Section A: Clarification on effectiveness data

Clinical trials

A1. **Priority question:** Please confirm the number of UK participants in each of the nintedanib trials (TOMORROW and INPULSIS) and provide their baseline characteristics (please replicate Tables 16 and 17 of the company submission for UK sites only).

Note that within the short timeframe, an analysis of UK patients from TOMORROW could not be provided; instead, please find below the characteristics of European participants in the study (Table 1).

Table 1: Characteristics of participants in the TOMORROW studies – EUROPE (Table 16 from original MS)

Baseline characteristic	Placebo (N=54)	Nintedanib				Total (N=264)
		50 mg Once daily (N=60)	50 mg Twice daily (N=53)	100 mg Twice Daily (N=52)	150 mg Twice Daily (N=45)	
Male, no. (%)	38 (70.4)	46 (76.7)	38 (71.7)	39 (75.0)	39 (86.7)	200 (75.8)
Age in years, mean (SD)	66.9 (8.3)	66.0 (10.2)	64.9 (8.5)	66.4 (8.5)	66.0 (7.5)	66.0 (8.7)
BMI, mean (SD)	27.69 (4.2)	27.93 (3.6)	28.11 (3.9)	27.65 (3.2)	27.84 (3.1)	27.85 (3.6)
Weight in Kg, mean (SD)	78.9 (14.1)	80.3 (12.6)	78.8 (14.9)	78.4 (14.5)	81.0 (12.3)	79.5 (13.7)
Smoking Status						
Never smoked	20 (37.0)	20 (33.3)	24 (45.3)	23 (44.2)	12 (26.7)	99 (37.5)
Former smoker	31 (57.4)	39 (65.0)	28 (52.8)	28 (53.9)	32 (71.1)	158 (59.9)
Current smoker	3 (5.6)	1 (1.7)	1 (1.9)	1 (1.9)	1 (2.2)	7 (2.7)
Time since IPF diagnosis, years, mean (SD)	1.5 (1.6)	1.3 (1.3)	1.0 (1.3)	1.4 (1.3)	0.7 (1.0)	1.2 (1.3)
Specimen from surgical lung biopsy available, no. (%)	-	-	-	-	-	-
FVC (L)						
Mean (SD)	2.8 (0.8)	2.8 (0.9)	2.7 (0.7)	2.9 (0.9)	2.9 (0.8)	2.8 (0.8)
Median FVC (L)	2.5	2.8	2.7	2.9	2.8	2.8
Percentage of	77.5	78.3	80.5	81.6	77.5	80.1

Baseline characteristic	Placebo (N=54)	Nintedanib				Total (N=264)
		50 mg Once daily (N=60)	50 mg Twice daily (N=53)	100 mg Twice Daily (N=52)	150 mg Twice Daily (N=45)	
predicted value,						
Median DLCO-mmol/min/kPa,	3.7	3.8	3.6	3.6	4.0	3.7
Median PaO2-mm Hg	-	-	-	-	-	-
Median SpO2 %, median	96.0	95.5	96.0	95.6	96.0	96.0

Table 2: Characteristics of participants in the INPULSIS studies – UK (Table 17 from original MS)

Baseline characteristic	INPULSIS-1		INPULSIS-2*	
	Nintedanib (N=33)	Placebo (N=12)	Nintedanib (N=0)	Placebo (N=0)
Male, no. (%)	25 (75.8)	9 (75.0)		
Age in years, mean (SD)	67.1 (9.1)	65.4 (6.6)		
BMI in kg/m^2, mean (SD)	30.3 (4.5)	29.7 (5.1)		
Weight in Kg, mean (SD)	88.8 (15.9)	84.7 (16.4)		
Smoking status, no. (%)				
Never smoked	7 (21.2)	2 (16.7)		
Former smoker	22 (66.7)	10 (83.3)		
Current smoker	4 (12.1)	0 (0)		
Time since IPF diagnosis, years, mean (SD)	1.4 (1.3)	1.7 (1.3)		
Specimen from surgical lung biopsy available, no. (%)	14 (42.4)	1 (8.3)		
FVC				
Mean-ml, (SD)	2954 (719)	3102 (971)		
Median-ml	2828	3273		
Percentage of predicted value, mean (SD)	83.7 (17.1)	87.6 (16.9)		
FEV1:FVC (%)	-	-		
DLco	-			
mmol/min/kPa, mean (SD)	4.5 (1.0)	4.2 (1.1)		
SpO2 %, mean (SD)	96.7 (1.5)	97.0 (0.9)		
Total SGRQ score$	38.4 (17.4)	40.8 (12.1)		

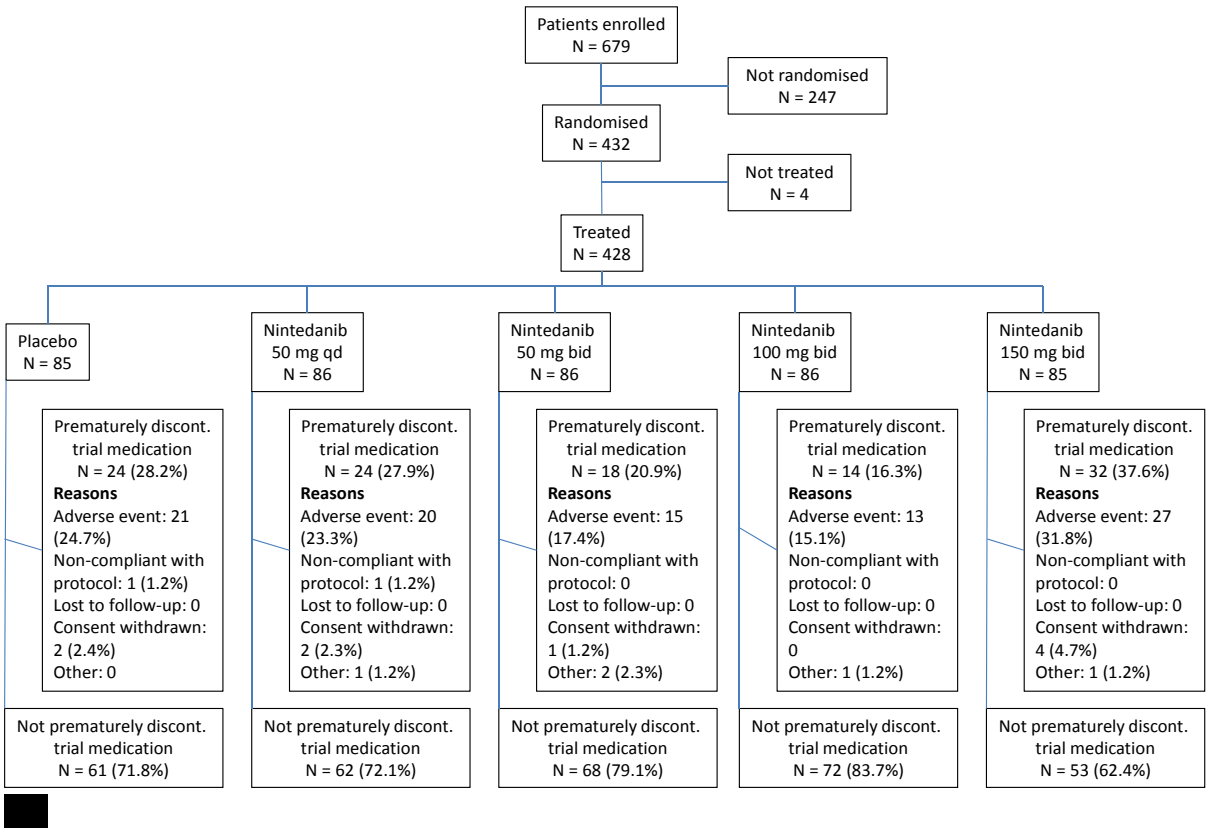
Please note there were no centres in the UK for INPULSIS-2.

