	Australian registry (no treatment)	Frequentist lognomal	Australian registry (AF treatment)	<£20,000 ([commercial-in-confidence information removed])
Frequentist lognormal	European IPF registry (non-AF treatment)	Frequentist exponential	European IPF registry (AF treatment)	<£25,000 ([commercial-in-confidence information removed])

AF, antifibrotic; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib

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Appendix 2: Consensus statement from 21 Clinical Leads of the 24 ILD specialist centres in England and Wales and 3 leading rheumatologists who treat PF-ILD patients

(please see list of clinicians below)

Immunosuppression is not used to treat fibrotic lung disease

The patient population with chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD) often have a wide range of underlying clinical conditions that have led to their ILD. These extra extrapulmonary manifestations such as arthritis, glomerulonephritis, pericarditis and dermatological manifestations may require treatment with corticosteroids and / or immunosuppressants, but these are not to treat the ILD, and they do not have any meaningful impact on the ILD. By definition, patients with PF-ILD have progressed despite treatment of the extrapulmonary manifestations with conventional therapies, including immunosuppressants and other restricted therapies.

The restriction of immunosuppression in the INBUILD study represents clinical practice

The INBUILD trial design allowed the introduction of restricted medications after 6 months. As stated in the BTS ILD expert committee NICE submission, the consensus from all of the ILD UK-based 23 clinical leads who manage patients with a confirmed diagnosis of PF-ILD in 23 tertiary ILD specialist centres advised that 'immunosuppressants are not given to treat the fibrotic component of an ILD, but the inflammatory component of the disease'. It is common clinical practice that when patients with predominantly fibrotic ILD present with lung function decline despite immunosuppression, clinical consideration would be to reduce or completely stop immunosuppressants due to a lack of efficacy. There are also significant safety concerns around the use of multiple immunosuppressants as evidenced in the IPF-focused PANTHER trial which clearly demonstrated an increased risk of mortality & hospitalisation in these patients.

The ILD clinical community are concerned about using non evidence-based immunosuppressants that lack efficacy in PF-ILD patients who phenotypically behave like IPF and have similar radiological features.

This is reflected in the very low levels of use of restricted immunosuppressants after 6 months in the INBUILD trial once these were allowed. Please see the table below.

Restricted therapies initiated between first and last trial drug intake over 52 weeks.

Restricted drugs	Patients who received restricted drugs >6 months n (%)	
	Nintedanib Group (n=206)	Placebo Group (n=206)
Azathioprine	1 (0.3%)	5 (1.5%)
Cyclophosphamide	0 (0%)	2 (0.6%)
Mycophenolate Mofetil	3 (0.9%)	7 (2.1%)
Tacrolimus	3 (0.9%)	3(0.9%)
High dose corticosteroids	33 (9.9%)	57 (17.2%)
Infliximab	0 (0%)	0 (0%)
Rituximab	2 (0.6%)	2 (0.6%)

The low use of restricted immunosuppressants once allowed (>6 months) in the placebo and nintedanib arms of the INBUILD trial further reflects the lack of evidence base for these therapies, thus supporting the clinical expert consensus that immunosuppressants are not a relevant comparator for progressive fibrotic ILD. The use of immunosuppression likely represents treatment of extrapulmonary manifestations of disease which may be responsive to this modality (such as arthritis).

In addition, a high proportion of patients (68.6% overall) in the INBUILD trial received systemic corticosteroids (<20 mg per day) at baseline or during the 52-week trial period (placebo, 70.1% vs nintedanib, 67.2%) and 39.8% had non-steroid anti-inflammatory agents at baseline). Please see table below.

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All baseline and on-treatment concomitant therapies over 52 weeks

Overall population

ATC3 category	Placebo		Nintedanib 150 mg bid		Total	
	N	%	N	%	N	%
Number of patients	331	100.0	332	100.0	663	100.0
Number of patients with at least 1 therapy	327	98.8	328	98.8	655	98.8
Adrenergics for systemic use	69	20.8	51	15.4	120	18.1
Adrenergics, inhalants	102	30.8	80	24.1	182	27.5
Agents for treatment of hemorrhoids and anal fissures for topical use	132	39.9	139	41.9	271	40.9
All other therapeutic products	103	31.1	89	26.8	192	29.0
Angiotensin II receptor blockers (ARBS), plain	60	18.1	72	21.7	132	19.9
Anti-acne preparations for topical use	92	27.8	78	23.5	170	25.6
Antihistamines for systemic use	73	22.1	60	18.1	133	20.1
Antiinfectives	113	34.1	105	31.6	218	32.9
Antiinflammatory agents	232	70.1	233	70.2	465	70.1
Antiinflammatory and antirheumatic products, non-steroids	126	38.1	138	41.6	264	39.8
Antipropulsives	35	10.6	138	41.6	173	26.1
Antithrombotic agents	107	32.3	107	32.2	214	32.3
Anxiolytics	69	20.8	61	18.4	130	19.6
Blood glucose lowering drugs, excl. insulins	59	17.8	67	20.2	126	19.0
Calcium	76	23.0	72	21.7	148	22.3
Corticosteroids	90	27.2	99	29.8	189	28.5
Corticosteroids for systemic use, plain	232	70.1	223	67.2	455	68.6
Corticosteroids, plain	170	51.4	158	47.6	328	49.5
Cough suppressants, excl. combinations with expectorants	69	20.8	69	20.8	138	20.8
Decongestants and other nasal preparations for topical use	179	54.1	175	52.7	354	53.4
Drugs for constipation	69	20.8	61	18.4	130	19.6
Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	200	60.4	238	71.7	438	66.1

Table continues on next page

The placebo arm in the INBUILD trial therefore reflects current standard treatment for the PF-ILD as well as underlying conditions.

From a clinical perspective, there are no treatments that are licensed for use, or really being consistently used in clinical practice for the management of UK patients with PF-ILD and therefore the placebo arm of the INBUILD trial is a true representation of UK clinical practice.
Until the recent marketing authorisation approval of nintedanib for PF-ILD, there were no evidence-based licensed treatments for patients with PF-ILD other than IPF. Nintedanib is the first pharmacological treatment to show clinical evidence of slowing disease progression in patients with PF-ILD, through the dedicated INBUILD trial, with demonstrable statistical significance for the primary endpoint in the overall patient population. This treatment effect was seen across all patients, regardless of the underlying ILD diagnosis.
The INBUILD trial clearly demonstrated that individuals with PF-ILD have a similar clinical disease course to that of patients with idiopathic pulmonary fibrosis (IPF), where there is a wealth of long term clinical and real world evidence that unequivocally supports the benefits of nintedanib in achieving a consistent reduction in FVC decline.

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The beneficial effects on reduction in FVC decline are similar to PF-ILD as demonstrated by the INBUILD trial. As such, nintedanib represents a step-change in the treatment of patients with PF-ILD other than IPF, providing a much-needed treatment option for patients with no evidence based approved therapies for their PF-ILD.

Clinical experts agreeing to the consensus document

The 21 clinical experts from ILD specialist centres in England and Wales and 3 leading rheumatologists who treat PF-ILD patients who have agreed to the consensus document are listed in the tables below. This consensus was reached in short timelines over a period of time when a lot of clinicians were out of office or on holiday.

ILD Specialist Centre	ILD Clinical Lead
Royal Brompton and Harefield NHS Foundation Trust	Dr Peter George
Manchester University NHS Foundation Trust.	Dr Nazia Chaudhuri
University Hospitals Birmingham NHS Foundation Trust	Dr Anjali Crawshaw
Royal Devon and Exeter NHS Foundation Trust	Professor Michael Gibbons
North Bristol NHS Trust	Dr Huzaifa Adamali
Leeds Teaching Hospitals NHS Trust	Dr Paul Beirne
Guy's and St Thomas' NHS Foundation Trust	DR Alex West
Royal Papworth Hospital NHS Foundation Trust	Dr Christine Fiddler
Hull University Teaching Hospitals	Dr Simon Hart
University Hospital Southampton NHS Foundation Trust	Professor Mark Jones Dr Katherine Spinks
University Hospitals of Morecambe Bay NHS Foundation Trust	Dr Timothy Gatheral
University College London Hospitals NHS Foundation Trust	Professor Joanna Porter
Oxford University Hospitals NHS Foundation Trust	Dr Rachel Hoyles
Portsmouth Hospitals University NHS Trust	Dr Suresh Babu
Newcastle Upon Tyne NHS Foundation Trust	Dr Ian Forrest
Norfolk and Norwich University Hospitals NHS Foundation Trust	Professor Andrew Wilson
University Hospitals of Leicester NHS Trust	Jane Scullion
University Hospitals of North Midlands NHS Trust	Dr Helen Stone
Nottingham University Hospitals NHS Trust	Dr Gauri Saini
Imperial College Healthcare NHS Trust	Dr Mel Wickremasinghe
Cardiff & Vale University Health Boards	Dr Ben Hope-Gill

Centre	Clinical Expert Rheumatologist
The Royal Free London NHS Foundation Trust	Professor Chris Denton
The Royal Free London NHS Foundation Trust	Dr Voon Ong
Manchester University NHS Foundation Trust.	Dr Rachel Gorodkin

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References

1. Boehringer Ingelheim. Data on file DOF NIN21-03. Analyses of time to absolute decline in FVC % predicted >=5% or >=10% over the whole trial.
2. Crestani B, Huggins JT, Kaye M, al. e. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. The Lancet Respiratory Medicine. 2019;7:60-8.
3. Antoniou K, Markopoulou K, Tzouvelekis A, Trachalaki A, Vasarmidi E, Organtzis J, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study. ERJ Open Res. 2020;6(1):00172-2019.
4. Vasakova M, Sterclova M, M M, et al. Long-term overall survival and progression-free survival in idiopathic pulmonary fibrosis treated by pirfenidone or nintedanib or their switch. Real world data from the EMPIRE registry. European Respiratory Journal. 2019;54:PA4720.
5. Guenther A, Krauss E, Tello S, Wagner J, Paul B, Kuhn S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respir Res. 2018;19(1):141.
6. Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. Eur Respir J. 2017;49(2).
7. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respiratory Soc; 2012.
8. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011;184(12):1382-9.
9. Boehringer Ingelheim. Clinical Trial Report for the INBUILD trial (study 1199.247). 2019.
10. Brown KK, Martinez FJ, Walsh SLF, Thannickal VJ, Prasse A, Schlenker-Herceg R, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J. 2020.
11. 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. ePoster presented at the American Thoracic Society Conference, 14-19th May 2021.
12. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071-82.
13. Cottin V, Richeldi L, Rosas I, Otaola M, Song JW, Tomassetti S, et al. Nintedanib and immunomodulatory therapies in progressive fibrosing interstitial lung diseases. Respir Res. 2021;22(1):84.
14. Boehringer Ingelheim. Descriptive statistics and absolute change from baseline in FVC over the whole trial. Data on file DOF NIN21-02.
15. Flaherty KR, Wells AU, Cottin V, Devaraj A, Inoue Y, Richeldi L, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. European Respiratory Journal. Article ahead of press.
16. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Medicine. 2016;14(1):18.
17. Cameli P, Refini RM, Bergantini L, d'Alessandro M, Alonzi V, Magnoni C, et al. Long-Term Follow-Up of Patients With Idiopathic Pulmonary Fibrosis Treated With Pirfenidone or Nintedanib: A Real-Life Comparison Study. Front Mol Biosci. 2020;7:581828.
18. National Institute for Health and Care Excellence. Nintedanib for treating idiopathic pulmonary fibrosis [TA379]. Manchester, UK; 2016.
19. Boehringer Ingelheim. Data on file DOF NIN21-04. Meta-analysis of mortality in nintedanib trials for IPF and PF-ILD. Data provided ahead of publication.
20. Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T. Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Chest. 2021.
21. Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Respiratory Investigation. 2014;52(4):242-50.
22. Boehringer Ingelheim. Data on file DOF NIN21-05. Data taken from BI response to the European Medicines Agency (EMA), 18th February 2020. Document number ra01054982-01.
23. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet journal of rare diseases. 2008;3:8.
24. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824.
25. du Bois RM. An earlier and more confident diagnosis of idiopathic pulmonary fibrosis. European Respiratory Review. 2012;21(124):141-6.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Action for Pulmonary Fibrosis**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
Name of commentator person completing form:	[redacted]

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1	**Overview** **Patients living with progressive fibrosing ILD (PF/ILD) are desperate to have access to nintedanib** for the reasons we explained in our earlier submission. There is clearly a gap between the views of the NICE and Boehringer-Ingelheim but, **on behalf of people living with PF/ILD, Action for Pulmonary Fibrosis calls on NICE and the company to put the interests of patients and their families first and do all they can to find a flexible and pragmatic way to bridge the gap between their two positions**. The up-coming Innovative Medicines Fund may provide a means to do this, as might approval of the drug with an independent 'registry' study by NICE to evaluate efficacy of the treatment as part of a risk-sharing agreement between the company and NICE. Whatever it takes, please find a way to ensure access for patients to this treatment. Action for Pulmonary Fibrosis will continue to raise awareness of the inequality in access to treatments until everyone with PF/ILD has the access the treatments they deserve.
2	**Impact on people living with PF/ILD** At Action for Pulmonary Fibrosis, we are deeply concerned that the NICE appraisal did not take sufficient account of the impact that its preliminary recommendation would have on people living with progressive fibrosing ILD (excluding IPF) and their families. Action for Pulmonary Fibrosis has discussed the NICE decision with a focus group of PF/ILD patients and had individual conversations with other patients and carers living with the disease in England and in Netherlands, where the drug is available to patients with PF/ILD. In total we have spoken to 17 patients over the last 3 weeks. All the English patients interviewed are extremely upset and disappointed by the NICE decision. The strength of their feelings can be gauged in the following quotes, which are typical of those we received:

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	Man living with Rheumatoid Arthritis-ILD (RA-ILD) Rejecting access to nintedanib for PF/ILD patients is devastating to patients and their families. Imagine that you are drowning in a lake, knowing that on the shore somebody has a lifeline to help you, but they will not throw that lifeline for you to catch. That is what this rejection feels like. Woman living with Pleuro-parenchymal fibroelastosis (PPFE) I feel very angry. I am in my 40s and have a young child and I work in the NHS. I have fibrosis at the top of my lungs but not at the bottom. My life expectancy is the same as someone with IPF. It seems unfair that I'm not given a chance. I tried to get the drug, but I was denied. Now I'm too ill and so it's too late. I think I will fade away before I get this drug. I have no hope. Steroids have caused me to have osteoporosis and have worn away my stomach lining, so I'm now fed through a tube. It's been awful. There are only 40 other people like me living with PPFE in England. Without this drug, we have no hope. Woman living with RA-ILD I was on steroids for a few years and had put on a huge amount of weight. Since being given nintedanib, in 2020, on compassionate grounds, I have been able to reduce my steroid intake and I have lost a lot of weight. I'm able to move around again. It's made a great improvement to my quality of life. This will also have saved money for the NHS because I am no longer diabetic and hopefully will not be susceptible to some of the comorbidities of obesity. I knew about the drug and was aware that it wasn't available to me. I felt so sad, that I wasn't even considered for it. But now I am furious that people living with PF/ILD in Scotland have it, but we will not. It's simply unfair. Woman in Netherlands living with desquamative interstitial pneumonia (DIP) I was taking steroids but the side effects were becoming difficult and eventually it became clear the drug was not working. I was offered the chance to go on the INBUILD clinical trial in Belgium. I have now been on nintedanib for nearly 2 years. I feel very much better using this medication. My situation is stable and my cough is very much less. There are side effects, but I have managed these with my doctor's help. Woman living with RA-ILD I was diagnosed with RA-ILD in 2012. It started with a funny little cough. I'm a former nurse, but I was unable to work in a way that was reliable, so I had to stop work. I was on methotrexate but it was stopped after a bronchoscopy. I was denied access to nintedanib on compassionate grounds, but I don't why. We are all lumped together and that means none of us get the drug.

