NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nintedanib for treating idiopathic pulmonary fibrosis [ID752]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Boehringer Ingelheim
     - PAS submission template
   - Action Pulmonary Fibrosis
   - British Thoracic Society
   - United Kingdom Clinical Pharmacy Association
   - Roche

   The Royal College of Physicians indicated that they supported the comments made by the British Thoracic Society. The Royal College of Nursing, Royal College of Pathologists and Department of Health informed us that they had no comments on this ACD.

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Evidence Review Group critique of the ACD response from Southampton Technology Assessments Centre**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Nintedanib for treating idiopathic pulmonary fibrosis

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
Action for Pulmonary Fibrosis	There is little evidence to restrict use of nintedanib to patients with an FVC between 50 and 80%, especially given the comment in para 3.3. Many patients with an FVC above 80% can have severe disease as assessed by Dlco. Patient data shows that between 35-40% of IPF patients have FVC>80% at presentation. Many of these have radiological and/or lung function data that confirms progressive disease. This is a limitation of measuring of FVC and it is unknown what is the person's "normal" FVC. Many people have normal FVC that is >100%.In addition INPULSIS data shows that the benefit of treatment (ie slowing decline in FVC) is equivalent in FVC>80% cohort compared to FVC 50-80% cohort. Patients who have taken part in patient access schemes for Nintedanib in the UK do have FVC <50% and FVC>80%.	The Committee understood the disadvantages with using percent predicted FVC, but heard that it is the most reliable and widely used measure of lung function in clinical practice (see FAD section 4.3). The Committee recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. Because pirfenidone is offered only to people with percent predicted FVC 50–80%, the Committee compared nintedanib with best supportive care for people with FVC above 80%. The Committee concluded that the ICERs for nintedanib as a replacement for best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost effective use of NHS resources, therefore could only recommend nintedanib in people with FVC of 50–80% (for whom nintedanib was cost effective compared with pirfenidone) (see FAD section 4.15).
Action for Pulmonary Fibrosis	Stopping criteria - suggest these are changed to reflect slowing of decline in FVC (from INPULSIS study Nintedanib slows decline in FVC ~50% compared to placebo over 1 year). This should be included in the treatment response. For instance a treatment that slows decline in FVC over 1 year from 30% to 15% should be considered effective.	Comments noted. The Committee understood that the stopping rule was determined during the pirfenidone appraisal. The Committee considered that this rule should also be applied to nintedanib because without it nintedanib would be more costly than pirfenidone for comparable benefits (see FAD section 4.14).
Boehringer	Boehringer Ingelheim is supportive of the exhaustive discussions carried out at the	Comments noted. The updated analyses were

Consultee	Comment [sic]	Response
Ingelheim	first Appraisal Committee Meeting regarding the potential FVC%predicted restriction and stopping rule. The general theme of the meeting suggested these restrictions would be unreasonable and unfair to patients, as well as being difficult to implement; this seemed to be accepted by the Committee during the Meeting. However, the conclusions drawn in the Appraisal Consultation Document (ACD) regarding restricted reimbursed population and stopping rule do not reflect the theme of the Meeting, and instead recommend both a restricted population and a stopping rule. Despite this, Boehringer Ingelheim has addressed the recommendations of the ACD, and as a result the following revised base case has been implemented in order to generate revised results: 1. NDB PAS discount. A PAS discount of [redacted] of the NDB daily price was applied: the discounted daily cost of NDB is [redacted]. All model results presented in the following sections used the NDB discounted cost. 2. Selection of NMA scenarios. Both the ERG and the NICE Committee seem to agree that Azuma et al. [2010] is a clear outlier and should be excluded from the pool of evidence for all analyses.	considered by the Committee (see FAD section 3.21 and 4.14).
Boehringer Ingelheim	An inconsistency was noted in the ACD reasoning regarding the NMA scenarios. In particular, in paragraph 4.6 it is mentioned that: *The Committee understood that the results of the network meta-analysis informed the relative effectiveness of nintedanib and pirfenidone in the company model. It heard that the company used the results of different sensitivity analyses (that is, using data from different sets of trials) for different outcomes in the model. The Committee agreed that this introduced a potential bias in favour of nintedanib because the analyses chosen by the company showed nintedanib more favourably than the results from analyses including all trials, and concluded that the same trials should be included for all outcomes.* It is a misconception that by using the all-evidence scenario for all outcomes the model would be using the same trials for all outcomes. Not all trials report evidence for all outcomes considered in the model. The approach was consistent in that for each outcome, the scenario with the lowest level of heterogeneity was used, but considered the widest possible range of data. If the same trials were to be used for all outcomes, as suggested by the Committee, there would be a reduction in the pool of studies to only: TOMORROW [Richeldi et al. 2011], INPULSIS [Richeldi et al. 2014] and CAPACITY [Noble et al. 2011]. It was assumed that the Committee's comment, to remove Azuma et al but keep all the other studies in is still the preferred approach for NICE. However, it should be	Comments noted. The FAD has been amended to reflect this (see FAD section 4.6) and the updated analyses were considered by the Committee (see FAD section 3.21, 4.6 and 4.14).

Consultee	Comment [sic]	Response
	clarified that it is not as described in the ACD as a selection of common trials for all outcomes. Therefore, the base-case selection of NMA scenarios was modified as follows: use scenario 1 (all evidence) or the scenario excluding Azuma 2005 where this study provides evidence for the outcome of interest. Specifically, the following were used: • OS: scenario 4 (excluding Azuma) • Acute exacerbations: scenario 5 (excluding Azuma) • Loss of lung function: scenario 1 (all evidence) - Azuma did not provide any data on progression. • Serious cardiac events: scenario 1 (all evidence) - Azuma did not provide any data on SAEs. • Serious GI events: scenario 1 (all evidence) – Azuma did not provide any data on SAEs. • Overall discontinuation: scenario 1 (all evidence) - Azuma did not provide any data on overall discontinuation. For all scenarios the fixed effects model was used – as discussed and accepted during the ACM.	
Boehringer Ingelheim	**Relaxing the conservative assumption on exacerbation.** A higher risk of death for patients who have experienced an exacerbation was applied (they only contribute by ~1% to the OS curves). A mortality hazard rate of 2.79% over 6 months was identified [Kondoh et al. 2010] for patients with exacerbations. This step reduces the ICER vs. BSC by about £2,000/QALY gained. Note, 2.79% is still a very conservative estimate as clinical opinion at the Committee Meeting suggested mortality is much higher.	Comments noted. The updated analyses were considered by the Committee (see FAD section 3.21 and 4.14).
Boehringer Ingelheim	Minor changes: • Correction of the EoL cost inflation. No impact on the model results. • Correction of the exacerbation-related disutility implemented in the model. No impact on the results. • Correction of the AE-disutility duration (1 year transformed to 1 month). No considerable impact on the results as AE disutilities are not a driver of the model. The following results were generated given the new model changes: • Base-case deterministic results for NDB vs. BSC and NDB vs. PFN (with all	Comments noted.

Consultee	Comment [sic]	Response
	levels of PFN discount). • One-way sensitivity analysis scenarios re-run with the proposed changes. • Full incremental analysis results. The revised results are presented Patient Access Scheme template. The remainder of this document aims to explain why the restrictions on the population for which nintedanib is recommended in the ACD should not be in place. Boehringer Ingelheim believes that nintedanib should be made available to all adults with IPF.	
Boehringer Ingelheim	**1. Although confirmed by the Committee as the best way to monitor decline in lung function over time (4.3 ACD), FVC%predicted is not a reliable way to distinguish between patients who should and should not receive treatment with Ofev.** NICE often restricts access for oncology treatments based on clinical markers. However, these markers tend to be clearer and more precise; eg. metastasis, size of the tumour etc. FVC%pred is subject to large intra and inter subject variability making it unsuitable as a measure for an initiation/stopping rule requiring a precise cut-off (from >80%FVCpred to 80%FVCpred) for treatment access. Patients who began their disease process with an FVC%pred at the upper end of the normal range (~120%), will have to endure a significant period of disease progression before they can be deemed suitable for reimbursed therapy, when compared to those whose disease occurs on a background of a low normal pre-morbid FVC (~80% predicted). Further to this, emphysema commonly co-exists with IPF, producing an elevated FVC in the face of significant pulmonary disease. Significant intra-subject variability gives rise to the risk of appropriate treatment being delayed or wrongly withheld due to performing slightly better (FVC%pred) on one day than the next. During that time those patients face increasing risks of progression and exacerbation that could have been otherwise mitigated (the existing ORs for progression and exacerbation are ~0.5 comparing to BSC). These conclusions were verified by the clinical expert on the Appraisal Committee and were unchallenged by the Committee.	The Committee understood the disadvantages with using percent predicted FVC, but heard that it is the most reliable and widely used measure of lung function in clinical practice (see FAD section 4.3). The Committee's remit, as defined by the NICE reference case, was to compare nintedanib with what is currently offered to patients in the NHS. Because pirfenidone is offered only to people with percent predicted FVC 50–80%, the Committee compared nintedanib with best supportive care for people with FVC above 80%. The Committee concluded that the ICERs for nintedanib as a replacement for best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost-effective use of NHS resources, therefore could only recommend nintedanib in people with FVC of 50–80% (for whom nintedanib was cost effective compared with pirfenidone). The Committee discussed the co-existence of emphysema, and understood that in people with both conditions percent predicted FVC can be less sensitive. The Committee recognised the limitations of FVC, but considered that in clinical practice the wider patient characteristics would be taken into account in interpreting percent predicted FVC (see FAD section 4.3).

Consultee	Comment [sic]	Response
Boehringer Ingelheim	**2. Patients >80%FVCpred have no other treatment** As mentioned in the ACD (section 4.10) people with >80%FVCpred represent a third of people with idiopathic pulmonary fibrosis. This group of patients currently have no reimbursed treatment options; Ofev is a clinically effective treatment which demonstrates no statistically significant differences between the clinical effectiveness of nintedanib in people with 50%-80%FVCpred compared with people who have >80%FVCpred (ACD section 3.3). **3. Nintedanib performs equally well in patients with >80%FVCpred and those with <80%FVCpred (Costabel et al. 2015).** As mentioned in the manufacturer submission and ACD (section 3.3) subgroup analyses showed that there were no statistically significant differences between the clinical effectiveness of nintedanib in people with 50%-80%FVCpred compared with people who have >80%FVCpred. Further, the placebo arms of these two subgroups showed similar rates of decline (-228 mL/year where the baseline FVC predicted was greater than 80% versus -220.5 ml/L where the FVC was equal to or less than 80% of that predicted). Disease progression is equally aggressive in those with an elevated baseline FVC predicted, and nintedanib's efficacy in slowing this progression is unaffected by the patient's baseline FVC predicted.	The Committee recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. The Committee concluded that the ICERs for nintedanib as a replacement for best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost effective use of NHS resources (see FAD section 4.15).
Boehringer Ingelheim	**4. Regarding the stopping rule suggested by the ACD: in section 4.3 of the ACD, it is stated that we can't know how a person's lung function would progress without treatment** A decline of >10%FVCpred in 12 months does not mean the treatment is not working. There is no reason to suggest that the same patient would not have progressed more had they not been receiving Ofev. There is also an increased likelihood that they would have suffered an exacerbation. These conclusions were verified by the clinical expert on the Appraisal Committee and were unchallenged by the Committee.	The Committee noted comments from consultation that there was no clinical basis for applying a stopping rule for nintedanib. However, the Committee was mindful of its consideration that the clinical effectiveness of nintedanib is similar to pirfenidone and was aware that not including a stopping rule for nintedanib would make it more costly than pirfenidone for comparable benefits. The Committee was not prepared to accept the additional costs associated with recommending nintedanib without a stopping rule (see FAD section 4.14).
Boehringer Ingelheim	**5. Emergent long term data** Subsequent to the finalisation of the original manufacturer's submission, further data for the open label roll over trial INPULSIS-ON has been published. INPULSIS-ON offered patients enrolled into the phase III INPULSIS trials to either continue or initiate nintedanib therapy in an open label fashion. The data relate to a mean (SD; min–max) total duration of exposure for patients treated with nintedanib in both	Comments noted.

Consultee	Comment [sic]	Response
	INPULSIS® and INPULSIS®-ON of 29.2 (6.6; 11.9–40.6) months. The decline in FVC in patients continuing or initiating nintedanib in INPULSIS®-ON was similar to the decline in FVC with nintedanib in INPULSIS®. This suggests that the treatment effect of nintedanib on slowing disease progression persists for 2 years. Long-term nintedanib treatment (up to 40 months) had a manageable safety and tolerability profile, with no new safety signals identified.	
British Thoracic Society	Thank you for the opportunity to respond to the appraisal committee's request for 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?*** We believe that the interpretation of the evidence has major flaws and we have the following comments: **Current practice** The committee acknowledge that median survival is 3-4 years and that around 1/3 of patients have an FVC of greater than 80%. Indeed in the INPULSIS trials the median FVC was approximately 80%. The committee state that patients with an FVC >80% are treated by best supportive care. In practice these patients need little clinical input other than education, psychological support and monitoring for deterioration. They wait for their condition to deteriorate. We see this as unethical, and regardless of the modeling, cannot justify waiting until the condition deteriorates before starting therapy. This is particularly pertinent in the face of robust clinical trial data that demonstrates that patients with an FVC >80% respond to nintedanib in the same manner as patients with an FVC <80%. Furthermore to ignore this data is to ignore half of the patients in the trials. The committee itself acknowledges this (clinical effectiveness, para 3.3 and para 4.5). There are extra costs associated with deterioration in patients with IPF and we would advocate treating early (when all that is required is drug therapy) rather than initiating therapy when patients need *increased* clinical care. The comparison with pirfenidone (which is expensive compared with best supportive care) does not seem logical. We urge NICE to re-appraise the recommendations so that patients with IPF are able to receive appropriate and effective treatment. **The technology**	The Committee recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. Because pirfenidone is offered only to people with percent predicted FVC 50–80%, the Committee compared nintedanib with best supportive care for people with FVC above 80%. The Committee concluded that the ICERs for nintedanib as a replacement for best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost effective use of NHS resources, therefore could only recommend nintedanib in people with FVC of 50–80% (for whom nintedanib was cost effective compared with pirfenidone) (see FAD section 4.14 and 4.15).

Consultee	Comment [sic]	Response
	We agree with all of these points. **Evidence for clinical effectiveness** We note the committee acknowledges that "there are no subgroups for which there is evidence of differential effectiveness".	
British Thoracic Society	**Evidence for cost effectiveness** The committee states that it is appropriate not to include people in the model with an FVC greater than 50%. Neither the company nor the ERG provided a model for patients with an FVC >80%. It is not clear to us why this was not requested. It is stated that nintedanib is cost effective when compared with pirfenidone, but not when compared with best supportive care. This does not seem logical nor clinically relevant.	The Committee would have preferred to see a model of only people with a percent predicted FVC of more than 80%, which the ERG provided following consultation on the appraisal consultation document. However, the ERG was concerned that this subgroup analysis (and its analysis in people with percent predicted FVC 50–79.9%) was subject to limitations because it did not include subgroup-specific estimates for parameters such as hazard ratios, mortality rates, and rates of discontinuing treatment. The Committee concluded that the company model (including patients with percent predicted FVC of 50% or above) was appropriate for its decision-making (see FAD section 4.8).
British Thoracic Society	The appraisal committee has also kindly asked for comments on the following: Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We would like to state that we do not believe that the recommendations are either sound or suitable. We strongly reject the FVC stopping rule. This is not based on clinical evidence.	Stopping rules in general improve cost effectiveness by minimising continued treatment in people for whom a drug is not effective. The Committee noted comments from consultation that there was no clinical basis for applying a stopping rule for nintedanib, and understood that the 10% value derived from expert advice about discontinuing treatment in clinical practice, during the evaluation of pirfenidone (technology appraisal guidance 282). However, the Committee was mindful of its consideration that the clinical effectiveness of nintedanib is similar to pirfenidone and was aware that not including a stopping rule for nintedanib would make it more costly for comparable benefits. The Committee was not prepared to accept the additional costs associated with recommending nintedanib without a stopping rule (see FAD section 4.14).

Consultee	Comment [sic]	Response
UK Clinical Pharmacy Association (UKCPA) Respiratory Group	We are concerned that the TA includes an upper limit FVC of 80% predicted. As noted in the TA document about a third of patients will have an FVC > 80% (4.10) and they will be significantly disadvantaged by the inclusion of this limitation, either being unable to access an evidence based disease modifying therapy, or expected to accrue additional, and irreversible, disability before they are able to access therapy. As discussed in our original submission, and those from other groups, a proportion of patients will have a relatively preserved FVC throughout the course of the condition and would develop moderate or severe disease, as defined by DLco and/or degree of functional disability, whilst maintaining an FVC > 80%.	The Committee discussed comments from consultation that people with percent predicted FVC over 80% may have had a substantial decline in lung function and may have 'severe' disease as defined by other criteria. The Committee recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. Because pirfenidone is offered only to people with percent predicted FVC 50–80%, the Committee compared nintedanib with best supportive care for people with FVC above 80%. The Committee concluded that the ICERs for nintedanib as a replacement for best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost effective use of NHS resources, therefore could only recommend nintedanib in people with FVC of 50–80% (for whom nintedanib was cost effective compared with pirfenidone) (see FAD section 4.14 and 4.15).
UK Clinical Pharmacy Association (UKCPA) Respiratory Group	With specific regard to the content of the TA evidence of efficacy in the group with an FVC > 80% is acknowledged by NICE (4.5), as is the fact that this group represents about 45% of patients in the manufacturer's model (3.19). Unfortunately, and for unclear reasons, this group was not included in the ERG model (4.10). The economic model appears to assume pirfendione as the standard of care only in patients with an FVC of 50 - 80% predicted and therefore assumes that use in patients with an FVC > 80% would not be cost effective compared to best supportive care. This position does not appear to have been applied to patients who have discontinued pirfenidone due to intolerance and for whom best supportive care would be the current treatment option, this group representing about 30% of patients trialling pirfendione (4.4).	The Committee acknowledged that clinical trials included people with FVC over 80% and recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC. However, it was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. The Committee would have preferred to see a model of only people with a percent predicted FVC of more than 80%, which the ERG provided following consultation on the appraisal consultation document. However, the ERG was concerned that this subgroup analysis (and its analysis in people with percent predicted FVC 50–79.9%) was subject to limitations because it did not include