A2. **Priority question:** Figures 9 and 10 of the company submission include reasons for treatment discontinuation and non-completion in the INPULSIS trials. Please provide

an updated Figure 8, to include the reasons for non-completion in the TOMORROW trial (this should also include patient numbers).

Patient disposition for the TOMORROW trial is shown in Figure 1 below. All patients not prematurely discontinuing trial medication completed the TOMORROW trial.

Figure 1: Patient Flow diagram for TOMORROW



A3. **Priority question:** On page 65 of the company submission it is stated that subgroup analyses of patients with a baseline forced vital capacity (FVC) of ≤70% compared with >70% of the predicted value were conducted using data from the INPULSIS trials. Please provide a rationale for why these FVC values were chosen.

This threshold had been chosen in consistency with a subgroup analysis performed in the preceding phase II TOMORROW trial [Richeldi et al. Eur Respir J 2011; 38 (55): 3S]. The 2011 ATS/ERS/JRS/ALAT evidence-based guidelines for diagnosis and management of IPF did not propose a formal staging system for classification of disease severity and there are no accepted criteria to define mild, moderate or severe IPF. There are no accepted thresholds of FVC %pred defining patient severity.

Additional post-hoc analyses using serial baseline FVC %pred thresholds of 80% and 90%, still resulting in subgroups with a sufficient number of patients, have also been conducted. Both subgroup analyses of pooled data from the INPULSIS trials confirm that nintedanib 150 mg bid reduced the decline in lung function by a similar magnitude in patients with IPF with

baseline FVC >80% and ≤80% predicted [Maher et al. ERS 2015] and with baseline FVC >90% and ≤90% [Kolb et al. Am J Respir Crit Care Med 191;2015:A1021], respectively.

A4. **Priority question:** Please provide the correct reference for the statement on page 66 of the company submission: "the results of the subgroup analysis for nintedanib did not find any statistically significant differences in outcomes by subgroup". The reference cited in the company submission (Costabel, 2014) is about pirfenidone.

The correct reference is the Summary of Clinical Efficacy (Ingelheim B. data on file - phase III trial (trial no 1199.32 and 1199.34) Summary of Clinical Efficacy. Nintedanib (BIBF 1120). 2014.), which was part of the list of references of the original submission.

Systematic literature review and network meta-analysis

A5. **Priority question:** Please supply the WinBUGS code for the network meta-analysis (section 4.10 of the company submission).

See Winbugs code_A5.docx

A6. **Priority question:** Tables 29–37 of the company submission present results of the network meta-analysis. These tables indicate that the denominator (for proportions of patients) for each outcome is 'patients at risk' (and for the INPULSIS trials it can be seen that there are fewer 'patients at risk' than 'patients randomised'). Please describe how 'patients at risk' was defined. Is the same definition used in the trials of comparator drugs which are presented in these tables?

Patients at risk were defined as treated randomised patients. In TOMORROW there were 2 patients in placebo and 1 in nintedanib arm that did not receive treatment. In INPULSIS-1 there were two patients in placebo that did not receive treatment. In INPULSIS-2 there was 1 patient in placebo and 2 in the nintedanib arm that did not receive treatment.

Boehringer Ingelheim has no information about the definition of patients at risk for the other trials.

A7. Please clarify the processes used for data extraction of the studies included in the systematic literature review. On page 37 of the company submission it is stated that "Data extraction was performed by one researcher, documented in Microsoft Excel data extraction forms and reviewed by a second researcher." Please clarify whether or not this means that the second reviewer checked the data extracted by the first for accuracy. Additionally, please clarify how discrepancies in the reviewers' judgements were resolved.

The second reviewer checked for accuracy. Discrepancies in reviewers' judgement were resolved by a third, more senior reviewer.

A8. In Figure 5 of the company submission it is stated that 6 references were identified from regulatory agencies (top right-hand side of the PRISMA diagram). Please clarify whether these are the 6 excluded studies listed in Table 9 of the company submission.

No. The regulatory agency documents were only used to verify the inclusion of all relevant trials for the RCT search for nintedanib. These searches are not formally required, but these sites and documents were reviewed and checked to ensure that they did not contain data which had not previously been published in the primary reference or CSRs. Regulatory documents were not required to provide information for nintedanib in the NMA.

A9. Please clarify if the search strategy used for the network meta-analysis was the same as the one used for the systematic review (section 4.10 of the company submission). If not, please specify any differences.

The search strategy for the systematic literature review was the same for the NMA. The only difference between the RCT search and the NMA search was the PICOS criteria to ensure the capture of additional comparators. The PICOS criteria for the NMA are in Table 21 of the submission.

Data clarifications and reference requests

A10. **Priority question:** Please provide a citation, and the reference document(s) for the acute exacerbations data presented in Table 30 of the company submission, for the TOMORROW trial. These data are not available in the publication provided (Richeldi 2011).

The AEs reported as "Progression of IPF" in Table 2 of the publication were used as a proxy. This was based on the following definition for acute exacerbations (Richeldi 2011, appendix): "Acute exacerbations were defined as progression of dyspnoea over several days to 4 weeks, new parenchymal ground glass abnormalities on X-ray or HRCT, and a decrease in PaO2 ≥10 mmHg or increase in alveolar-arterial (A-a) oxygen gradient, within a 1 month period that could not be otherwise explained."
Using this proxy does not have any material effect on the results.

A11. **Priority question:** Table 31 of the company submission presents the results from the network meta-analysis for loss of lung function, defined as a decline of 10% or more in forced vital capacity percent predicted (FVC%Pred; a standardisation of forced vital capacity). On page 93 of the company submission it is stated that the FVC%Pred data for the nintedanib trials (TOMORROW and INPULSIS) were obtained from a post-hoc analysis, based on observed data only.

i. Table 31 presents 2 sets of data for each trial (one set excluding deaths, one set including deaths). Please provide a justification for presenting 2 data sets.

The analysis on Loss of Lung Function (LoLF) was performed twice to explore the changes in the results if the definition of the outcomes FVC%Pred drop and death were combined. Excluding death from the outcome was useful for the economic model; however, data were not always reported in this way. For example King et al. 2014 includes death, whereas evidence was found for both from Noble et al. 2011:

Table 3: Evidence from CAPACITY trial

	Treatment	**Observed events**	**Patients at risk**	**Source**
Excluding death	PFN	59	345	EMA report 2010
	PBO	80	347	
Including death	PFN	74	345	Publication Noble 2011
	PBO	106	347	

ii. Please provide a citation, and the reference document(s), for the post-hoc analysis of the TOMORROW and INPULSIS trials.

There were analyses performed as per protocol on TOMORROW and INPULSIS 1 and 2; data presented in the publications and in other section of the MS. The post-hoc analysis refers to additional retrospective analysis of the individual patient data (IPD) that were performed solely with the objective to obtain model inputs for the cost-effectiveness analysis. There is no publication for the post-hoc analyses of the IPD (for the cost-effectiveness model). For your consideration, please see additional information about this analysis both here are in other questions where it is requested.

Specifically for the outcome of the loss of lung function analyses please find below the summary tables describing the number of observations of 10-points drop in FVC%Pred. from the INPULSIS trial.