	I appreciate the aims of NICE, but SMC looked at the bigger picture and gave greater weight to the benefits nintedanib will bring to people living with this rare disease. In view of the recently announced £680 million Innovative Medicines Fund, I am hopeful that NICE will change its mind, but in the meantime, I am having to spend my hard-earned pension buying the drug from India. I can just about afford it, but what about all those people who cannot? Man living with chronic hypersensitivity pneumonitis (CHP) I was diagnosed with CHP in 2020 but was told that I would not be able to get nintedanib from the NHS for at least a year, if at all. Knowing that it is available in some European countries, we decided, with the support of relatives from abroad, to move to another country, where we could get the drug. At a time when Covid-19 was playing havoc with international travel, we managed to leave the UK and have moved abroad. The stress that this has caused and the heartache of leaving beloved relations, friends and our house is something which is difficult to accept or convey in words, it has been a monumental change to our lives. I cannot understand why other nations, having seen the same evidence and rationale as NICE have decided to authorise the drugs but NICE has not. It smacks of heartless cost saving. For me, this is unacceptable.
3	**Impact on inequality and disability** APF is also concerned about the implications NICE's decision will have on inequality and on the wellbeing of PF/ILD patients all of whom become disabled for the last 1-2 years of their lives. There are three aspects of this: 1. **People living in poverty will be the hardest hit** as 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 nintedanib from India – an increasing number of people with PF/ILD are already doing this, or • moving to Scotland or an EU or other country which has approved the drug for reimbursement, such as Netherlands. 2. **PF/ILD patients will feel a heightened sense of injustice compared to IPF patients** if NICE denies them access to nintedanib. The experience of people living with all types of progressive pulmonary fibrosis – PF/ILD and IPF is similar. Over time they become increasingly breathless, come to depend on supplementary and then home oxygen, and eventually die from respiratory failure or

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	a related cause. Given these similarities of experience, PF/ILD patients feel discriminated against because NICE has approved antifibrotic medications, such as nintedanib, for IPF patients but not for PF/ILD. While the majority of IPF patients are white men over 70 years of age, the PF/ILD community is more diverse with slightly more women than men and a higher proportion of people of Asian and Afro-Caribbean heritage. The NICE decision could be seen, by some, as having a differential impact on groups protected by equality legislation. 3. **All PF/ILD patients become disabled.** The NICE instructions for this consultation ask whether NICE's preliminary recommendation could have an adverse impact on people living with disability? They certainly will because all PF/ILD patients become disabled as the disease progresses and are generally disabled for periods between one and three years. Initially they find it difficult to walk up hills or flights of stairs but by the time they need supplementary oxygen they will be 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.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or

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not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Scleroderma and Raynaud's UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the action taken to suspend consultation ID1420 which considered the use of nintedanib within systemic sclerosis ILD (SSc-ILD) and its replacement with this current and broader consultation has overlooked the needs of patients with systemic sclerosis. Systemic sclerosis is a rare autoimmune disease characterised by fibrosis which affects multiple organs including the lungs which may be affected through progressive fibrosing interstitial lung disease which is a major contributory factor to death from the condition. There are limited effective treatments options for systemic sclerosis in general and even less for SSc-ILD, immunosuppressants for SSc-ILD are prescribed off-label and in most cases are unsuccessful in slowing progression. Patients may be offered lung transplantation in severe cases, but the grim reality is that few patients will be deemed 'fit' to undergo transplantation. The current outcomes of this consultation will contribute to the treatment inequalities experienced by rare disease patients in the UK, denying them an effective treatment option (as evidenced by the SENSCIS study, where SSc-ILD patients treated with nintedanib in combination with Mycophenolate mofetil had much slower lung progression than those taking MMF alone).
2	Nintedanib has been FDA approved for use in SSc-ILD since 2019 and has EMA approval for SSc-ILD and other chronic fibrosing lung conditions. The decision to deny patients with SSc-ILD and other chronic fibrosing conditions access to this effective treatment will contribute to global health inequalities where UK-based patients with fibrosing lung conditions will have poorer outcomes and reduced quality of life than those from other western economies.
3	Drug development and clinical trials are extremely challenging in the rare disease area; commercial interest is limited due to the relatively small number of patients affected. Whilst this drug is licenced and approved for other uses, we are concerned that lack of support from NICE may mean that companies may be discouraged from venturing into drug discovery in the rare disease arena or may not seek approval for treatments to be used in the UK market.
4	We take on board the point made by the committee that there is a lack of long-term data to show long term effectiveness of nintedanib against progression of lung fibrosis and its effects on survival. This 'gap' would be best met through 'real world evidence'. By blocking the use of nintedanib in a comprehensive data-rich health care setting such as the NHS we may never gain insights into the full benefits of nintedanib for this group of patients.
5	
6	

Insert extra rows as needed

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of Respiratory Nurse Specialists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Example 1	We are concerned that this recommendation may imply that ……..
1	Having read the document, it is clear how the conclusion has been reached. The study could and should have been more robust. However, it is disappointing that Nintedanib has not been approved for patients with Progressive Pulmonary Fibrosis and the resulting inequity with those living in Scotland who can already access this essential treatment. This decision will significantly limit treatment options for this cohort of patients and affect quality of life. More research is needed as a priority to provide a larger and superior evidence base enabling the company to resubmit with as little delay as possible. If the trials can include as many patients accessing the treatment as feasible then the benefits and cost effectiveness can be established. For patients we believe, the addition of Nintedanib in their treatment plan has made a significant difference to their progression and symptom burden.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Rheumatology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	Lung fibrosis is an important contributing cause for mortality in autoimmune related ILD in particular scleroderma and this being a fibrotic disease, the clinical significance of INBUILD and another important trial SENSCIS are consistent with significant effect of nintedanib on lung function decay.
2	The relationship of lung function decline to long term mortality (15 years follow up) has been confirmed in scleroderma related mortality. Accepting INBUILD is too short to show this, translating the behaviour of lung function trajectory linking to mortality, any significant impact of nintedanib on halting of lung function decline will likely to manifest in decline in mortality in scleroderma-lung fibrosis.
3	In SENSCIS study, half of patients recruited were on mycophenolate and within this group there was numerical improvement in rate of decline in FVC (-40 mls) with combination nintedanib and mycophenolate, compared to no-mycophenolate (-63.9 mls). This provides additional evidence that nintedanib with or without mycophenolate is beneficial in prevention of decline of FVC – an important surrogate for long term mortality.
4	The utility of an anti-fibrotic without additional risk of immunosuppression from immunosuppressants/biologics with associated increased risks of infection in autoimmune diseases is a step up novel agent in our armamentarium in treatment of this complication – and this is an increasing important consideration with the risk of COVID pandemic.
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Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Thoracic Society**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	The appraisal consultation document states that "Current treatment for fibrosing interstitial lung disease (ILD) starts with immunosuppressants." This is an incorrect interpretation of the evidence. There is currently no evidence based therapy for the treatment of fibrotic interstitial lung disease, other than antifibrotics for Idiopathic Pulmonary Fibrosis and mycophenolate for systemic sclerosis ILD. Fibrosing ILDs comprise a number of diseases including chronic hypersensitivity pneumonitis, non-specific interstitial pneumonia, asbestosis, unclassifiable ILDs and other connective tissue diseases eg Rheumatoid arthritis ILD for which there are no evidence based therapies. Immunosuppression is not an established treatment for all causes of fibrosing ILD. Many ILD clinicians would only recommend use when diseases have an inflammatory onset or an extra thoracic systemic component eg for extra pulmonary manifestations of Connective tissue diseases or where there is evidence of co-existent inflammatory hypersensitivity pneumonitis (as evidenced by ground glass shadowing on CT or cytological support from a BAL).
2	The appraisal consultation document states that "if recommended, nintedanib would be given at the same time" – This comment is not evidence based as only those with systemic extra pulmonary manifestations of CTD or inflammatory hypersensitivity pneumonitis would have received immunosuppression. All other patients would not receive immunosuppression in clinical practice if they have fibrotic ILD eg asbestosis, RA-ILD, chronic HSP as there is no evidence base for giving it. In deed in line with the PANTHER study for IPF where immunosuppression was deemed to be harmful, there is growing evidence from studies in chronic HSP that immunosuppression may be harmful (especially in the context of specific genetic phenotypes) References: (https://www.atsjournals.org/doi/10.1164/rccm.201809-1646OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed) and in more recent CHP data (https://www.atsjournals.org/doi/full/10.1164/rccm.201902-0360OC). If patients are on immunosuppression and develop progressive fibrotic ILD then this is seen as a treatment failure and often immunosuppression is withdrawn due to the concerns about infection risk. Nintednaib would NOT be introduced at the same time as immunosuppressive therapy but only when immunosuppressive therapy had failed. As a result, in clinical practice a significant proportion of patients would not be on immunosuppression which reflects the trial design where immunosuppression was restricted for 6 months. However, in the trial 68% of patients remained on prednisolone doses less than 20mg which is reflective of clinical practise. The document also comments it is uncertain what the effect would be in clinical practice because the trial restricted use of immunosuppressants for 6 months. It is clear from the clinical trial that patients with progressive fibrotic ILD would benefit from nintedanib in that there is a reduction of FVC decline – these patients are reflective of clinical practice. There is evidence that in SSc-ILD, RA-ILD, HP and idiopathic NSIP, decline in FVC despite management is associated with a much higher mortality. Once treatment has failed, mortality increases strikingly, whatever subsequent additional treatments are used. Clinicians continue immunosuppression despite disease progression because until now, no better treatment has been available. NHS practice exists as it currently does and will continue to do so precisely because nintedanib is not approved.
3	Section 3.4. Steroids, azathioprine, rituximab and infliximab are not evidence based treatments for fibrosing ILD as per this statement and thus this is not evidence based.
4	Section 3.6. The statement that "the committee interpreted this to show that fewer patients randomised to nintedanib than placebo needed immunosuppresants" is an incorrect conclusion and not statistically valid. The study was not powered to look at this and this finding could have occurred by chance. Also that "a substantial proportion of participants needed the treatment that was restricted earlier in

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	the trial" again is factually incorrect as only 16% of patients were prescribed immunosuppressants after 6 months which means a significant greater proportion 84% DID NOT require immunosuppression after 6 months. "ERG noted that immunosuppressants are not restricted in clinical practise" – this is clinically inaccurate. There are a number of patients with progressive fibrotic ILD in whom immunosuppressants would not be given in clinical practise, notably Rheumatoid arthritis ILD, asbestosis and those with concerns about infection with immunosuppression. "Placebo without conventional standard treatments does not reflect NHS clinical practise. Therefore it is not an appropriate comparator" – again this is factually incorrect for all the reasons described in 1,2,4 and 5 above. "The clinical experts explained that nintedanib would be offered to reduce the dosage and use of corticosteroids" – This is factually incorrect as nintedanib would not be added to reduce dosage of prednisolone – this is the role of second line immunosuppressants. Nintedanib is not used as a steroid sparing agent. "The committee concluded that the INBUILD trial does not represent NHS clinical practice'; again factually incorrect for all the reasons stated in previous comments.
5	Section 3.7. A 107ml difference in FVC is significant in clinical practise whether it reaches the 10% threshold or not. The document noted the committee felt it was unclear whether this 107ml difference is clinically meaningful as it was uncertain the 10% threshold was achieved. The clinical experts at the meeting felt 107ml is clinically significant in line with other ILD colleagues. This difference is identical to the IPF treatment effect in the larger UIP sub-group in the IPF Clinical trials and nintedanib is an approved therapy in IPF. So questioning the significance of this effect for PF-ILD is not valid as its established already in IPF as a significant difference. Normal ageing experiences a 20-30ml decline per year so this 107ml difference is 5 x the normal ageing process especially cumulatively year on year. "The committee noted that the decrease of treatment effect suggested either a waning effect of nintedanib in the long term or a treatment effect of immunosuppressants, which more people had in the placebo arm than in the nintedanib arm" – this statement has no evidence base at all and is not corroborated with the evidence that has been given for the 84 week data of the study. The effects seen are not statistically robust and MUST be taken with caution. Also, only 16% of the whole population was given immunosuppression and such a statement that this is an effect of immunosuppression is unsubstantiated and not evidence based and based on speculation rather than evidence that has been presented.
6	Section 3.8 "The committee concluded that there is uncertainty about whether nintedanib was associated with a 'clinically meaningful change' in FVC% predicted, compared with placebo" The experts and ILD clinicians defend the premise that 107ml difference is clinically meaningful irrespective of the FVC % change. Normal ageing experiences a 20-30ml decline per year so this 107ml difference is 5 x the normal ageing process especially cumulatively year on year.
7	Section 3.29: There would be unlawful discrimination of all English patients with progressive fibrotic ILD as this therapy has been approved in Scotland for Scottish patients.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Clinical Pharmacy Association (UKCPA)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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1.2/3.6	We note that NICE appraisal documentation states that "It is also uncertain what its effects would be in clinical practice because the trial restricted use of some immunosuppressants in the first 6 months" Patients in the trial were being treated with immunosuppresants in the form of prednisolone tablets (only patients with >20mg prednisolone daily were excluded). 68.6% of patients (70.1% in the placebo arm and 67.2% in the nintedanib arm) used corticosteroids over the 52-week period in INBUIILD. Corticosteroids are the current first line immunosuppressant treatment for PF-ILD. Long-term use of corticosteroids has become the backbone of immunosuppressive therapy in PF-ILD but it is evident that such an approach is associated with significant morbidity to the patient. For this reason, other immunosuppressant agents, such as methotrexate, azathioprine and mycophenolate, are often prescribed to act as steroid sparing agents to enable the clinician to reduce the overall burden of oral corticosteroids. There is limited evidence for the role of second line immunosuppressants in PF-ILD with insufficient high-quality studies available to confirm their place in therapy. However, the national guideline advise that such treatments should be considered if corticosteroids do not control the disease or if the person experiences intolerable adverse effects. In practice many patients will be initially treated with 6 months oral corticosteroid therapy before second line immunosuppressant agents are added in. Such agents are unlicensed, have significant risk of adverse side effects and require intensive monitoring during therapy, adding increased resources and cost to the prescription cost. We believe the INBUILD trial design to not be dis-similar to the treatment approach to a patient in practice and the background therapy should be regarded as standard practice.
3.6	"The clinical experts explained that nintedanib would be offered to reduce the dosage and use of corticosteroids, but the committee was not presented with any evidence for this." We believe this statement was misinterpreted as it is the second line immunosuppressant therapy (such as mycophenolate, methotrexate) prescribed as an adjuvant has the aim to reduce oral corticosteroid dose.
3.6	The post hoc analysis of SENSCIS study supports a synergistic benefit of both approaches immunosuppressant and nintedanib together in SSc-ILD. https://www.nejm.org/doi/full/10.1056/NEJMoa1903076

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Lisa Spencer

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Example 1	We are concerned that this recommendation may imply that ……..
1	**Page 3 of ACD states "Why the committee made these recommendations Current treatment for fibrosing interstitial lung disease starts with immunosuppressants. If recommended, nintedanib would be given at the same time."** This statement is not quite accurate in my view. Some PF-ILD subtypes would be offered immunosuppressants (IS) but not all. Only in one sub type (scleroderma CTD ILD) is there any evidence for IS). In many sub types of PF-ILD, nintedanib would not be 'added in'. IS would be stopped and nintedanib given instead particularly where disease progression had occurred despite being on IS.
2	**Page 3 of ACD states: "It is also uncertain what its effects would be in clinical practice because the trial restricted use of some immunosuppressants in the first 6 months."** I do not feel this statement is quite correct. Almost 70% of patients were actually on a drug suppressing their immune system i.e. prednisolone. Prednisolone is considered equivalent broadly to other immunosuppressant drugs used e.g. mycophenolate, methotrexate. We use these types of drugs interchangeably broadly to try and treat lung diseases. The 30% not on prednisolone was likely either because IS drugs had been tried and were not helpful or the underlying ILD sub type did not merit use of IS type drugs e.g IS not advised in rheumatoid arthritis fibrotic ILD or asbestosis for example. So I believe the INBUILD trial and its results does absolutely reflect real clinical practice. One of the main reasons we do no just use prednisolone in everyone, where we wish to try and IS, is because of its side effect profile over longer time periods. We employ a "steroid sparring strategy" and switch prednisolone to other drugs such as methotrexate or mycophenolate for example. The effect of these different types of IS drugs however is thought to be similar.
3	**Point 3.4, page 7: this paragraph mentions that nintedanib would be an "add on therapy"** As above in 1). Sometimes it might be – mainly in CTD or autoimmune ILD but in many other forms of PF-ILD IS would be stopped and nintedanib alone would be used if progression had occurred on IS.
4	**Point 3.6 page 9: states "Concurrent treatments in the INBUILD trial do not reflect current NHS care"** I do not agree with this conclusion above by NICE. The INBUILD study does reflect current NHS care as outlined above in my point 2. **"Patients could not have IS other than systemic corticosteroids for first 6 months of study".** Corticosteroids are a perfectly good IS to give and comparable to other IS drugs as outlined above. The main reason why they are not given longer term is due to their side effect profile not because they are not as effective. The only exception to this is in scleroderma ILD where the scleroderma lung study I showed that mycophenolate was an effective treatment to slow progressive ILD over the shorter term. Scleroderma patients were a small number overall in cohort.

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	Point 3.6 page 9: ACD states"Approximately 16% of patients started immunosuppressants during the second 6 months of the initial 52-week period (21% in the placebo arm and 11% in the nintedanib arm). The committee interpreted this to show that fewer patients randomised to nintedanib than placebo needed immunosuppressants, but that a substantial proportion of participants needed the treatments that the protocol restricted earlier in the trial." Starting IS after first 6 months of study may also have been needed to treat joint disease or other features of the systemic disease components that these patients have rather than to treat their ILD. Do the company know what the indications were for addition of IS to these patients? It would be useful to know this. This paragraph 3.6 goes on to state again the trial design does not reflect clinical practice but I believe strongly it does. I do not support that conclusion by the ERG.
5	Paragraph 3.7 page 10 of ACD states: **The committee noted it was unclear whether a between-group difference of 107 ml/year in adjusted rate of decline in FVC over 52 weeks equals a 10% difference (relative or absolute) in FVC% predicted, which would indicate a clinically meaningful change in FVC (see section 3.3).** The reduction in FVC seen in the nintedanib group in trial is definitely clinically significant. Patients on nintedanib on average had 107mls more of lung left at end of study. Falling FVC ultimately leads to death in this patient group so preventing that fall is significant and important to outcome. The drug does not need to hit a 10% reduction in FVC to prolong life. A healthy person without lung disease loses only 30mls of lung volume per year. These ILD patients are losing lung at a significantly accelerated rate and this leads to premature death in the end.
6	Overall all I would request that NICE reconsider its first decision here. Hopefully the company can provide NICE with relevant modelling information which will help further assessments. I am not statistically trained and cannot comment much on modelling queries. I do not support ERGs conclusion that the INBUILD trial does not reflect UK clinical practice. The changes in FVC seen with nintedanib are clinically important and relevant to prognosis and outcome. Nintedanib would be an add on therapy only in some sub types of PF-ILD (not all). In a similar disease Idiopathic pulmonary fibrosis these anti fibrotic drugs have been proven to have a sustained effect on disease progression over time. I note that NICE would usually review any negative decision 3 years later and if a negative decision is final decision here I request that NICE mark this proposal for an earlier review than this as more data re the effectiveness of this drug is likely to be available well before 3 years have passed.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

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NICE National Institute for Health and Care Excellence

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 August 2021. Please submit via NICE Docs.

- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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.