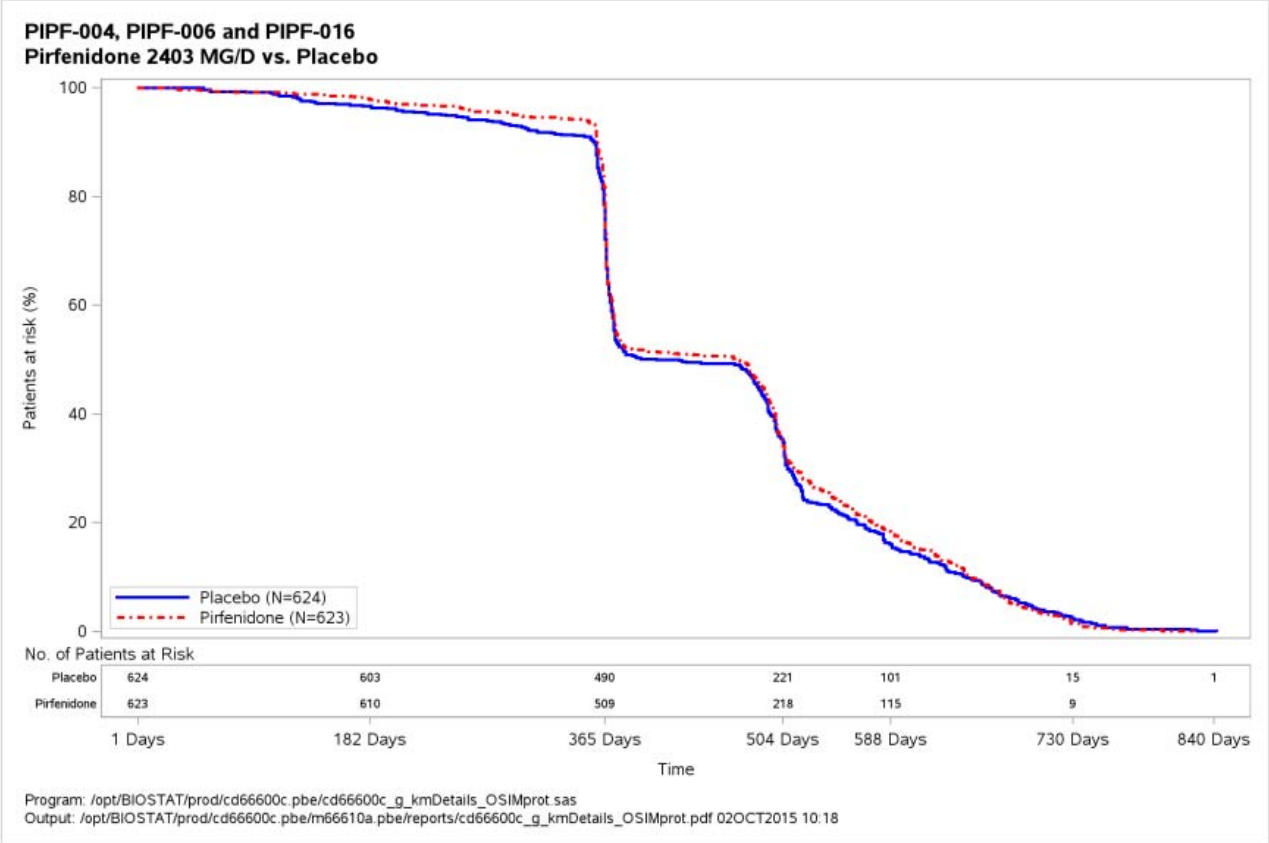
Consultee	Comment [sic]	Response
		subgroup-specific estimates for parameters such as hazard ratios, mortality rates, and rates of discontinuing treatment. The Committee concluded that the company model (including patients with percent predicted FVC of 50% or above) was appropriate for its decision-making (see FAD section 4.8). The Committee did not see cost-effectiveness evidence specific to people who have discontinued pirfenidone due to intolerance and for whom best supportive care would be the treatment option.
UK Clinical Pharmacy Association (UKCPA) Respiratory Group	It is also important to note that due to the availability of patient access schemes over the last 4 years patients with an FVC > 80% managed by centres treating IPF have had access to either pirfendione or nintedanib under a number of patient access schemes - i.e. the contemporary management of patients with IPF and an FVC > 80% has included disease modifying therapies in addition to best supportive care. The statement in the TA that *'patients already on nintedanib to continue on treatment until they and their clinician consider it appropriate to stop'* (1.3) exacerbating an inequitable scenario by allowing patients initiated under these schemes with an FVC > 80% to continue on treatment while barring access to those diagnosed with IPF after this.	Comments noted. NICE guidance is prospective. NICE recognise that people may have access to treatments before the marketing authorisation is granted or before NICE guidance is issued. NICE technology appraisals make allowances for people who have accessed new treatments before its formal guidance is released.
UK Clinical Pharmacy Association (UKCPA) Respiratory Group	We are also concerned about the introduction of a stopping rule for patients with an FVC decline > 10% over 1 year. This appears to have been included because of its inclusion in the pirfendione TA (4.15) but without any reference to an evidence base supporting this as evidence of a lack of efficacy.	Stopping rules in general improve cost effectiveness by minimising continued treatment in people for whom a drug is not effective. The Committee noted comments from consultation that there was no clinical basis for applying a stopping rule for nintedanib, and understood that the 10% value derived from expert advice about discontinuing treatment in clinical practice, during the evaluation of pirfenidone (technology appraisal guidance 282). However, the Committee was mindful of its consideration that the clinical effectiveness of nintedanib is similar to pirfenidone and was aware that not including a stopping rule for nintedanib would make it more costly for comparable benefits. The Committee was not

Consultee	Comment [sic]	Response
		prepared to accept the additional costs associated with recommending nintedanib without a stopping rule (see FAD section 4.14).

Comments received from commentators

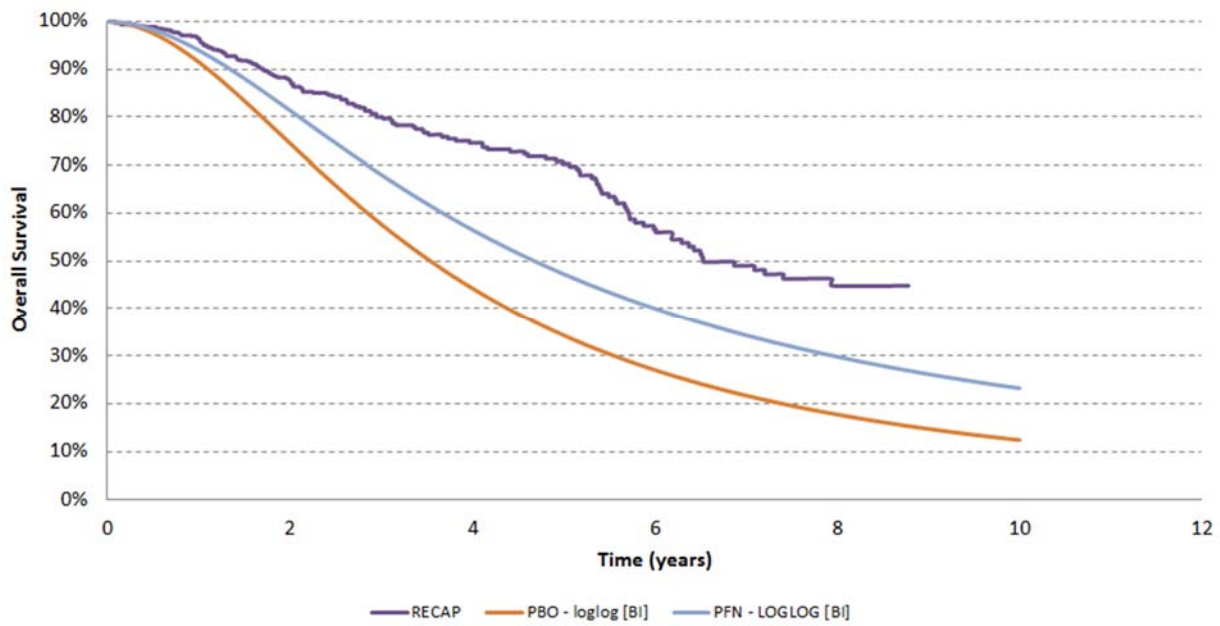
Commentator	Comment [sic]	Response
Roche	Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of nintedanib (Ofev®) in the treatment of idiopathic pulmonary fibrosis (IPF). We believe it is important patients have an alternative treatment to pirfenidone (Esbriet®). We are, however, concerned with a several aspects of the evidence submitted and assessed through the appraisal process to date. Specifically, we believe a more robust assessment of the impact of the available treatment options on overall survival, and the relative differences between treatments with regard to this endpoint, is warranted, We also remain concerned that the Committee has failed to recognise the importance of treating patients with mild IPF (FVC>80%). Idiopathic pulmonary fibrosis is a chronic, progressive, and fatal lung disease that is characterised by irreversible loss of lung function. Early treatment to delay progression should, therefore, be an important goal for the management of the condition. We note that clinical opinion strongly advocates for earlier access to treatments, but this is not reflected in the prevailing guidance from NICE, which is ultimately at the determinant of patients. The following appendix provides further detail on our concerns with the evidence supporting the ACD and suggested approaches to allow the Committee to make a more considered recommendation.	Comments noted, detailed responses are provided for each individual comment below. Regarding the importance of treating people with percent predicted FVC over 80%, the Committee recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS.
Roche	**<u>Conclusion that nintedanib may be more clinically effective than pirfenidone is not supported by the available evidence</u>** The ACD states *"the clinical effectiveness of nintedanib is similar to, if not slightly better than, pirfenidone based on the results of the network meta-analysis"* (ACD, p30). We do not consider this to be an accurate reflection of the available evidence for the following reasons: 1. Pirfenidone is the only treatment for IPF with phase III randomised clinical data demonstrating a significant survival benefit [Esbriet SmPC, Ofev SmPC, ASCEND 20141] 2. The network meta-analysis developed for the appraisal has used different time-points in comparing overall survival. The impact of this mismatch biases the analysis in favour of nintedanib, and	The Committee reviewed the clinical evidence and results of the network meta-analysis. The conclusion that nintedanib may be more clinically effective than pirfenidone has been removed from the FAD - see FAD sections

Commentator	Comment [sic]	Response
	explains the non-significant finding for pirfenidone vs. placebo, which is in contrast to the analysis by the EMA [Esbriet SmPC] 3. The manufacturer has not systematically selected studies to assess the acute exacerbations outcome, or provided a clear rationale for the exclusion of some studies, as noted by the ERG (ACD; 3.8, see Table 1). When all data are included, the point estimates for the rate of acute exacerbations are very similar between nintedanib and pirfenidone. The manufacturer's analysis is therefore biased in favour of nintedanib (see Table 2). 4. The 6MWD is a valid and responsive clinical endpoint, which provides objective and clinically meaningful information on the functional status of a patient with IPF [Nathan et al, 20152]. Similar to FVC, 6MWD is an independent predictor of mortality, but is not fully collinear to FVC [Puxeddu et al, 20153& Nathan SD et al 20152]. We do not believe the Committee has recognised the importance of the pirfenidone data which shows a significant improvement in 6MWD. 5. NICE state that benefits of nintedanib *"may not be fully reflected in the cost-effectiveness results"* (ACD, p32), due *to "its improved tolerability profile compared with pirfenidone".* There is no clear rationale why such benefits are not captured in the assessment. We believe this statement is misleading and unsupported by evidence. 6. There is no evidence – including that within the manufacturers submission – which supports the view that nintedanib has a benefit over pirfenidone in FVC. The FDA analysis of the cumulative distribution of patients by change in percent predicted FVC from baseline is consistent between the two treatments. In conclusion, there is no robust evidence or assessment which supports the claim of a beneficial effect of nintedanib over pirfenidone in any relevant clinical outcome. We, therefore, strongly disagree with the statement that the clinical effectiveness of nintedanib may be "slightly better than" pirfenidone, and request the Committee reconsider this view.	4.5 and 4.6.
Roche	**<u>Incorrect data used to estimate overall survival associated with pirfenidone</u>** The pooled overall survival analysis for pirfenidone was a pre-specified to occur at 52 weeks. In their analysis of overall survival, the manufacturer has compared pooled results from their clinical trial programme assessed at a 52 week time point with survival data from trials with pirfenidone taken at 120 weeks. The analysis for pirfenidone at this time point were exploratory in nature. This discrepancy in time point assessment heavily biases the results against pirfenidone, and leads to an incorrect overall survival ratio being used in the economic model. The pirfenidone analyses was pre-specified to be conducted at 52 weeks as all patients from the three studies contributing to the analysis were to be followed up until at least 52 weeks. As described in Figure 1 below, the number of patients at risk beyond weeks 52 and weeks 72 falls dramatically in the pooled analysis of pirfenidone: at 2 years (730 days) less than 5% of the initial population are still being followed up. As the 52 week analysis was pre-specified, and nintedanib has survival data at 52 weeks, a comparative	Comments noted. The data that cost effectiveness estimates were based on results of the company network meta-analysis, which used 72-week data for pirfenidone. The ERG stated that this had the potential to introduce bias in favour of nintedanib because the company used 52-week data for nintedanib, but considered

Commentator	Comment [sic]	Response
	analysis of overall survival should be based on this common time point. **Figure 1: Proportion of patients still at risk by days after randomisation**  	that a difference of 20 weeks might be too short to observe a difference in mortality and concluded that it was not a source of substantial uncertainty. The company's model assumed equal survival for nintedanib and pirfenidone.
Roche	**<u>Bias caused by selection of studies to inform the network meta-analysis</u>** As discussed during the Appraisal Committee meeting, and alluded to in the ACD (p28), there is concern with the selective choice of studies used in the manufacturers network meta-analysis (NMA): in particular, the use of different studies to inform the analyses for different outcomes. The ACD states that this inconsistent approach – which is summarised in Table 1 – *"potentially biased the results in favour of nintedanib",* and these inconsistencies do not seem to be sufficiently justified by the manufacturer. Despite the concerns expressed by members of the Committee during the meeting, as reported in the ACD,	Comments noted. Following consultation on the appraisal consultation document, the company updated its analysis in line with the Committee's preferred assumptions for the network meta-analysis

<table>
<tr><th>Commentator</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>the Determination concludes the NMA “generally provided an adequate basis for decision-making”, with the NMA also being used to conclude “the clinical effectiveness of nintedanib is similar to, <u>if not slightly better than</u>, pirfenidone based on the results of the network meta-analysis”. On the basis of the Committee discussions and acknowledged potential for bias, we are surprised that NICE would reach these conclusions without further analyses being performed.
Table 1: Inconsistent selection of studies across the outcomes of the NMA for the economic evaluation*
<table>
<tr><th>Studies</th><th>Timeponts (weeks)</th><th>Overall survival</th><th>Exacerbation rate</th><th>FVC % predicted 10% decline</th><th>PFS</th><th>6MWD</th></tr>
<tr><td>CAPACITY I & II</td><td>72</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>ASCEND</td><td>52</td><td>✓</td><td>n/a</td><td>✗</td><td>✗</td><td>✗</td></tr>
<tr><td>SP2</td><td>36</td><td>✓</td><td>✗</td><td>n/a</td><td>n/a</td><td>✗</td></tr>
<tr><td>SP3</td><td>52</td><td>✓</td><td>✗</td><td>n/a</td><td>✗</td><td>✗</td></tr>
<tr><td>PANTHER (NAC)</td><td>60</td><td>✓</td><td>✓</td><td>✓</td><td>✗</td><td>✓</td></tr>
<tr><td>INPULSIS I & II</td><td>52</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>n/a</td></tr>
<tr><td>TOMORROW</td><td>52</td><td>✓</td><td>✓</td><td>✓</td><td>✗</td><td>✓</td></tr>
<tr><td>HOMMA</td><td>48</td><td>✗</td><td>✓</td><td>✗</td><td>✗</td><td>✗</td></tr>
</table>
*There appears to be inconsistencies in the studies which the manufacturer lists as being part of the network (Table 38 MS Submission) with the actual inputs in the economic model base case.
n/a evidence not available</td><td>The Committee concluded that the updated network meta-analysis provided a more appropriate basis for its decision-making (see FAD sections 3.21, 4.6 and 4.14).</td></tr>
<tr><td>Roche</td><td><u>Approach used to assess exacerbations is biased against pirfenidone</u>
Selective use of clinical evidence from the network meta-analysis
Using all the available evidence for this outcome (including SP-25 and SP-36) has a significant impact on the point estimate for the exacerbation rate in the network meta-analysis. This can be seen in Table 2, which presents data assessed from the manufacturer’s submission and economic model. No clear reason is provided for this exclusion, and we are concerned that the reported outcome results in a bias in favour of nintedanib.
Table 2: Exacerbation rates for pirfenidone and nintedanib</td><td>Comments noted. The Committee concluded that SP2 was an outlier and the company excluded this study from the analysis of acute exacerbations in its updated network meta-analysis. It included SP3. The Committee</td></tr>
</table>

Commentator	Comment [sic]	Response
	<table><tr><td></td><td colspan="2">Exacerbation rate:</td></tr><tr><td></td><td colspan="2">Based on all trial evidence</td></tr><tr><td></td><td>NIN vs PBO</td><td>PFN vs PBO</td></tr><tr><td>Fixed effects</td><td>0.56</td><td>0.59</td></tr><tr><td>Random effects</td><td>0.47</td><td>0.37</td></tr><tr><td></td><td colspan="2">Manufacturer's economic model *</td></tr><tr><td></td><td>NIN vs PBO</td><td>PFN vs PBO</td></tr><tr><td>Fixed effects</td><td>0.56</td><td>1.01</td></tr><tr><td>Random effects</td><td>0.5</td><td>1</td></tr><tr><td colspan="3">* Excludes SP-2 and SP-3</td></tr></table> *Inappropriate use of different time-points to calculate an odds ratio for exacerbation* The manufacturer and ERG fail to make note of the methods for calculating the odds ratio for exacerbation risk in the network meta-analysis. From the documents available, it is apparent that the manufacturer calculates the overall rate of exacerbation through totalling all exacerbation events over 52 weeks, despite some of the studies included only reporting data to 36 weeks. This is a questionable approach, and raises concerns about the relative differences in rates in the model: particularly when such differences are used to come to the conclusion that *"nintedanib is likely to be more clinically effective than pirfenidone…at preventing acute exacerbations"* (ACD, p27-28). These concerns are compounded through the potential bias introduced through the inconsistent use of clinical trials in the assessment of different clinical outcomes, as described above.	concluded that the company's updated network meta-analysis provided a more appropriate basis for its decision-making (see FAD sections 3.21, 4.6 and 4.14). The conclusion that nintedanib may be more clinically effective than pirfenidone has been removed from the FAD - see FAD sections 4.5 and 4.6.
Roche	**<u>Approach used to extrapolate overall survival is not robust</u>** *Lack of face validity in the manufacturer's extrapolation of overall survival* The extrapolation for overall survival within the manufacturer's economic model poorly reflects the long term survival of IPF patients in the UK. Figure 2 presents the survival estimates for pirfenidone and placebo (extracted from the manufacturer's economic model), and compares this to the Kaplan Meier data from the RECAP study11 through overlaying the KM curve from this study. The RECAP study is the long term follow up of patients enrolled in the CAPACITY I & II4 trials. From Figure 2, it is clear that this important outcome of the model lacks face validity: the extrapolated pirfenidone estimate from the manufacturer's model [light blue] has diverged from the observed KM data by 1 year, with this gap growing over time: by year 3, the model under-predicts survival for patients initially receiving pirfenidone by over 10%. **Figure 2: Manufacturer's model poorly reflects the long term survival of IPF patients**	The ERG raised concerns about the company's extrapolation of overall survival and the company's literature review to validate the estimates, but was satisfied by responses provided during the clarification stage of the appraisal. The Committee agreed that the survival modelling was uncertain, but noted that it had little

Commentator	Comment [sic]	Response
	 *Systematic literature review for non-randomised studies* As part of the evidence submission, the manufacturer states an ad-hoc targeted literature review for non-randomised studies to validate long term survival estimates was performed. We are not confident that a systematic approach has been employed, and are concerned that evidence from the Kondoh et al12 publication – a study based on 74 Japanese patients – is not generalisable to the UK patient population. Furthermore, the low patient numbers in this study leads to concern as to whether this is an appropriate study to validate the long term survival of this chronic long term condition. *Pirfenidone and Nintedanib survival estimates – not tested in sensitivity analysis* Given the inherent uncertainty created through basing overall survival estimates on the Kondoh et al12 study, along with the importance of this outcome as the key driver of the economic model, we were surprised to note that no scenario analyses had been performed to investigate the impact of adjusting the relative difference between pirfenidone and nintedanib in this outcome. While analyses were run for the choice of parametric function, at no point did was the relative difference between pirfenidone and nintedanib tested in the analysis. Pirfenidone – unlike nintedanib – has demonstrated a statistically significant overall survival benefit when	effect on the ICER when comparing nintedanib with pirfenidone. The ICER for nintedanib compared with best supportive care was more sensitive to survival extrapolation and the Committee considered that the base case was probably an underestimate, but it was already above the range considered to be cost effective (see FAD section 4.9). The network meta-analysis indicated that company performed one-way sensitivity analyses around the 95% confidence intervals. The Committee concluded that the company model was appropriate for decision-making.