Table 4: Summary table describing the number of observations of 10-points drop in FVC%Pred (Nintedanib arm, INPULSIS)

			Interval starting before 1st exacerbation (investigator)		Interval starting after 1st exacerbation (investigator)		Interval starting before 1st exacerbation (adjudicator)		Interval starting after 1st exacerbation (adjudicator)	
FVCpp at start of 3-month interval	**Number of observations**	**Number of 10-pt drop**	**Number of observations**	**Number of 10-pt drop**	**Number of observations**	**Number of 10-pt drop**	**Number of observations**	**Number of 10-pt drop**	**Number of observations**	**Number of 10-pt drop**
20-29	0	0	0	0	0	0	0	0	0	0
30-39	1	0	1	0	0	0	1	0	0	0
40-49	50	2	44	2	6	0	49	2	1	0
50-59	271	9	266	8	5	1	268	9	3	0
60-69	467	16	464	15	3	1	466	15	1	1
70-79	500	15	496	14	4	1	500	15	0	0
80-89	403	19	402	19	1	0	403	19	0	0
90-99	286	9	286	9	0	0	286	9	0	0
100-109	152	6	152	6	0	0	152	6	0	0
110-119	85	3	85	3	0	0	85	3	0	0
120-129	37	3	37	3	0	0	37	3	0	0
130-139	7	2	7	2	0	0	7	2	0	0
140-149	2	2	2	2	0	0	2	2	0	0
150-159	0	0	0	0	0	0	0	0	0	0

Table 5: Summary table describing the number of observations of 10-points drop in FVC%Pred (Placebo arm, INPULSIS)

			Interval starting before 1st exacerbation (investigator)		Interval starting after 1st exacerbation (investigator)		Interval starting before 1st exacerbation (adjudicator)		Interval starting after 1st exacerbation (adjudicator)	
FVCpp at start of 3-month interval	**Number of observations**	**Number of 10-pt drop**	**Number of observations**	**Number of 10-pt drop**	**Number of observations**	**Number of 10-pt drop**	**Number of observations**	**Number of 10-pt drop**	**Number of observations**	**Number of 10-pt drop**
20-29	1	0	1	0	0	0	1	0	0	0
30-39	7	0	7	0	0	0	7	0	0	0
40-49	41	0	38	0	3	0	41	0	0	0
50-59	204	15	203	15	1	0	204	15	0	0
60-69	336	14	334	14	2	0	334	14	2	0
70-79	314	14	313	14	1	0	313	14	1	0
80-89	253	16	251	15	2	1	251	15	2	1
90-99	164	12	163	12	1	0	163	12	1	0
100-109	102	5	102	5	0	0	102	5	0	0
110-119	55	7	55	7	0	0	55	7	0	0
120-129	17	3	17	3	0	0	17	3	0	0
130-139	10	2	10	2	0	0	10	2	0	0
140-149	5	0	5	0	0	0	5	0	0	0
150-159	4	1	4	1	0	0	4	1	0	0

iii. What was the quantity of missing data in each arm of each trial in the post-hoc analysis of the TOMORROW and INPULSIS trials? For each trial arm, please provide the number of participants not contributing data and the total number of participants (n/N).

In TOMORROW, out of 170 patients there were 47 patients (29 nintedanib and 18 placebo), that did not have FVC%Pred data over the entire 12 months period and for which no progression was observed. It was assumed that these patients had not progressed. There were more instances with incomplete FVC%Pred data, but on those cases we observed progression in following timepoints and therefore, they were classified them as progressers and are not missing as such.
In INPULSIS, out of 1061 patients we had 181 patients (114 nintedanib and 67 placebo) with incomplete data and no progression observed; it was assumed that these patients did not progress.

A12. **Priority question:** On page 95 of the company submission it is stated that the progression free survival data for the nintedanib trial presented in Table 32 (Richeldi 2014) were obtained from a post-hoc analysis. Please provide a citation, and the reference document, for this post-hoc analysis.

Please refer to A11 regarding the post-hoc analysis reference.
The nintedanib trial data was analysed to obtain a HR for nintedanib vs. placebo, by replicating the methods presented in the Noble et al. 2011 paper. A composite endpoint of progression-free survival (PFS) was defined: time to confirmed ≥10% decline in FVC%pred, or ≥15% decline in Dlco%Pred, or death [Noble et al. 2011]. A Cox proportional hazard model was run with geographic region (USA vs. non-USA) as a stratum. The HR value for nintedanib vs. placebo was estimated to be 0.74 (0.60, 0.91).

A13. **Priority question:** The data for the INPULSIS trials (Richeldi 2014) presented in Table 37 of the company submission do not correlate with the data in Figure 9 of the company submission. Have data for INPULSIS II been omitted from Table 37 in error? Alternatively, was a different source used for the INPULSIS data in Table 37? If so, please provide the reference.

Tables 35, 37, 83, 87, 88, 90, 91 and 122 in the submission contained small errors in values due to an earlier version of the NMA report being used to write up the submission. These values have been corrected (along with any corresponding forest plots) in this corrected version. Please note that the correct values were originally used in the cost effectiveness model to generate results i.e. the results section is not affected by this error, and the results in the original submission are correct.

Table 6: Serious GI events evidence

Study	Treatment	Observed events	Patients at risk

Richeldi 2011	NDB	4	85
Richeldi 2011	PBO	0	85
Richeldi 2014	NDB	19	638
Richeldi 2014	PBO	7	423
Noble 2011	PFN	8	345
Noble 2011	PBO	13	347
Martinez 2014	NAC	0	133
Martinez 2014	PBO	6	131

Abbreviations: NDB: nintedanib, PBO: placebo, PFN: pirfenidone, NAC: N-acetylcysteine

Table 7: Overall discontinuation evidence

Study	Treatment	Observed events	Patients at risk
Richeldi 2011	NDB	32	85
Richeldi 2011	PBO	24	85
Richeldi 2014	NDB	156	638
Richeldi 2014	PBO	80	423
Noble 2011	PFN	72	345
Noble 2011	PBO	62	347
King 2014	PFN	55	278
King 2014	PBO	39	277
Taniguchi 2010*	PFN	40	109
Taniguchi 2010*	PBO	31	107
Martinez 2014	NAC	34	133
Martinez 2014	PBO	29	131

*Values for patients who withdrew/discontinued the study; NDB: nintedanib, PBO: placebo, PFN: pirfenidone, NAC: N-acetylcysteine

Table 8: N-acetylcysteine vs. placebo; scenario 1 discontinuation due to AEs

Study	OR (95% CI)	p-value
Martinez 2014	0.65 (0.11, 3.96)	0.642

Table 9: Nintedanib vs. placebo; scenario 1 discontinuation overall

Study	OR (95% CI)	Weights FE (%)	Weights RE (%)
Richeldi 2011	1.54 (0.81, 2.92)	17.1	18.1
Richeldi 2014	1.39 (1.03, 1.88)	82.9	81.9
Pooled OR (95% CI)		1.41 (1.07, 1.86)	1.41 (1.07, 1.86)
p-value (test OR=1)		0.014	0.013
Heterogeneity	I^2=0%, chi-square p-value=0.782		

Table 10: Pirfenidone vs. placebo; scenario 1 discontinuation overall

Study	OR (95% CI)	Weights FE (%)	Weights RE (%)

Noble 2011	1.21 (0.83, 1.77)	48.9	46.6
King 2014	1.51 (0.96, 2.36)	31.3	33.0
Taniguchi 2010	1.42 (0.80, 2.52)	19.8	20.4
Pooled OR (95% CI)		1.35 (1.04, 1.74)	1.34 (1.04, 1.74)
p-value (test OR=1)		0.024	0.024
Heterogeneity	I^2=0%, chi-square p-value=0.753		