Please return to: **NICE DOCS**

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

The large INBUILD RCT has been the main focus for this submission. It includes a very heterogeneous group of conditions with different aetiologies and different pathogeneses but has interstitial lung disease as the common denominator. It includes a subgroup of patients with autoimmune-related interstitial lung disease (25.6%). Approximately 13% of patients recruited had rheumatoid arthritis-ILD and approximately 5-6% of the total study population had systemic sclerosis-ILD.

Progressive ILD is a significant problem in patients with systemic sclerosis and I suspect only a small number of patients were recruited to the INBUILD study as immunosuppressants that are frequently used to treat interstitial lung disease such as cyclophosphamide and mycophenolate were not allowed during the first 6 months of the study. However, very importantly there is a very relevant large multicentre randomised controlled trial which compares nintedanib with placebo in patients with systemic sclerosis who have associated interstitial lung disease (the SENCIS trial, NEJM 2019; 380:2518-28). The entry criteria for the SENSCIS study were slightly different to the INBUILD study. Patients had relatively early disease; they were allowed to enter the study if they were within 7 years of their first nonRaynaud's symptom and the median disease duration was 3.4 years for study participants. An HRCT chest scan had to show fibrosis affecting at least 10% of the lungs but to enter the SENSCIS study they did not have to demonstrate progression of ILD prior to entry, in contrast to the INBUILD study. This study also had the primary end point as the annual rate of decline of FVC assessed over a 52 week period. Five hundred and seventy-six patients received at least one dose of nintedanib or placebo. 51.9% had diffuse cutaneous systemic sclerosis, approximately 60% participants were Scl-70 positive and 48.4% were receiving mycophenolate mofetil at baseline. The adjusted annual rate of change in FVC was -52.4 mils per year in the nintedanib group and -93.3 mils per year in the placebo group (P = 0.04). As mentioned previously, approximately 50% of patients were on mycophenolate mofetil at baseline and this had an additional positive effect on progression of inflammatory lung disease in both arms of the study. The patients on mycophenolate mofetil deteriorated more slowly than patients who were not on mycophenolate mofetil. These results suggest that nintedanib should be add on therapy where clinically indicated.

Systemic sclerosis-ILD has its own marketing authorisation for nintedanib but I note from the public slides that no NICE submission is currently planned by the company. However, I hope that patients with systemic sclerosis-ILD will have access to nintedanib through some appropriate route.

Systemic sclerosis associated pulmonary disease is the leading cause of systemic sclerosis related death. Pulmonary fibrosis accounts for 35% of these deaths. Pulmonary fibrosis can occur in both diffuse cutaneous and limited cutaneous systemic sclerosis. Up to 80% of patients with diffuse cutaneous systemic sclerosis develop interstitial lung disease. A third of these will develop clinically significant interstitial lung disease. Evidence has accumulated through small studies and the larger Scleroderma Lung Studies (I and II) and shown cyclophosphamide and mycophenolate mofetil to have a positive effect on the progression of SSc-ILD. Other immunosuppressants, including rituximab and tocilizumab, have been evaluated in RCTs and shown promising results. However, approximately 15% of this cohort with clinically significant ILD will develop progressive disease that does not respond to the currently available immunosuppressants in England, namely IV cyclophosphamide and mycophenolate mofetil.

A deterioration in lung function occurs early in disease i.e. less than 5 years from disease onset. From early studies, we know that a forced vital capacity less than 50% of predicted at baseline is highly predictive of mortality in a patient with systemic sclerosis. Prior to using immunosuppressants in these patients, systemic sclerosis-ILD patients with a DLCO less than 40% had a 5 year survival of only 9%. We know that with the early use of immunosuppression such as cyclophosphamide and mycophenolate mofetil that we can slow the deterioration in forced vital capacity and so improve outcome and life expectancy. However unfortunately not all patients will respond to immunosuppression and thus there is an unmet need for other treatment options in these patients with severe rapidly progressive pulmonary fibrosis.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

t is usual for RCTs in ILD to be of 12 months duration. I note that in the recommendations under section 1 it states that follow up was short so it was unclear if these people live longer. By extrapolation of the currently available treatments for patients with ILD, it would seem logical that any treatment that slows the rate of lung progression will lead to people living longer; this is what has happened in patients with systemic sclerosis associated ILD who have received and responded to IV methylprednisolone and IV cylopshosphamide and/or mycophenolate mofetil. Such long-term data for nintedanib could be collected via a managed access scheme/registry/ commissioning through evaluation process. It appears that the data are being collected by the company in the extension study but data are only available for a couple of years currently and there needs to be longer follow up to establish this but it does not seem appropriate to wait for these data.

SSc-ILD patients were eligible for recruitment into the INBUILD study. We know from the SENSCIS trial that SSc-ILD patients who were also taking mycophenolate, whether they were in the nintedanib or placebo arms experienced a slower rate of annual fall in FVC. Such immunosuppressive drugs were not permitted in the first 6 months of the INBUILD study, which has been the main focus of this application and only 16% started these drugs during the second 6 months of the study. The results and modelling may therefore not reflect usual practice in managing patients with autoimmune-related ILD in England as stated in section 3.6. However, the earlier mentioned SENSCIS trial in SSc-ILD permitted the use of mycophenolate mofetil so does more accurately represent NHS clinical practice in the management of SSc-ILD. Perhaps more data from the SENSCIS trial should be included in this application.

It was disappointing to learn that it was not possible to estimate nintedanib's cost

effectiveness. I think the models could be reviewed so that it is possible. I agree with the statement in section 3.11 that there will be higher mortality rates with lower levels of lung function and so another reason to review the economic model.

These patients experience significant morbidity and mortality without treatment. The aim of treatment in patients with autoimmune-related ILDs is to supress disease activity to prevent damage and maintain quality of life. The use of immunosuppression has improved outcomes in some patients with autoimmune-related ILDs but unfortunately not all patients respond so there remains an unmet need. Nintedanib, together with pirfenidone, are novel treatments that have slowed the rate of deterioration in lung function. I think these drugs do reflect a 'step change' in treatment and should be included in the final steps of a treatment algorithm for these patients living with ILD in England (section 3.28).

I would anticipate that nintedanib would be taken for several years if it is tolerated and effective. Some patients are unable to tolerate it primarily due to gastro-intestinal side effects. Although, for clinical and cost-effectiveness reasons it should be discontinued if it is ineffective in a patient. A robust definition and assessment of response should be incorporated in a treatment algorithm.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Nintedanib has a marketing authorisation for the treatment of chronic fibrosing ILD with a progressive phenotype. We all recognise that finance in the NHS is finite and drugs have to be proven to be cost-effective. Hopefully a subgroup of patients with progressive ILD can be identified and be eligible to receive this drug via a NICE TA. For example, in the autoimmune patients with progressive ILD it may be most beneficial for nintedanib to be approved for use in patients who are progressing (FVC declined by 10% in 12 months with an increase in extent of fibrotic changes on HR chest imaging), despite maximal tolerated immunosuppression and/or who have the UIP pattern of fibrosis. Nintedanib should be stopped if there is no improvement/stabilisation of FVC decline. Stabilisation of FVC can be a good outcome in this cohort of patients with progressive disease.

Name	[redacted]
Role	
Other role	
Organisation	UK Scleroderma Study Group
Location	
Conflict	
Notes	

Comments on the ACD: Comments from [redacted]

I am commenting on behalf of the clinical members of the UK Scleroderma Study Group (UKSSG) that includes medical specialists and NHS consultant rheumatologists from all of the major centres across UK that manage systemic sclerosis patients. Lung fibrosis (ILD) is the commonest cause of death related to systemic sclerosis that is the most lethal of the rhematic diseases. It is ta great disappointment that patients in England will not have access to the first drug approved in most countries for systemic sclerosis associated ILD (SSc-ILD).

In recognition of the importance of SSc-ILD for our patients, and consequent high unmet medical need, UKSSG members would like to make the following points.

- SSc-ILD is a major cause of death and poor quality of life in SSc, affecting up

to half of patients during the course of disease. Impact is due to symptoms and also the absence of approved therapies that has a very detrimental effect on mental wellbeing for patients.

- SSc-ILD can be progressive over a short period of time, and so some cases were included in the INBUILD trial, but more often is a slowly progressive complication that leads to death after years of progression. This means that even modest slowing of progression is likely to improve survival, but this will not emerge from short term clinical trial results.
- Link between lung function decline and survival in SSc-ILD has been shown in several high quality published academic studies that decline of lung function over 12 or 24 months is associated with significantly worse survival and so slowing this lung function decline is likely to improve outcome.
- The positive SENSCIS clinical trial in SSc-ILD showed that nintedanib is effective in slowing decline in lung function in SSc-ILD compared with placebo. The trial results also suggest that benefit was numerically greater for cases receiving mycophenolate mofetil (MMF), an immunosuppressive drug that is recommended in SSc-ILD. These data suggest that for SSc-ILD there is a strong justification for using nintedanib in cases that progress on standard treatment with MMF.
- In addition, infected digital ulceration occurs in SSc and may preclude use of immunosuppression such as MMF. In these cases, a non-immunosuppressant treatment for SSc-ILD would address an important unmet medical need.
- From analysis of UK SSc patient cohorts, it has been shown that approximately 1 in 5 patients with SSc-ILD that are already treated with immunosuppression show significant decline in lung function to levels that predict poor survival within 5 years of onset of SSc. This equates to approximately 1 in 10 of the overall SSc population and these patients deserve access to approved drug therapy for SSc-ILD. The total UK SSc population is estimated as fewer than 12,000, and so inability to access nintedanib would directly impact around 1200 patients.

Has all of the relevant evidence been taken into account?

The committee has focused on progressive ILD in several diseases but not on systemic sclerosis associated ILD (SSc-ILD) that is the main cause of death in this rheumatic disease with high mortality. The SENSCIS trial examined nintedanib in SSc-ILD and provides robust evidence of benefit and suggests added benefit to that obtained by MMF treatment.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Impact of treatment that slows progression of ILD in SSc-ILD and prevents decline of lung function would be expected to reduce mortality from SSc-ILD based on robust observational cohort data from multiple large datasets and publications. Alternative treatments such as stem cell transplantation are expensive and have high treatment related mortality. Nintedanib may be more cost-effective if this comparator treatment was considered.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations are not a suitable basis for guidance to the NHS. The recommendations would deny patients with SSc-ILD that could not receive immunosuppression or those that had progressive disease despite immunosuppression of a licensed treatment when no alternative therapy is available. This is outside best practice in other similar countries in Europe and elsewhere with

comparable healthcare systems.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Women are much more likely to be affected by SSc than me. Black patients have a much worse outcome and survival form SSc and SSc-ILD than white patients.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

See below

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

See below

Are the recommendations sound and a suitable basis for guidance to the NHS?

The drug is approved for Ideopathic pulmonary fibrosis but not for sarcoidosis fibrosis for which it potentially has better outcomes.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The treatment is available in Wales and Scotland which discriminates on country of residence. The drug is approved for Ideopathic pulmonary fibrosis but not for sarcoidosis fibrosis for which it potentially has better outcomes.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	

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Comments on the ACD:

Has all of the relevant evidence been taken into account?

No it hasn't. There is a substantial body of evidence that individuals who have fibrosis as a result of sarcoidosis would also benefit from this treatment and indeed have longer life and better prospects

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

The cost of treatment is only just over the quality of life year limit and with an NHS discount would be below it. Clinical research suggests that lung transplant prognosis is improving all the time.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not. They are based solely on cost and not the ability of this treatment, which is approved in many other countries, to improve the lives of those who have sarcoidosis related pulmonary fibrosis. This treatment is already available in Scotland and Wales to people with Sarcoidosis.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes. The recommendations discriminate between groups of individuals who suffer from pulmonary fibrosis from different causes. This seems to be based on how well known such causes are rather than the effectiveness of the treatment on pulmonary fibrosis regardless of cause. The actual number of individuals with Sarcoidosis fibrosis requiring this treatment on an annual basis would be small and therefore the overall cost to the NHS would be relatively low. It is discriminating against an underrepresented group whose prognosis is actually better than for those with IPF who are able to access this treatment.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

I firmly believe that pulmonary fibrosis is generally terminal and there should be no discrimination between its various types. or even United Kingdom boarders. in general terms this disease is not self inflicted, effecting many people who still have much to offer society, and should be available to all who qualify.

Are the summaries of clinical and and cost effectiveness reasonable

interpretations of the evidence?

I believe there is a substantial imbalance when a 90 year old person whose life remains valuable following a lifetime of contributing to society is rightly given all the most expensive resources of the NHS following exposure to Covid. A pulmonary fibrosis sufferer may not qualify for a drug that can prolong there lives.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations should be based on the same criteria that allowed the drug to be approved in Scotland, consequently the Nintendanib drug should be given the same approval in England.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I thought it would assist my case if I supplied a few bullet points about myself . In light of my current condition I believe that my only hope for a prolonged life is to be prescribed with Nintendanib.

1. MY AGE. I have always felt that I carry my age better than most and apart from my lung condition am in excellent health and feel very confident that I can well endure any side effects.
2. FITNESS. I have good musculature and continue to exercise on a daily basis.
3. MY WEIGHT. Despite being on a high dose of steroids I have managed to lose over a stone and a half in weight and continue to do so. I would of course ensure that I will be match fit if offered this Medication.
4. ACHIEVEMENTS I AM PROUD OF.

A. 12 years as a medic and Physiotherapist in the RAF.
B. Selection for the RAF and Olympic Gymnastic team,
C. Helicopter winch man on mountain desert rescue.
D. 40 years as volunteer Managing Director, Chairman and Trustee of a MENCAP charity.
E. 8 years as swimming coach and lifeguard for a disabled swimming club.
F. 30 Years as co-Founder, Owner and CEO with my wife of the largest Envelope Print and Mail-house businesses in the south west

In conclusion I have been married for 54 years with a loving family unit. Our two daughters are sadly handicapped, one severely Autistic and the other with Crohns Disease and congenital deafness. Also my employees and their families rely on me to continue running a very successful Print & Mail House business, so I therefore request that you present my case and put me forward for consideration or trial. Thank you.

Name	[redacted]
Role	
Other role	
Organisation	SarcoidosisUK
Location	
Conflict	

Notes	
Comments on the ACD:	
Nintedanib has been shown to slow progress of pulmonary fibrosis in patients with ILD however it is currently not available to these patients in England. Our members consider this to be an equality issue, especially considering that the drug is available in Scotland. "Sarcoidosis is a 'rare' multi system disease of unknown origin with no known cure and it is one of the most common types of interstitial lung disease (ILD). End stage (i.e. Stage 4) sarcoidosis includes the presence of pulmonary fibrosis. About 20% of sarcoidosis patients develop pulmonary fibrosis. Our members report that many aspects of their lives have been compromised due to sarcoidosis induced pulmonary fibrosis, for example being housebound or unable to work. One of our members has commented, "I have been unable to follow my vocation, I am very ill most of the time and even with conventional treatment (Azathioprine and Hydroxychloroquine) have largely been housebound throughout the last decade. We desperately need better medication so fibrosis won't halt our lives in the way it does now." When pulmonary fibrosis progresses, our members find their activities are limited and their quality of life suffers. Another patient commented, "I had considered myself 'comparatively lucky' until recently. I have now been told the fibrosis has progressed, and find my activities are limited and I pass my responsibilities to others, hence having a lesser quality future to look forward to with my family."" Our members comment that there are not currently enough treatment options for sarcoidosis patients with pulmonary fibrosis. Sarcoidosis patients tend to have a very individual experience of the condition, and one patient can experience completely different symptoms and responses to medications to another. Sarcoidosis-induced fibrosis can also manifest differently from patient to patient. Some of our members report adverse reactions to the currently available medications but there are often no other options. Our members believe that there needs to be more choice for patients in order to have better outcomes. The more treatments available to patients, the better the outcomes will be for patients. "Sarcoidosis is a rare disease which does not get the funding that is required. Whilst Nintedanib may be expensive in the short term, in the medium to long term it is far more expensive to have those with chronic sarcoidosis and fibrosis being unable to work or live a normal life. The impact of sarcoidosis-induced pulmonary fibrosis is not only financial but also emotional. One of our members has commented, "it hits not just the patient but also the family of the patient, their friends, relatives and work colleagues. With Nintedanib we have a chance to make a real difference to so many sarcoidosis patients' lives. Please give us back more of our life."	

Name	[redacted]
Role	
Other role	
Organisation	
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Conflict	
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account?	

I have been advised that Nintedanib has been approved for use in the US and Europe since 2014 and that it is also used in Scotland and Wales. I am wondering if there is evidence from these experiences which could/should be considered?

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

I am not an expert (or a patient) but am not wholly convinced they are. See comments below.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, I do not believe so. The committee notes a number of uncertainties and on that basis I would argue that it is premature to make a decision about the use of Nintedanib. The clinical trial suggests decline of lung function is slowed and I would think this provides encouragement to undertake further research or trials if a decision to approve use of the drug can not be made at this juncture. I would prefer that this treatment be made available as it is elsewhere.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

I don't think there is discrimination in relation to the above protected characteristics per se but I do think there is in relation to medical conditions. My lay persons view is that expensive treatments are approved for high profile or well-known conditions such as most forms of cancer but not for those lesser known/rarer conditions. This can not be right, particularly when life expectancy for those with interstitial lung disease is shorter than for those with many cancers

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments on the ACD:

Has all of the relevant evidence been taken into account?

There have been been many studies demonstrating the effectiveness of this drug with non ipf fibrosing lung disease as well as ipf. It has been approved in the US and many countries worlwide since 2014 with great success, the average life extension being 7 more years. Effectively tripling life expectancy in many people.
Fibrotic lung disease carries a prognosis much worse than many cancers and should be afforded every practicable intervention.
The Quality of Life year assessment of cost is under £20 pa. This drug falls into that category with bulk purchase.
Only 170 extra people roughly each year will make use of the drug, but for that 170 people the drug is life changing.