Commentator	Comment [sic]	Response
	compared to placebo. We, therefore, believe this is a key omission from the manufacturer's evidence submission and the ERG's assessment. Further analyses, extending past the point estimate and including confidence intervals, are warranted to reflect the range of uncertainty. We would also propose more exhaustive sensitivity analyses to ensure the Committee are best informed on the uncertainty associated with the point estimates presented by the manufacturer.	
Roche	**Choice of model structure** The manufacturer has chosen a model structure which they believes represents the natural history of the disease. While we agree that FVC is an important clinical outcome, we are concerned that the quantity and quality of the evidence which the manufacturer has identified does not meet the amount required through the use of this relatively complex approach. Specifically, with the increased number of health states, the manufacturer has had to make a number of assumptions to incorporate the transition probabilities between health states. In assessing the outputs of the model, there is little difference in both the incremental benefits and costs between the health states. It could therefore be suggested that the added complexity has increased the level uncertainty with limited benefit. We do not believe this has been properly addressed in the ERG's report.	Comments noted. The Committee concluded that the company model was appropriate for decision-making (see FAD section 4.8).
Roche	**Nintendanib is associated with a 'different' vs. 'improved' tolerability profile** The ACD states "*nintedanib may be considered innovative because the benefits of its improved tolerability profile compared with pirfenidone".* Whilst the two treatments clearly have different tolerability profiles, this statement does not seem to be fully reflect that fact that nintendanib exhibits some toxicities (atherothrombotic and gastrointestinal events, bleeding, etc.) which pirfenidone does not have. Indeed, the manufacturer's submission was criticised by the ERG and Committee for the exclusion of costs and disutility associated with diarrhoea in the economic model, given it led to treatment discontinuation in 4.4% vs. 0.23% of patients randomised to nintedanib and placebo, respectively (INPULSIS I & II8). The INPULSIS 1&2 clinical trials identified a higher incidence of myocardial infarction in patients treated with nintedanib vs. placebo (INPULSIS I & II8). We are not aware of any evidence of serious cardiac events in the pirfenidone trials (CAPACITY4 & ASCEND1). The patient population enrolled in the nintedanib trials also excluded many patients at risk of cardiac events, meaning the trial population may not be representative of those likely to receive the treatment in clinical practice. Pirfenidone is associated with a higher incidence of photosensitivity than nintedanib, although clinical and patient feedback is that – with appropriate education and support – this can be adequately managed.	Comments noted. In discussing innovation, the Committee considered whether nintedanib made a significant and substantial impact on health-related benefits. The Committee took into account comments from clinical and patient experts that people may tolerate nintedanib better than pirfenidone and also that the reduced dosing frequency with nintedanib was an advantage. The Committee acknowledged that nintedanib is associated with adverse events that are not commonly associated with pirfenidone, such as

Commentator	Comment [sic]	Response
		serious gastrointestinal events, but noted that the model included costs and disutilities for serious cardiac events, serious gastrointestinal events, photosensitivity and rash. The Committee acknowledged that diarrhoea is more common with nintedanib than pirfenidone and expressed some concern that the company did not include a disutility for diarrhoea, but concluded that the model was appropriate for decision-making. See FAD section 4.16.
Roche	**Other notable inaccuracies** We have identified a number of further inaccuracies/errors within the ACD and economic model. *ACD, 3.3* - We believe it should be made clear that this statement only applies to nintedanib's effect on FVC in this subpopulation, rather than a broader clinical effectiveness	Comments noted. Section 3.3 of the FAD has been updated accordingly.
Roche	*ACD, 3.5* - Regarding the final sentence of this paragraph (on discontinuation due to AE), it should be made clear that this difference is not statistically significant	Comments noted. Section 3.5 of the FAD has been updated accordingly.
Roche	*ACD, 4.1* - The clearly different clinical indications for pirfenidone and lung transplant should be made more explicit in this statement	Comments noted. Section 4.1 of the FAD has been updated accordingly. The Committee's discussion of treatment options is also presented in section 4.4 of the FAD.
Roche	*ACD, 4.4* - It is not clear why it is believed that RECAP underestimated the incidence of rash by 50%, and	The Committee heard from the clinical expert that

Commentator	Comment [sic]	Response
	request that this point is referenced	RECAP was an open-label extension of the CAPACITY trials of pirfenidone. It heard that half of the patients in the RECAP study had been taking pirfenidone for 72 weeks and would have already experienced rash, and it would have already resolved, or would not experience it at all; because rash occurs within the first 3 months of treatment or not at all. Therefore the clinical expert considered that RECAP underestimated the incidence of rash by 50%.
Roche	*Economic model* - The dosing of pirfenidone is not reflective of the clinical practice. The model appears to assume 9 pills in accordance with the label, but the clinical studies had an average of 7.88 pills per day. This reduces the total cost of treatment by 12%. The manufacturer has assumed a higher discontinuation rate for nintedanib than pirfenidone in accordance with the clinical trial data. However, due to their assumptions on overall survival, the model estimates that patients treated with nintedanib would live longer post therapy than those previously treated with pirfenidone. This is the driver for the incremental cost in the manufacturer's analysis. In the manufacturer's model, the rate of exacerbation is assumed to be higher in the pirfenidone arm than in the placebo arm. This does not reflect the clinical evidence for pirfenidone and lacks face validity.	Comments noted. The Committee discussed the limitations of the model, including the limitations of the network meta-analysis, and concluded that the model provided an appropriate basis for its decision-making
Roche	*Manufacturer's submission* - No clear rationale is presented in the manufacturer's submission why odds rations have been chosen in preference to hazard ratios. We are concerned that – as outcomes across studies report at various time points – the risk and uncertainty associated with this selection has not be adequately addressed.	Comments noted.
Roche	**References** 1. King TE, Bradford WZ, Castro-Bernardini S et al: The ASCEND study group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083-92.	Comments noted.

Commentator	Comment [sic]	Response
	2. Nathan SD, du Bois RM et al. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respir Med. 2015; 109(7):914-22 3. Puxeddu E, Pezzuto G, Pallante M et al. A six minute walking test (6MWT) derived index (O2-GAP) predicts mortality in IPF. Presentation to ERS Annual Congress; September 26–30, 2015; Amsterdam. Available at: http://www.ers-education.org/media/share.aspx?id=149463#sthash.hk92hSEc.dpuf 4. Noble PWA, Bradford C, Costabel WZ et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): Two randomised trials. The Lancet 2011;377(9779):1760-9. 5. Azuma A, Nukiwa T, Tsuboi E et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005; 171(9):1040-7 6. Taniguchi HE, Kondoh M, Ogura Y et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35(4):821-9 7. Martinez FJ, de Andrade JA, Anstrom KJ et al. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. New Engl J Med. 2014;370(22):2093-101 8. Richeldi LdB, Raghu RM, Azuma G et al. INPULSIS trial investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New Engl J Med. 2014;370(22):2071-82 9. Richeldi L, Costabel U, Selman M et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. New Engl J Med 2011;365(12):1079-87. 10. Homma SA, Taniguchi A, Ogura H et al. Efficacy of inhaled N-acetylcysteine monotherapy in patients with early stage idiopathic pulmonary fibrosis. Respirology 2012; 17(3):467-77 11. Fisher M, Maher T, Hill C, Marshall J. Disease-progression modeling in idiopathic pulmonary fibrosis: a prediction of time to disease progression and life expectancy with pirfenidone. Presentation to ATS International Conference; May 15–20, 2015; Denver, Colorado, USA. Available at: http://mapbiopharma.com/wp-content/uploads/2015/05/201505-HLR73269D_Fisher.pdf 12. Kondoh Y, Taniguchi H, Katsuta T et al. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. Sarcoidosis, vasculitis, and diffuse lung diseases: official journal of WASOG / World Association of Sarcoidosis and Other Granulomatous Disorders. 2010;27(2):103-10.	

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS Professional	1	Using the criteria of FVC 50-80% stratified as mild to moderate disadvantages up to 40% of patients who have significant fibrosis when one looks at other parameters such as DLCO and fibrosis score on HRCT. These patients do not have mild disease and the majority do not have emphysema. This is just normal population variation in lung function (abnormal value can be 75-140%. The clinical trials with nintedanib DID NOT exclude patients with FVC above 80%. The reduction in decline in FVC was seen in patients with FVC 50-80% and those with FVC above 80%. This is clearly documented in the NICE appraisal. Nintedanib offers a treatment option for patients that donot tolerate side effects with pirfenidone, but also the clinical trails recruit patients with ""milder"" disease and thus offers a treatment option for 40% of patients who's FVC is above 80%. It is not evidence based to restrict prescribing of nintedanib to those with FVC 50-80%. Seeing a 10% decline in FVC as a treatment failure is a figure plucked out of the air and there is now post hoc data to demonstrate that there are fewer patient with >10% decline on pirfenidone a NICE approved antifibrotic compared to placebo, demonstrating that antifibrotics slow disease progression despite how progressive the disease. IPF is very heterogenous and patients behave very differently in their disease course and discriminating those that deteriorate more rapidly as treatment failure is not guided by any evidence. The FVC criteria and discontinuation criteria is not evidence based and discriminates a significant proportion of patients who have a severe and devastating disease	The Committee understood the disadvantages with using percent predicted FVC, but heard that it is the most reliable and widely used measure of lung function in clinical practice (see FAD section 4.3). The Committee discussed comments from consultation that people with percent predicted FVC over 80% may have had a substantial decline in lung function and may have 'severe' disease as defined by other criteria (see FAD section 4.15). The Committee recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. Because pirfenidone is offered only to people with percent predicted FVC 50–80%, the Committee compared nintedanib with best supportive care for people with FVC above 80%. The Committee concluded that the ICERs for nintedanib as a replacement for best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost effective use of NHS resources, therefore could only recommend nintedanib in people with FVC of 50–80% (for whom nintedanib was cost effective compared with pirfenidone) (see FAD section 4.14 and 4.15). The Committee noted comments from consultation that there was no clinical basis for applying a stopping rule for nintedanib, and understood that the 10% value derived from expert advice about

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patient', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
			discontinuing treatment in clinical practice, during the evaluation of pirfenidone (technology appraisal guidance 282). However, the Committee was mindful of its consideration that the clinical effectiveness of nintedanib is similar to pirfenidone and was aware that not including a stopping rule for nintedanib would make it more costly than pirfenidone for comparable benefits. The Committee was not prepared to accept the additional costs associated with recommending nintedanib without a stopping rule (see FAD section 4.14).
Patient organisation	1	One of the biggest problems that patients face with the prescribing of drugs such as Pirfenidone is the fact that the drugs are not available outside the range of FVCs quoted. i.e. 50% to 80%. The argument many patients make is that if the drug is helpful why not prescribe it for all patients. Some patients are quite ill but still have an FVC of more than 80% and some patients are still very well even though their FVC is below 50%, With Idiopathic Pulmonary Fibrosis nobody knows what range can be called mild, moderate, or severe.	The Committee understood the disadvantages with using percent predicted FVC, but heard that it is the most reliable and widely used measure of lung function in clinical practice (see FAD section 4.3). The Committee discussed comments from consultation that people with percent predicted FVC over 80% may have had a substantial decline in lung function and may have 'severe' disease as defined by other criteria. The Committee recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. Because pirfenidone is offered only to people with percent predicted FVC 50–80%, the Committee compared nintedanib with best supportive care for people with FVC above 80%. The Committee concluded that the ICERs for nintedanib as a replacement for best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost effective use of NHS resources, therefore could only recommend nintedanib in people with FVC of 50–80% (for whom nintedanib was cost effective compared with

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			pirfenidone) (see FAD section 4.14 and 4.15).
NHS Professional	1	Response to NICE consultation Nintedanib for treating idiopathic pulmonary fibrosis We are pleased to review the appraisal consultation document Nintedanib for treating idiopathic pulmonary fibrosisâ (IPF) and welcome its recommendation of Nintedanib as an option for treating IPF. However, we are concerned by the upper forced vital capacity (FVC) threshold of 80% and feel that Nintedanib should be available to IPF patients with an FVC >50% with no upper threshold. The natural course of IPF is difficult to predict at diagnosis with no baseline measure able to accurately predict those at risk of disease progression. It is widely recognised that a decline in FVC of >10% over 6-12 months is associated with increased mortality and indeed this was confirmed in a large observational study by Schmidt et al. However, despite this clear association with mortality, FVC decline in 1 year was not necessarily associated with decline in subsequent years [1]. Given that the efficacy of Nintedanib relates to slowing the rate of FVC decline, delaying treatment until FVC decline has already occurred may reduce any potential mortality benefit. There is therefore an argument that early initiation of therapy may be fruitful [2]. Indeed, our local data from the North of England on the use of Nintedanib under the patient access scheme reveals that over 40% of patients currently receiving Nintedanib have an FVC >80% (n=75; S. Hart, N. Chaudhuri, unpublished data). These patients have been assessed as suitable for treatment by experienced ILD clinicians in specialist centres, but would be denied treatment under the proposed NICE recommendations. The cost effectiveness calculations presented in the consultation document are based on trying to model a disease that is both unpredictable and presently poorly understood. In our opinion, baseline FVC does not reliably reflect an individuals disease severity in clinical practice and therefore sole reliance on this measure is flawed. Furthermore, it appears counterintuitive to limit a therapy that is known to reduce disease progression to those with more advanced disease rather than intervening at a time when a lower symptom burden could be prolonged. This is particularly true as published data from the INPULSIS trials demonstrate similar reductions in disease progression in patients across the spectrum of FVC [3]. We recognise the need to rationalise the use of expensive medications, but to do so on the	The Committee understood the disadvantages with using percent predicted FVC, but heard that it is the most reliable and widely used measure of lung function in clinical practice (see FAD section 4.3). The Committee discussed comments from consultation that people with percent predicted FVC over 80% may have had a substantial decline in lung function and may have 'severe' disease as defined by other criteria. The Committee recognised that nintedanib is clinically effective regardless of the person's baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. Because pirfenidone is offered only to people with percent predicted FVC 50–80%, the Committee compared nintedanib with best supportive care for people with FVC above 80%. The Committee concluded that the ICERs for nintedanib as a replacement for best supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost effective use of NHS resources, therefore could only recommend nintedanib in people with FVC of 50–80% (for whom nintedanib was cost effective compared with pirfenidone) (see FAD section 4.14 and 4.15). The Committee noted comments from consultation that there was no clinical basis for applying a stopping rule for nintedanib, and understood that the 10% value derived from expert advice about discontinuing treatment in clinical practice, during the evaluation of pirfenidone (technology appraisal guidance 282). However, the Committee was mindful of its consideration that the clinical effectiveness of nintedanib is similar to pirfenidone and was aware that not including a stopping rule

Role*	Section	Comment [sic]	Response
		basis of statistical economic models of a disease that does not follow a predictable course with outcomes that are not predicted by baseline FVC appears unreasonable. References 1. Scmidt SL, Tayob N, Han MK, Zappala C, Kervitsky D, Murray S, Wells AU, Brown KK, Martinez FJ, Flaherty KR. Predicting pulmonary fibrosis disease course from past trends in pulmonary function. Chest. 20144;145(3):579-85 2. Crooks MG, Hart SP. A new era of drug therapy for idiopathic pulmonary fibrosis. Lancet Respir Med. 2014;2(12):964-6 3. Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, Azuma A. Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis Across Pre-specified Subgroups in INPULSIS. Am J Respir Crit Care Med. 2015 [Epub ahead of print].	for nintedanib would make it more costly for comparable benefits. The Committee was not prepared to accept the additional costs associated with recommending nintedanib without a stopping rule (see FAD section 4.14).
NHS Professional	1	We note with interest the provisional recommendation of this consultation document that nintedanib be approved by NICE for patients diagnosed with IPF with an FVC between 50-80%. It appears that this conclusion has been reached based upon cost calculations and interpretation of clinical trial data. Whilst the approval of nintedanib would provide a valuable treatment option for patients with IPF, as clinicians in this highly specialised area we are concerned that the application of an upper FVC limit for nintedanib prescription will significantly disadvantage the patients above this threshold who currently have no treatment option. Pirfenidone approval by NICE in 2013 represented a landmark moment for the care of patientâ€™s with IPF in the UK. Technology Appraisal 282 (Pirfenidone for treating idiopathic pulmonary fibrosis), which informed the approval, identified that there was no statistically significant difference between the pirfenidone and placebo group in patients with a baseline % predicted FVC of greater than 80%. In addition, it was stated that it was rare for patients with confirmed IPF to have an FVC greater than 80% predicted. Pirfenidone was therefore approved for patients with an FVC between 50 â€“ 80%.	The Committee heard from clinical experts that people with a percent predicted FVC of more than 80% represent around one third of people with idiopathic pulmonary fibrosis. It discussed comments from consultation that people with percent predicted FVC over 80% may have had a substantial decline in lung function and may have ‘severe’ disease as defined by other criteria. The Committee recognised that nintedanib is clinically effective regardless of the person’s baseline percent predicted FVC but was mindful that its recommendations are based on both clinical and cost effectiveness, compared with what is currently offered to patients in the NHS. Because pirfenidone is offered only to people with percent predicted FVC 50–80%, the Committee compared nintedanib with best supportive care for people with FVC above 80%. The Committee concluded that the ICERs for nintedanib as a replacement for best

Role*	Section	Comment [sic]	Response
		We do not believe that direct translation of this upper prescription threshold is approproriate for nintedanib, and that to do so would be entirely arbitrary. Firstly, in our clinical experience approximately one third of patients with IPF at diagnosis have an FVC greater than 80% predicted. Secondly, as the consultation document acknowledges, subgroup analyses identify no difference in clinical effectiveness of nintedanib when comparing patients with an FVC of 50 â€“ 80 % versus greater than 80%. IPF is a chronic, progressive, life-threatening disease. Patients with an FVC above 80% do not have mild disease, they have early disease. Just as those with cancer in the early stages, still have cancer. Any loss of lung function is irreversible. Given this, it makes little practical sense, having made an early diagnosis (with an FVC over 80%), to wait for the disease to advance (to an FVC below 80%) before offering treatment with clear evidence of efficacy. In particular, the commencement of early treatment would be anticipated to delay the onset of the significant symptom burden that patients with IPF bear. We therefore believe that no upper limit to the commencement of nintedanib is appropriate, and that to do so arbitrarily disadvantages a patient group with no current treatment option who would be anticipated to derive sustained long term benefit from nintedanib.	supportive care in people with a percent predicted FVC of more than 80% were not within the range considered to be a cost effective use of NHS resources, therefore could only recommend nintedanib in people with FVC of 50–80% (for whom nintedanib was cost effective compared with pirfenidone) (see FAD section 4.14 and 4.15).

Comments received from clinical experts and patient experts

None

Boehringer Ingelheim Limited's Response to Appraisal Consultation Document (ACD) for Nintedanib for the Treatment of Adults with Idiopathic Pulmonary Fibrosis

Boehringer Ingelheim is supportive of the exhaustive discussions carried out at the first Appraisal Committee Meeting regarding the potential FVC%predicted restriction and stopping rule. The general theme of the meeting suggested these restrictions would be unreasonable and unfair to patients, as well as being difficult to implement; this seemed to be accepted by the Committee during the Meeting. However, the conclusions drawn in the Appraisal Consultation Document (ACD) regarding restricted reimbursed population and stopping rule do not reflect the theme of the Meeting, and instead recommend both a restricted population and a stopping rule. Despite this, Boehringer Ingelheim has addressed the recommendations of the ACD, and as a result the following revised base case has been implemented in order to generate revised results:

1. **NDB PAS discount**. A PAS discount of [redacted] of the NDB daily price was applied: the discounted daily cost of NDB is [redacted]. All model results presented in the following sections used the NDB discounted cost.