Table 11: NMA; scenario 1 discontinuation overall

	FIXED-EFFECTS (DIC=81.9, tot res dev 9.6)	**RANDOM-EFFECTS (DIC=83.6, tot res dev 10.1)**
Comparison	**Median OR (95% CrI)**	**Median OR (95% CrI)**
All vs. placebo		
placebo vs. placebo	1.00 (-)	1.00 (-)
nintedanib vs. placebo	1.42 (1.08, 1.87)	1.43 (0.79, 2.63)
pirfenidone vs. placebo	1.34 (1.04, 1.73)	1.35 (0.83, 2.24)
N-acetylcysteine vs. placebo	1.21 (0.68, 2.15)	1.21 (0.48, 3.01)
All vs. nintedanib		
placebo vs. nintedanib	0.71 (0.54, 0.93)	0.70 (0.38, 1.26)
nintedanib vs. nintedanib	1.00 (-)	1.00 (-)
pirfenidone vs. nintedanib	0.95 (0.65, 1.38)	0.94 (0.43, 2.05)
N-acetylcysteine vs. nintedanib	0.85 (0.45, 1.62)	0.85 (0.28, 2.48)
Nintedanib vs. all		
nintedanib vs. placebo	1.42 (1.08, 1.87)	1.43 (0.79, 2.63)
nintedanib vs. nintedanib	1.00 (-)	1.00 (-)
nintedanib vs. pirfenidone	1.06 (0.73, 1.54)	1.06 (0.49, 2.32)
nintedanib vs. N-acetylcysteine	1.17 (0.62, 2.21)	1.18 (0.40, 3.54)

Table 12: Ranking matrix; scenario 1 discontinuation overall

	Fixed effects				**Random effects**			
Ranking*	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
placebo	71.2%	27.7%	1.1%	0.0%	58.0%	34.8%	6.6%	0.7%
nintedanib	0.8%	10.6%	28.9%	59.8%	4.8%	13.0%	29.4%	52.8%
pirfenidone	2.8%	32.1%	46.4%	18.7%	8.2%	29.2%	41.4%	21.2%
N-acetylcysteine	25.3%	29.7%	23.5%	21.5%	29.0%	23.0%	22.7%	25.3%

*1: best, 4: worst

Table 13: OR values for overall discontinuation - NMA results

Comparison	OR median value	95% Confidence interval
NDB vs. PBO	1.42	1.08 – 1.87
PFN vs. PBO	1.34	1.04 – 1.73

A14. **Priority question:** Table 122 of the company submission presents odds ratios for overall discontinuation from the all evidence scenario of the network meta-analysis (fixed effects model). These data are used in the cost-effectiveness model. The data in Table 122 do not match the data in Table 90, suggesting that there is an error in one of these tables. Please check the data in these tables and provide corrected tables. Please also provide a corrected model if appropriate.

Please see response to question A13.

A15. On page 28 of the company submission, it is stated that each year 5000 patients with IPF die. Please provide the correct reference for this statement. The reference provided is a conference abstract report of the INPULSIS trial and does not provide this mortality information.

This was a referencing error. The correct reference should be: Navaratnam V, Fleming KM, West J, Smith CJ, Jenkins RG, Fogarty A, et al. The rising incidence of idiopathic pulmonary fibrosis in the U.K. Thorax. 2011;66(6):462-7.

See Navaratnam_2011_A15.pdf

A16. The company submission does not present the results of the sensitivity analyses to investigate missing data effects, using multiple imputation approaches. For the INPULSIS trials this is available in the supplementary appendix to the published paper. Please provide the equivalent results for the TOMORROW trial.

For TOMORROW, a sensitivity analysis corresponding to the INPULSIS sensitivity analysis 3 has been conducted. This is a conservative analysis, as it uses the slope (SE) estimates in placebo patients from the primary model as a basis for the multiple imputation of missing week 52 data, assuming the treatment effect does not persist after drug discontinuation. Data selection and derivations were performed as for the primary analysis of TOMORROW but with the analysis method for MI sensitivity analysis 3 as performed on the INPULSIS data. Results are presented in Table 14.

Results of this sensitivity analysis show that the adjusted annual rate of decline in FVC was lower in the nintedanib group (-0.093 L/yr) than in the placebo group (-0.198 L/yr). The adjusted difference in the annual rate of decline between nintedanib and placebo was 0.105 L/yr (95% CI: 0.020, 0.189) and was statistically significant (p=0.015).

Table 14: Rate of decline in FVC (L/yr) over 52 weeks in TOMORROW Period 1 – Multiple Imputation Sensitivity Analysis 3 - Randomised Set

1199.32	Placebo	Nintedanib 150 mg bid
Number of patients in RS	87	86
Number of analysed patients	87	86
Rate of decline over 52 weeks		
Adjusted[1] rate (SE)	-0.198 (0.030)	-0.093 (0.030)
95% CI	(-0.257, -0.138)	(-0.152, -0.034)
Comparison vs. Placebo		
Adjusted[1] difference (SE)		0.105 (0.043)
95% CI		(0.020, 0.189)
p-value		0.0152

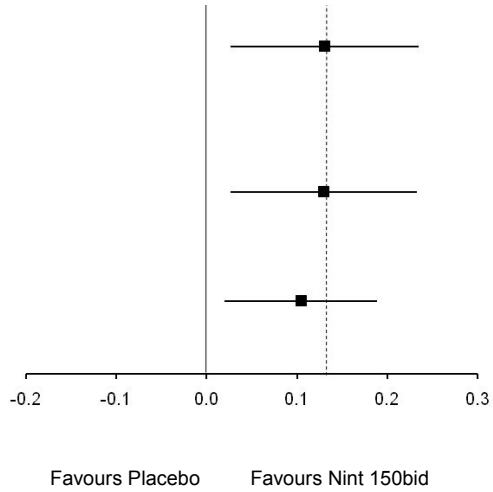
RS: Randomised Set; SE: Standard Error
Data selection was based on original derivation rules in used in 1199.30 (FVC data up to visit 9; no time windowing applied). For patients with no on−treatment FVC data, baseline value was included.
[1] For each imputation: Based on a random coefficient regression with fixed effects for treatment, gender, age, height and random effect of patient-specific intercept and time. Within−patient errors are modelled by an unstructured variance−covariance matrix. Inter-individual variability is modelled by a variance−components variance−covariance matrix.

Multiple imputation of missing Week 52 data:
Sensitivity analysis 3: Imputation in pattern 3 is based on based on the slope (SE) estimates in placebo patients from the Phase III primary analysis model (MMRM). Imputation in pattern 4 is based on the slope (SE) estimates in all placebo patients, but using a truncated distribution. **Pattern 3:** Patients without a 52-week FVC value who were alive at Week 52 **Pattern 4:** Patients without a 52-week FVC value that died before Week 52.

The results of the analyses performed are consistent with the primary analysis results presented in the CTR for Study TOMORROW Period 1 i.e. treatment effect estimates were similar to those of the primary analysis, with overlapping confidence intervals (See Figure 2).

Figure 2: Sensitivity analyses for the rate of decline in FVC (L/yr) over 52 weeks in TOMORROW Period 1 – Randomised Set

Event	N analysed Placebo	N analysed Nint 150 bid	Adjusted[1] difference vs. placebo [95% CI]	Nint 150bid – Placebo adjusted difference in rate of decline of FVC at 52 weeks [L/yr] and 95% confidence interval	p-value
Primary Analysis[1]	83	84	0.131 [0.027;0.235]		0.0136
Sensitivity to data handling:					
Primary analysis model from the Phase III trials[2]	83	84	0.130 [0.027;0.233]		0.0134
Multiple Imputation Sensitivity Analysis 3	87	86	0.105 [0.020;0.189]		0.0152



[1] Based on a MMRM with terms for treatment* time, gender* height, gender* age, patient effect, patient* time (patient effect and patient* time random, all other effects fixed) and a variance component variance−covariance matrix

[2] Based on a random coefficient regression with fixed effects for treatment, gender, age, height and random effect of patient-specific intercept and time. Within−patient errors are modelled by an unstructured variance−covariance matrix. Inter-individual variability is modelled by a variance−components variance−covariance matrix.

Multiple imputation of missing Week 52 data:
Sensitivity analysis 3: Imputation in pattern 3 is based on based on the slope (SE) estimates in placebo patients from the Phase III primary analysis model (MMRM). Imputation in pattern 4 is based on the slope (SE) estimates in all placebo patients, but using a truncated distribution. **Pattern 3:** Patients without a 52-week FVC value who were alive at Week 52 **Pattern 4:** Patients without a 52-week FVC value that died before Week 52.