This is a very useful document supporting its use.

https://err.ersjournals.com/content/26/145/170053

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No. The cost fits within the criteria of cost per QOLY when bulk purchase is considered. cost is c £21 k without NHS discount. With the discount it falls well below the £20 k pa threshhold

Are the recommendations sound and a suitable basis for guidance to the NHS?

Whilst decisions need to be made, ignoring substantial research carried out on the global stage is counter productive. As we have seen with Covid, when health systems work together and build on each others research, treatments and research prospers. There is ample evidence globally that this is a life changing drug for many people. To deny this treatment is inhumane.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

All fibrosing lung disease carries a dire prognosis without treatment. This drug is the best available treatment for substantially prolonging life. To differentiate different fibrosing lung diseases including ipf for treatment but not other fibrotic lung diseases is discriminatory.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

A fundamental assumption in the appraisal process is that ""Current treatment for fibrosing interstitial lung disease starts with immunosuppressants"". This is incorrect. There is no evidence base for immunosuppressants in a range of progressive fibrosing interstitial lung diseases (PF-ILD), nor are they licensed, and in IPF (which has many clinical and molecular features in common with PF-ILD) immunosuppressant-based treatment caused major harm (more deaths and hospitalisations compared with placebo)(1).
Confusion may have arisen because some patients with PF-ILD receive immunosuppressants for extrapulmonary manifestations, such as rheumatoid arthritis and connective tissue diseases. Here, immunosuppressants are not used to treat the PF-ILD. Furthermore, the appraisal mixes up 'ILD' and 'PF-ILD', often apparently using these terms interchangeably (e.g. ERG comment on page 20 of the committee papers). Patients with a steroid-responsive inflammatory ILD (who likely represent most patients in the physician survey, Figure 1, page 17 of the committee papers) are not relevant to this appraisal since clearly, they do not fulfil the criteria for progression (by definition, patients with PF-ILD have progressive fibrosis).
There are no treatments that are being consistently used for the management of patients with PF-ILD. Immunosuppressants are not a relevant comparator for novel therapies for PF-ILD, and that the placebo arm of the INBUILD trial is a good representation of UK clinical practice. "No treatment" is the correct comparator for a cost effectiveness analysis of nintedanib.

1. Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ, Network IPFCR. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968-77.

Has all of the relevant evidence been taken into account?

Yes

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I would like to add that I have a friend who is suffering from progressive lung sarcoidosis and would greatly benefit in regard to her life expectancy from this drug becoming available in the UK.	

NICE National Institute for Health and Care Excellence

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 August 2021. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Boehringer Ingelheim

NICE National Institute for Health and Care Excellence

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 August 2021. Please submit via NICE Docs.

Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Abby Tebboth

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 August 2021. Please submit via NICE Docs.

Comment number	Comments	ERG response
	Key points **1. The committee have commented that nintedanib's treatment effect may decrease in the long term, but available data do not support this conclusion.** o The INBUILD trial was not designed to assess data beyond 52 weeks. The analysis of change in FVC (mL) up to database lock (DBL) 2 has important methodological limitations due to a healthy survivor bias observed in the placebo arm which underestimates the treatment effect of nintedanib. o Time-to-event analyses (absolute decline in FVC % predicted >5% and >10%) show consistent treatment effect over time up to DBL2.(1) o Data from INPULSIS-ON and a Greek registry in idiopathic pulmonary fibrosis (IPF) have shown that nintedanib has a sustained treatment effect over time.(2, 3) o Data from registries and meta-analyses have shown that nintedanib is associated with a significant long-term survival benefit compared with non-antifibrotic treatments.(4-6) o Overall, the conclusion that there is insufficient evidence of survival benefit, or that there is substantial likelihood of a treatment waning effect is not a reasonable interpretation of the evidence. It also does not take into account the full body of relevant evidence. **2. The committee have commented that they were not presented with the algorithm chosen by the company to estimate FVC % predicted and that they would like to see how this was done.** o FVC % predicted was reported as a secondary endpoint in the INBUILD trial. This was calculated according to the Global Lung Initiative (GLI) equation.(7) **3. The committee have commented that it is unclear whether the primary endpoint measured by FVC in millilitres per year over 52 weeks reflects a clinically meaningful change as measured by FVC % predicted.** o Published literature suggests that the change in FVC % predicted reported in INBUILD is clinically meaningful.(8) o Pre-specified analyses from INBUILD showed that treatment with nintedanib reduced the proportion of patients with both a relative and absolute decline from baseline of >10% and >5% at week 52.(9) These declines are associated with mortality in ILD.(10) o Meta-analysis of nintedanib clinical trials in IPF, PF-ILD and systemic sclerosis-associated ILD show a strong association between annual rate of change in FVC % predicted and risk of	**Please see responses to each Key point below.**

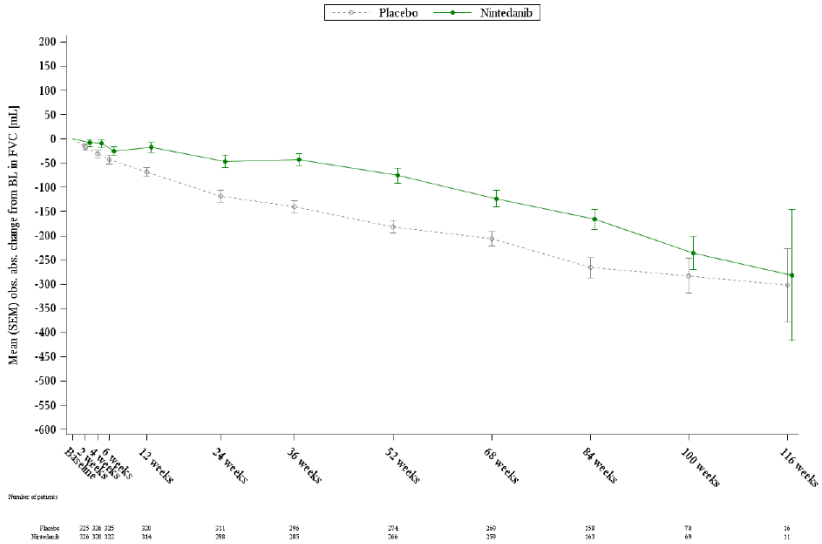
	death.(11) ○ The difference in FVC reported in INBUILD, measured in both mL and % predicted, was similar to that reported in INPULSIS.(9, 12) Clinical experts and patient groups agree that this difference has been meaningful for patients with IPF, as well as those receiving nintedanib for PF-ILD under named patient supply. **4. The committee have commented that the impact of restricted concurrent NHS treatments on the treatment effect of nintedanib is unclear.** ○ Post-hoc analyses of the INBUILD trial excluding all patients who took prohibited or restricted medications over 52 weeks were very similar to the primary analysis. This indicates that the treatment effect was not influenced by the use of restricted and prohibited medications.(13) ○ Post-hoc subgroup analyses from INBUILD have shown that the effect of nintedanib on reducing FVC decline was not influenced by the use of glucocorticoids, a type of immunomodulatory medication, at baseline.(13) ○ Clinical experts treating interstitial lung diseases at specialist tertiary centres in the UK also agree that restricted medications would not be expected to have any meaningful efficacy in the treatment of progressive fibrosing disease. **5. The committee have commented that there are uncertainties in the company's modelling and validation for overall survival in the placebo arm, and that this likely overpredicts deaths in the placebo arm.** ○ If plausible alternative survival curves with more optimistic survival for the placebo arm are selected, nintedanib remains cost-effective. ○ The ICER for nintedanib is only not cost-effective if clinically implausible curves are selected. **6. The committee have commented that there are uncertainties in fitting individual parametric distributions to the nintedanib and placebo arms, and that modelling resulted in ever-increasing survival benefits for nintedanib compared with placebo in the extrapolated periods.** ○ Independent survival models were used for consistency across outcomes, as the proportional hazards assumption was not met for the time to discontinuation outcome. ○ The original company base case is based on Bayesian analysis, the shape of which is informed by the long-term clinical trial data for nintedanib in IPF. However, we take the committee's point of view that there is uncertainty particularly for the placebo arm. ○ If reasonable alternative survival curves are selected that reduce the modelled difference in survival between nintedanib and BSC, the ICER remains cost-effective. **7. The committee have commented that there are uncertainties in the company's modelling of exacerbations and decline in lung function because of their lack of a link with mortality in the**	

	model. ○ We acknowledge that this is a limitation of the current model, which was necessary to avoid double counting deaths. We did look into changing the structure of the model to include a link between mortality and exacerbations and decline in lung function, but this model generated unrealistically high life years for both BSC and nintedanib due to additional uncertainties generated by this approach. ○ Since the committee commented that the modelling of exacerbations and decline in lung function was acceptable, and since the main driver of the cost-effectiveness is the survival analysis, we do not believe that these limitations significantly impact the economic case for nintedanib. **8. The committee have commented that the modelling of stopping treatment was uncertain and may have underestimated the costs of nintedanib.** ○ Exploratory analyses have shown that selecting a different distribution for discontinuations still results in a plausibly cost-effective ICER for nintedanib. ○ The modelling of discontinuations was deemed to be acceptable by the Evidence Review Group. **9. The committee have commented that nintedanib does not meet NICE's criteria for an innovative treatment, due to shortcomings in the company's modelling.** ○ Clinical experts and patient groups unanimously agree that nintedanib is a step change in the treatment of PF-ILD, as there are no other evidence-based treatments available to slow disease progression. ○ The clinical relevance of nintedanib has been demonstrated in the INBUILD trial, and is independent of the economic modelling. ○ Therefore, the committee's view of uncertainties in the economic model should not impact on whether nintedanib is determined to be a step change in the treatment of PF-ILD.	

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

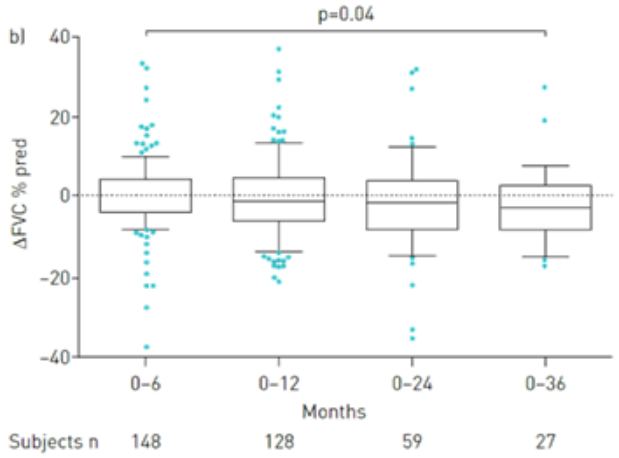
Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 August 2021. Please submit via NICE Docs.

1	**The committee have commented that nintedanib's treatment effect may decrease in the long term, but available data do not support this conclusion.** **The INBUILD trial was not designed to assess data beyond 52 weeks. The analysis of change in FVC (mL) up to DBL2 has important methodological limitations due to a healthy survivor bias observed in the placebo arm which underestimates the treatment effect of nintedanib.** According to the clinical trial protocol, the objective of the INBUILD trial was "to investigate the efficacy and safety of 150 mg bid nintedanib in patients with PF-ILD compared to placebo over 52 weeks in Part A" and the primary objective was "to demonstrate a reduction in lung function decline, as measured by the annual rate of decline in FVC for nintedanib compared to placebo over 52 weeks". The objectives of part B were "to collect supportive, longer term efficacy (time to event endpoints) and safety data on the effect of nintedanib compared to placebo." Therefore, the study focussed on the primary endpoint of annual rate of decline in FVC (mL/year) over 52 weeks. The annual rate of decline in FVC (mL/year) including data collected after 52 weeks up to DBL2 was not pre-specified in the protocol or the trial statistical analysis plan (TSAP) and was added as a purely post-hoc exploratory analysis. In addition, the latter analysis has some methodological limitations which make interpretation of the results challenging. Due to the study design, the follow-up times of the patients differ for those in part B (i.e. beyond 52 weeks), and the number of patients attending the visits beyond 52 weeks decreases per visit. It should be noted that the mean change from baseline presented in response to clarification questions was based on DBL1. Figure 1 shows data up to DBL2. It can be seen that with further follow-up and additional patients reaching the week 84 timepoint (321 at DBL2 vs. 180 at DBL1), the treatment difference has increased, and the variability decreased, compared to the data from DBL1. This shows the uncertainty of the mean change from baseline beyond 52 weeks at timepoints when only few patients were observed in the trial. **Figure 1: Mean of observed absolute change from baseline in FVC (mL) over time (overall population)**	The ERG would argue that the annual rate of decline in FVC post-52 weeks not being in the protocol is not a reason for not considering it in deliberations about the treatment effect post-52 weeks. Differing follow-up times and loss to follow-up are also not reasons to ignore outcomes, but instead are limitations to the extent of credibility of the evidence on treatment effect post-52 weeks. The company argue that the reason for decrease in the treatment effect post-52 weeks is because patients drop out of the placebo arm because of disease worsening and of the nintedanib arm because of adverse events. However, in the ACD response this has not been empirically demonstrated. The company claim that the fact that the intercept term in the RS&I model increases for follow-up beyond 52 weeks that the slope decreases and thus the treatment effect of nintedanib is also decreased. The ERG cannot fully understand this reasoning. The company also claim that the change in intercept term is evidence of lack of linearity. If what the company are asserting is that there the treatment effect of nintedanib vs. comparator is best not estimated by assuming a single linear trend over the entire follow-up period then, as shown by the company in Figure 1, notwithstanding the limitations due to loss to follow-up, that does appear to be the case. This would not imply

	 Variable follow-up leads to methodological limitations for the analysis of the annual rate of decline in FVC (mL/year) including data collected after 52 weeks. Data beyond 52 weeks seem to be associated with a healthy survivor bias, i.e. there seem to be healthier patients in the placebo arm compared to the nintedanib arm.(14) Table 1 (page 35, based on data up to DBL1) shows that initial mean baseline FVC actually increased in patients with longer follow-up in the placebo group, but not in the nintedanib group (mean difference placebo-nintedanib at 52 weeks = -8 mL vs. 60–74 mL at 68–100 weeks). This is consistent with the assumption that patients in the nintedanib arm drop out due to adverse events, whereas placebo patients drop out due to disease worsening. A healthy survivor bias might lead to biased differences for the FVC decline between the treatment groups beyond 52 weeks. This might decrease the advantage of nintedanib as the more severely affected patients (with stronger FVC decline) are underrepresented in the placebo arm (as for example more patients have died in the placebo group). In the Random slope & intercept (RS&I) model, patients with long term data and more available assessments are given a higher weight in the analysis compared to patients with shorter follow-up times. Thus, biased data beyond 52 weeks particularly affects the results of the RS&I model.	limiting data to a follow-up to 52 weeks in order to fit a linear model, but perhaps changing the statistical model to better fit the data beyond 52 weeks. The time to event results are as presented in the CS and reported in Table 3.7 of the ERG report. The company show that the annual rate of decline for nintedanib increased by 22 mL to -135.1 mL from -113.6 between 52 and 140 weeks with a comparison to -205 at 52 weeks for placebo. However, the equivalent value for placebo at 140 weeks is not reported and so the change cannot be compared to the value of 22mL for nintedanib. Again, as shown in Figure 1, it is possible that the rate of change for placebo decreases in comparison to nintedanib, thus reducing the treatment effect post-52 weeks. The Greek registry data dose seem to show that change in FVC% predicted remains relatively stable over three years on nintedanib. However, there does appear to be weak evidence of a trend downwards. The EMPIRE study was presented in the original CS and used to validate the survival curve for nintedanib. The European and Australian IPF registries were also presented in the original CS and

	Another methodological challenge for the analysis of annual rate of decline is the linearity assumption. The RS&I model assumes that FVC declines are linear and that treatment effect is captured by the difference in slopes. This fits well over 52 weeks but not necessarily over longer time periods. This can be illustrated when considering the intercept term for treatment in the RS&I models. For the annual rate of decline in FVC (mL/year) over 52 weeks (primary endpoint) the effect of nintedanib vs. placebo on the intercept is 13.7 mL and non-significant. This effect is not included in the slope (annual rate of decline in FVC) and could be interpreted as the "acute" effect of nintedanib. In contrast, the treatment intercept for annual rate of decline in FVC [mL/year] including data collected up to DBL2 is about 2 times higher (27.3 mL) as in the primary endpoint model and significant (p=0.0072). As this higher intercept value is also not included in the treatment effect this leads to a reduced estimate for the slope, i.e. a reduced annual rate of decline in FVC, compared to the annual rate of decline over 52 weeks. Therefore, the effect of nintedanib on the annual rate of decline in FVC (mL/year) is underestimated compared to the primary endpoint model. The higher intercept term for treatment is a hint that the linearity assumption, which is a requirement for the application of the RS&I models, might be violated for this analysis and reduces the effect size measured by the slope. All in all, the validity of the analysis of annual rate of decline in FVC (mL/year) including data collected up to DBL2 is limited and likely underestimates the treatment effect of nintedanib compared to placebo. To evaluate efficacy endpoints beyond 52 weeks, time to event endpoints should be considered instead. As by study design, the follow-up times of the patients differ in Part B (i.e. beyond 52 weeks). Time to event endpoints are a valid approach to evaluate longer term efficacy as they can deal with variable follow-up by censoring. Pre-specified time to event endpoints such as time to progression or death and time to first acute exacerbation or death became statistically significant at DBL2 (see below, data provided ahead of publication).(15) • Proportion of patients who had ILD progression (decline in FVC ≥10% predicted) or died up to DBL2: HR for nintedanib vs placebo 0.66 (95% CI: 0.53, 0.83; p=0.0003) • Proportion of patients who had an acute exacerbation or died: HR for nintedanib vs placebo 0.67 (95% CI: 0.46, 0.98; p=0.04) Absolute decline in FVC % predicted ≥5% and ≥10% was also consistent at 52 weeks and at DBL2 (see Table 2).(1) These analyses strengthen the evidence that nintedanib has a consistent effect over time, as the hazard ratios	used to validate the survival curve for BSC: lack of separate data on nintedanib reduces their applicability to validate the nintedanib curve.