2. **Selection of NMA scenarios**. Both the ERG and the NICE Committee seem to agree that Azuma et al. [2010] is a clear outlier and should be excluded from the pool of evidence for all analyses.

An inconsistency was noted in the ACD reasoning regarding the NMA scenarios. In particular, in paragraph 4.6 it is mentioned that:

> *The Committee understood that the results of the network meta-analysis informed the relative effectiveness of nintedanib and pirfenidone in the company model. It heard that the company used the results of different sensitivity analyses (that is, using data from different sets of trials) for different outcomes in the model. The Committee agreed that this introduced a potential bias in favour of nintedanib because the analyses chosen by the company showed nintedanib more favourably than the results from analyses including all trials, and concluded that the same trials should be included for all outcomes.*

It is a misconception that by using the all-evidence scenario for all outcomes the model would be using the same trials for all outcomes. Not all trials report evidence for all outcomes considered in the model. The approach was consistent in that for each outcome, the scenario with the lowest level of heterogeneity was used, but considered the widest possible range of data. If the same trials were to be used for all outcomes, as suggested by the Committee, there would be a reduction in the pool of studies to only: TOMORROW [Richeldi et al. 2011], INPULSIS [Richeldi et al. 2014] and CAPACITY [Noble et al. 2011].

It was assumed that the Committee's comment, to remove Azuma et al but keep all the other studies in is still the preferred approach for NICE. However, it should be clarified that it is not as described in the ACD as a selection of common trials for all outcomes.

Therefore, the base-case selection of NMA scenarios was modified as follows: use scenario 1 (all evidence) or the scenario excluding Azuma 2005 where this study provides evidence for the outcome of interest. Specifically, the following were used:

- OS: scenario 4 (excluding Azuma)
- Acute exacerbations: scenario 5 (excluding Azuma)
- Loss of lung function: scenario 1 (all evidence) - Azuma did not provide any data on progression.
- Serious cardiac events: scenario 1 (all evidence) - Azuma did not provide any data on SAEs.
- Serious GI events: scenario 1 (all evidence) – Azuma did not provide any data on SAEs.
- Overall discontinuation: scenario 1 (all evidence) - Azuma did not provide any data on overall discontinuation.

For all scenarios the fixed effects model was used – as discussed and accepted during the ACM.

- **Relaxing the conservative assumption on exacerbation**. A higher risk of death for patients who have experienced an exacerbation was applied (they only contribute by ~1% to the OS curves). A mortality hazard rate of 2.79% over 6 months was identified [Kondoh et al. 2010] for patients with exacerbations. This step reduces the ICER vs. BSC by about £2,000/QALY gained. Note, 2.79% is still a very conservative estimate as clinical opinion at the Committee Meeting suggested mortality is much higher.

3. **Minor changes**:

- Correction of the EoL cost inflation. No impact on the model results.
- Correction of the exacerbation-related disutility implemented in the model. No impact on the results.
- Correction of the AE-disutility duration (1 year transformed to 1 month). No considerable impact on the results as AE disutilities are not a driver of the model.

The following results were generated given the new model changes:

- Base-case deterministic results for NDB vs. BSC and NDB vs. PFN (with all levels of PFN discount).
- One-way sensitivity analysis scenarios re-run with the proposed changes.
- Full incremental analysis results.

The revised results are presented Patient Access Scheme template.

The remainder of this document aims to explain why the restrictions on the population for which nintedanib is recommended in the ACD should not be in place. Boehringer Ingelheim believes that nintedanib should be made available to all adults with IPF.

1. **Although confirmed by the Committee as the best way to monitor decline in lung function over time (4.3 ACD), FVC%predicted is not a reliable way to distinguish between patients who should and should not receive treatment with Ofev.**

NICE often restricts access for oncology treatments based on clinical markers. However, these markers tend to be clearer and more precise; eg. metastasis, size of the tumour etc. FVC%pred is subject to large intra and inter subject variability making it unsuitable as a measure for an initiation/stopping rule requiring a precise cut-off (from >80%FVCpred to 80%FVCpred) for treatment access. Patients who began their disease process with an FVC%pred at the upper end of the normal range (~120%), will have to endure a significant period of disease progression before they can be deemed suitable for reimbursed therapy, when compared to those whose disease occurs on a background of a low normal pre-morbid FVC (~80% predicted). Further to this, emphysema commonly co-exists with IPF, producing an elevated FVC in the face of significant pulmonary disease. Significant intra-subject variability gives rise to the risk of appropriate treatment being delayed or wrongly withheld due to performing slightly better (FVC%pred) on one day than the next. During that time those patients face increasing risks of progression and exacerbation that could have been otherwise mitigated (the existing ORs for progression and exacerbation are ~0.5 comparing to BSC). These conclusions were verified by the clinical expert on the Appraisal Committee and were unchallenged by the Committee.

2. **Patients >80%FVCpred have no other treatment**

As mentioned in the ACD (section 4.10) people with >80%FVCpred represent a third of people with idiopathic pulmonary fibrosis. This group of patients currently have no reimbursed treatment options; Ofev is a clinically effective treatment which demonstrates no statistically significant differences between the clinical effectiveness of nintedanib in people with 50%-80%FVCpred compared with people who have >80%FVCpred (ACD section 3.3).

3. **Nintedanib performs equally well in patients with >80%FVCpred and those with <80%FVCpred (Costabel et al. 2015).**

As mentioned in the manufacturer submission and ACD (section 3.3) subgroup analyses showed that there were no statistically significant differences between the clinical effectiveness of nintedanib in people with 50%-80%FVCpred compared with people who have >80%FVCpred. Further, the placebo arms of these two subgroups showed similar rates of decline (-228 mL/year where the baseline FVC predicted was greater than 80% versus -220.5 ml/L where the FVC was equal to or less than 80% of that predicted). Disease progression is equally aggressive in those with an elevated baseline FVC predicted, and nintedanib's efficacy in slowing this progression is unaffected by the patient's baseline FVC predicted.

4. Regarding the stopping rule suggested by the ACD: in section 4.3 of the ACD, it is stated that we can't know how a person's lung function would progress without treatment

A decline of >10%FVCpred in 12 months does not mean the treatment is not working. There is no reason to suggest that the same patient would not have progressed more had they not been receiving Ofev. There is also an increased likelihood that they would have suffered an exacerbation. These conclusions were verified by the clinical expert on the Appraisal Committee and were unchallenged by the Committee.

5. Emergent long term data

Subsequent to the finalisation of the original manufacturer's submission, further data for the open label roll over trial INPULSIS-ON has been published. INPULSIS-ON offered patients enrolled into the phase III INPULSIS trials to either continue or initiate nintedanib therapy in an open label fashion. The data relate to a mean (SD; min–max) total duration of exposure for patients treated with nintedanib in both INPULSIS® and INPULSIS®-ON of 29.2 (6.6; 11.9–40.6) months. The decline in FVC in patients continuing or initiating nintedanib in INPULSIS®-ON was similar to the decline in FVC with nintedanib in INPULSIS®. This suggests that the treatment effect of nintedanib on slowing disease progression persists for 2 years. Long-term nintedanib treatment (up to 40 months) had a manageable safety and tolerability profile, with no new safety signals identified.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Ofev (nintedanib) for the treatment of adult patients with Idiopathic Pulmonary Fibrosis (IPF). This patient access scheme also applies to nintedanib under the brand name of Vargatef; nintedanib in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

3.2 Please outline the rationale for developing the patient access scheme.

The patient access scheme has been developed in order to support the cost effectiveness case for Ofev.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The scheme is a commercial in confidence simple discount patient access scheme (PAS). A confidential discount will be applied to the list price of Ofev.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS for Ofev applies to the entire licensed population. This patient access scheme also applies to nintedanib under the brand name of Vargatef;

nintedanib in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme is not dependent on any criteria and the discounted price will be reflected on all original invoices for the product.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

100%

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

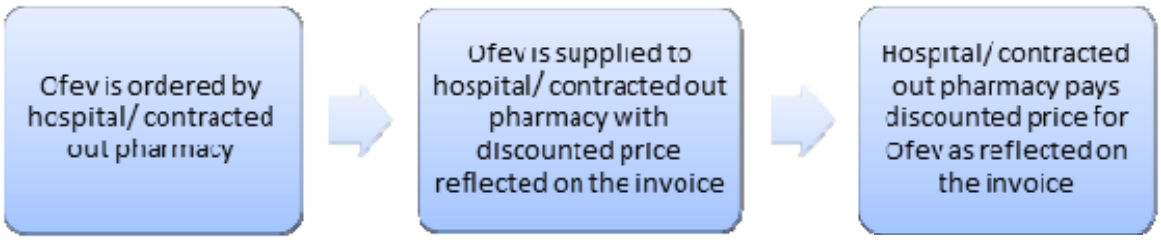
A fixed net price (which will not vary with any change to the UK list price) will apply to all packs of Ofev (nintedanib). The approved discounted price in the scheme will be the price paid by the NHS at the point of sale so there is no requirement for the calculation of rebates.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

NHS organisations will be required to sign a Confidential Disclosure Agreement to take part in the scheme. There are no associated administrative processes required with the scheme as stock for the product will be ordered in

the usual way and the approved discounted price will be paid at the point of sale by the NHS and will be reflected on all original invoices.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.



3.10 Please provide details of the duration of the scheme.

The scheme will remain in place until NICE next reviews the guidance on the product.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No issues have been identified by Boehringer Ingelheim Ltd in this regard.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

A Confidential Disclosure Agreement will need to be signed by NHS stakeholders before the discounted price can be shared.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

N/A

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Given the comments of the NICE Committee and the ERG [NICE ACD, September 2015], the following were modified in the cost-effectiveness model:

1. **NDB PAS discount**. A PAS discount of [redacted] of the NDB daily price was applied: the discounted daily cost of NDB is [redacted]. All model results presented in the following sections used the NDB discounted cost.
2. **Selection of NMA scenarios**. Both the ERG and the NICE Committee seem to agree that Azuma et al. [2010] is a clear outlier and should be excluded from the pool of evidence for all analyses.

An inconsistency was noted in the ACD reasoning regarding the NMA scenarios. In particular, in paragraph 4.6 it is mentioned that:

> *The Committee understood that the results of the network meta-analysis informed the relative effectiveness of nintedanib and pirfenidone in the company model. It heard that the company used the results of different sensitivity analyses (that is, using data from different sets of trials) for different outcomes in the model. The Committee agreed that this introduced a potential bias in favour of nintedanib because the analyses chosen by the*

company showed nintedanib more favourably than the results from analyses including all trials, and concluded that the same trials should be included for all outcomes.

It is a misconception that by using the all-evidence scenario for all outcomes the model would be using the same trials for all outcomes. Not all trials report evidence for all outcomes considered in the model. The approach was consistent in that for each outcome, the scenario with the lowest level of heterogeneity was used, but considered the widest possible range of data. If the same trials were to be used for all outcomes, as suggested by the Committee, there would be a reduction in the pool of studies to only 3: TOMORROW [Richeldi et al. 2011], INPULSIS [Richeldi et al. 2014] and CAPACITY [Noble et al. 2011].

It was assumed that the Committee's comment, to remove Azuma et al but keep all the other studies in, is still the preferred approach for NICE. However, it should be clarified that it is not as described in the ACD as a selection of common trials for all outcomes.

Therefore, the base-case selection of NMA scenarios was modified as follows: use scenario 1 (all evidence) or the scenario excluding Azuma 2005 where this study provides evidence for the outcome of interest. Specifically, the following were used:

- OS: scenario 4 (excluding Azuma)
- Acute exacerbations: scenario 5 (excluding Azuma)
- Loss of lung function: scenario 1 (all evidence) - Azuma did not provide any data on progression.
- Serious cardiac events: scenario 1 (all evidence) - Azuma did not provide any data on SAEs.
- Serious GI events: scenario 1 (all evidence) – Azuma did not provide any data on SAEs.
- Overall discontinuation: scenario 1 (all evidence) - Azuma did not provide any data on overall discontinuation.

For all scenarios the fixed effects model was used – as discussed and accepted during the ACM.

- **Relaxing the conservative assumption on exacerbation**. A higher risk of death for patients who have experienced an exacerbation was applied (they only contribute by ~1% to the OS curves). A mortality hazard rate of 2.79% over 6 months was identified [Kondoh et al. 2010]

for patients with exacerbations. Note, 2.79% is still a very conservative estimate as clinical opinion at the Committee Meeting suggested mortality is much higher.

3. **Minor changes**:

- Correction of the EoL cost inflation. No impact on the model results.
- Correction of the exacerbation-related disutility implemented in the model. No impact on the results.
- Correction of the AE-disutility duration (1 year transformed to 1 month). No considerable impact on the results as AE disutilities are not a driver of the model.

The following results were generated given the new model changes:

- Base-case deterministic results for NDB vs. BSC and NDB vs. PFN (with all levels of PFN discount).
- One-way sensitivity analysis scenarios re-run with the proposed changes.
- Full incremental analysis results.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the “Costs” tab, cell D8 allows the user to enter the discounted daily cost for nintedanib (NDB). As the patient access scheme is submitted at the same time as the main submission, there is no change made to the model at the time of preparing this document. The daily cost for nintedanib is changed to [redacted] in order to implement the PAS.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The patient access scheme does not change the clinical data; the clinical data is the same as in the main submission document.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

N/A

Table 1 Costs associated with the implementation and operation of the patient access scheme (PAS)

	Calculation of cost	Reference source
Stock management		
Administration of claim forms		
Staff training		
Other costs…		
…		
…		
Total implementation/ operation costs		

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

N/A

Table 2 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)

	Intervention without PAS		Intervention with PAS		Reference source
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Interventions					
Monitoring tests					
Diagnostic tests					
Appointments					
Other costs…					
…					
…					
Total treatment-related costs					

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

4.7.1. Base-case analysis results - without patient access scheme discount

Table 3 Base-case cost-effectiveness results (Nintedanib versus pirfenidone) - without PAS

	PFN	NDB	Incremental
Treatment costs	£59,121.16	£57,582.92	-£1,538.24
Adverse event costs	£1,002.64	£702.54	-£300.10
Liver panel tests	£9.06	£8.83	-£0.24
Patient monitoring and O_2 use	£10,026.61	£10,119.06	£92.45
Acute exacerbation costs	£1,486.63	£1,127.31	-£359.32
End of life costs	£8,828.27	£8,810.06	-£18.21
Total costs	**£80,474.37**	**£78,350.71**	**-£2,123.65**
Total QALYs	**3.4509**	**3.5013**	**0.0503**
LYs	4.5682	4.6026	0.0345
Exacerbation events	0.3596	0.2727	-0.0869
Net monetary benefit	£23,053.86	£26,687.68	
Cost-effectiveness	£23,319.54	£22,377.73	
ICER (per QALY)			**NDB dominates**
ICER (per LY)			NDB dominates
ICER (per exacerbation avoided)			NDB dominates

Table 4 Base-case cost-effectiveness results (nintedanib versus best supportive care) - without PAS

	BSC	NDB	Incremental
Treatment costs	£0.00	£57,582.92	£57,582.92
Adverse event costs	£589.13	£702.54	£113.40
Liver panel tests	£0.00	£8.83	£8.83
Patient monitoring and O2 use	£9,231.78	£10,119.06	£887.27
Acute exacerbation costs	£1,265.38	£1,127.31	-£138.07
End of life costs	£8,942.94	£8,810.06	-£132.87
Total costs	**£20,029.23**	**£78,350.71**	**£58,321.48**
Total QALYs	**3.0999**	**3.5013**	**0.4014**
LYs	4.1035	4.6026	0.4991
Exacerbation events	0.3061	0.2727	-0.0334
Net monetary benefit	£72,968.39	£26,687.68	
Cost-effectiveness	£6,461.21	£22,377.73	
ICER (per QALY)			**£145,309.98**
ICER (per LY)			£116,841.94
ICER (per exacerbation avoided)			£1,746,047.07

Table 5: Full incremental cost-effectiveness analysis for all comparators – without PAS

Treatment	Total costs	Total QALYs	ICER

BSC	£20,029.23	3.0999	
PFN	£80,474.37	3.4509	Dominated by NDB
NDB	£78,350.71	3.5013	£145,309.98 per QALY gained

4.7.2. Base-case analysis results - with patient access scheme discount

Table 6 Base-case cost-effectiveness results for nintedanib versus pirfenidone - with PAS

	PFN	NDB	Incremental
Treatment costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Liver panel tests	[redacted]	[redacted]	[redacted]
Patient monitoring and O_2 use	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	**3.4509**	**3.5013**	**0.0503**
LYs	4.5682	4.6026	0.0345
Exacerbation events	0.3596	0.2727	-0.0869
Net monetary benefit	[redacted]	[redacted]	
Cost-effectiveness	[redacted]	[redacted]	
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 7 Base-case cost-effectiveness results for nintedanib versus best supportive care - with PAS

	BSC	NDB	Incremental
Treatment costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Liver panel tests	[redacted]	[redacted]	[redacted]
Patient monitoring and O_2 use	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	**3.0999**	**3.5013**	**0.4014**
LYs	4.1035	4.6026	0.4991
Exacerbation events	0.3061	0.2727	-0.0334
Net monetary benefit	[redacted]	[redacted]	
Cost-effectiveness	[redacted]	[redacted]	
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 8: Full incremental cost-effectiveness analysis for all comparators – with PAS

Treatment	Total costs	Total QALYs	ICER
BSC	£20,029.23	3.0999	
PFN	[redacted]	3.4509	[redacted]
NDB	[redacted]	3.5013	[redacted]

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 9 Base-case incremental results without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BSC	20,029.23	4.1035	3.0999	-	-	-	-	-
Nintedanib	78.350.71	4.6026	3.5013	58,321.48	0.4991	0.4014	145,309.98	145,309.98
Pirfenidone	80,474.37	4.5682	3.4509	2,391.65	-0.0036	-0.0471	176,077.26	Dominated

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 10 Base-case incremental results with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BSC	20,029.23	4.1035	3.0999	-	-	-	-	-
Nintedanib	[redacted]	4.6026	3.5013	[redacted]	0.4991	0.4014	[redacted]	[redacted]
Pirfenidone	[redacted]	4.5682	3.4509	[redacted]	0.0345	0.0503	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

The tornado diagrams for this section were run in the same way as described in the main submission document.

4.9.1. Deterministic sensitivity analysis results for nintedanib versus pirfenidone

1. Without patient access scheme discount

Deterministic sensitivity analysis results show that nintedanib dominates pirfenidone. Please note that a tornado diagram is not presented for this comparison because dominance cannot be represented in such a graph.