A17. Please explain the following discrepancies in the reporting of adverse events leading to discontinuations:

i. Figure 9 (24 people in the placebo group of INPULSIS-1 prematurely discontinued due to adverse events) compared with Table 93 (22 people in the placebo group of INPULSIS-1 had adverse events leading to discontinuation)

ii. Figure 10 (37 people receiving nintedanib in the of INPULSIS-2 trial prematurely discontinued due to adverse events) compared with Table 93 (58 people in the nintedanib arm of INPULSIS-2 had adverse events leading to discontinuation)

iii. Figure 10 (25 people receiving placebo in the INPULSIS-2 trial prematurely discontinued due to adverse events) compared with Table 93 (33 people in the placebo group of INPULSIS-2 had adverse events leading to discontinuation).

The discrepancy is due to a subtle difference in reporting:

- premature discontinuation due to adverse events
- adverse events leading to discontinuation

The former (as reported in Figures 9 and 10 in the submission) is derived from the Termination of Trial Medication eCRF page:

Boehringer Ingelheim
Patient X3 Trial 1199_0032
Investigator John Smith
TTM Blank page ☐

DCM: TTM DCI: TTM View(s): TTM

TERMINATION OF TRIAL MEDICATION

DG = DRUGDISC

Date of last administration of trial drug [DRGYMD] DRGSTPDT (d)

DG = TERMC

☐ 1 = The patient did not prematurely stop the trial medication TERMCDC.TERMCF

OR the patient prematurely stopped the trial drug due to:

☐ 2 = (Adverse event) unexpected worsening of disease under study
☐ 3 = (Adverse event) unexpected worsening of other pre-existing disease
☐ 4 = (Adverse event) other adverse event

If 2, 3 or 4 is chosen, be sure there is a corresponding entry on AE page

☐ 5 = Non compliant with protocol (please explain below)
☐ 6 = Lost to follow-up (please explain below)
☐ 7 = Patient refusal to continue taking trial medication
☐ 8 = Other (please explain below)

ATRCD1 (d)
ATRSDT1 (d)
ATRSTTM1 (d)
ATRCD2 (d)
ATRSDT2 (d)
ATRSTTM2 (d)
TERMPOP (d)

Explanation/Comment (Primary reason 5, 6 or 8):
[TERMX]

The latter (as reported in Table 93 in the submission) is derived from the Adverse Events eCRF page:

Boehringer Ingelheim
Patient X3 Trial 1199_0032
Investigator John Smith
AE Blank page ☐

DCM: AE DCI: ADV_EVENTS
View(s): AE ADVERSE EVENTS

QG = AED

Adverse Event Number [ ] AENUM (d)

Event [AEMNM]

Start date [AEONYMD] AEOUT.AEOUTF Outcome of event End date [AEENDYMD] Complete if Outcome of event is Recovered or Fatal

☐ 1=Recovered
☐ 2=Not yet recovered
☐ 3=Sequelae
☐ 4=Fatal
☐ 5=Unknown

AECMSIG (d)
AEENDCEN (d)
AEENDIMP(d)
AELLT (d)
AELLTCD (d)
AEONIMP(d)
AEONDT (d)
AEENDDT (d)

AETHPA.YNF
Therapy for event
☐ 0=No
☐ 1=Yes, enter drug or non-drug therapy on the Concomitant Therapy form

AEINT.AEINTF
Intensity of event
Indicate the most severe intensity
☐ 1=Mild
☐ 2=Moderate
☐ 3=Severe

AEACTE.AEACTEF
Action taken with trial drug due to AE?
☐ 1=Neither discontinued nor reduced (Includes temporary discontinuation and reintroduction at previous dose/dose increase and NA)
☐ 2=Dose permanently reduced
☐ 3=Drug permanently discontinued

This information is only reconciled in one direction. Patients with a response of 2, 3 or 4 on the Termination of Trial Medication page must either have an AE with action taken=3 (drug permanently discontinued) or outcome=4 (fatal) [or both]. It is possible for a patient to have had a fatal AE whilst still taking trial drug in which case no explicit action would have been taken with the trial drug due to the AE hence the action taken with trial drug due to AE may be 1 (neither discontinued nor dose reduced). Conversely, patients with action taken=3 (drug permanently discontinued) on the Adverse Events eCRF page are not required to have the reason for trial termination recorded as AE. The patient may have more than one reason for

discontinuing the trial medication but only the primary reason can be captured on the Termination of Trial Medication page.

A18. Please provide a citation and the reference document(s) used for the TOMORROW trial data in Table 33 of the company submission (6 Minute Walk Test). These data are not presented in Table 18 of the submission and are not available in the TOMORROW publication (Richeldi 2011).

The correct reference is the TOMORROW clinical trial report, which was part of the list of references of the original submission (Brun M, Luedtke D, Kluglich M, Juhel N, Roulot S. A 52 week, double blind, randomized, placebo-controlled trial evaluating the effect of BIBF 1120 administered at oral doses of 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid on Forced Vital Capacity decline during one year, in patients with Idiopathic Pulmonary Fibrosis, with optional active treatment extension until last patient out. [Clinical trial report].).

A19. Table 34 of the company submission presents the results from the network meta-analysis for serious cardiac events.

i. What is the definition of serious cardiac events?

The definition of serious cardiac events varied across the studies analysed. Moreover, it was noted that given that this definition represents a larger group of AEs based on the system organ class (SOC) (cardiac), there may be additional heterogeneity of the nature of the serious cardiac event. As data were not always broken down for all studies, no attempt was made to address such clinical heterogeneity in the composition of the SAE classes. Heterogeneity analysis was performed across the study outcomes (defined broadly as serious cardiac events).
The SAE data for PFN were extracted from the NICE submission Manufacturer's Submission (MS) report [2011] for the CAPACITY trial – no clear definition was reported in any of the sources that we identified for this trial.
In both INPULSIS trials, a SAE was defined as any AE which resulted in death, was immediately life-threatening, resulted in persistent or significant disability or incapacity, required or prolonged patient hospitalisation, was a congenital anomaly or birth defect, or was deemed serious for any other reason if it was an important medical event when based upon appropriate medical judgement which may have jeopardised the patient and may have required medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Additionally in Japan, an AE which possibly led to disability was to be reported as an SAE.
In the TOMORROW trial a SAE was defined as defined as fatal, life-threatening, disabling, incapacitating, requiring hospitalisation, or medically significant.

ii. Please provide a citation and the reference document(s) used for the TOMORROW trial data in Table 34. These data are not presented in Table 18 and not available in the TOMORROW publication (Richeldi 2011).

The source of the data is provided below (reference Summary of Clinical Safety 2014). Note values below have been cross-checked for the outcomes of interest with the IPD.

Table 2.1.7.2: 1 Serious adverse events with an incidence of more than 2% of patients in either treatment group in SG-1.2, by SOC and preferred term, sorted by incidences in the nintedanib 150 mg bid arm / TS

System organ class Preferred term	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	85 (100.0)	85 (100.0)
Patients with any SAE	26 (30.6)	23 (27.1)
Respiratory, thoracic and mediastinal disorders	14 (16.5)	7 (8.2)
Idiopathic pulmonary fibrosis	9 (10.6)	3 (3.5)
Dyspnoea	3 (3.5)	1 (1.2)
Infections and infestations	11 (12.9)	6 (7.1)
Bronchitis	2 (2.4)	1 (1.2)
Pneumonia	5 (5.9)	1 (1.2)
Respiratory tract infection	2 (2.4)	1 (1.2)
Gastrointestinal disorders	0 (0.0)	4 (4.7)
Diarrhoea	0 (0.0)	3 (3.5)
General disorders and administration site conditions	0 (0.0)	2 (2.4)
Investigations	1 (1.2)	2 (2.4)
Musculoskeletal and connective tissue disorders	2 (2.4)	2 (2.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (1.2)	2 (2.4)
Cardiac disorders	7 (8.2)	1 (1.2)
Nervous system disorders	2 (2.4)	1 (1.2)
Surgical and medical procedures	2 (2.4)	0 (0.0)

MedDRA version used for reporting: 13.0

iii. Please clarify the source used for the INPULSIS trial data in Table 34. Is it Table S10 of the appendix to the published paper ('serious adverse event cardiac disorder')?