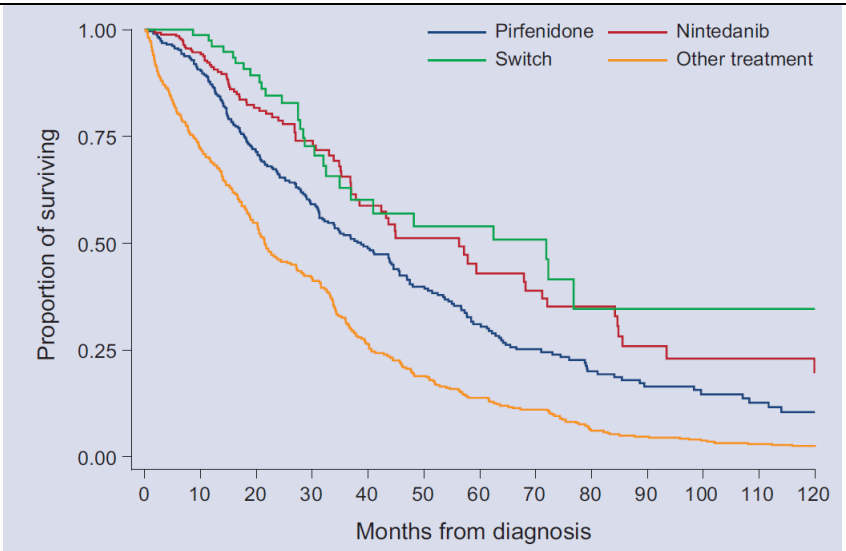
	for 52 weeks and over the whole trial are similar and the 95% confidence intervals largely overlap. **Real-world data from a registry in IPF and longer term data from INPULSIS-ON have also shown that nintedanib has a consistent treatment effect over time.** Data from INPULSIS-ON, a long-term extension of the INPULSIS trials in IPF, showed that the adjusted rate of decline in FVC over 192 weeks was comparable to that shown over 52 weeks in patients treated with nintedanib: • Adjusted annual rate of decline in FVC over 192 weeks (all patients treated with nintedanib): -135.1 mL.(2) • Adjusted annual rate of decline in FVC over 52 weeks (nintedanib) -113.6 mL.(2) This is a 22mL difference in the adjusted rate of decline at 192 weeks vs. 52 weeks for nintedanib (a period of 140 weeks) compared with an annual rate of decline in FVC over 52 weeks of 205.0 mL for placebo.(12) As noted below, the minimum clinically important difference in FVC % predicted is 2-6%, which equates to 75-80 mL in the patients in INPULSIS-ON.(2) This further suggests that the small difference seen between 52 and 192 weeks is not clinically meaningful. Data from a Greek registry of IPF patients across 7 hospitals has also shown that FVC % predicted was largely stable at 3 years for nintedanib patients, with no significant difference from baseline (see Figure 4 below). **Figure 4: Change from baseline in FVC% predicted at 0-6, 6-12, 12-24 and 24-36 months taken from the Greek INDULGE-IPF registry in IPF.(3)**	



Data from registries and meta-analyses have shown that nintedanib is associated with a long-term survival benefit compared with non-antifibrotic treatments.

Long-term comparative data for IPF patients treated with nintedanib are available from the EMPIRE registry. This shows significantly longer median overall survival for the nintedanib group compared with those who received non-antifibrotic treatment (median survival 56.3 months for nintedanib vs. 21.4 months for other treatment, for a 34.9 month or 2.91 year difference in median survival; p<0.001).(4) This is comparable to the life years (LYs) gained in the company's base case in the economic model (LYs gained = [redacted] years for nintedanib vs. BSC). The median survival difference is also similar to that reported in the Greek INDULGE-IPF registry (54.7 months for nintedanib).(3)

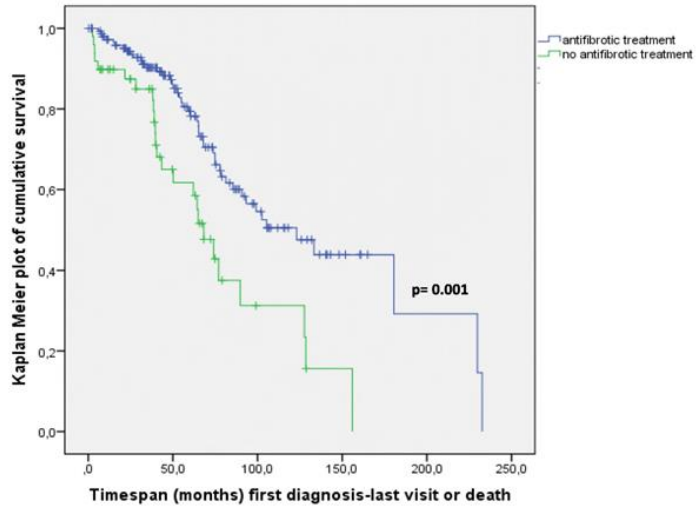
Figure 5: Long-term survival reported in the EMPIRE IPF registry(4)



Although the European IPF registry does not report survival data specifically for nintedanib, it does report long-term survival data on the use of antifibrotics, which included pirfenidone and nintedanib.(5) Previous meta-analysis and other real-world data have shown that nintedanib treated patients have similar or better survival compared with pirfenidone treated patients in IPF.(4, 16, 17) Similar efficacy of nintedanib and pirfenidone was also accepted by the committee in the appraisal of nintedanib for IPF (TA379).(18) Therefore, the antifibrotic treatment arm should provide an indication of the survival benefit of nintedanib in the European IPF registry population.

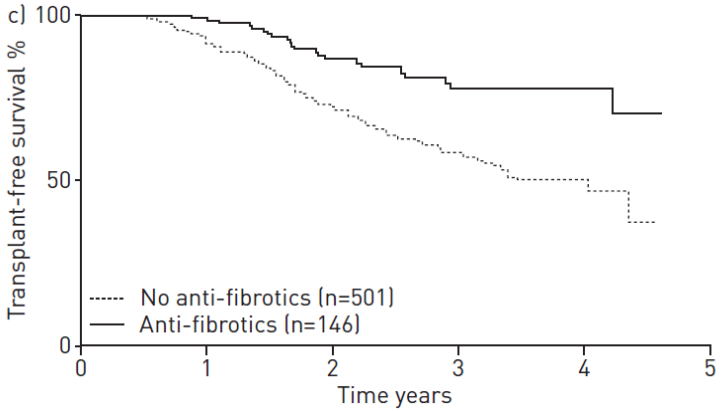
This registry also reported a significant survival benefit for antifibrotic treatment compared with non-antifibrotic treatment (median survival on antifibrotics 123.1 months vs 68.3 months for prednisolone or other treatment, for a 54.8 month or 4.6 year difference in median survival, p=0.001).(5) This is a greater difference in overall survival than is modelled in the company base case.

Figure 6: Overall survival of IPF patients upon first diagnosis depending on treatment from the European IPF registry(5)



Similarly, although the Australian registry does not report survival specifically for nintedanib, it does report long-term survival for patients treated with antifibrotics (including pirfenidone and nintedanib).(6) This registry also reported significantly improved survival for patients who received antifibrotic therapy compared with patients who did not (HR 0.56; 95% CI 0.34, 0.92; p=0.022).

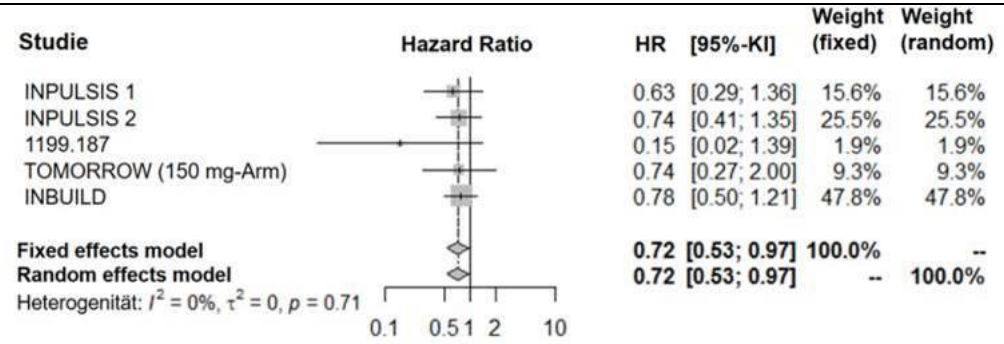
Figure 7: Kaplan-Meier survival analysis of patients with IPF with or without antifibrotic treatment(6)



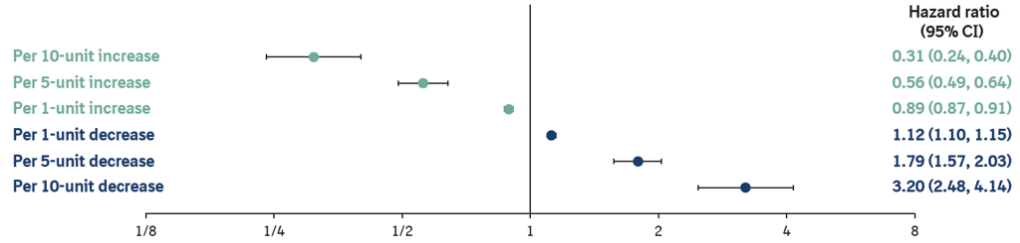
These registries all report a survival difference that is maintained, or could be said to increase, over time.

Finally, a meta-analysis of randomised controlled trials in IPF (4 studies) and PF-ILD (1 study) has also shown that nintedanib treatment is associated with significantly improved survival compared with placebo (Figure 8).(19) This is confirmed by another meta-analysis of 8 randomised controlled trials and 18 cohort studies that found that antifibrotic treatment was associated with a significantly decreased risk of all-cause mortality (RR 0.55; 95% CI 0.45, 0.66).(20)

Figure 8: Meta-analysis of randomised controlled trials for nintedanib in IPF and PF-ILD

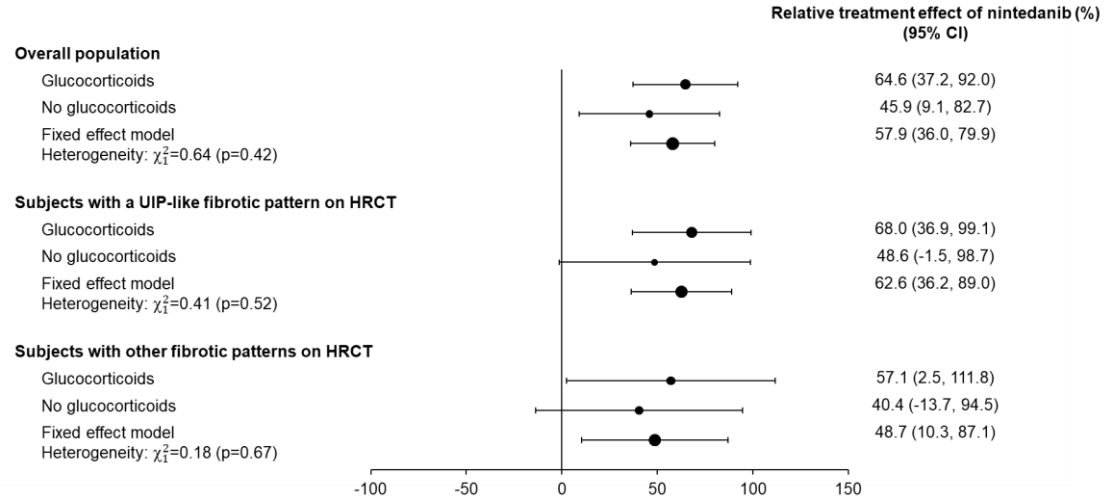
	 **Overall, the conclusion that there is insufficient evidence of survival benefit with nintedanib, or that there is a substantial likelihood of a treatment waning effect is not a reasonable interpretation of the evidence. It also does not take into account the full body of relevant evidence.**	
2	**The committee have commented that they were not presented with the algorithm chosen by the company to estimate FVC % predicted and that they would like to see how this was done.** FVC % predicted was reported as a secondary endpoint in the INBUILD trial. This was calculated according to the Global Lung Initiative (GLI) equation which takes the form of the equation below, and varies depending on individual patients' race, age, gender and height. This approach is described and validated in publications by Quanjer et al and Kubota et al.(7, 21) Predicted value = $e^{a} \times H^{b} \times A^{c} \times e^{d \times group} \times e^{spline}$ where a is the intercept, H is the height (cm), b is the exponent for the height, A is age (years), c is the exponent for age and spline is the contribution from the age spline. Group is Caucasian, African-American, South or North East Asian and takes a value of 1 or 0 depending on the group.	The ERG can confirm that the equation presented is the exponential of an equation presented in the paper by Quanjer 2012 cited by the company: log(Y) = a + b*log(H) + c*log(A) + age-spline + d*group
3	**The committee have commented that it is unclear whether the primary endpoint measured by FVC in millilitres per year over 52 weeks reflects a clinically meaningful change as measured by FVC % predicted.** The committee accepted that nintedanib is associated with a slower decline in lung function (page 10 of the	The ERG can confirm that those 52 week values for change from baseline in FVC% predicted are those that were reported in the CSR (see Table 11.1.3.1.2). They correspond to values for change in FVC of -192.20 and -

	ACD). They state that a decline in FVC of at least 10% predicted defines disease progression and is associated with disease deterioration and mortality in PF-ILD (page 6 of the ACD). However, they question whether this is clinically meaningful as measured by FVC % predicted. **Published literature in IPF suggests that the change in FVC % predicted reported in the INBUILD trial is clinically meaningful.** In the overall population of the INBUILD trial, the adjusted mean absolute change from baseline to week 52 in FVC % predicted was a secondary endpoint, and reported change was -2.62% in the nintedanib group and -5.86% in the placebo group (see Table 3 and section 11.1.3.1.2 of the Clinical Trial Report).(9) The adjusted mean difference showed that treatment with nintedanib reduced FVC % predicted decline by 3.24% (95% CI 2.09, 4.40) compared with placebo at week 52. Published literature in patients with IPF suggest that the minimum clinically important difference for percent predicted FVC is between 2-6%.(8) This is therefore a clinically meaningful change in FVC % predicted. **Pre-specified analyses from INBUILD showed that treatment with nintedanib reduced the proportion of patients with both a relative and absolute decline from baseline in FVC of >10% and >5% at week 52.** In the overall population, fewer patients treated with nintedanib had an absolute decline from baseline in FVC % predicted of >10% (adjusted odds ratio 0.68; 95% CI 0.49, 0.95) or >5% (adjusted odds ratio 0.63; 95% CI 0.46, 0.85) at week 52.(9) Analyses of the proportions of patients with a relative decline from baseline in FVC % predicted of >10% (adjusted odds ratio 0.63; 95% CI 0.43, 0.94) or >5% (adjusted odds ratio 0.46; 95% CI 0.31, 0.69) at week 52 were also in favour of nintedanib vs. placebo.(9) In the overall population, treatment with nintedanib also reduced the risk of progression (defined as ≥10% absolute decline in FVC % predicted) or death by 35% vs. placebo (HR 0.65; 95% CI 0.49, 0.85).(9) Declines in FVC of both >10% and >5% have been associated with mortality.(10) In INBUILD a decline of >10% was associated with a more than three-fold increase in the risk of death over 52 weeks (hazard ratio 3.64; 95% CI 1.29, 10.28; p=0.015).(10) This is similar to the risk reported in the INPULSIS trials (HR 3.95; 95% CI: 1.87 to 8.33; P<0.001).(10) These differences vs. placebo are therefore clinically meaningful.	85.45 that correspond to the values of annual rate of decline of −175.67 and −118.14 respectively reported in the CS and reproduced in the ERG report Table 3.7. The ERG can report that the MCID reported in the paper cited by the company was reported to be one of several values, i.e. 2.2%, 2.7%, 4.3% or 5.8%, depending on the method used. The company also presents evidence of the effect on proportion of patients experiencing a >5% or 10% absolute or relative decline in FVC% predicted, which are consistent with the evidence on the time to progression (>10%) already reported in the CS and reproduced in Table 3.7 of the ERG report. The ERG notes the clear direct relationship between FVC% predicted difference and HR for mortality as reported in the paper by Maher 2021. Very little information was available on this study given that it was a conference abstract, although it might be worth noting that all of the data were from nintedanib trials with a maximum 52 week follow-up. The company also shows the similarity between INBUILD and pooled INPULSIS trial data in 52 week FVC% predicted change from baseline and the perception by clinical experts and patient groups that nintedanib

	Meta-analysis of nintedanib clinical trials in IPF, PF-ILD and SSc-ILD show a strong association between annual rate of change in FVC % predicted and risk of death. A meta-analysis was published at the 2021 American Thoracic Society Conference, assessing the strength of FVC as a surrogate marker for mortality. This analysis pooled data from patients who received nintedanib or placebo in the placebo-controlled periods of trials in IPF (TOMORROW, INPULSIS-1 and -2, Phase IIIb trial NCT01979952), PF-ILD (INBUILD) and systemic sclerosis-associated ILDs (SENSCIS). The authors then assessed the association between FVC % predicted and time to death over 52 weeks. This analysis showed a strong association between annual rate of change in FVC % predicted and risk of death (see Figure 9 below). The p-value for association between rate of change in FVC % predicted as a continuous variable and death was <0.0001.(11) **Figure 9: Association between annual rate of change in FVC % and risk of death over 52 weeks(11)**  **The difference in FVC reported in INBUILD, measured both in mL and % predicted, was similar to that reported in INPULSIS. Clinical experts and patient groups agree that this difference has been meaningful for patients with IPF, as well as those receiving nintedanib for PF-ILD as part of a named patient supply programme.** The adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks reported in INBUILD was similar to that reported in INPULSIS: • INBUILD, nintedanib vs. placebo: 106.96 mL (95% CI 65.42, 148.50; p<0.0001)(9) • INPULSIS (pooled), nintedanib vs. placebo: 110.6 mL (95% CI, 83.2-137.9, p<0.001)(12) (information	has made a clinically meaningful difference.