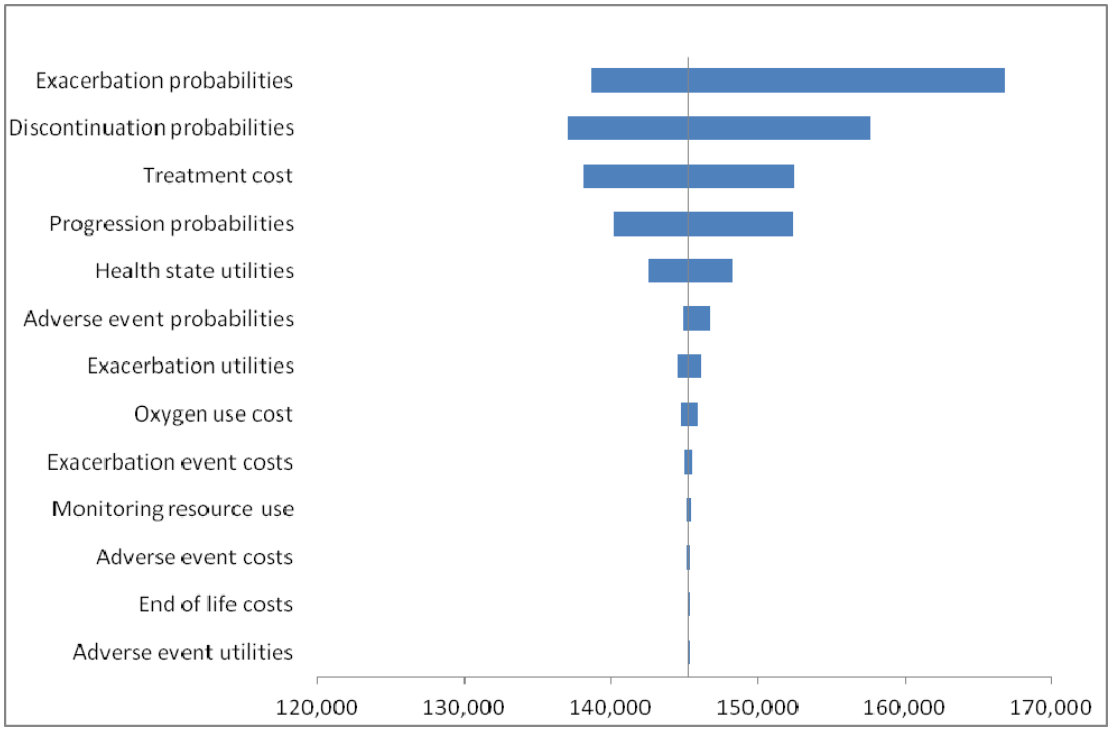
2. With patient access scheme discount

Deterministic sensitivity analysis results show that nintedanib dominates pirfenidone. Please note that a tornado diagram is not presented for this comparison because dominance cannot be represented in such a graph.

4.9.2. Deterministic sensitivity analysis results for nintedanib versus best supportive care (BSC)

1. Without patient access scheme discount

Figure 1: Tornado diagram of nintedanib versus BSC excluding the effect of mortality probabilities; without PAS



2. With patient access scheme discount

[redacted]

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

4.10.1. Probabilistic sensitivity analysis results for nintedanib versus pirfenidone

1. Without patient access scheme discount

Table 11: Comparison of ICERs obtained from deterministic and probabilistic sensitivity analyses for nintedanib versus pirfenidone without PAS

	Incremental cost	Incremental QALY	ICER
Deterministic	-£2,123.65	0.05034	NDB dominates
Average value from PSA	-£1,655.79	0.0939	NDB dominates

Figure 3: Incremental cost-effectiveness scatter-plot (nintedanib versus pirfenidone) without PAS

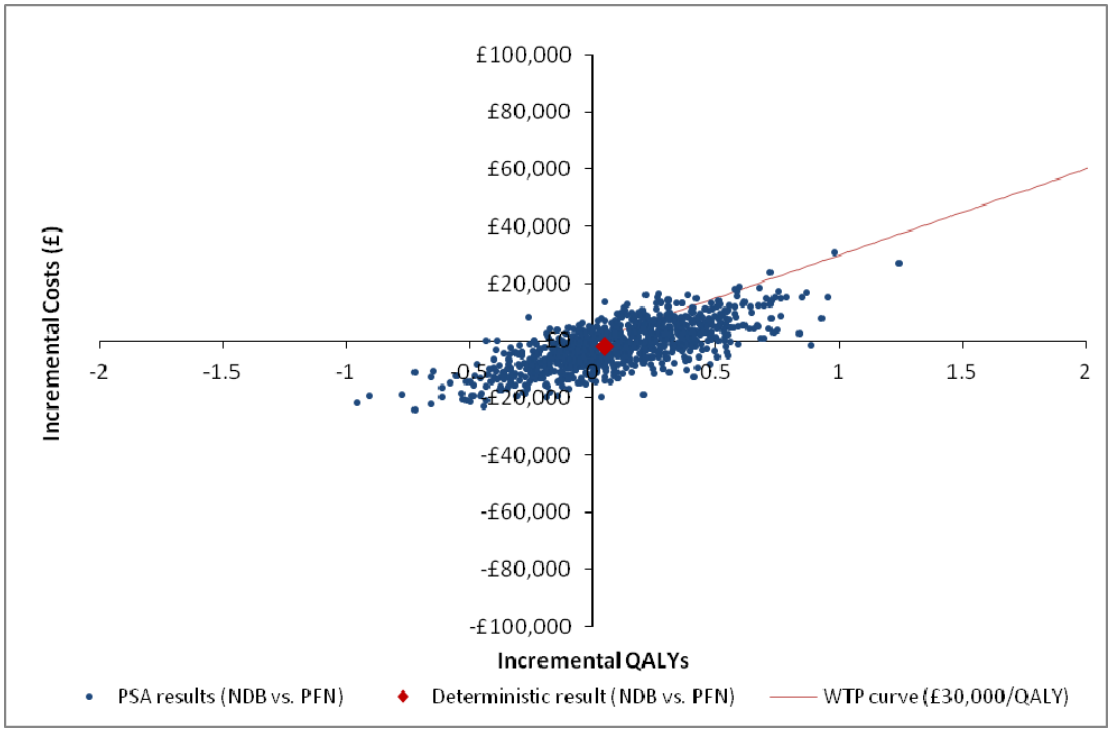
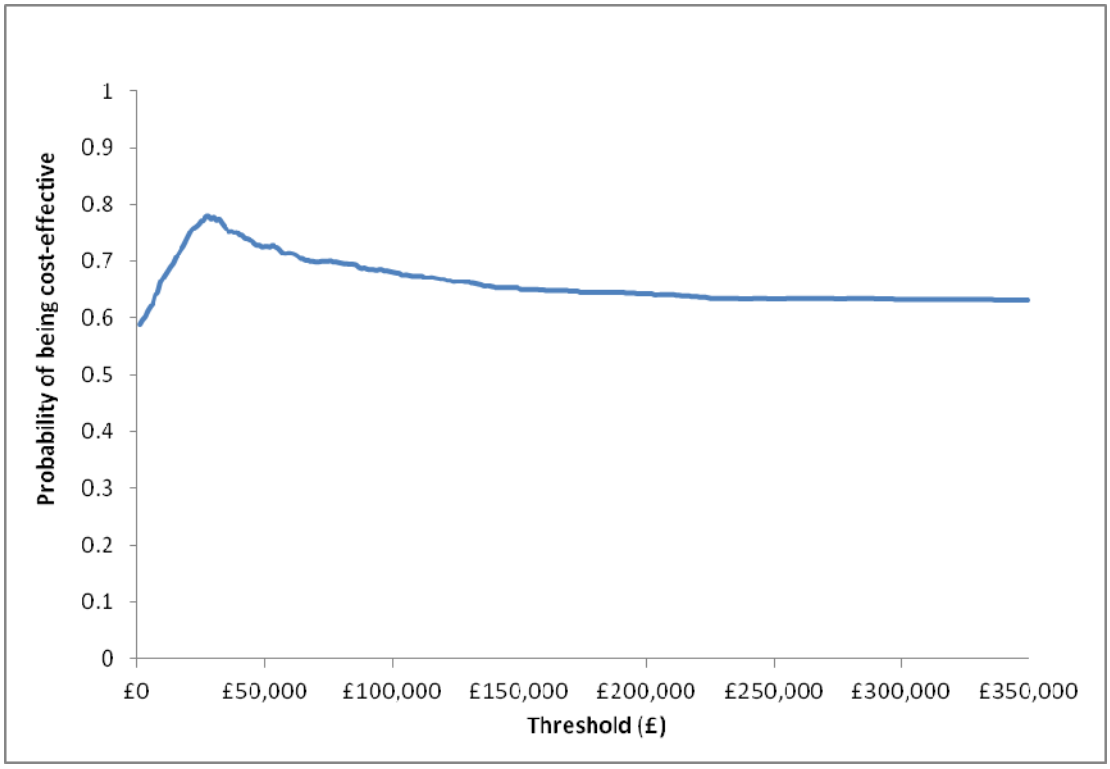


Figure 4: CEAC (nintedanib versus pirfenidone) without PAS



2. With patient access scheme discount

Table 12: Comparison of ICERs obtained from deterministic and probabilistic sensitivity analyses for nintedanib versus pirfenidone with PAS

	Incremental cost	Incremental QALY	ICER
Deterministic	[redacted]	0.0503	[redacted]
Average value from PSA	[redacted]	0.0929	[redacted]

[redacted]

4.10.2. Probabilistic sensitivity analysis results for nintedanib versus best supportive care

Table 13: Comparison of ICERs obtained from deterministic and probabilistic sensitivity analyses for nintedanib versus best supportive care without PAS.

	Incremental cost	Incremental QALY	ICER
Deterministic	£58,321.48	0.4014	£145,309.98

	Incremental cost	Incremental QALY	ICER
Average value from PSA	£58,435.13	0.4088	£142,939.12

Figure 7: Incremental cost-effectiveness scatter-plot (nintedanib versus BSC) without PAS

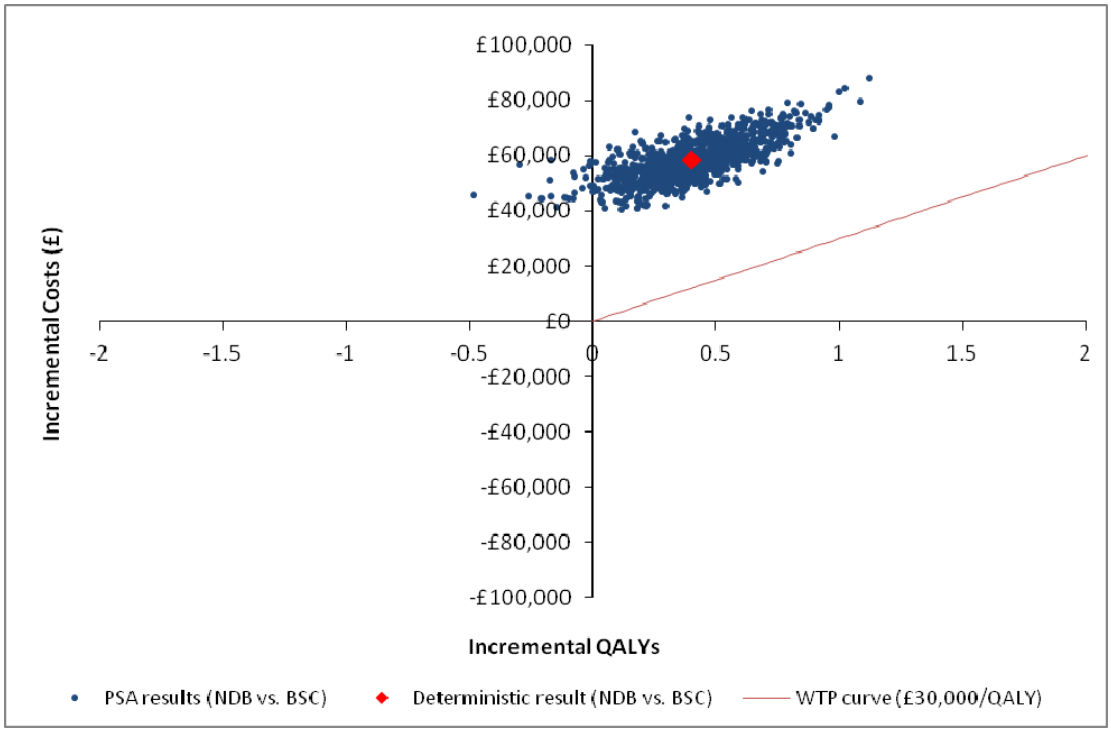
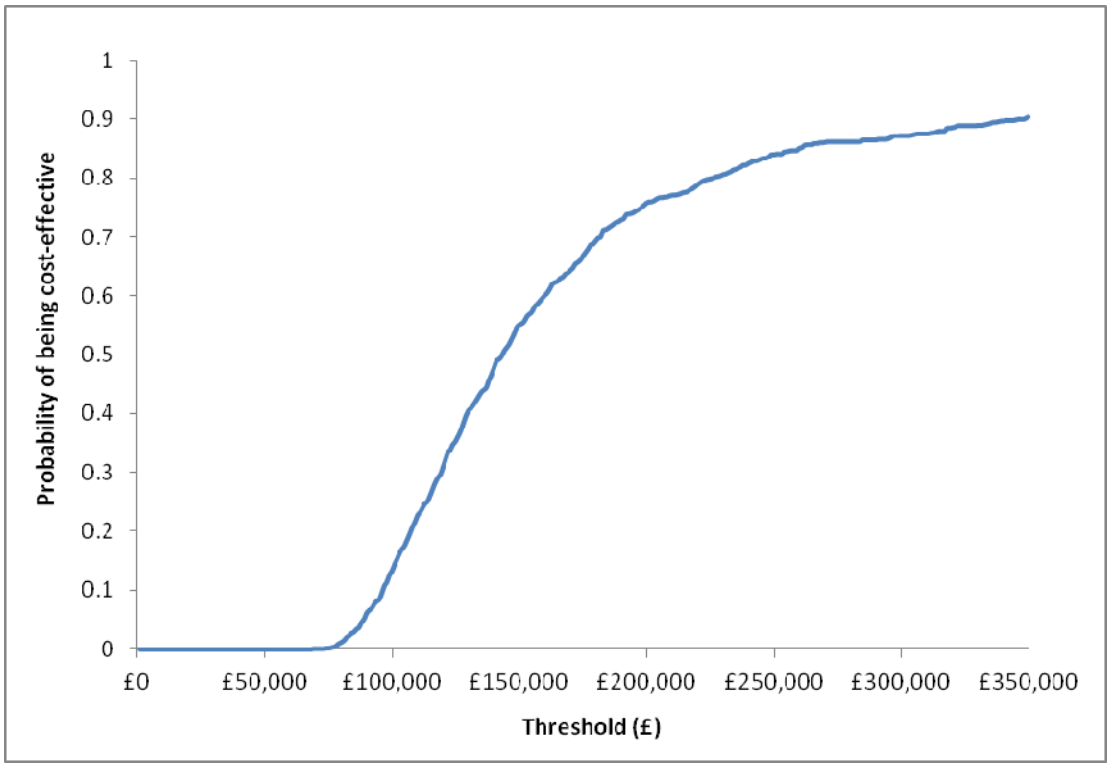


Figure 8: CEAC (nintedanib versus BSC) – without PAS



2. With patient access scheme discount

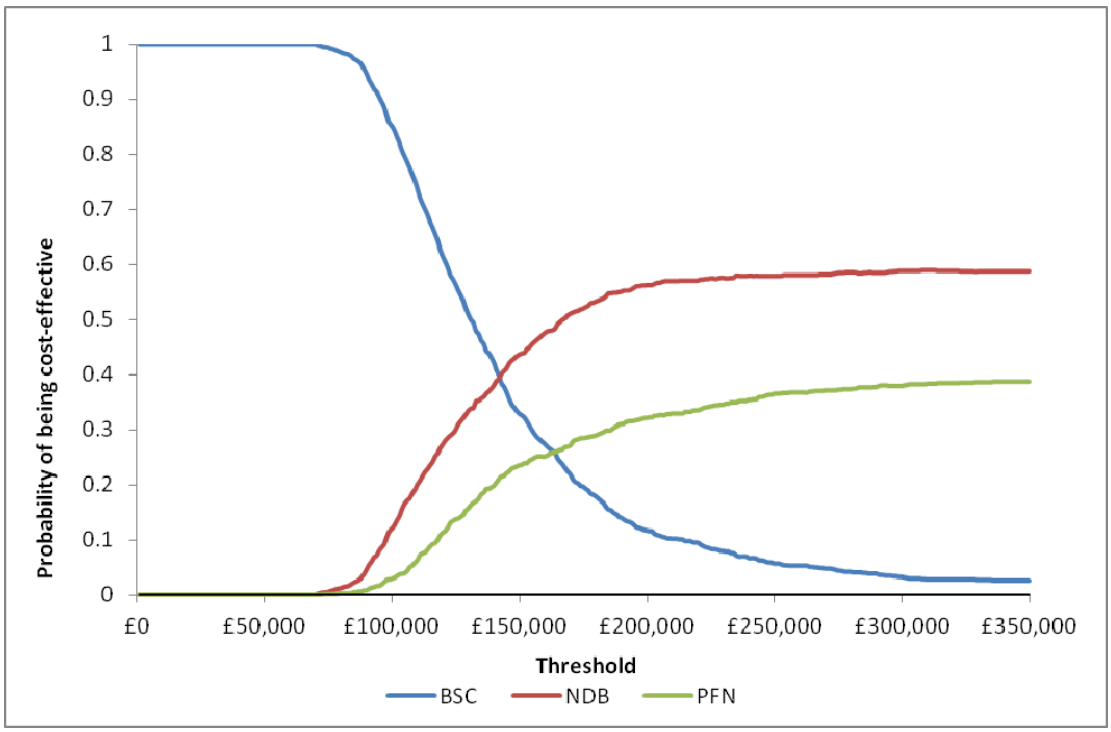
Table 14: Comparison of ICERs obtained from deterministic and probabilistic sensitivity analyses for nintedanib versus best supportive care with PAS

	Incremental cost	Incremental QALY	ICER
Deterministic	[redacted]	0.4014	[redacted]
Average value from PSA	[redacted]	0.4108	[redacted]

[redacted]

4.10.3. Cost-effectiveness acceptability curves and scatter-plots comparing multiple interventions

Figure 11: Multiple CEACs - without patient access scheme



BSC – best supportive care; NDB – Nintedanib; PFN – pirfenidone

[redacted]

Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

The same scenarios as described in the main submission (Section 5.8.5 – 5.8.9) were explored in this section for nintedanib versus pirfenidone treatment comparison and nintedanib versus best supportive care.