The source is provided below (reference: Summary of Clinical Safety 2014):

Table 2.1.7.1: 1 Serious adverse events with an incidence of more than 1% of patients in either treatment group in SG-1.1, by SOC and preferred term, sorted by frequency in the nintedanib 150 mg bid group / TS

System organ class/ Preferred term	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	423 (100.0)	638 (100.0)
Patients with SAEs	127 (30.0)	194 (30.4)
Respiratory, thoracic and mediastinal disorders	61 (14.4)	77 (12.1)
Idiopathic pulmonary fibrosis	39 (9.2)	42 (6.6)
Pulmonary hypertension	9 (2.1)	11 (1.7)
Dyspnoea	6 (1.4)	3 (0.5)
Respiratory failure	8 (1.9)	2 (0.3)
Infections and infestations	36 (8.5)	54 (8.5)
Pneumonia	16 (3.8)	23 (3.6)
Bronchitis	2 (0.5)	8 (1.3)
Lower respiratory tract infection	5 (1.2)	1 (0.2)
Cardiac disorders	23 (5.4)	32 (5.0)
Myocardial infarction	2 (0.5)	7 (1.1)
Gastrointestinal disorders	7 (1.7)	19 (3.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	15 (3.5)	18 (2.8)
Squamous cell carcinoma	5 (1.2)	1 (0.2)
General disorders and administration site conditions	9 (2.1)	12 (1.9)
Nervous system disorders	10 (2.4)	11 (1.7)
Vascular disorders	10 (2.4)	11 (1.7)
Investigations	2 (0.5)	8 (1.3)
Musculoskeletal and connective tissue disorders	4 (0.9)	8 (1.3)
Hepatobiliary disorders	1 (0.2)	7 (1.1)
Injury, poisoning and procedural complications	10 (2.4)	7 (1.1)
Metabolism and nutrition disorders	5 (1.2)	3 (0.5)

MedDRA version used for reporting: 16.1

A20. Table 35 of the company submission presents the results from the network meta-analysis for serious gastrointestinal (GI) events:

i. What is the definition of serious GI events?

ii. Please clarify the source used for the TOMORROW trial data in Table 35. Is it Table S7 of the appendix to the published paper ('severe diarrhoea')? If so, please provide a justification for why the 'serious diarrhoea' data in Table S7 were not used.

iii. Please provide a citation and the reference document(s) used for the INPULSIS trial data in Table 35.

Please see responses to question A19.

Section B: Clarification on cost-effectiveness data

Utility values

B1. **Priority question:** Please provide more details on collection of utility values in the INPULSIS clinical trials, including:

i. how the data were collected

Utility values were captured as part of the INPULSIS clinical trials using the EQ-5D (3-level version) in its local adaptations. The EQ-5D was administered after the other PRO questionnaires (SGRQ, UCSD-SOBQ, CASA-Q cough domains, and PGI-C) and before any other trial-related procedures were performed.

ii. how frequently the data were collected

EQ-5D data were collected at visits 2, 6, 7, and 9, corresponding to weeks 0, 12, 24, and 52, respectively.

iii. how many patients contributed data

Please see below a breakdown of the observations by week for each trial arm (INPULSIS 1 and 2 pooled):

Table 15: Number of observations of utility values in INPULSIS 1 and 2 trials

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

iv. the quantity of missing data.

See Table 15. Please note that as only the correlation of EQ-5D and patient status (FVC%Pred category membership) was of interest, all available observations have been used. That is, regardless if patients were missing data in previous weeks/visits.
The distribution of EQ-5D at the beginning and the end of follow-up (1-year) is similar:
[redacted]

B2. Please provide the correct reference for the disutility values reported in section 5.4.6 of the company submission. These data are not available in the reference cited (Ara and Brazier 2010).

Instead of:
Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010;13(5):509-18.

The correct reference should be the HEDS Discussion Paper:
Ara R and Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition specific data are not available. Running head: EQ-5D scores with/without prevalent conditions. HEDS Discussion Paper 2010/11.

See Ara_201011_B2.pdf

Other model inputs

B3. **Priority question:** Please provide more details on collection of resource values in the INPULSIS clinical trials used in the model including:

i. how the data were collected

In the INPULSIS trials, healthcare resource utilisation was routinely captured during every study visit as part of the electronic case report form (eCRF). For example, pp.46-47 of the eCRF shows the corresponding questions for visit.
[redacted]See eCRF_B3i.pdf

ii. how frequently the data were collected

HCRU data were captured at every scheduled study visit from visit 3, i.e. at weeks 2, 4, 6, 12, 24, 36, and 52.

iii. how many patients contributed data

Please see below the number of patients contributing to the HCRU data broken down by visit.[redacted]Table 16: Number of patients with hospitalisations in INPULSIS clinical trials

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]Table 17: Number of visits with healthcare professions in INPULSIS trials

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[redacted]**Table 18: Number of procedures in INPULSIS trials**

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iv. the quantity of missing data.

Please note that, similarly to the EQ-5D analysis, the correlation between the resource use and the patient status (FVC%Pred) was of interest. If readings for a patient at an interval were not available it was assumed that the resource was not used.
Overall, after the synthesis of resource use and costs, a logical increase in annual costs with progression to lower FVC%Pred categories was observed (Figure 3). It was noted that deteriorating patients might contribute more to the missing data, and therefore, the resource use estimates might be underestimated for lower FVC%Pred categories. In terms of the incremental cost-effectiveness results this is likely to favour the active treatments that delay progression.

[redacted]**Figure 3: Total annual costs for each FVC%pred group**

[redacted]

B4. **Priority question:** In the model, only severe adverse events that occurred in the best supportive care arm were included (as described on pages 180–1 of the company submission). Please provide details of any severe adverse events that occurred during treatment with nintedanib or pirfenidone that did not occur in the best supportive care arms of the clinical trials included in the network meta-analysis. Please describe the potential cost and clinical effectiveness impacts of these severe adverse events.

Regarding the selection of AEs for the economic model all arms were considered (not only events that occurred in BSC [or PBO]) and from all relevant clinical trials. Contrary to the ERG's interpretation of the AEs selection, events that might not have occurred in such high

numbers in the control arm but occurred in the active treatment arms of the trials were selected. The criteria that were set covered the severity and seriousness of the event (1st criterion), and its significance in absolute terms (2nd) and relative to the comparator (3rd). In addition to the evidence presented in the MS, the serious adverse events from each relevant trial are presented below:

Figure 4: Richeldi et al. 2011 (TOMORROW) – Source Summary of Clinical Safety 2014

Table 2.1.7.2: 1 Serious adverse events with an incidence of more than 2% of patients in either treatment group in SG-1.2, by SOC and preferred term, sorted by incidences in the nintedanib 150 mg bid arm / TS