	taken from the supplementary appendix) The difference in adjusted absolute mean change from baseline in FVC % predicted over 52 weeks was also similar in INBUILD and INPULSIS: • INBUILD, nintedanib vs. placebo: 3.24% (95% CI 2.09, 4.40)(9) • INPULSIS (pooled), nintedanib vs. placebo: 3.2% (95% CI 2.4, 4.0)(12) (information taken from the supplementary appendix) Clinical experts and patient groups unanimously agree that the effect of nintedanib in IPF has been highly meaningful for patients. This is highlighted in the previous submissions by the British Thoracic Society (BTS), Action for Pulmonary Fibrosis (APF) and clinical expert. In addition, BI have received requests for 'Named Patient Supply' (NPS) for nintedanib in PF-ILD from 19 out of 24 ILD specialist centres in the UK between 2018 and 2021. Named patient supply was considered in response to unsolicited requests from expert ILD physicians to access treatment with nintedanib in exceptional, life-threatening cases of PF-ILD. In total 258 patients have commenced NPS for nintedanib in PF-ILD, including patients from 19 different ILD specialist centres. This affirms that the ILD community, as stated in both clinician and patient submissions to NICE, view nintedanib as an innovation or 'step change' in the treatment of PF-ILD. This information also suggests that patients are receiving important benefit from nintedanib in PF-ILD in the UK. Previous submissions from Action for Pulmonary Fibrosis have also reinforced the benefit that patients have received from nintedanib in IPF: *"Anti-fibrotic treatments like nintedanib have been a 'game changer' for people living with IPF, slowing disease progression and increasing life expectancy."* "[redacted], *an RA-ILD patient, from Devon* *When I look around my support group, I see friends with IPF who have been diagnosed much longer than me and seem to be doing much better. They have all been on nintedanib or pirfenidone for a few years."* *"PF/ILD patients urgently want access to nintedanib because it directly targets their lung fibrosis and has been shown to slow progression, which a high priority for them."*	

	Overall, it is <u>not</u> a reasonable interpretation of the evidence to conclude that the treatment effect of nintedanib shown in INBUILD is not clinically relevant.	
4	**The committee have commented that the impact of restricted concurrent NHS treatments on the treatment effect of nintedanib is unclear.** **However, post-hoc analyses of the INBUILD trial excluding all patients who took prohibited or restricted medications over 52 weeks were very similar to the primary analysis. This indicates that the treatment effect was not influenced by the use of restricted and prohibited medications.** A post-hoc analysis was performed to assess the impact of restricted and prohibited medications on the primary endpoint (annual rate of decline in FVC).(13, 22) This was done by excluding all patients who took prohibited or restricted medications at baseline or on-treatment or post-study drug discontinuation over 52 weeks. As shown in Table 4, the results of the primary analysis and that of the analysis excluding all patients who took prohibited or restricted medications through the trial to 52 weeks are very similar (rate of decline in FVC [mL/year] over 52 weeks was 107.8 mL vs. 107.0 mL in the primary analysis, both p<0.001), indicating that the treatment effect was not influenced by the use of restricted and prohibited medications.(13, 22) **Post-hoc subgroup analyses from the INBUILD trial have shown that the effect of nintedanib on reducing FVC decline was not influenced by the use of glucocorticoids at baseline.** A post-hoc analysis of the rate of decline in FVC over 52 weeks in subgroups by glucocorticoid use at baseline has also been done.(13) This analysis found that there was no significant difference in the treatment effect of nintedanib between subjects taking glucocorticoids at baseline and those who were not (interaction p=0.18, see Figure 10). **Figure 10: Relative treatment effect of nintedanib vs placebo on rate of FVC decline over 52 weeks in subgroups by use of glucocorticoids at baseline(13)**	The company demonstrate in Table 4 that the exclusion of restricted medication did not have much of an effect on the difference between nintedanib and placebo in rate of rate of FVC decline over 52 weeks. It might be worth noting that it did seem to have a substantial effect on the per arm values:- 187.78 and -80.82 versus -157.17 and -49.41 respectively. Figure 10 does seem to show little effect of glucocorticoid use on the treatment effect on rate of FVC decline over 52 weeks. The BTS consensus statement seems to contradict the finding of an effect of restricted medications on the per arm values (as opposed to the treatment effect of nintedanib vs. placebo): "…they do not have any meaningful impact on the ILD."



Clinical experts treating interstitial lung diseases at specialist tertiary centres in the UK also agree that restricted medications would not be expected to have any meaningful efficacy in the treatment of progressive fibrosing disease.

As stated in the British Thoracic Society's previous submission to NICE, the clinical consensus is that 'immunosuppressants are not given to treat the fibrotic component of an ILD, but the inflammatory component of the disease'. A consensus document agreed by the majority (21/24) of the clinical leads in ILD centres in England and Wales, plus 3 rheumatology experts, collated in short timelines has reaffirmed this statement.

The consensus document also states the following:

'The patient population with chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD) often have a wide range of underlying clinical conditions that have led to their ILD. These extrapulmonary manifestations such as arthritis, glomerulonephritis, pericarditis and dermatological manifestations may require treatment with corticosteroids and/or immunosuppressants, but these are not to treat the ILD, and they do not have any meaningful impact on the ILD. By definition, patients with PF-ILD have progressed <u>despite treatment with conventional therapies, including immunosuppressants and other restricted therapies</u>.'

	'It is common clinical practice that when patients with predominantly fibrotic ILD present with lung function decline despite immunosuppression, clinical consideration would be to reduce or completely stop immunosuppressants due to a lack of efficacy. There are also significant safety concerns around the use of multiple immunosuppressants as evidenced in the IPF-focused PANTHER trial which clearly demonstrated an increased risk of mortality & hospitalisation in these patients.' *'The ILD clinical community are concerned about using non evidence-based immunosuppressants that lack efficacy in PF-ILD patients who phenotypically behave like IPF and have similar radiological features. This is reflected in the very low levels of use of restricted immunosuppressants after 6 months in the INBUILD trial once these were allowed.'* *'From a clinical perspective, there are no treatments that are licensed for use, or really being consistently used in clinical practice for the management of UK patients with PF-ILD and therefore the placebo arm of the INBUILD trial is a true representation of UK clinical practice.'* Please see Appendix 2 (page 38) for the full consensus statement. **In summary, it is not a reasonable interpretation of the evidence to conclude that the impact of restricted therapies on the treatment effect of nintedanib is unclear. It is clear that the restriction of these treatments in INBUILD has not biased the results of the trial, or reduced the relevance of the trial to UK clinical practice, when all relevant evidence is considered.**	
5	**The committee have commented that there are uncertainties in the company's modelling and validation for overall survival in the placebo arm, and that this likely overpredicts deaths in the placebo arm.** **If an alternative survival curve with more optimistic survival for the placebo arm is selected, nintedanib remains cost-effective.** The committee noted that the Bayesian survival curves dropped more quickly (had a higher death rate) than the registries survival, and that this meant that the company may be underestimating survival of patients who do not take nintedanib by using Weibull Bayesian curves. Whilst we accept that there is uncertainty in the placebo analysis, this is due to there being no long-term placebo clinical trial data available for patients with IPF or other PF-ILD. Nevertheless, the use of placebo	The ERG has provided Figure 1.1 in Appendix 3 of this document, showing a range of potentially plausible placebo curves compared to the European and Australian registries and the nintedanib Weibull Bayesian curve. This should enable the committee to select the curve they consider most plausible. The corresponding ICERs for each scenario are presented in Table 1.1 of Appendix 3. The ERG notes that in all but one scenario tested, the ICER remains approximately equal to or below the £30,000

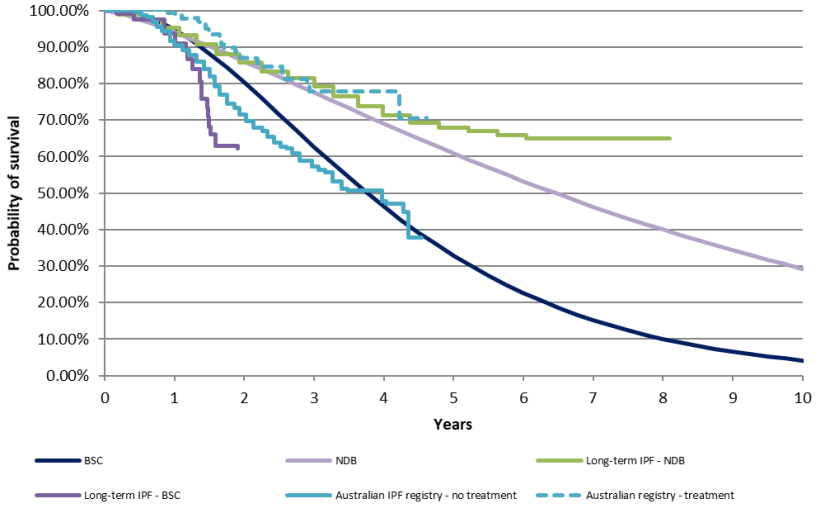
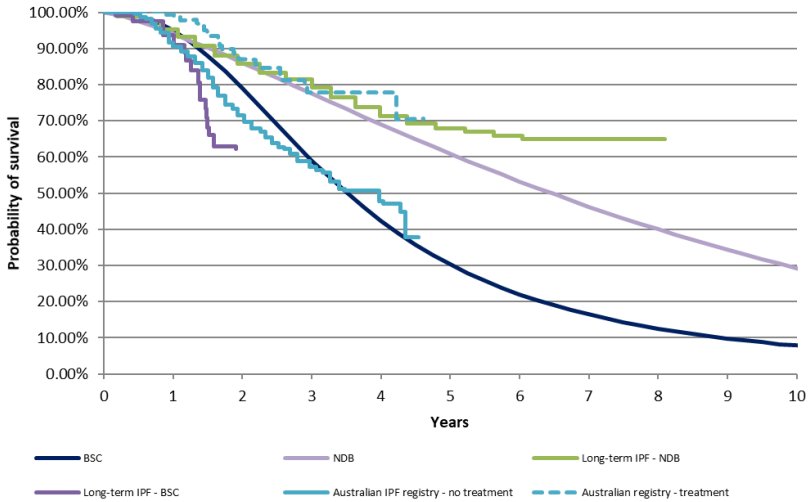
	clinical trial data from patients with IPF to generate an informative prior goes some way to reduce uncertainty in the survival estimates of control within the trial timeframe, which may in turn help produce more realistic long-term survival estimates. If an alternative curve that has a lower death rate over the long term is selected for placebo, namely the Bayesian gamma or log logistic curves, this results in an ICER that is <£25,000/QALY [redacted] and [redacted] per QALY, respectively). These curves provide a good visual match to the Australian registry, which ILD expert clinicians believed to be the most appropriate registry to use in our Advisory Board in December 2020 due to similarities with UK clinical practice and how the registry is managed (see Figures 11 and 12). **Figure 11: BSC arm modelled using the Bayesian Gamma distribution, NDB modelled using Bayesian Weibull (company base case)**  	per QALY gained threshold.

Figure 12: BSC arm modelled using the Bayesian log-logistic distribution, NDB modelled using Bayesian Weibull (company base case)



It is also possible to select a survival curve for nintedanib that is a good visual match for the group receiving antifibrotic treatment in the Australian registry (the frequentist lognormal curve). If this is used together with the curves that provide the best visual match to the no treatment group in the Australian registry (Bayesian gamma or Bayesian log-logistic) this gives ICERs <£20,000/QALY [redacted] and [redacted] respectively).

Figure 13: NDB arm modelling to match on-treatment group from the Australian registry (frequentist lognormal), BSC arm modelled using Bayesian gamma

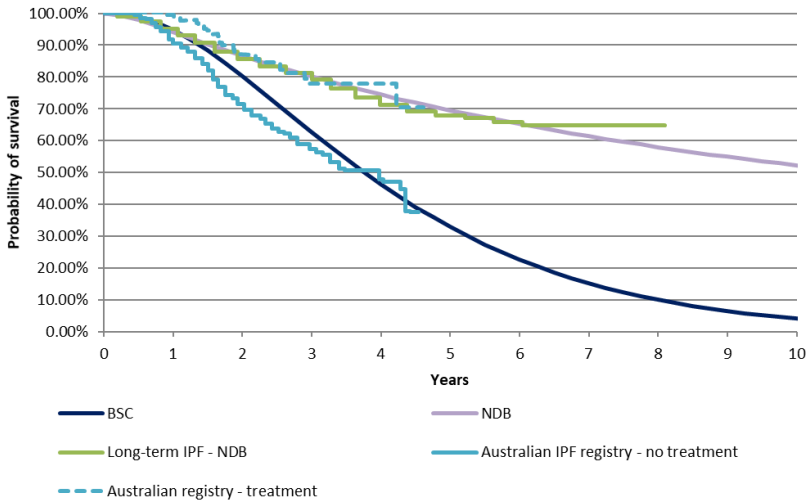
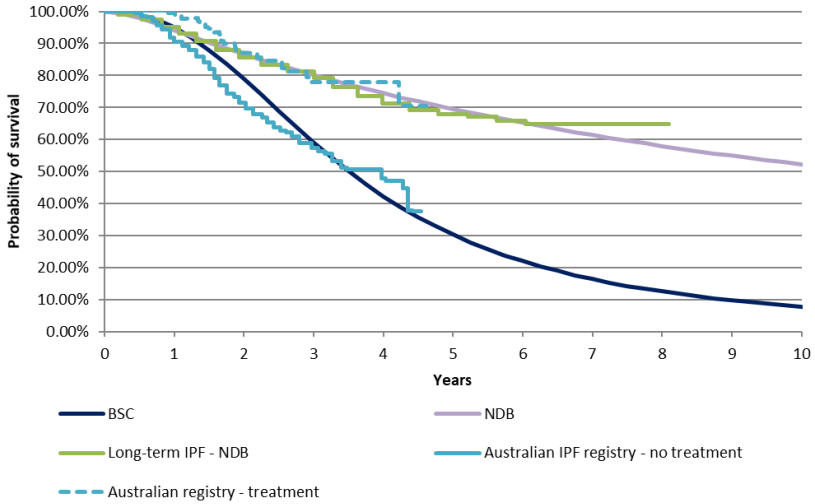


Figure 14: NDB arm modelled to match on-treatment group from the Australian registry (frequentist lognormal), BSC arm modelled using Bayesian log-logistic



The committee commented that the European IPF registry may be the best source to validate the placebo arm survival estimates. Although data on nintedanib specifically are not reported in this registry, it does report long-term survival data on the use of antifibrotics, which included pirfenidone and nintedanib.(5) Previous meta-analysis and other real-world data have shown that nintedanib treated patients have similar or better survival compared with pirfenidone treated patients in IPF.(4, 16, 17) Similar efficacy of nintedanib and pirfenidone was also accepted by the committee in the appraisal of nintedanib for IPF (TA379).(18) Therefore, the antifibrotic treatment arm should provide an indication of the survival benefit of nintedanib in the European IPF registry population.

The European IPF registry reported considerably higher survival estimates for both the no treatment and antifibrotic treated groups, compared with other registries and the long-term clinical trial data for IPF. This may be because no central HRCT scans or histology samples were performed to validate whether patients had IPF, which may have led to the inclusion of some patients without true IPF.(6) Therefore, if we select a survival curve for placebo that matches the data from the European registry, we must also select an alternative curve for nintedanib survival, otherwise nintedanib survival is underestimated by a considerable margin (see Figure 15). If alternative curves are selected that better match the European IPF registry data for both arms

(frequentist lognormal for BSC and frequentist exponential for nintedanib, see Figure 16), the ICER is under £25,000/QALY [redacted]).

These alternative scenarios are summarised in Table 6 in Appendix 1 (page 37).