4.11.1 Nintedanib versus pirfenidone

1. Without patient access scheme discount

Table 15: Sensitivity analysis results (nintedanib versus pirfenidone) – without PAS

Scenario	Parameter	Description of parameter varied	ICER (IC/IQALYs)	
			Low value of the parameter	High value of the parameter
Base case		*N/A*	*NDB dominates*	
Tests around the 95% confidence interval values of model parameters				
1	Probabilities	Mortality probabilities	£4,624,248	NDB dominates
2		Exacerbation probabilities	£139,901	NDB dominates
3		Progression probabilities	NDB dominates	NDB dominates
4		Discontinuation probabilities	NDB dominates	NDB dominates
5	Costs	Treatment costs	NDB dominates	NDB dominates
6		Background follow-up costs	NDB dominates	NDB dominates
7		Oxygen use costs	NDB dominates	NDB dominates
8		Exacerbation event costs	NDB dominates	NDB dominates
9		EoL costs	NDB dominates	NDB dominates
10	Utilities	Health state baseline utilities	NDB dominates	NDB dominates
11		Exacerbation-related utilities	NDB dominates	NDB dominates

12	Adverse events	Adverse events probabilities	NDB dominates	NDB dominates
13		Adverse events costs	NDB dominates	NDB dominates
14		Adverse events related utilities	NDB dominates	NDB dominates
Tests on other model parameters				
Scenario	**Parameter**	**Description of parameter varied**	**ICER (IC/IQALYs)**	
15	Overall survival	Baseline risk: Weibull parametric model	NDB dominates	
16		Baseline risk: Gompertz parametric model	NDB dominates	
17		Baseline risk: do not allow progression from FVC40-49.9%Pred to FVC30-39.9%Pred (death)	NDB dominates	
18		Relative risk: NMA results, scenario 1, all evidence	NDB dominates	
19		Relative risk: NMA results, scenario 2, excluding King, Azuma and Taniguchi (patient characteristics)	NDB dominates	
20		Relative risk: NMA results, scenario 3 excluding Richeldi 2011, King, Azuma and Taniguchi	£991.57	
21		Relative risk: NMA results, scenario 5 excluding Japanese studies (European studies only)	NDB dominates	
22	Exacerbations	Baseline risk: use adjudication committee estimate	NDB dominates	
23		Baseline risk: exclude recurrent exacerbation risk	NDB dominates	
24		Relative risk: NMA results, scenario 1, all evidence	£113,037.71	
25		Relative risk: NMA results, scenario 2 excluding Homma (route of administration and study bias)	£113,037.71	
26		Relative risk: NMA results, scenario 3 excluding Azuma, Taniguchi and Homma (patient characteristics)	NDB dominates	
27		Relative risk: NMA results, scenario 4 excluding Richeldi 2011, Azuma, Taniguchi and Homma)	NDB dominates	
28		Relative risk: NMA results, scenario 6 excluding Azuma and Homma	NDB dominates	
29	Loss of lung function	Baseline risk: include exacerbation coefficient	NDB dominates	
30		Relative risk: NMA results, scenario 2, excluding King (heterogeneity/study population)	NDB dominates	
31		Relative risk: NMA results, scenario 3, excluding Richeldi 2011	NDB dominates	

		and King	
32		Relative risk: NMA results, scenario 4, include death (without Noble)	NDB dominates
33		Relative risk: NMA results, scenario 5, include death (with Noble)	NDB dominates
34	Safety	Relative risk: serious cardiac events, NMA results, scenario 2, excluding Richeldi 2011	NDB dominates
35		Relative risk: serious GI events, NMA results, scenario 2, excluding Richeldi 2011	NDB dominates
36		SAE disutility value: use alternative value for serious cardiac events	NDB dominates
37		SAE disutility value: use alternative value for GI perforation	NDB dominates
38		SAE disutility value: use extreme value for all SAEs: maximum disutility - serious cardiac events value	NDB dominates
39	Overall discontinuation	Baseline risk: discontinuation rate of 22% in 9.5 months for NDB and PFN (6.71% per cycle)	NDB dominates
40		Relative risk: NMA results, scenario 2,excluding King and Taniguchi	NDB dominates
41		Relative risk: NMA results, scenario 3, excluding King, Taniguchi, and Richeldi 2011	NDB dominates
42		Relative risk: NMA results, scenario 4, excluding King	NDB dominates
43		Relative risk: NMA results, scenario 5, excluding Taniguchi	NDB dominates
44	FVC%Pred values	Use the lowest value of each FVC%Pred category (e.g. 50 for the 50-59.9 FVC%Pred category) as starting point	NDB dominates
45		Use the highest value of each FVC%Pred category (e.g. 59.9 for the 50-59.9 FVC%Pred category) as starting point	NDB dominates
46	PFN stopping rule	Progressors in the PFN arm discontinue and lose treatment effect	£72,054.14
47	Direct evidence for NDB	Use clinical trial data for both NDB and PBO for all efficacy parameters (OS, exacerbations, loss of lung function) and discontinuation	N/A for this comparison

2. With patient access scheme discount

Table 16: Sensitivity analysis results (Nintedanib versus Pirfenidone) – with PAS

Scenario	Parameter	Description of parameter varied	ICER (IC/IQALYs)	
			Low value of the parameter	High value of the parameter
Base case		*N/A*	[redacted]	
Tests around the 95% confidence interval values of model parameters				
1	Probabilities	Mortality probabilities	[redacted]	[redacted]
2		Exacerbation probabilities	[redacted]	[redacted]
3		Progression probabilities	[redacted]	[redacted]
4		Discontinuation probabilities	[redacted]	[redacted]
5	Costs	Treatment costs	[redacted]	[redacted]
6		Background follow-up costs	[redacted]	[redacted]
7		Oxygen use costs	[redacted]	[redacted]
8		Exacerbation event costs	[redacted]	[redacted]
9		EoL costs	[redacted]	[redacted]
10	Utilities	Health state baseline utilities	[redacted]	[redacted]
11		Exacerbation-related utilities	[redacted]	[redacted]
12	Adverse events	Adverse events probabilities	[redacted]	[redacted]
13		Adverse events costs	[redacted]	[redacted]
14		Adverse events related utilities	[redacted]	[redacted]
Tests on other model parameters				
Scenario	**Parameter**	**Description of parameter varied**	**ICER (IC/IQALYs)**	
15	Overall survival	Baseline risk: Weibull parametric model	[redacted]	
16		Baseline risk: Gompertz parametric model	[redacted]	
17		Baseline risk: do not allow progression from FVC40-49.9%Pred to FVC30-39.9%Pred (death)	[redacted]	
18		Relative risk: NMA results, scenario 1, all evidence	[redacted]	
19		Relative risk: NMA results, scenario 2, excluding King, Azuma and Taniguchi (patient characteristics)	[redacted]	

20		Relative risk: NMA results, scenario 3 excluding Richeldi 2011, King, Azuma and Taniguchi	[redacted]
21		Relative risk: NMA results, scenario 5 excluding Japanese studies (European studies only)	[redacted]
22	Exacerbations	Baseline risk: use adjudication committee estimate	[redacted]
23		Baseline risk: exclude recurrent exacerbation risk	[redacted]
24		Relative risk: NMA results, scenario 1, all evidence	[redacted]
25		Relative risk: NMA results, scenario 2 excluding Homma (route of administration and study bias)	[redacted]
26		Relative risk: NMA results, scenario 3 excluding Azuma, Taniguchi and Homma (patient characteristics)	[redacted]
27		Relative risk: NMA results, scenario 4 excluding Richeldi 2011, Azuma, Taniguchi and Homma)	[redacted]
28		Relative risk: NMA results, scenario 6 excluding Azuma and Homma	[redacted]
29	Loss of lung function	Baseline risk: include exacerbation coefficient	[redacted]
30		Relative risk: NMA results, scenario 2, excluding King (heterogeneity/study population)	[redacted]
31		Relative risk: NMA results, scenario 3, excluding Richeldi 2011 and King	[redacted]
32		Relative risk: NMA results, scenario 4, include death (without Noble)	[redacted]
33		Relative risk: NMA results, scenario 5, include death (with Noble)	[redacted]
34	Safety	Relative risk: serious cardiac events, NMA results, scenario 2, excluding Richeldi 2011	[redacted]
35		Relative risk: serious GI events, NMA results, scenario 2, excluding Richeldi 2011	[redacted]
36		SAE disutility value: use alternative value for serious cardiac events	[redacted]
37		SAE disutility value: use alternative value for GI perforation	[redacted]
38		SAE disutility value: use extreme value for all SAEs: maximum disutility - serious cardiac events value	[redacted]

39	Overall discontinuation	Baseline risk: discontinuation rate of 22% in 9.5 months for NDB and PFN (6.71% per cycle)	[redacted]
40		Relative risk: NMA results, scenario 2,excluding King and Taniguchi	[redacted]
41		Relative risk: NMA results, scenario 3, excluding King, Taniguchi, and Richeldi 2011	[redacted]
42		Relative risk: NMA results, scenario 4, excluding King	[redacted]
43		Relative risk: NMA results, scenario 5, excluding Taniguchi	[redacted]
44	FVC%Pred values	Use the lowest value of each FVC%Pred category (e.g. 50 for the 50-59.9 FVC%Pred category) as starting point	[redacted]
45		Use the highest value of each FVC%Pred category (e.g. 59.9 for the 50-59.9 FVC%Pred category) as starting point	[redacted]
46	PFN stopping rule	Progressors in the PFN arm discontinue and lose treatment effect	[redacted]
47	Direct evidence for NDB	Use clinical trial data for both NDB and PBO for all efficacy parameters (OS, exacerbations, loss of lung function) and discontinuation	[redacted]

4.11.2. Nintedanib versus Best Supportive Care

1. Without patient access scheme discount

Table 17: Sensitivity analysis results (Nintedanib versus best supportive care) – without PAS

Scenario	Parameter	Description of parameter varied	ICER (IC/IQALYs)	
			Low value of the parameter	High value of the parameter
Base case		*N/A*	*£145,309.98*	
Tests around the 95% confidence interval values of model parameters				
1	Probabilities	Mortality probabilities	£87,917.06	£1,295,818.84
2		Exacerbation probabilities	£138,658.40	£166,811.16
3		Progression probabilities	£140,205.02	£152,416.08
4		Discontinuation probabilities	£137,050.27	£157,665.76
5	Costs	Treatment costs	£138,120.64	£152,505.01
6		Background follow-up costs	£145,124.24	£145,505.96
7		Oxygen use costs	£144,782.40	£145,837.57
8		Exacerbation event costs	£145,542.92	£144,972.29
9		EoL costs	£145,409.30	£145,210.67
10	Utilities	Health state baseline utilities	£148,242.92	£142,490.93
11		Exacerbation-related utilities	£144,544.34	£146,089.01
12	Adverse events	Adverse events probabilities	£144,878.65	£146,722.71
13		Adverse events costs	£145,184.89	£145,400.11
14		Adverse events related utilities	£145,319.99	£145,299.97
Tests on other model parameters				
Scenario	**Parameter**	**Description of parameter varied**	**ICER (IC/IQALYs)**	
15	Overall survival	Baseline risk: Weibull parametric model	£227,076.04	
16		Baseline risk: Gompertz parametric model	£440,352.40	
17		Baseline risk: do not allow progression from FVC40-49.9%Pred	£146,684.38	

		to FVC30-39.9%Pred (death)	
18		Relative risk: NMA results, scenario 1, all evidence	£145,309.98
19		Relative risk: NMA results, scenario 2, excluding King, Azuma and Taniguchi (patient characteristics)	£145,309.98
20		Relative risk: NMA results, scenario 3 excluding Richeldi 2011, King, Azuma and Taniguchi	£141,722.47
21		Relative risk: NMA results, scenario 5 excluding Japanese studies (European studies only)	£145,309.98
22	Exacerbations	Baseline risk: use adjudication committee estimate	£145,240.24
23		Baseline risk: exclude recurrent exacerbation risk	£145,502.05
24		Relative risk: NMA results, scenario 1, all evidence	£145,309.98
25		Relative risk: NMA results, scenario 2 excluding Homma (route of administration and study bias)	£145,309.98
26		Relative risk: NMA results, scenario 3 excluding Azuma, Taniguchi and Homma (patient characteristics)	£148,452.68
27		Relative risk: NMA results, scenario 4 excluding Richeldi 2011, Azuma, Taniguchi and Homma)	£148,452.68
28		Relative risk: NMA results, scenario 6 excluding Azuma and Homma	£145,309.98
29	Loss of lung function	Baseline risk: include exacerbation coefficient	£144,224.93
30		Relative risk: NMA results, scenario 2, excluding King (heterogeneity/study population)	£145,309.98
31		Relative risk: NMA results, scenario 3, excluding Richeldi 2011 and King	£144,865.89
32		Relative risk: NMA results, scenario 4, include death (without Noble)	£145,309.98
33		Relative risk: NMA results, scenario 5, include death (with Noble)	£145,309.98
34	Safety	Relative risk: serious cardiac events, NMA results, scenario 2, excluding Richeldi 2011	£145,438.34
35		Relative risk: serious GI events, NMA results, scenario 2, excluding Richeldi 2011	£145,227.06
36		SAE disutility value: use alternative value for serious cardiac	£145,310.94

		events	
37		SAE disutility value: use alternative value for GI perforation	£145,319.07
38		SAE disutility value: use extreme value for all SAEs: maximum disutility - serious cardiac events value	£145,370.32
39	Overall discontinuation	Baseline risk: discontinuation rate of 22% in 9.5 months for NDB and PFN (6.71% per cycle)	N/A for this comparison
40		Relative risk: NMA results, scenario 2,excluding King and Taniguchi	£145,370.72
41		Relative risk: NMA results, scenario 3, excluding King, Taniguchi, and Richeldi 2011	£144,914.41
42		Relative risk: NMA results, scenario 4, excluding King	£145,370.72
43		Relative risk: NMA results, scenario 5, excluding Taniguchi	£145,218.80
44	FVC%Pred values	Use the lowest value of each FVC%Pred category (e.g. 50 for the 50-59.9 FVC%Pred category) as starting point	£145,613.76
45		Use the highest value of each FVC%Pred category (e.g. 59.9 for the 50-59.9 FVC%Pred category) as starting point	£144,965.87
46	PFN stopping rule	Progressors in the PFN arm discontinue and lose treatment effect	N/A for this comparison
47	Direct evidence for NDB	Use clinical trial data for both NDB and PBO for all efficacy parameters (OS, exacerbations, loss of lung function) and discontinuation	£185,836.20

2. With patient access scheme discount

Table 18: Sensitivity analysis results (Nintedanib versus best supportive care) – with PAS

Scenario	Parameter	Description of parameter varied	ICER (IC/IQALYs)	
			Low value of the parameter	High value of the parameter
Base case		*N/A*		[redacted]
Tests around the 95% confidence interval values of model parameters				

1	Probabilities	Mortality probabilities		[redacted]	
2		Exacerbation probabilities		[redacted]	
3		Progression probabilities		[redacted]	
4		Discontinuation probabilities		[redacted]	
5	Costs	Treatment costs		[redacted]	
6		Background follow-up costs		[redacted]	
7		Oxygen use costs		[redacted]	
8		Exacerbation event costs		[redacted]	
9		EoL costs		[redacted]	
10	Utilities	Health state baseline utilities		[redacted]	
11		Exacerbation-related utilities		[redacted]	
12	Adverse events	Adverse events probabilities		[redacted]	
13		Adverse events costs		[redacted]	
14		Adverse events related utilities		[redacted]	
Tests on other model parameters					
Scenario	**Parameter**	**Description of parameter varied**	**ICER (IC/IQALYs)**		
15	Overall survival	Baseline risk: Weibull parametric model	[redacted]		
16		Baseline risk: Gompertz parametric model	[redacted]		
17		Baseline risk: do not allow progression from FVC40-49.9%Pred to FVC30-39.9%Pred (death)	[redacted]		
18		Relative risk: NMA results, scenario 1, all evidence	[redacted]		
19		Relative risk: NMA results, scenario 2, excluding King, Azuma and Taniguchi (patient characteristics)	[redacted]		
20		Relative risk: NMA results, scenario 3 excluding Richeldi 2011, King, Azuma and Taniguchi	[redacted]		
21		Relative risk: NMA results, scenario 5 excluding Japanese studies (European studies only)	[redacted]		
22	Exacerbations	Baseline risk: use adjudication committee estimate	[redacted]		
23		Baseline risk: exclude recurrent exacerbation risk	[redacted]		
24		Relative risk: NMA results, scenario 1, all evidence	[redacted]		
25		Relative risk: NMA results, scenario 2 excluding Homma (route of	[redacted]		

		administration and study bias)	
26		Relative risk: NMA results, scenario 3 excluding Azuma, Taniguchi and Homma (patient characteristics)	[redacted]
27		Relative risk: NMA results, scenario 4 excluding Richeldi 2011, Azuma, Taniguchi and Homma)	[redacted]
28		Relative risk: NMA results, scenario 6 excluding Azuma and Homma	[redacted]
29	Loss of lung function	Baseline risk: include exacerbation coefficient	[redacted]
30		Relative risk: NMA results, scenario 2, excluding King (heterogeneity/study population)	[redacted]
31		Relative risk: NMA results, scenario 3, excluding Richeldi 2011 and King	[redacted]
32		Relative risk: NMA results, scenario 4, include death (without Noble)	[redacted]
33		Relative risk: NMA results, scenario 5, include death (with Noble)	[redacted]
34	Safety	Relative risk: serious cardiac events, NMA results, scenario 2, excluding Richeldi 2011	[redacted]
35		Relative risk: serious GI events, NMA results, scenario 2, excluding Richeldi 2011	[redacted]
36		SAE disutility value: use alternative value for serious cardiac events	[redacted]
37		SAE disutility value: use alternative value for GI perforation	[redacted]
38		SAE disutility value: use extreme value for all SAEs: maximum disutility - serious cardiac events value	[redacted]
39	Overall discontinuation	Baseline risk: discontinuation rate of 22% in 9.5 months for NDB and PFN (6.71% per cycle)	[redacted]
40		Relative risk: NMA results, scenario 2,excluding King and Taniguchi	[redacted]
41		Relative risk: NMA results, scenario 3, excluding King, Taniguchi, and Richeldi 2011	[redacted]
42		Relative risk: NMA results, scenario 4, excluding King	[redacted]
43		Relative risk: NMA results, scenario 5, excluding Taniguchi	[redacted]

44	FVC%Pred values	Use the lowest value of each FVC%Pred category (e.g. 50 for the 50-59.9 FVC%Pred category) as starting point	[redacted]
45		Use the highest value of each FVC%Pred category (e.g. 59.9 for the 50-59.9 FVC%Pred category) as starting point	[redacted]
46	PFN stopping rule	Progressors in the PFN arm discontinue and lose treatment effect	[redacted]
47	Direct evidence for NDB	Use clinical trial data for both NDB and PBO for all efficacy parameters (OS, exacerbations, loss of lung function) and discontinuation	[redacted]

4.11.3. Impact of Discount Rate Variation (Pirfenidone PAS)

As Boehringer Ingelheim does not have access to the net price of pirfenidone used in practise, scenario analyses were performed by reducing the list price for pirfenidone in 5% increments from a 5% discount to a 95% discount. Results are shown in Table 21 and Table 22.

Table 19: Impact of pirfenidone discount rate on ICER; nintedanib without PAS

Level of PFN discount	Incremental total cost	ICER (£ per QALY)*
0%	-£2,123.65	NDB dominates
5%	£832.41	£16,536.00
10%	£3,788.46	£75,259.06
15%	£6,744.52	£133,982.11
20%	£9,700.58	£192,705.17
25%	£12,656.64	£251,428.22
30%	£15,612.70	£310,151.27
35%	£18,568.75	£368,874.33
40%	£21,524.81	£427,597.38
45%	£24,480.87	£486,320.43
50%	£27,436.93	£545,043.49
55%	£30,392.99	£603,766.54
60%	£33,349.04	£662,489.60
65%	£36,305.10	£721,212.65
70%	£39,261.16	£779,935.70
75%	£42,217.22	£838,658.76
80%	£45,173.28	£897,381.81
85%	£48,129.33	£956,104.86
90%	£51,085.39	£1,014,827.92
95%	£54,041.45	£1,073,550.97

Table 20: Impact of pirfenidone discount rate on ICER; nintedanib with PAS

Level of PFN discount	Incremental total cost	ICER (£ per QALY)*
0%		
5%		
10%		
15%		
20%		
25%		
30%		
35%		
40%		
45%		
50%		
55%		
60%		
65%		
70%		
75%		

80%		[redacted]			[redacted]	
85%		[redacted]			[redacted]	
90%		[redacted]			[redacted]	
95%		[redacted]			[redacted]	

4.11 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

N/A

Impact of patient access scheme on ICERs

4.12 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 21 Results showing the impact of patient access scheme on ICERs

	ICER for intervention (nintedanib) versus:			
	Pirfenidone		Best Supportive Care	
	Without PAS	With PAS	Without PAS	With PAS
Base-case deterministic values	Nintedanib dominates	[redacted]	£145,309.98	[redacted]
Average for PSA	Nintedanib dominates	[redacted]	£142,939.12	[redacted]

PAS - patient access scheme; PSA – probabilistic sensitivity analysis

Appendices

4.13 Appendix A: Additional documents

4.13.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Response

4.14 Appendix B: Details of outcome-based schemes

4.14.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

4.14.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

4.14.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

4.14.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

4.14.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

4.14.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

4.14.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

4.14.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

4.14.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

ACD Comments - IPF Nintedanib 752

1.1
There is little evidence to restrict use of nintedanib to patients with an FVC between 50 and 80%, especially given the comment in para 3.3. Many patients with an FVC above 80% can have severe disease as assessed by Dlco.