System organ class Preferred term	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	85 (100.0)	85 (100.0)
Patients with any SAE	26 (30.6)	23 (27.1)
Respiratory, thoracic and mediastinal disorders	14 (16.5)	7 (8.2)
Idiopathic pulmonary fibrosis	9 (10.6)	3 (3.5)
Dyspnoea	3 (3.5)	1 (1.2)
Infections and infestations	11 (12.9)	6 (7.1)
Bronchitis	2 (2.4)	1 (1.2)
Pneumonia	5 (5.9)	1 (1.2)
Respiratory tract infection	2 (2.4)	1 (1.2)
Gastrointestinal disorders	0 (0.0)	4 (4.7)
Diarrhoea	0 (0.0)	3 (3.5)
General disorders and administration site conditions	0 (0.0)	2 (2.4)
Investigations	1 (1.2)	2 (2.4)
Musculoskeletal and connective tissue disorders	2 (2.4)	2 (2.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (1.2)	2 (2.4)
Cardiac disorders	7 (8.2)	1 (1.2)
Nervous system disorders	2 (2.4)	1 (1.2)
Surgical and medical procedures	2 (2.4)	0 (0.0)

MedDRA version used for reporting: 13.0

Figure 5: Richeldi et al. 2014 (INPULSIS pooled) – Source Summary of Clinical Safety 2014

Table 2.1.7.1: 1 Serious adverse events with an incidence of more than 1% of patients in either treatment group in SG-1.1, by SOC and preferred term, sorted by frequency in the nintedanib 150 mg bid group / TS

System organ class/ Preferred term	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	423 (100.0)	638 (100.0)
Patients with SAEs	127 (30.0)	194 (30.4)
Respiratory, thoracic and mediastinal disorders	61 (14.4)	77 (12.1)
Idiopathic pulmonary fibrosis	39 (9.2)	42 (6.6)
Pulmonary hypertension	9 (2.1)	11 (1.7)
Dyspnoea	6 (1.4)	3 (0.5)
Respiratory failure	8 (1.9)	2 (0.3)
Infections and infestations	36 (8.5)	54 (8.5)
Pneumonia	16 (3.8)	23 (3.6)
Bronchitis	2 (0.5)	8 (1.3)
Lower respiratory tract infection	5 (1.2)	1 (0.2)
Cardiac disorders	23 (5.4)	32 (5.0)
Myocardial infarction	2 (0.5)	7 (1.1)
Gastrointestinal disorders	7 (1.7)	19 (3.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	15 (3.5)	18 (2.8)
Squamous cell carcinoma	5 (1.2)	1 (0.2)
General disorders and administration site conditions	9 (2.1)	12 (1.9)
Nervous system disorders	10 (2.4)	11 (1.7)
Vascular disorders	10 (2.4)	11 (1.7)
Investigations	2 (0.5)	8 (1.3)
Musculoskeletal and connective tissue disorders	4 (0.9)	8 (1.3)
Hepatobiliary disorders	1 (0.2)	7 (1.1)
Injury, poisoning and procedural complications	10 (2.4)	7 (1.1)
Metabolism and nutrition disorders	5 (1.2)	3 (0.5)

MedDRA version used for reporting: 16.1

Figure 6: Noble et al. 2011 (Source NICE TA – MS)

Table B5.9.3 Treatment-emergent SAEs that occurred in >2 patients and at a greater incidence in either pirfenidone group than in the placebo group in the randomised patient subset

Treatment-Emergent SAEs	Number of Patients, n (%)		
System Organ Class Preferred Term	Pirfenidone 1197 mg/day (N = 87)	Pirfenidone 2403 mg/day (N = 345)	Placebo (N = 347)
Patients with Any TE SAE	28 (32.2%)	113 (32.8%)	109 (31.4%)
Cardiac Disorders	11 (12.6%)	21 (6.1%)	17 (4.9%)
Coronary Artery Disease	3 (3.4%)	6 (1.7%)	2 (0.6%)
Atrial Fibrillation	3 (3.4%)	3 (0.9%)	2 (0.6%)
Angina Pectoris	2 (2.3%)	3 (0.9%)	2 (0.6%)
Cardiac Failure Congestive	0	2 (0.6%)	1 (0.3%)
Sick Sinus Syndrome	0	2 (0.6%)	0
Gastrointestinal Disorders	**3 (3.4%)**	**8 (2.3%)**	**13 (3.7%)**
Colitis	0	2 (0.6%)	1 (0.3%)
Gastrooesophageal Reflux Disease	0	2 (0.6%)	0
General Disorders and Administration Site Conditions	**3 (3.4%)**	**8 (2.3%)**	**5 (1.4%)**
Chest Pain	0	4 (1.2%)	0
Infections and Infestations	**10 (11.5%)**	**27 (7.8%)**	**32 (9.2%)**
Respiratory Tract Infection	0	2 (0.6%)	0
Injury, Poisoning and Procedural Complications	**1 (1.1%)**	**10 (2.9%)**	**2 (0.6%)**
Fall	0	3 (0.9%)	1 (0.3%)
Hip Fracture	0	2 (0.6%)	0
Investigations	**1 (1.1%)**	**2 (0.6%)**	**3 (0.9%)**
Liver Function Test Abnormal	1 (1.1%)	2 (0.6%)	0
Musculoskeletal and Connective Tissue Disorders	**3 (3.4%)**	**7 (2.0%)**	**4 (1.2%)**
Intervertebral Disc Protrusion	0	2 (0.6%)	0
Bladder Cancer	0	3 (0.9%)	1 (0.3%)
Small Cell Lung Cancer Stage Unspecified	0	2 (0.6%)	1 (0.3%)
Rectal Cancer	2 (2.3%)	0	0
Nervous System Disorders	**3 (3.4%)**	**8 (2.3%)**	**10 (2.9%)**
Syncope	1 (1.1%)	3 (0.9%)	1 (0.3%)
Cerebrovascular Accident	0	2 (0.6%)	1 (0.3%)
Psychiatric Disorders	**0**	**2 (0.6%)**	**2 (0.6%)**
Suicidal Ideation	0	2 (0.6%)	0
Renal and Urinary Disorders	**2 (2.3%)**	**8 (2.3%)**	**5 (1.4%)**
Renal Failure Acute	2 (2.3%)	3 (0.9%)	2 (0.6%)
Nephrolithiasis	0	2 (0.6%)	0
Respiratory, Thoracic and Mediastinal Disorders	**11 (12.6%)**	**40 (11.6%)**	**46 (13.3%)**
Pneumothorax	2 (2.3%)	4 (1.2%)	1 (0.3%)
Pleural Effusion	1 (1.1%)	2 (0.6%)	0
Pulmonary Embolism	3 (3.4%)	1 (0.3%)	1 (0.3%)
Vascular Disorders	**3 (3.4%)**	**6 (1.7%)**	**3 (0.9%)**
Aortic Aneurysm	1 (1.1%)	2 (0.6%)	1 (0.3%)
Hypotension	0	2 (0.6%)	1 (0.3%)

Table 19: King et al. 2014 (extracted from the text)

	PFN		**PBO**	
Total number of patients	278		277	
Serious adverse events (excluding IPF)	52	(18.71%)	56	(20.22%)
Serious adverse events (including IPF)	55	(19.78%)	69	(24.91%)

For nintedanib, the events that occurred only in the active treatment arm and not in the control, in addition to what we have already included in the analysis, were “general disorders

and administration site conditions”; occurring twice. All the other SAEs were balanced between nintedanib and placebo.
For pirfenidone, King et al. 2014 did not report a breakdown of SAEs and therefore there is uncertainty as to the nature of the events and their occurrence. In the NICE TA for pirfenidone (MS) we found a table that contains evidence on SAEs. The SAEs that were unique to pirfenidone are: sick sinus syndrome, chest pain, respiratory tract infection, hip fracture, intervertebral disc protrusion, suicidal ideation, nephrolithiasis, and pleural effusion. The above events for pirfenidone could lead to substantial cost and clinical impairment for patients. However, given their low incidence and since the time on treatment is similar for nintedanib and pirfenidone, it is not expected that their inclusion to the model will have a material effect to the incremental costs and incremental clinical effectiveness; the inclusion of these additional events would most likely improve the cost-effectiveness of nintedanib.