Figure 15: Modelled survival curves (BSC = frequentist lognormal; NDC = Bayesian Weibull) compared with data from the European IPF registry

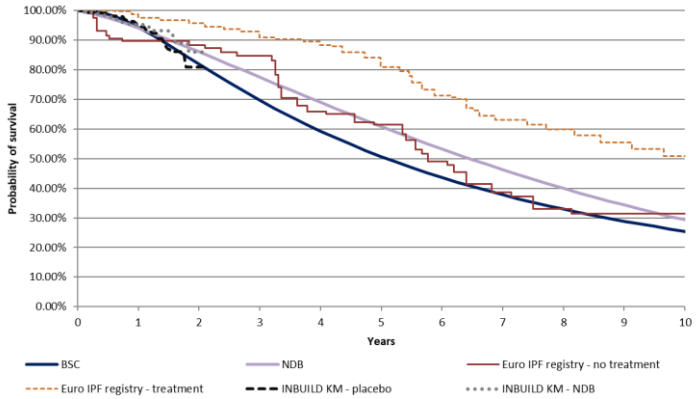
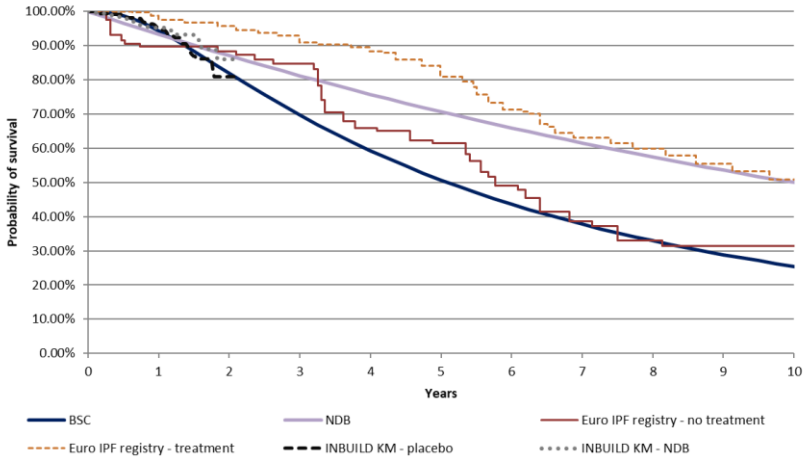
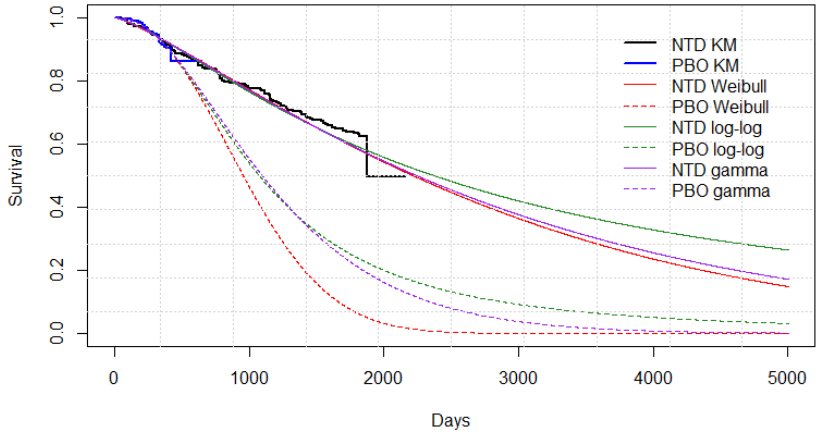


Figure 16: Alternative survival curves that better match the European registry data for no treatment and antifibrotic treated patients (BSC = frequentist lognormal; NDB = frequentist exponential)

	 It is possible to select alternative curves for BSC where the ICER is >£30,000, for example the frequentist or Bayesian exponential and frequentist or Bayesian lognormal). However, these are implausible and unrealistic compared with survival data reported in IPF registries. **In summary, the survival modelling of BSC can be validated by comparison with real-world registries. If extrapolated curves are selected that provide a good visual match for data reported in these registries, nintedanib is still cost-effective. Therefore, the conclusion that modelling and validation of overall survival for the placebo arm is uncertain and its impact on the model results is not clear does not take account of all the relevant evidence.**	
6	**The committee have commented that there are uncertainties in fitting individual parametric distributions to the nintedanib and placebo arms, and that the modelling resulted in ever-increasing survival benefits for nintedanib compared with placebo in the extrapolated periods.** **The ACD also states that the committee was not provided with evidence that the company had explored the proportionality of treatment effects in the observed data and had not been presented with information on the treatment effect over time implied by the company's chosen curves. It concluded that the company should explore the proportionality of hazards assumptions observed in the data and provide information on the treatment effect implied by the alternative survival modelling approaches**	The company have not included any additional survival modelling approaches within the model. Neither did the company provide a comparison of the observed hazard over time and the predicted hazard for the various modelled survival curves. Thus, the ERG cannot provide new thoughts regarding the selection of the best OS curve for the placebo group.

	considered. The proportional hazards assumption was tested for all survival analysis outcomes in the economic model (overall survival, time to discontinuation, and time to first acute exacerbation) and these analyses were provided in response to clarification questions. Independent survival models were used for consistency across outcomes, as the proportional hazards assumption was not met for the time to discontinuation outcome. The general model (using treatment as a covariate) is unlikely to have been an appropriate approach for the Bayesian survival analysis. In the Bayesian survival analysis, the best-fit models were informed by the matched IPF data, where the Kaplan-Meier curves crossed. This suggests that the proportional hazards assumption is unlikely to have been met (see Figure 17 below). Additionally, due to the difference in the duration of observed events between nintedanib (5.9 years) and placebo (1.8 years) arms, any analysis of a general model with treatment as a covariate is unlikely to reach any meaningful results. **Figure 17: Modelled survival curves and Kaplan-Meier data from INBUILD**  The original company base case is based on Bayesian analysis, the shape of which is informed by the long-term clinical trial data for nintedanib in IPF. However, we take the committee's point of view that there is uncertainty in these long-term survival estimates based on clinical trial data, particularly for the placebo arm. It is possible to select a different survival distribution for placebo that more closely matches the Australian	The ERG has provided a Figure and range of scenarios selecting a range of different potentially plausible placebo curves, while maintaining the Weibull Bayesian curve in Figure 1.1 and Table 1.1 of Appendix 3 of this document.

registry. This could be justified, as the ILD clinical experts (Leads at ILD Specialist Centres) consulted in our Advisory Board in 2020 considered this to be the best registry to validate the long term survival for placebo due to similarities in clinical practice and the way the registry is managed compared with the UK. As stated above, this results in an ICER that is <£25,000/QALY.

Selecting these alternative curves for placebo also reduces the modelled difference in survival between nintedanib and BSC compared with the company base case (Figures 18-20). If alternative survival curves are selected that give the best visual match to the European IPF registry, the modelled difference in survival between nintedanib and BSC is also reduced compared with the company base case (see Figure 16 above), with an ICER <£25,000/QALY [redacted]).

Figure 18: Company base case survival modelling (Bayesian Weibull for NDB and BSC)

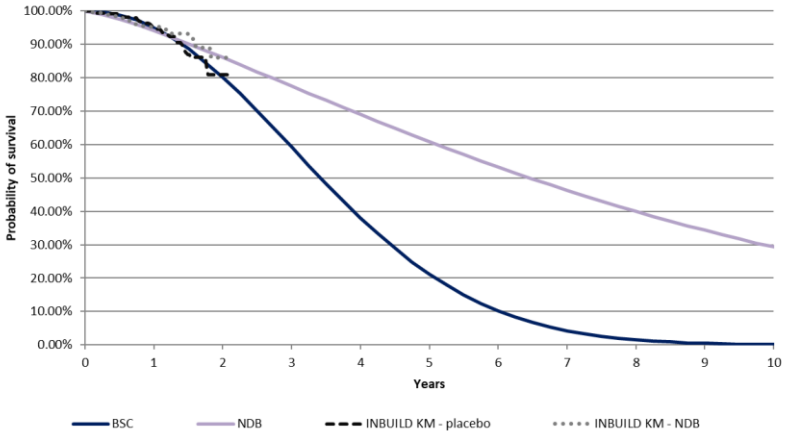


Figure 19: Alternative modelling using a Bayesian Gamma distribution for BSC (Bayesian Weibull for NDB)

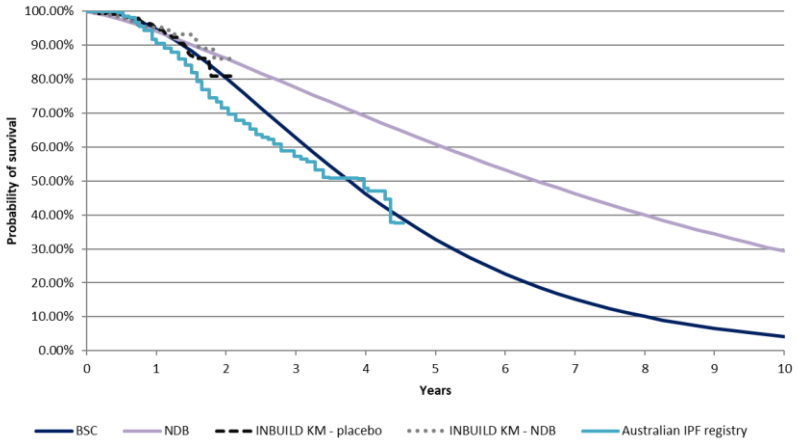
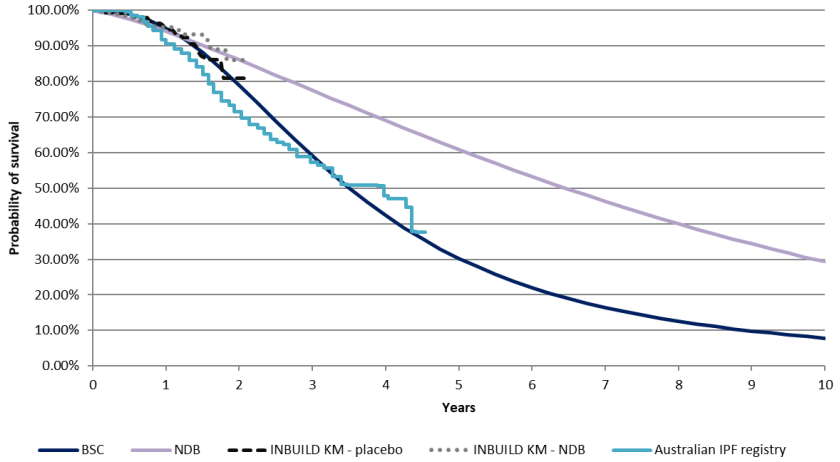


Figure 20: Alternative modelling using a Bayesian loglogistic distribution for BSC (Bayesian Weibull for NDB)



	Although survival data from the INBUILD trial were immature, long-term survival data are available from registries of IPF patients. As stated in row 1 above, three registries report long-term comparative data and all show a statistically significant survival benefit for nintedanib/antifibrotic treatment compared with non-antifibrotic treatment that is maintained over time.(4-6) These report similar survival difference for nintedanib vs non-antifibrotic treatment as reported in the company modelling (base case) and greater survival difference compared with the modelling when the alternative survival curves for placebo are used (see Table 5). **Overall, evidence from registries in IPF suggest that the modelled difference in survival for nintedanib vs. placebo is reasonable. If a plausibly reduced difference in survival is modelled, nintedanib is still cost-effective.** In our view, taking all relevant evidence into account substantially addresses the uncertainties highlighted by the committee. However, BI is open to exploring approaches to address any remaining material uncertainty, if the committee believes this still exists.	
7	**The committee have commented that there are uncertainties in the company's modelling of exacerbations and decline in lung function because of their lack of a link with mortality in the model.** We acknowledge that this is a limitation of the current model, which as noted in the ACD was necessary to avoid double counting deaths. In general, the committee accepted this model structure as relevant for decision making. We did look into changing the structure of the model to include a link between mortality and exacerbations and decline in lung function. However, the adapted model produced increased and unrealistic life years for both placebo and nintedanib, compared with the current model. This is likely because there is additional uncertainty generated by this approach, as a separate risk of death is needed for each health state in the model, and this is in itself uncertain. Although an important event for individual patients, exacerbations are relatively rare in patients with ILD. The ACD also states that the committee was aware that both the company and the ERG's varying risk of exacerbation in scenario analyses had little impact on the cost effectiveness. Since the committee commented that the modelling of exacerbations and decline in lung function was acceptable, and since the main driver of the cost-effectiveness is the survival analysis, we do not believe that these limitations significantly impact the economic case for nintedanib.	The ERG notes that the limited impact of varying the risk of exacerbation on cost effectiveness is most likely due to the lack of link with mortality. The true impact remains unknown. Given that no new evidence has been presented, the ERG has nothing further to add.

8	**The committee have commented that the modelling of stopping treatment was uncertain and may have underestimated the costs of nintedanib.** **Exploratory analyses have shown that selecting a different distribution for discontinuations still results in a plausibly cost-effective ICER for nintedanib.** Exploratory analyses provided at technical engagement and presented at the committee meeting showed alternative modelling of discontinuations. Using the Bayesian Weibull distribution for nintedanib and the ERG's preferred distribution for discontinuation (Weibull), the exploratory ICER was [redacted]/QALY. Although the ERG state that this analysis "does not provide correct ICERs" they agreed that it does give an idea of the impact of changing the distribution for discontinuation and shows that alternative modelling still results in a plausibly cost-effective ICER for nintedanib. The Evidence Review Group noted at the technical engagement meeting that a different model structure or assumptions might not be possible or necessary, given the additional uncertainties this would introduce. The modelling of discontinuations was therefore deemed to be acceptable by the ERG.	No new evidence has been presented in relation to this issue. The ERG has nothing to add beyond their comments in the technical engagement response that the discontinuation scenario ICERs presented do not correspond to the correct ICERs in the model and therefore can only be used as a guide for the rough impact on results.
9	**The committee have commented that nintedanib does not meet NICE's criteria for an innovative treatment, due to shortcomings in the company's modelling. However, clinical experts and patient groups agree that nintedanib is a step change in the treatment of PF-ILD, as there are no other treatments available that slow disease progression in PF-ILD. These factors are independent of the economic modelling as they have been demonstrated in the INBUILD trial.** As discussed in point 3 above, the change in FVC reported in INBUILD, both in mL and % predicted, has been demonstrated to be clinically relevant. FVC has been shown to be a strong indicator of mortality in patients with ILD.(11) There is also evidence from registries that nintedanib treatment results in longer median survival compared with other non-antifibrotic treatments.(4-6) This benefit is in the treatment of a disease which, if left untreated, has a median post-diagnosis survival that is worse than several types of cancer.(23-25) Clinicians and patient groups unanimously agree that nintedanib is a step change in treatment for patients with PF-ILD, based on the benefit demonstrated in the pivotal clinical trial and their experience of using nintedanib in IPF. As stated above, BI have also received requests for 'Named Patient Supply' (NPS) for nintedanib in PF-ILD from 19 out of 24 ILD specialist centres in the UK between 2018 and 2021. In total 258 patients have commenced NPS for nintedanib in PF-ILD, including patients from 19 different ILD specialist centres. This affirms that the ILD community, as stated in both clinician and patient submissions to NICE, view nintedanib as	

	an innovation or ‘step change’ in the treatment of PF-ILD. These factors are separate from the economic modelling. Therefore, the committee’s view of uncertainties in the economic model should not impact on whether nintedanib is determined to be a step change in the treatment of patients with PF-ILD. Evidence and feedback from clinical and patient groups is clear that nintedanib is a step change, and should be considered to be innovative. **Therefore, it is not a reasonable interpretation of the evidence to say that nintedanib is not innovative.**	

Nintedanib for treating progressive fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis [ID1599]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 August 2021. Please submit via NICE Docs.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix 1: Additional data tables

Table 1: Initial mean baseline FVC values of patients attending visits beyond 52 weeks

Visit at…	Placebo		Nintedanib		Placebo-Nintedanib
	N	Mean (ml)	N	Mean (ml)	Mean difference (ml)
52 weeks	274	2,339	265	2,347	-8
68 weeks	204	2,380	205	2,320	60
84 weeks	91	2,454	89	2,380	74
100 weeks	19	2,370	16	2,298	72

Source: Boehringer Ingelheim. Descriptive statistics and absolute change from baseline in FVC over the whole trial (DBL1).
FVC, forced vital capacity

Table 2: Time to absolute decline in FVC % predicted ≥5% or ≥10% at 42 weeks and up to DBL2

	Nintedanib			Placebo				
	N	Patients with event (%)	Observation time (patient-years)	N	Patients with event (%)	Observation time (patient-years)	HR (95% CI)	P value
Time to absolute decline in FVC % predicted ≥5%								
52 weeks	332	170 (51.2)	217.4	331	222 (67.1)	185.7	0.68 (0.56, 0.83)	0.0001
DBL2	332	217 (65.4)	299.8	331	263 (79.5)	233.1	0.67 (0.56, 0.81)	<0.0001
Time to absolute decline in FVC % predicted ≥10%								
52 weeks	332	73 (22.0)	295.2	331	115 (34.7)	283.9	0.60 (0.45, 0.80)	0.0005
DBL2	332	114 (34.3)	432.0	331	160 (48.3)	393.5	0.64 (0.50, 0.81)	0.0002

Source: Boehringer Ingelheim. Analyses of time to absolute decline in FVC % predicted >=5% or >=10% over the whole trial.
CI, confidence interval; DBL2, database lock 2; FVC, forced vital capacity

Table 3: Absolute change from baseline in FVC (mL) and FVC % predicted at week 52 – treated set, overall population

	Baseline[1]	Change from baseline in FVC	Comparison vs. placebo

				at week 52					
Treatment	**N**	**Mean**	**SD**	**Adjusted mean**	**SE**	**95% CI**	**Adjusted mean**	**SE**	**95% CI**
Absolute change from baseline in FVC (mL)									
Placebo	331	2321.15	727.97	-192.20	13.83	(-219.37, -165.03)			
Nintedanib 150 mg bid	332	2340.07	740.19	-85.45	14.05	(-113.04, -57.86)	106.75	19.72	(68.03, 145.48)
Absolute change from baseline in FVC % predicted									
Placebo	331	69.27	15.21	-5.86	0.41	(-6.67, -5.05)			
Nintedanib 150 mg bid	332	68.70	16.04	-2.62	0.42	(-3.44, -1.80)	3.24	0.59	(2.09, 4.40)

Source: Table 11.1.3.1.2:1 of the Clinical Trial Report(9)
CI, confidence interval; FVC, forced vital capacity; SE, standard error; SD, standard deviation
1 Based on the number of patients that were included in the model and had baseline data available.
2 Based on MMRM, with fixed effects for baseline, HRCT pattern, visit, treatment-by-visit interaction, baseline-by-visit interaction and random effect for patient. Within-patient error were modelled by unstructured variance-covariance structure

Table 4: Annual rate of decline in FVC (mL/year) over 52 weeks – treated set, overall population