Patient data shows that between 35-40% of IPF patients have FVC>80% at presentation. Many of these have radiological and/or lung function data that confirms progressive disease. This is a limitation of measuring of FVC and it is unknown what is the person's "normal" FVC. Many people have normal FVC that is >100%.In addition INPULSIS data shows that the benefit of treatment (ie slowing decline in FVC) is equivalent in FVC>80% cohort compared to FVC 50-80% cohort. Patients who have taken part in patient access schemes for Nintedanib in the UK do have FVC <50% and FVC>80%.

1.2
Stopping criteria - suggest these are changed to reflect slowing of decline in FVC (from INPULSIS study Nintedanib slows decline in FVC ~50% compared to placebo over 1 year). This should be included in the treatment response. For instance a treatment that slows decline in FVC over 1 year from 30% to 15% should be considered effective.

[redacted]
Chair of Trustee
Action for Pulmonary Fibrosis

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NICE
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28 September 2015

Dear Colleague

ACD - Consultees & Commentators: Idiopathic pulmonary fibrosis - nintedanib [752]

Thank you for the opportunity to respond to the appraisal committee's request for 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?

We believe that the interpretation of the evidence has major flaws and we have the following comments:

Current practice
The committee acknowledge that median survival is 3-4 years and that around 1/3 of patients have an FVC of greater than 80%. Indeed in the INPULSIS trials the median FVC was approximately 80%.

The committee state that patients with an FVC >80% are treated by best supportive care. In practice these patients need little clinical input other than education, psychological support and monitoring for deterioration. They *wait* for their condition to deteriorate. We see this as unethical, and regardless of the modeling, cannot justify waiting until the condition deteriorates before starting therapy.
This is particularly pertinent in the face of robust clinical trial data that demonstrates that patients with an FVC >80% respond to nintedanib in the same manner as patients with an FVC <80%.
Furthermore to ignore this data is to ignore half of the patients in the trials. The committee itself acknowledges this (clinical effectiveness, para 3.3 and para 4.5).

There are extra costs associated with deterioration in patients with IPF and we would advocate treating early (when all that is required is drug therapy) rather than initiating therapy when patients

need *increased* clinical care. The comparison with pirfenidone (which is expensive compared with best supportive care) does not seem logical.

We urge NICE to re-appraise the recommendations so that patients with IPF are able to receive appropriate and effective treatment.

The technology

We agree with all of these points.

Evidence for clinical effectiveness

We note the committee acknowledges that "there are no subgroups for which there is evidence of differential effectiveness".

Evidence for cost effectiveness

The committee states that it is appropriate not to include people in the model with an FVC greater than 50%. Neither the company nor the ERG provided a model for patients with an FVC >80%. It is not clear to us why this was not requested. It is stated that nintedanib is cost effective when compared with pirfenidone, but not when compared with best supportive care. This does not seem logical nor clinically relevant.

The appraisal committee has also kindly asked for comments on the following:

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

We would like to state that we <u>do not</u> believe that the recommendations are either sound or suitable. We strongly reject the FVC stopping rule. This is not based on clinical evidence.

Yours sincerely

Single Technology Appraisal (STA)

Nintedanib for treating idiopathic pulmonary fibrosis [ID752]

Appraisal consultation document

Comments from the UK Clinical Pharmacy Association (UKCPA) Respiratory Group

We are concerned that the TA includes an upper limit FVC of 80% predicted. As noted in the TA document about a third of patients will have an FVC > 80% (4.10) and they will be significantly disadvantaged by the inclusion of this limitation, either being unable to access an evidence based disease modifying therapy, or expected to accrue additional, and irreversible, disability before they are able to access therapy. As discussed in our original submission, and those from other groups, a proportion of patients will have a relatively preserved FVC throughout the course of the condition and would develop moderate or severe disease, as defined by DLco and/or degree of functional disability, whilst maintaining an FVC > 80%.

With specific regard to the content of the TA evidence of efficacy in the group with an FVC > 80% is acknowledged by NICE (4.5), as is the fact that this group represents about 45% of patients in the manufacturer's model (3.19). Unfortunately, and for unclear reasons, this group was not included in the ERG model (4.10). The economic model appears to assume pirfendione as the standard of care only in patients with an FVC of 50 - 80% predicted and therefore assumes that use in patients with an FVC > 80% would not be cost effective compared to best supportive care. This position does not appear to have been applied to patients who have discontinued pirfenidone due to intolerance and for whom best supportive care would be the current treatment option, this group representing about 30% of patients trialling pirfendione (4.4).

It is also important to note that due to the availability of patient access schemes over the last 4 years patients with an FVC > 80% managed by centres treating IPF have had access to either pirfendione or nintedanib under a number of patient access schemes - i.e. the contemporary management of patients with IPF and an FVC > 80% has included disease modifying therapies in addition to best supportive care. The statement in the TA that '*patients already on nintedanib to continue on treatment until they and their clinician consider it appropriate to stop*' (1.3) exacerbating an inequitable scenario by allowing patients initiated under these schemes with an FVC > 80% to continue on treatment while barring access to those diagnosed with IPF after this.

We are also concerned about the introduction of a stopping rule for patients with an FVC decline > 10% over 1 year. This appears to have been included because of its inclusion in the pirfendione TA (4.15) but without any reference to an evidence base supporting this as evidence of a lack of efficacy.

Response written by:

[redacted]

Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT

BY EMAIL

2nd October 2015

RE: Idiopathic pulmonary fibrosis – nintedanib [ID752]

Dear Meindert,

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of nintedanib (Ofev®) in the treatment of idiopathic pulmonary fibrosis (IPF). We believe it is important patients have an alternative treatment to pirfenidone (Esbriet®).

We are, however, concerned with a several aspects of the evidence submitted and assessed through the appraisal process to date. Specifically, we believe a more robust assessment of the impact of the available treatment options on overall survival, and the relative differences between treatments with regard to this endpoint, is warranted,

We also remain concerned that the Committee has failed to recognise the importance of treating patients with mild IPF (FVC>80%). Idiopathic pulmonary fibrosis is a chronic, progressive, and fatal lung disease that is characterised by irreversible loss of lung function. Early treatment to delay progression should, therefore, be an important goal for the management of the condition. We note that clinical opinion strongly advocates for earlier access to treatments, but this is not reflected in the prevailing guidance from NICE, which is ultimately at the determinant of patients.

The following appendix provides further detail on our concerns with the evidence supporting the

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ACD and suggested approaches to allow the Committee to make a more considered recommendation.

Yours sincerely,

[redacted], Head of Health Economics and Strategic Pricing

Roche Products Limited

Conclusion that nintedanib may be more clinically effective than pirfenidone is not supported by the available evidence

The ACD states *"the clinical effectiveness of nintedanib is similar to, if not slightly better than, pirfenidone based on the results of the network meta-analysis*" (ACD, p30). We do not consider this to be an accurate reflection of the available evidence for the following reasons:

1. Pirfenidone is the only treatment for IPF with phase III randomised clinical data demonstrating a significant survival benefit [Esbriet SmPC, Ofev SmPC, ASCEND 2014[1]]
2. The network meta-analysis developed for the appraisal has used different time-points in comparing overall survival. The impact of this mismatch biases the analysis in favour of nintedanib, and explains the non-significant finding for pirfenidone vs. placebo, which is in contrast to the analysis by the EMA [Esbriet SmPC]
3. The manufacturer has not systematically selected studies to assess the acute exacerbations outcome, or provided a clear rationale for the exclusion of some studies, as noted by the ERG (ACD; 3.8, see Table 1). When all data are included, the point estimates for the rate of acute exacerbations are very similar between nintedanib and pirfenidone. The manufacturer's analysis is therefore biased in favour of nintedanib (see Table 2).
4. The 6MWD is a valid and responsive clinical endpoint, which provides objective and clinically meaningful information on the functional status of a patient with IPF [Nathan et al, 2015[2]]. Similar to FVC, 6MWD is an independent predictor of mortality, but is not fully collinear to FVC [Puxeddu et al, 2015[3]& Nathan SD et al 2015[2]]. We do not believe the Committee has recognised the importance of the pirfenidone data which shows a significant improvement in 6MWD.
5. NICE state that benefits of nintedanib "*may not be fully reflected in the cost-effectiveness results*" (ACD, p32), due to "*its improved tolerability profile compared with pirfenidone*". There is no clear rationale why such benefits are not captured in the assessment. We

believe this statement is misleading and unsupported by evidence.

6. There is no evidence – including that within the manufacturers submission – which supports the view that nintedanib has a benefit over pirfenidone in FVC. The FDA analysis of the cumulative distribution of patients by change in percent predicted FVC from baseline is consistent between the two treatments.

In conclusion, there is no robust evidence or assessment which supports the claim of a beneficial effect of nintedanib over pirfenidone in any relevant clinical outcome. We, therefore, strongly disagree with the statement that the clinical effectiveness of nintedanib may be "*slightly better* than" pirfenidone, and request the Committee reconsider this view.

Incorrect data used to estimate overall survival associated with pirfenidone

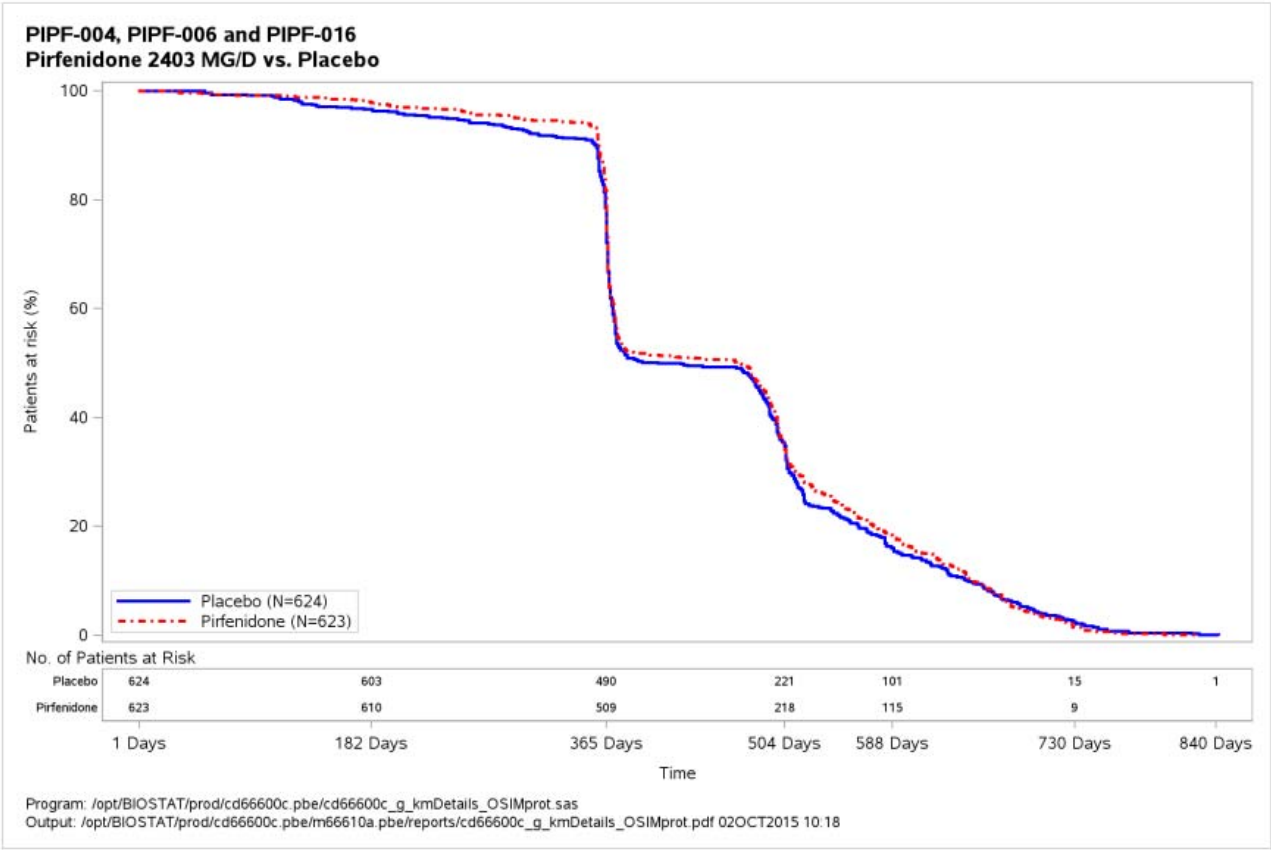
The pooled overall survival analysis for pirfenidone was a pre-specified to occur at 52 weeks. In their analysis of overall survival, the manufacturer has compared pooled results from their clinical trial programme assessed at a 52 week time point with survival data from trials with pirfenidone taken at 120 weeks. The analysis for pirfenidone at this time point were exploratory in nature. This discrepancy in time point assessment heavily biases the results against pirfenidone, and leads to an incorrect overall survival ratio being used in the economic model.

The pirfenidone analyses was pre-specified to be conducted at 52 weeks as all patients from the three studies contributing to the analysis were to be followed up until at least 52 weeks. As described in Figure 1 below, the number of patients at risk beyond weeks 52 and weeks 72 falls dramatically in the pooled analysis of pirfenidone: at 2 years (730 days) less than 5% of the initial population are still being followed up.

As the 52 week analysis was pre-specified, and nintedanib has survival data at 52 weeks, a

comparative analysis of overall survival should be based on this common time point.

Figure 1: Proportion of patients still at risk by days after randomisation



Bias caused by selection of studies to inform the network meta-analysis

As discussed during the Appraisal Committee meeting, and alluded to in the ACD (p28), there is concern with the selective choice of studies used in the manufacturers network meta-analysis (NMA): in particular, the use of different studies to inform the analyses for different outcomes. The ACD states that this inconsistent approach – which is summarised in Table 1 – "*potentially biased the results in favour of nintedanib*", and these inconsistencies do not seem to be sufficiently justified by the manufacturer.

Despite the concerns expressed by members of the Committee during the meeting, as reported in

the ACD, the Determination concludes the NMA "*generally provided an adequate basis for decision-making*", with the NMA also being used to conclude "*the clinical effectiveness of nintedanib is similar to, if not slightly better than, pirfenidone based on the results of the network meta-analysis*". On the basis of the Committee discussions and acknowledged potential for bias, we are surprised that NICE would reach these conclusions without further analyses being performed.

Table 1: Inconsistent selection of studies across the outcomes of the NMA for the economic evaluation*

Studies	Timeponts (weeks)	Overall survival	Exacerbation rate	FVC % predicted 10% decline	PFS	6MWD
CAPACITY I & II	72	✓	✓	✓	✓	✓
ASCEND	52	✓	n/a	✗	✗	✗
SP2	36	✓	✗	n/a	n/a	✗
SP3	52	✓	✗	n/a	✗	✗
PANTHER (NAC)	60	✓	✓	✓	✗	✓
INPULSIS I & II	52	✓	✓	✓	✓	n/a
TOMORROW	52	✓	✓	✓	✗	✓
HOMMA	48	✗	✓	✗	✗	✗

*There appears to be inconsistencies in the studies which the manufacturer lists as being part of the network (Table 38 MS Submission) with the actual inputs in the economic model base case.
n/a evidence not available

Approach used to assess exacerbations is biased against pirfenidone

Selective use of clinical evidence from the network meta-analysis

Using all the available evidence for this outcome (including SP-2[5] and SP-3[6]) has a significant impact on the point estimate for the exacerbation rate in the network meta-analysis. This can be seen in Table 2, which presents data assessed from the manufacturer's submission and economic model. No clear reason is provided for this exclusion, and we are concerned that the reported outcome results in a bias in favour of nintedanib.

Table 2: Exacerbation rates for pirfenidone and nintedanib

	Exacerbation rate:	
	Based on all trial evidence	
	NIN vs PBO	PFN vs PBO
Fixed effects	0.56	0.59
Random effects	0.47	0.37
	Manufacturer's economic model *	
	NIN vs PBO	PFN vs PBO
Fixed effects	0.56	1.01
Random effects	0.5	1

* Excludes SP-2 and SP-3

Inappropriate use of different time-points to calculate an odds ratio for exacerbation

The manufacturer and ERG fail to make note of the methods for calculating the odds ratio for exacerbation risk in the network meta-analysis. From the documents available, it is apparent that the manufacturer calculates the overall rate of exacerbation through totalling all exacerbation events over 52 weeks, despite some of the studies included only reporting data to 36 weeks. This is a questionable approach, and raises concerns about the relative differences in rates in the model: particularly when such differences are used to come to the conclusion that "*nintedanib is likely to be more clinically effective than pirfenidone…at preventing acute exacerbations*" (ACD, p27-28). These concerns are compounded through the potential bias introduced through the inconsistent use of clinical trials in the assessment of different clinical outcomes, as described above.

Approach used to extrapolate overall survival is not robust

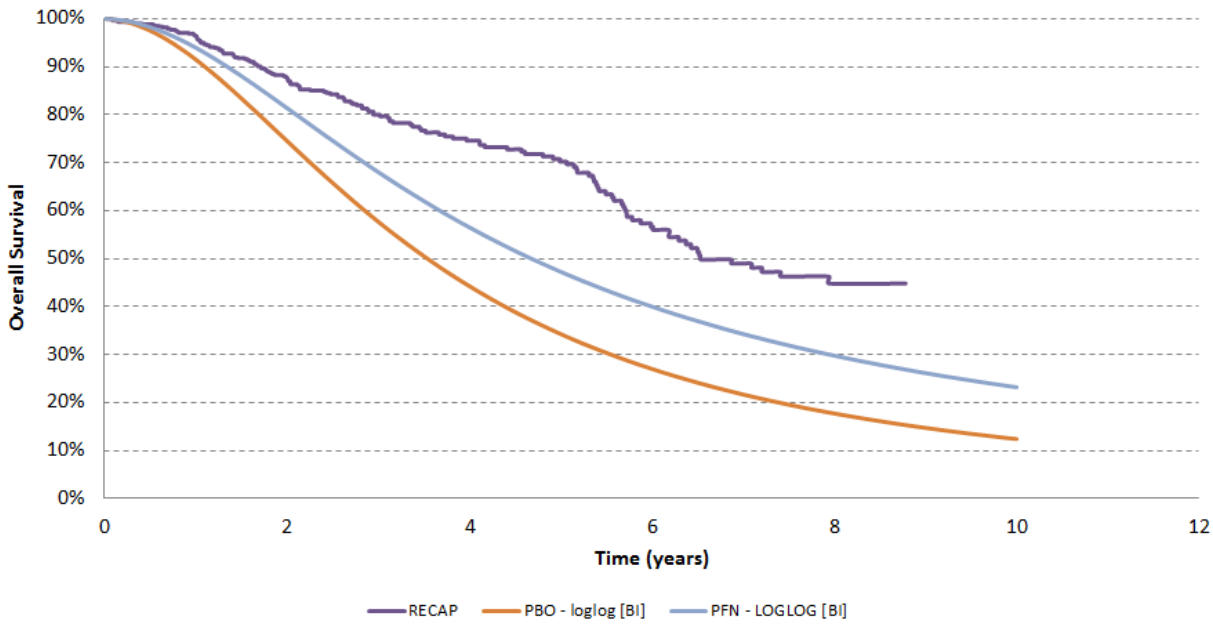
Lack of face validity in the manufacturer's extrapolation of overall survival

The extrapolation for overall survival within the manufacturer's economic model poorly reflects the long term survival of IPF patients in the UK. Figure 2 presents the survival estimates for pirfenidone and placebo (extracted from the manufacturer's economic model), and compares this

to the Kaplan Meier data from the RECAP study[11] through overlaying the KM curve from this study. The RECAP study is the long term follow up of patients enrolled in the CAPACITY I & II[4] trials.