	Rate of FVC decline over 52 weeks				Comparison vs. placebo			
Treatment	**N**	**Adjusted rate**	**SE**	**95% CI**	**Adjusted difference**	**SE**	**95% CI**	**p-value**
Overall population (primary analysis)								
Placebo	331	-187.78	14.84	(216.92, -158.64)				
Nintedanib 150 mg bid	332	-80.82	15.07	(-110.42, -51.22)	106.96	21.15	(65.42, 148.50)	<0.0001
Overall population (excluding patients with restricted or prohibited medication use)								
Placebo	240	-157.17	15.31	(-187.26, -127.08)				
Nintedanib 150 mg bid	279	-49.41	14.47	(-77.84, -20.98)	107.75	21.07	(66.36, 149.15)	<0.0001

Source: Table 8:3 of the Response Document to 1st Request for Supplementary Information sent to the EMA(22)
CI, confidence interval; FVC, forced vital capacity; SE, standard error

Table 5: LYs gained in the economic model compared with difference in median survival reported in IPF registries

Source	Difference for nintedanib vs non-antifibrotic treatment	Unit
Company base case model	[redacted] years	LYs gained
Company alternative model (Bayesian gamma for BSC, Bayesian Weibull for NDB)	[redacted] years	LYs gained
Company alternative model (Bayesian loglogistic for BSC, Bayesian Weibull for NDB)	[redacted] years	LYs gained
Company alternative model (frequentist lognormal for BSC, frequentist exponential for NDB)	[redacted] years	LYs gained
EMPIRE registry	2.91 years (p<0.001)	Median survival
European IPF registry	4.6 years (p=0.001)	Median survival

BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; LYs, life years; NDB, nintedanib

Table 6: Summary of alternative scenarios for survival analysis

BSC		NDB		ICER
Model selected	**Data source used to validate**	**Model selected**	**Data source used to validate**	
Bayesian gamma	Australian registry (no treatment)	Bayesian Weibull	Long-term IPF trial data (company base case)	<£25,000 [redacted])
Bayesian loglogistic	Australian registry (no treatment)	Bayesian Weibull	Long-term IPF trial data (company base case)	<£25,000 [redacted])
Bayesian gamma	Australian registry (no treatment)	Frequentist lognormal	Australian registry (AF treatment)	<£20,000 [redacted])
Bayesian loglogistic	Australian registry (no treatment)	Frequentist lognomal	Australian registry (AF treatment)	<£20,000 [redacted])
Frequentist lognormal	European IPF registry (non-AF treatment)	Frequentist exponential	European IPF registry (AF treatment)	<£25,000 [redacted])

AF, antifibrotic; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib

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Appendix 2: Consensus statement from 21 Clinical Leads of the 24 ILD specialist centres in England and Wales and 3 leading rheumatologists who treat PF-ILD patients

(please see list of clinicians below)

Immunosuppression is not used to treat fibrotic lung disease

The patient population with chronic fibrosing interstitial lung diseases with a progressive phenotype (PF-ILD) often have a wide range of underlying clinical conditions that have led to their ILD. These extra extrapulmonary manifestations such as arthritis, glomerulonephritis, pericarditis and dermatological manifestations may require treatment with corticosteroids and / or immunosuppressants, but these are not to treat the ILD, and they do not have any meaningful impact on the ILD. By definition, patients with PF-ILD have progressed despite treatment of the extrapulmonary manifestations with conventional therapies, including immunosuppressants and other restricted therapies.

The restriction of immunosuppression in the INBUILD study represents clinical practice

The INBUILD trial design allowed the introduction of restricted medications after 6 months. As stated in the BTS ILD expert committee NICE submission, the consensus from all of the ILD UK-based 23 clinical leads who manage patients with a confirmed diagnosis of PF-ILD in 23 tertiary ILD specialist centres advised that 'immunosuppressants are not given to treat the fibrotic component of an ILD, but the inflammatory component of the disease'. It is common clinical practice that when patients with predominantly fibrotic ILD present with lung function decline despite immunosuppression, clinical consideration would be to reduce or completely stop immunosuppressants due to a lack of efficacy. There are also significant safety concerns around the use of multiple immunosuppressants as evidenced in the IPF-focused PANTHER trial which clearly demonstrated an increased risk of mortality & hospitalisation in these patients.

The ILD clinical community are concerned about using non evidence-based immunosuppressants that lack efficacy in PF-ILD patients who phenotypically behave like IPF and have similar radiological features.

This is reflected in the very low levels of use of restricted immunosuppressants after 6 months in the INBUILD trial once these were allowed. Please see the table below.

Restricted therapies initiated between first and last trial drug intake over 52 weeks.

Restricted drugs	Patients who received restricted drugs >6 months n (%)	
	Nintedanib Group (n=206)	Placebo Group (n=206)
Azathioprine	1 (0.3%)	5 (1.5%)
Cyclophosphamide	0 (0%)	2 (0.6%)
Mycophenolate Mofetil	3 (0.9%)	7 (2.1%)
Tacrolimus	3 (0.9%)	3(0.9%)
High dose corticosteroids	33 (9.9%)	57 (17.2%)
Infliximab	0 (0%)	0 (0%)
Rituximab	2 (0.6%)	2 (0.6%)

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The low use of restricted immunosuppressants once allowed (>6 months) in the placebo and nintedanib arms of the INBUILD trial further reflects the lack of evidence base for these therapies, thus supporting the clinical expert consensus that immunosuppressants are not a relevant comparator for progressive fibrotic ILD. The use of immunosuppression likely represents treatment of extrapulmonary manifestations of disease which may be responsive to this modality (such as arthritis).
In addition, a high proportion of patients (68.6% overall) in the INBUILD trial received systemic corticosteroids (<20 mg per day) at baseline or during the 52-week trial period (placebo, 70.1% vs nintedanib, 67.2%) and 39.8% had non-steroid anti-inflammatory agents at baseline). Please see table below.

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All baseline and on-treatment concomitant therapies over 52 weeks

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Overall population

ATC3 category	Placebo		Nintedanib 150 mg bid		Total	
	N	%	N	%	N	%
Number of patients	331	100.0	332	100.0	663	100.0
Number of patients with at least 1 therapy	327	98.8	328	98.8	655	98.8
Adrenergics for systemic use	69	20.8	51	15.4	120	18.1
Adrenergics, inhalants	102	30.8	80	24.1	182	27.5
Agents for treatment of hemorrhoids and anal fissures for topical use	132	39.9	139	41.9	271	40.9
All other therapeutic products	103	31.1	89	26.8	192	29.0
Angiotensin II receptor blockers (ARBS), plain	60	18.1	72	21.7	132	19.9
Anti-acne preparations for topical use	92	27.8	78	23.5	170	25.6
Antihistamines for systemic use	73	22.1	60	18.1	133	20.1
Antiinfectives	113	34.1	105	31.6	218	32.9
Antiinflammatory agents	232	70.1	233	70.2	465	70.1
Antiinflammatory and antirheumatic products, non-steroids	126	38.1	138	41.6	264	39.8
Antipropulsives	35	10.6	138	41.6	173	26.1
Antithrombotic agents	107	32.3	107	32.2	214	32.3
Anxiolytics	69	20.8	61	18.4	130	19.6
Blood glucose lowering drugs, excl. insulins	59	17.8	67	20.2	126	19.0
Calcium	76	23.0	72	21.7	148	22.3
Corticosteroids	90	27.2	99	29.8	189	28.5
Corticosteroids for systemic use, plain	232	70.1	223	67.2	455	68.6
Corticosteroids, plain	170	51.4	158	47.6	328	49.5
Cough suppressants, excl. combinations with expectorants	69	20.8	69	20.8	138	20.8
Decongestants and other nasal preparations for topical use	179	54.1	175	52.7	354	53.4
Drugs for constipation	69	20.8	61	18.4	130	19.6
Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	200	60.4	238	71.7	438	66.1

Table continues on next page

The placebo arm in the INBUILD trial therefore reflects current standard treatment for the PF-ILD as well as underlying conditions.

From a clinical perspective, there are no treatments that are licensed for use, or really being consistently used in clinical practice for the management of UK patients with PF-ILD and therefore the placebo arm of the INBUILD trial is a true representation of UK clinical practice.
Until the recent marketing authorisation approval of nintedanib for PF-ILD, there were no evidence-based licensed treatments for patients with PF-ILD other than IPF. Nintedanib is the first pharmacological treatment to show clinical evidence of slowing disease progression in patients with PF-ILD, through the dedicated INBUILD trial, with demonstrable statistical significance for the primary endpoint in the overall patient population. This treatment effect was seen across all patients, regardless of the underlying ILD diagnosis.
The INBUILD trial clearly demonstrated that individuals with PF-ILD have a similar clinical disease course to that of patients with idiopathic pulmonary fibrosis (IPF), where there is a wealth of long term clinical and real world evidence that unequivocally supports the benefits of nintedanib in achieving a consistent reduction in FVC decline. The beneficial effects on reduction in FVC decline are similar to PF-ILD as demonstrated by the INBUILD trial. As such, nintedanib represents a step-change in the treatment of patients with PF-ILD other than IPF, providing a much-needed treatment option for patients with no evidence based approved therapies for their PF-ILD.

Clinical experts agreeing to the consensus document

The 21 clinical experts from ILD specialist centres in England and Wales and 3 leading rheumatologists who treat PF-ILD patients who have agreed to the consensus document are listed in the tables below. This consensus was reached in short timelines over a period of time when a lot of clinicians were out of office or on holiday.

ILD Specialist Centre	ILD Clinical Lead
Royal Brompton and Harefield NHS Foundation Trust	Dr Peter George
Manchester University NHS Foundation Trust.	Dr Nazia Chaudhuri
University Hospitals Birmingham NHS Foundation Trust	Dr Anjali Crawshaw
Royal Devon and Exeter NHS Foundation Trust	Professor Michael Gibbons
North Bristol NHS Trust	Dr Huzaifa Adamali
Leeds Teaching Hospitals NHS Trust	Dr Paul Beirne
Guy's and St Thomas' NHS Foundation Trust	DR Alex West
Royal Papworth Hospital NHS Foundation Trust	Dr Christine Fiddler
Hull University Teaching Hospitals	Dr Simon Hart
University Hospital Southampton NHS Foundation	Professor Mark Jones

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Trust	Dr Katherine Spinks
University Hospitals of Morecambe Bay NHS Foundation Trust	Dr Timothy Gatheral
University College London Hospitals NHS Foundation Trust	Professor Joanna Porter
Oxford University Hospitals NHS Foundation Trust	Dr Rachel Hoyles
Portsmouth Hospitals University NHS Trust	Dr Suresh Babu
Newcastle Upon Tyne NHS Foundation Trust	Dr Ian Forrest
Norfolk and Norwich University Hospitals NHS Foundation Trust	Professor Andrew Wilson
University Hospitals of Leicester NHS Trust	Jane Scullion
University Hospitals of North Midlands NHS Trust	Dr Helen Stone
Nottingham University Hospitals NHS Trust	Dr Gauri Saini
Imperial College Healthcare NHS Trust	Dr Mel Wickremasinghe
Cardiff & Vale University Health Boards	Dr Ben Hope-Gill

Centre	**Clinical Expert Rheumatologist**
The Royal Free London NHS Foundation Trust	Professor Chris Denton
The Royal Free London NHS Foundation Trust	Dr Voon Ong
Manchester University NHS Foundation Trust.	Dr Rachel Gorodkin

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Appendix 3: ERG appendix

Figure 1.1: Placebo extrapolations compared to the European IPF registry for "no treatment" group and the Weibull Bayesian extrapolation for nintedanib

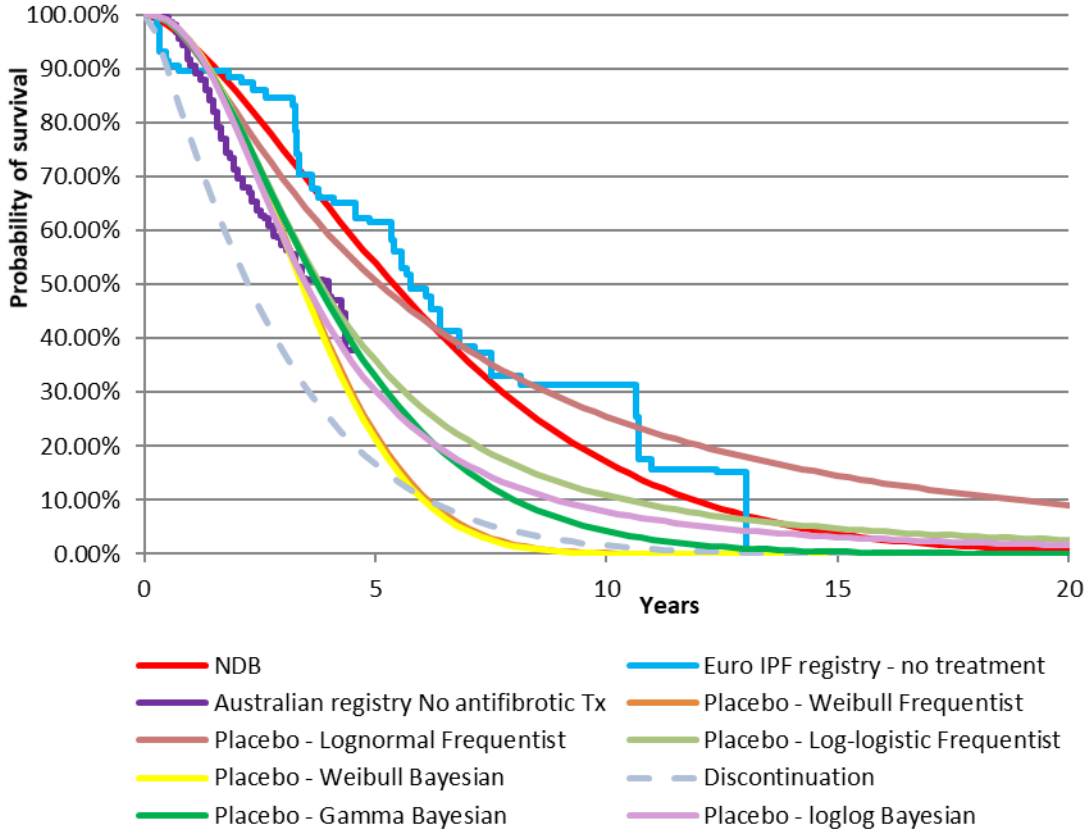

Table 0.1: Scenarios placebo extrapolation (compared to Weibull Bayesian for nintedanib)

Placebo OS	Nintedanib		BSC		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Lognormal frequentist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic frequentist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic Bayesian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma Bayesian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull Bayesian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull frequentist	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG preferred base case, applied in electronic model from the response to the clarification letter.
BC = base-case; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; OS = overall survival; QALYs = quality adjusted life years.

References

1. Boehringer Ingelheim. Data on file DOF NIN21-03. Analyses of time to absolute decline in FVC % predicted >=5% or >=10% over the whole trial.
2. Crestani B, Huggins JT, Kaye M, al. e. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. The Lancet Respiratory Medicine. 2019;7:60-8.
3. Antoniou K, Markopoulou K, Tzouvelekis A, Trachalaki A, Vasarmidi E, Organtzis J, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: a retrospective, observational, cohort study. ERJ Open Res. 2020;6(1):00172-2019.
4. Vasakova M, Sterclova M, M M, et al. Long-term overall survival and progression-free survival in idiopathic pulmonary fibrosis treated by pirfenidone or nintedanib or their switch. Real world data from the EMPIRE registry. European Respiratory Journal. 2019;54:PA4720.
5. Guenther A, Krauss E, Tello S, Wagner J, Paul B, Kuhn S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respir Res. 2018;19(1):141.
6. Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. Eur Respir J. 2017;49(2).
7. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respiratory Soc; 2012.
8. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011;184(12):1382-9.
9. Boehringer Ingelheim. Clinical Trial Report for the INBUILD trial (study 1199.247). 2019.
10. Brown KK, Martinez FJ, Walsh SLF, Thannickal VJ, Prasse A, Schlenker-Herceg R, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J. 2020.
11. 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. ePoster presented at the American Thoracic Society Conference, 14-19th May 2021.
12. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071-82.
13. Cottin V, Richeldi L, Rosas I, Otaola M, Song JW, Tomassetti S, et al. Nintedanib and immunomodulatory therapies in progressive fibrosing interstitial lung diseases. Respir Res. 2021;22(1):84.
14. Boehringer Ingelheim. Descriptive statistics and absolute change from baseline in FVC over the whole trial. Data on file DOF NIN21-02.
15. Flaherty KR, Wells AU, Cottin V, Devaraj A, Inoue Y, Richeldi L, et al. Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial. European Respiratory Journal. Article ahead of press.
16. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Medicine. 2016;14(1):18.
17. Cameli P, Refini RM, Bergantini L, d'Alessandro M, Alonzi V, Magnoni C, et al. Long-Term Follow-Up of Patients With Idiopathic Pulmonary Fibrosis Treated With Pirfenidone or Nintedanib: A Real-Life Comparison Study. Front Mol Biosci. 2020;7:581828.
18. National Institute for Health and Care Excellence. Nintedanib for treating idiopathic pulmonary fibrosis [TA379]. Manchester, UK; 2016.
19. Boehringer Ingelheim. Data on file DOF NIN21-04. Meta-analysis of mortality in nintedanib trials for IPF and PF-ILD. Data provided ahead of publication.
20. Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T. Impact of Antifibrotic Therapy on Mortality and Acute Exacerbation in Idiopathic Pulmonary Fibrosis: A Systematic Review and Meta-Analysis. Chest. 2021.
21. Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Respiratory Investigation. 2014;52(4):242-50.
22. Boehringer Ingelheim. Data on file DOF NIN21-05. Data taken from BI response to the European Medicines Agency (EMA), 18th February 2020. Document number ra01054982-01.
23. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. Orphanet journal of rare diseases. 2008;3:8.

24. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824.
25. du Bois RM. An earlier and more confident diagnosis of idiopathic pulmonary fibrosis. European Respiratory Review. 2012;21(124):141-6.