From Figure 2, it is clear that this important outcome of the model lacks face validity: the extrapolated pirfenidone estimate from the manufacturer's model [light blue] has diverged from the observed KM data by 1 year, with this gap growing over time: by year 3, the model under-predicts survival for patients initially receiving pirfenidone by over 10%.

Figure 2: Manufacturer's model poorly reflects the long term survival of IPF patients



Systematic literature review for non-randomised studies

As part of the evidence submission, the manufacturer states an ad-hoc targeted literature review for non-randomised studies to validate long term survival estimates was performed. We are not confident that a systematic approach has been employed, and are concerned that evidence from the Kondoh *et al*[12] publication – a study based on 74 Japanese patients – is not generalisable to the UK patient population. Furthermore, the low patient numbers in this study leads to concern as

to whether this is an appropriate study to validate the long term survival of this chronic long term condition.

Pirfenidone and Nintedanib survival estimates – not tested in sensitivity analysis

Given the inherent uncertainty created through basing overall survival estimates on the Kondoh *et al*[12] study, along with the importance of this outcome as the key driver of the economic model, we were surprised to note that no scenario analyses had been performed to investigate the impact of adjusting the relative difference between pirfenidone and nintedanib in this outcome. While analyses were run for the choice of parametric function, at no point did was the relative difference between pirfenidone and nintedanib tested in the analysis.

Pirfenidone – unlike nintedanib – has demonstrated a statistically significant overall survival benefit when compared to placebo. We, therefore, believe this is a key omission from the manufacturer's evidence submission and the ERG's assessment. Further analyses, extending past the point estimate and including confidence intervals, are warranted to reflect the range of uncertainty. We would also propose more exhaustive sensitivity analyses to ensure the Committee are best informed on the uncertainty associated with the point estimates presented by the manufacturer.

Choice of model structure

The manufacturer has chosen a model structure which they believes represents the natural history of the disease. While we agree that FVC is an important clinical outcome, we are concerned that the quantity and quality of the evidence which the manufacturer has identified does not meet the amount required through the use of this relatively complex approach. Specifically, with the increased number of health states, the manufacturer has had to make a number of assumptions to incorporate the transition probabilities between health states.

In assessing the outputs of the model, there is little difference in both the incremental benefits and costs between the health states. It could therefore be suggested that the added complexity has increased the level uncertainty with limited benefit. We do not believe this has been properly addressed in the ERG's report.

Nintendanib is associated with a 'different' vs. 'improved' tolerability profile

The ACD states "*nintedanib may be considered innovative because the benefits of its improved tolerability profile compared with pirfenidone*". Whilst the two treatments clearly have different tolerability profiles, this statement does not seem to be fully reflect that fact that nintendanib exhibits some toxicities (atherothrombotic and gastrointestinal events, bleeding, etc.) which pirfenidone does not have. Indeed, the manufacturer's submission was criticised by the ERG and Committee for the exclusion of costs and disutility associated with diarrhoea in the economic model, given it led to treatment discontinuation in 4.4% vs. 0.23% of patients randomised to nintedanib and placebo, respectively (INPULSIS I & II[8]).

The INPULSIS 1&2 clinical trials identified a higher incidence of myocardial infarction in patients treated with nintedanib vs. placebo (INPULSIS I & II[8]). We are not aware of any evidence of serious cardiac events in the pirfenidone trials (CAPACITY[4] & ASCEND[1]). The patient population enrolled in the nintedanib trials also excluded many patients at risk of cardiac events, meaning the trial population may not be representative of those likely to receive the treatment in clinical practice.

Pirfenidone is associated with a higher incidence of photosensitivity than nintedanib, although clinical and patient feedback is that – with appropriate education and support – this can be

adequately managed.

Other notable inaccuracies

We have identified a number of further inaccuracies/errors within the ACD and economic model.

Reference	Description
ACD, 3.3	We believe it should be made clear that this statement only applies to nintedanib's effect on FVC in this subpopulation, rather than a broader clinical effectiveness
ACD, 3.5	Regarding the final sentence of this paragraph (on discontinuation due to AE), it should be made clear that this difference is not statistically significant
ACD, 4.1	The clearly different clinical indications for pirfenidone and lung transplant should be made more explicit in this statement
ACD, 4.4	It is not clear why it is believed that RECAP underestimated the incidence of rash by 50%, and request that this point is referenced
Economic Model	The dosing of pirfenidone is not reflective of the clinical practice. The model appears to assume 9 pills in accordance with the label, but the clinical studies had an average of 7.88 pills per day. This reduces the total cost of treatment by 12%.
Economic Model	The manufacturer has assumed a higher discontinuation rate for nintedanib than pirfenidone in accordance with the clinical trial data. However, due to their assumptions on overall survival, the model estimates that patients treated with nintedanib would live longer post therapy than those previously treated with pirfenidone. This is the driver for the incremental cost in the manufacturer's analysis.
Economic Model	In the manufacturer's model, the rate of exacerbation is assumed to be higher in the pirfenidone arm than in the placebo arm. This does not reflect the clinical evidence for pirfenidone and lacks face validity.
Manufacturers submission	No clear rationale is presented in the manufacturer's submission why odds rations have been chosen in preference to hazard ratios. We are concerned that – as outcomes across studies report at various time points – the risk and uncertainty associated with this selection has not be adequately addressed.

References

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Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant respiratory physician with specialist interest in ILD
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"Using the criteria of FVC 50-80% stratified as mild to moderate disadvantages up to 40% of patients who have significant fibrosis when one looks at other parameters such as DLCO and fibrosis score on HRCT. These patients do not have mild disease and the majority do not have emphysema. This is just normal population variation in lung function (abnormal value can be 75-140%. The clinical trials with nintedanib DID NOT exclude patients with FVC above 80%. The reduction in decline in FVC was seen in patients with FVC 50-80% and those with FVC above 80%. This is clearly documented in the NICE appraisal. Nintedanib offers a treatment option for patients that donot tolerate side effects with pirfenidone, but also the clinical trails recruit patients with ""milder"" disease and thus offers a treatment option for 40% of patients who's FVC is above 80%. It is not evidence based to restrict prescribing of nintedanib to those with FVC 50-80%. Seeing a 10% decline in FVC as a treatment failure is a figure plucked out of the air and there is now post hoc data to demonstrate that there are fewer patient with >10% decline on pirfenidone a NICE approved antifibrotic compared to placebo, demonstrating that antifibrotics slow disease progression despite how progressive the disease. IPF is very heterogenous and patients behave very differently in their disease course and discriminating those that deteriorate more rapidly as treatment failure is not guided by any evidence. The FVC criteria and discontinuation criteria is not evidence based and discriminates a significant proportion of patients who have a severe and devastating disease"

Name	[redacted]
Role	[redacted]
Other role	[redacted]
Organisation	Pulmonary Fibrosis Trust
Location	England
Conflict	No
Notes	None
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	One of the biggest problems that patients face with the prescribing of drugs such as Pirfenidone is the fact that the drugs are not available outside the range of FVCs quoted. i.e. 50% to 80%. The argument many patients make is that if the drug is helpful why not prescribe it for all patients. Some patients are quite ill but still have an FVC of more than 80% and

	some patients are still very well even though their FVC is below 50%, With Idiopathic Pulmonary Fibrosis nobody knows what range can be called mild, moderate, or severe.

Name	[redacted]
Role	NHS Professional
Other role	NIHR Academic Clinical Lecturer
Organisation	Hull and East Yorkshire Hospitals NHS Trust
Location	England
Conflict	MC and SH have received personal fees and non-financial support from Boehringer Ingelheim. SH has received personal fees from Roche and MC and SH have received non-financial support from Roche. MC and SH have approved funding for an investigator led study by Boehringer Ingelheim. None of the disclosed relate to the submitted comment.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Response to NICE consultation â€˜Nintedanib for treating idiopathic pulmonary fibrosis We are pleased to review the appraisal consultation document â€˜Nintedanib for treating idiopathic pulmonary fibrosis (IPF) and welcome its recommendation of Nintedanib as an option for treating IPF. However, we are concerned by the upper forced vital capacity (FVC) threshold of 80% and feel that Nintedanib should be available to IPF patients with an FVC >50% with no upper threshold. The natural course of IPF is difficult to predict at diagnosis with no baseline measure able to accurately predict those at risk of disease progression. It is widely recognised that a decline in FVC of >10% over 6-12 months is associated with increased mortality and indeed this was confirmed in a large observational study by Schmidt et al. However, despite this clear association with mortality, FVC decline in 1 year was not necessarily associated with decline in subsequent years [1]. Given that the efficacy of Nintedanib relates to slowing the rate of FVC decline, delaying treatment until FVC decline has already occurred may reduce any potential mortality benefit. There is therefore an argument that early initiation of therapy may be fruitful [2]. Indeed, our local data from the North of England on the use of Nintedanib under the patient access scheme reveals that over 40% of patients currently receiving Nintedanib have an FVC >80% (n=75; S. Hart, N. Chaudhuri, unpublished data). These patients have been assessed as suitable for treatment by experienced ILD clinicians in specialist centres, but would be denied treatment under the proposed NICE recommendations. The cost effectiveness calculations presented in the consultation document are based on trying to model a disease that is both unpredictable and presently poorly understood. In our opinion, baseline FVC does not reliably reflect an individuals disease severity in clinical practice and therefore sole reliance on this measure is flawed. Furthermore, it appears counterintuitive to limit a therapy that is known to reduce

	disease progression to those with more advanced disease rather than intervening at a time when a lower symptom burden could be prolonged. This is particularly true as published data from the INPULSIS trials demonstrate similar reductions in disease progression in patients across the spectrum of FVC [3]. We recognise the need to rationalise the use of expensive medications, but to do so on the basis of statistical economic models of a disease that does not follow a predictable course with outcomes that are not predicted by baseline FVC appears unreasonable. [redacted], academic clinical lecturer [redacted] specialist nurse [redacted], consultant physician [redacted] [redacted] [redacted] References 1. Scmidt SL, Tayob N, Han MK, Zappala C, Kervitsky D, Murray S, Wells AU, Brown KK, Martinez FJ, Flaherty KR. Predicting pulmonary fibrosis disease course from past trends in pulmonary function. Chest. 20144;145(3):579-85 2. Crooks MG, Hart SP. A new era of drug therapy for idiopathic pulmonary fibrosis. Lancet Respir Med. 2014;2(12):964-6 3. Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, Azuma A. Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis Across Pre-specified Subgroups in INPULSIS. Am J Respir Crit Care Med. 2015 [Epub ahead of print].

Name	[redacted]
Role	NHS Professional
Other role	Consultant Respiratory Physician, clinical lead ILD (Interstital Lung Disease)
Organisation	University Southampton NHS Trust
Location	England
Conflict	I have recieved funding to attend advisory boards for both

	Intermune and Boehringer Ingelheim
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	"We note with interest the provisional recommendation of this consultation document that nintedanib be approved by NICE for patients diagnosed with IPF with an FVC between 50-80%. It appears that this conclusion has been reached based upon cost calculations and interpretation of clinical trial data. Whilst the approval of nintedanib would provide a valuable treatment option for patients with IPF, as clinicians in this highly specialised area we are concerned that the application of an upper FVC limit for nintedanib prescription will significantly disadvantage the patients above this threshold who currently have no treatment option. Pirfenidone approval by NICE in 2013 represented a landmark moment for the care of patients with IPF in the UK. Technology Appraisal 282 (Pirfenidone for treating idiopathic pulmonary fibrosis), which informed the approval, identified that there was no statistically significant difference between the pirfenidone and placebo group in patients with a baseline % predicted FVC of greater than 80%. In addition, it was stated that it was rare for patients with confirmed IPF to have an FVC greater than 80% predicted. Pirfenidone was therefore approved for patients with an FVC between 50 â€“ 80%. We do not believe that direct translation of this upper prescription threshold is approproriate for nintedanib, and that to do so would be entirely arbitrary. Firstly, in our clinical experience approximately one third of patients with IPF at diagnosis have an FVC greater than 80% predicted. Secondly, as the consultation document acknowledges, subgroup analyses identify no difference in clinical effectiveness of nintedanib when comparing patients with an FVC of 50 â€“ 80 % versus greater than 80%. IPF is a chronic, progressive, life-threatening disease. Patients with an FVC above 80% do not have mild disease, they have early disease. Just as those with cancer in the early stages, still have cancer. Any loss of lung function is irreversible. Given this, it makes little practical sense, having made an early diagnosis (with an FVC over 80%), to wait for the disease to advance (to an FVC below 80%) before offering treatment with clear evidence of efficacy. In particular, the commencement of early treatment would be anticipated to delay the onset of the significant symptom burden that patients with IPF bear. We therefore believe that no upper limit to the commencement of nintedanib is appropriate, and that to do so arbitrarily disadvantages a patient group with no current treatment option who would be anticipated to derive sustained long term benefit from nintedanib. "

Nintedanib for treating idiopathic pulmonary fibrosis

Evidence Review Group Commentary on Boehringer Ingelheim Limited's Response to the Appraisal Consultation Document

Southampton Health Technology Assessments Centre (SHTAC)

9th October 2015

Commercial in confidence (CIC) data have been redacted: [redacted]

Contents

List of Tables

1 Introduction

The Evidence Review Group (ERG) has provided commentary and critique on the company's response to the Appraisal Consultation Document (ACD). The ERG received the company's response document on 5th October 2015. The focus of the ERG commentary has been on the information provided, in particular the cost-effectiveness analyses presented in the company's response document, as requested by NICE.

2 Clarifications relating to cost-effectiveness

The company has presented a "revised base case" with a new patient access scheme (PAS) taking into account issues raised in the "Summary of Appraisal Committee's key conclusions" in the ACD. In particular the model was amended to reflect:

- A new PAS discount of [redacted] of the nintedanib daily price was applied. The discounted daily cost of nintedanib is [redacted].
- Change in the Network meta analysis scenarios. Use scenario 1 (all evidence) or the scenario excluding the trial by Azuma *et al.* 2005 where this study provides evidence for the outcome of interest.
- Correction of the end of life cost.
- Correction of the exacerbation-related disutility implemented in the model.
- Correction of the adverse events-disutility duration (from 1 year to 1 month)

The company's revised base case also incorporated an increased risk of mortality for patients who have experienced an exacerbation (Hazard ratio 1.395).

The company justifies including an increased risk of mortality for patients who have an exacerbation by stating that, at the first appraisal committee meeting, it had been suggested that the mortality rate is much higher. They have obtained this hazard ratio, based upon a mortality hazard rate of 2.79% over 6 months found in Kondoh *et al*. 2010 for patients with exacerbations.

The ERG notes that the company has not changed the incidence of photosensitivity and rash that occurs in the pirfenidone arm, however as the company has changed the adverse events disutility duration, the adverse events for photosensitivity and rash no longer affect the model results.

The company has shown the revised base case analysis results with and without the PAS in the PAS submission template Tables 3 – 8. The ERG has checked these analyses by

replicating them in the original company model with the changes listed above and obtained the same results.

The ERG notes that the base case results for nintedanib with the PAS have been compared against pirfenidone using the list price in PAS template Table 6 – 8 and has shown the impact of different pirfenidone discount rates in the PAS template Table 20. The ERG provides the base case results for nintedanib versus pirfenidone with the PAS price for both nintedanib and pirfenidone below (Table 1).

Table 1 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£20,029.23	3.0999	
Pirfenidone	[redacted]	3.4509	[redacted]
Nintedanib	[redacted]	3.5013	[redacted]

BSC – Best supportive care; NDB - nintedanib

The ERG also notes that the company has not provided the revised analysis incorporating a treatment stopping rule if the disease progresses by a 10% or more decline in percent predicted FVC, and including a restricted population with percent predicted FVC of 50-80%. The ERG provides these analyses in Tables 2 - 5. These analyses show similar results to the company's revised base case analyses.

Table 2 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib and a treatment stopping rule for both treatments if the disease progresses by more than a 10% decline in percent predicted FVC

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£20,029.23	3.0999	
Pirfenidone	[redacted]	3.3573	[redacted]
Nintedanib	[redacted]	3.4023	[redacted]

BSC – Best supportive care; NDB - nintedanib

Table 3 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib and a restricted population with percent predicted FVC of 50-80%

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£22,539.29	2.9227	
Pirfenidone	[redacted]	3.2669	[redacted]
Nintedanib	[redacted]	3.3139	[redacted]

BSC – Best supportive care; NDB - nintedanib

Table 4 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib and a restricted population with percent predicted FVC of 50-80% and a treatment stopping rule if the disease progresses by more than a 10% decline in percent predicted FVC for both treatments

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£22,539.29	2.9227	
Pirfenidone	[redacted]	3.1939	[redacted]
Nintedanib	[redacted]	3.2376	[redacted]

BSC – Best supportive care; NDB - nintedanib

Table 5 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib and a restricted population with percent predicted FVC of 50-80% and a treatment stopping rule if the disease progresses by more than a 10% decline in percent predicted FVC for pirfenidone only

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£22,539.29	2.9227	
Pirfenidone	[redacted]	3.1939	[redacted]
Nintedanib	[redacted]	3.3139	[redacted]

BSC – Best supportive care

The ERG also provides analyses for the milder IPF population with percent predicted FVC >= 80% (Table 6) which showed a similar ICER to the whole population. The ERG urges caution in comparing the results for subgroups defined according to percent predicted FVC. In the model, the discontinuation rate is assumed to be similar for all percent predicted FVC population groups and so the treatment cost is similar for all percent predicted FVC populations. The ERG is unclear whether the discontinuation rate may vary between percent predicted FVC populations in clinical practice. Similarly, it is unclear whether there would be

differences in the treatment efficacy or other model parameters for different subgroups defined by percent predicted FVC.

Table 6 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib and a restricted population with a percent predicted FVC of greater than 80%

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£17,049.09	3.3238	
Pirfenidone	[redacted]	3.6830	[redacted]
Nintedanib	[redacted]	3.7376	[redacted]

BSC – Best supportive care; NDB - nintedanib

Table 7 shows an analysis for the whole population with a stopping rule for pirfenidone but not for nintedanib.

Table 7 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib and a treatment stopping rule for pirfenidone only if the disease progresses by more than a 10% decline in percent predicted FVC

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£20,029.23	3.0999	
Pirfenidone	[redacted]	3.3573	[redacted]
Nintedanib	[redacted]	3.5013	[redacted]

BSC – Best supportive care

The ERG has also run sensitivity analyses using the Weibull distribution for the survival distribution, rather than the log-logistic distribution. These results are shown in Table 8 for the whole population and for a restricted population with percent predicted FVC of >=80% respectively (Table 9).

Table 8 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib for the whole population with Weibull distribution for survival

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£17,381.37	2.3619	
Pirfenidone	[redacted]	2.5696	[redacted]
Nintedanib	[redacted]	2.5975	[redacted]

BSC – Best supportive care

Table 9 Full incremental cost effectiveness analysis for all comparators – with PAS for pirfenidone and nintedanib for a restricted population with percent predicted FVC >=80% with Weibull distribution for survival

Treatment	Total costs	Total QALYs	ICER (£/QALY)
BSC	£14,742.34	2.4851	
Pirfenidone	[redacted]	2.6957	[redacted]
Nintedanib	[redacted]	2.7243	[redacted]

BSC – Best supportive care; NDB - nintedanib