B5. **Priority question:** Please provide a justification for using the outpatient procedure (OPROC) code instead of inpatient costs (NEL, NES) for the cost of mechanical ventilation during an inpatient stay (Table 141 and 159 of the company submission).

The difference in costs between the NEI_L/ NEI_S (Table 21 and Table 22) and OPROC (Table 20) was noted. The OPROC was selected because it had a much higher number of procedures comparing to the alternatives. Sensitivity analysis with the alternatives costs of mechanical ventilation were performed. The model results are not affected by the unit cost of mechanical ventilation.

Table 20: Calculation of the mechanical ventilation unit cost - outpatient procedure code (OPROC) (National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts, Procedures in Outpatients)

Currency Code	Currency Description	Service Code	Service Description	Procedures	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Data Submissions
DZ37A	Non-Invasive Ventilation Support Assessment, 19 years and over	340	Respiratory Medicine	6,351	£148	£127	£142	34
DZ37A	Non-Invasive Ventilation Support Assessment, 19 years and over	341	Respiratory Physiology	1,125	£147	£57	£ 304	8
Weighted average*					**£147.52**			

*Weights: procedures values

Table 21: Calculation of the mechanical ventilation unit cost – non-elective inpatients long stay procedure code (NEI_L) (National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts, Non-Elective Inpatients Long Stay)

Currency Code	Currency Description	Service Code	Service Description	FCEs	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average Length of Stay - Days	Data Submissions
DZ37A	Non-Invasive Ventilation Support Assessment, 19 years and over	340	Respiratory Medicine	201	£2,830	£2,640	£3,376	8.90	11
Average cost per day					=£2,830 / 8.90 = **£318**				

Table 22: Calculation of the mechanical ventilation unit cost – non-elective inpatients short stay procedure code (NEI_S) (National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts, Non-Elective Inpatients Short Stay)

Currency Code	Currency Description	Service Code	Service Description	FCEs	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Data Submissions
DZ37A	Non-Invasive Ventilation Support Assessment, 19 years and over	340	Respiratory Medicine	1,206	£770	£368	£789	96
DZ37A	Non-Invasive Ventilation Support Assessment, 19 years and over	341	Respiratory Physiology	1	£1,531	£1,531	£1,531	1
Weighted average*					**£770**			

*Weights: FCE values (finished consultant episodes)

The cost-effectiveness deterministic and full-incremental analysis results are presented below for the NDB list price model.

Table 23: Model results NDB vs. BSC, alternative mechanical ventilation cost (non-elective inpatients long stay procedure code NEI_L), NDB list price

	BSC	NDB	Incremental
Treatment costs	£0.00	£59,037.76	£59,037.76
Adverse event costs	£625.98	£781.97	£155.98
Liver panel tests	£0.00	£9.05	£9.05
Patient monitoring and O_2 use	£9,957.63	£10,827.17	£869.54
Acute exacerbation costs	£1,336.83	£1,191.50	-£145.33
End of life costs	£13,440.51	£13,242.07	-£198.44
Total costs	£25,360.96	£85,089.52	£59,728.56
Total QALYs	3.2721	3.6720	0.3999
LYs	4.3602	4.8593	0.4992
Exacerbation events	0.3234	0.2882	-0.0352
Net monetary benefit	£72,801.45	£25,069.69	
Cost-effectiveness	£7,750.71	£23,172.69	
ICER (per QALY)			£149,361.27
ICER (per LY)			£119,656.78
ICER (per exacerbation avoided)			£1,698,845.10

Table 24: Model results NDB vs. PFN, alternative mechanical ventilation cost (non-elective inpatients long stay procedure code NEI_L), NDB list price

	PFN	NDB	Incremental
Treatment costs	£60,707.68	£59,037.76	-£1,669.92
Adverse event costs	£1,054.92	£781.97	-£272.95
Liver panel tests	£9.31	£9.05	-£0.26
Patient monitoring and O_2 use	£10,955.83	£10,827.17	-£128.66
Acute exacerbation costs	£1,501.72	£1,191.50	-£310.22
End of life costs	£13,251.74	£13,242.07	-£9.67
Total costs	£87,481.20	£85,089.52	-£2,391.68
Total QALYs	3.6249	3.6720	0.0471
LYs	4.8558	4.8593	0.0036
Exacerbation events	0.3633	0.2882	-0.0750
Net monetary benefit	£21,264.99	£25,069.69	
Cost-effectiveness	£24,133.59	£23,172.69	
ICER (per QALY)			NDB dominates
ICER (per LY)			NDB dominates
ICER (per exacerbation avoided)			NDB dominates

Table 25: Model results NDB vs. BSC, alternative mechanical ventilation cost (non-elective inpatients short stay procedure code NEI_S), NDB list price

	BSC	NDB	Incremental
Treatment costs	£0.00	£59,037.76	£59,037.76
Adverse event costs	£625.98	£781.97	£155.98
Liver panel tests	£0.00	£9.05	£9.05
Patient monitoring and O_2 use	£9,962.58	£10,832.54	£869.96
Acute exacerbation costs	£1,336.83	£1,191.50	-£145.33
End of life costs	£13,440.51	£13,242.07	-£198.44
Total costs	£25,365.91	£85,094.89	£59,728.98
Total QALYs	3.2721	3.6720	0.3999
LYs	4.3602	4.8593	0.4992
Exacerbation events	0.3234	0.2882	-0.0352
Net monetary benefit	£72,796.50	£25,064.32	
Cost-effectiveness	£7,752.23	£23,174.16	
ICER (per QALY)			£149,362.33
ICER (per LY)			£119,657.62
ICER (per exacerbation avoided)			£1,698,857.08

Table 26: Model results NDB vs. PFN, alternative mechanical ventilation cost (non-elective inpatients short stay procedure code NEI_S), NDB list price

	PFN	NDB	Incremental
Treatment costs	£60,707.68	£59,037.76	-£1,669.92
Adverse event costs	£1,054.92	£781.97	-£272.95
Liver panel tests	£9.31	£9.05	-£0.26
Patient monitoring and O_2 use	£10,961.27	£10,832.54	-£128.73
Acute exacerbation costs	£1,501.72	£1,191.50	-£310.22
End of life costs	£13,251.74	£13,242.07	-£9.67
Total costs	£87,486.64	£85,094.89	-£2,391.75
Total QALYs	3.6249	3.6720	0.0471
LYs	4.8558	4.8593	0.0036
Exacerbation events	0.3633	0.2882	-0.0750
Net monetary benefit	£21,259.55	£25,064.32	
Cost-effectiveness	£24,135.09	£23,174.16	
ICER (per QALY)			NDB dominates
ICER (per LY)			NDB dominates
ICER (per exacerbation avoided)			NDB dominates

The cost-effectiveness deterministic and full-incremental analysis results are presented below for the NDB PAS discount price model.

Table 27: Model results NDB vs. BSC, alternative mechanical ventilation cost (non-elective inpatients long stay procedure code NEI_L), NDB PAS discount price

	BSC	NDB	Incremental
Treatment costs	£0.00	[redacted]	[redacted]
Adverse event costs	£625.98	[redacted]	[redacted]
Liver panel tests	£0.00	[redacted]	[redacted]
Patient monitoring and O_2 use	£9,957.63	[redacted]	[redacted]
Acute exacerbation costs	£1,336.83	[redacted]	[redacted]
End of life costs	£13,440.51	[redacted]	[redacted]
Total costs	£25,360.96	[redacted]	[redacted]
Total QALYs	3.2721	3.6720	0.3999
LYs	4.3602	4.8593	0.4992
Exacerbation events	0.3234	0.2882	-0.0352
Net monetary benefit	£72,801.45	[redacted]	
Cost-effectiveness	£7,750.71	[redacted]	
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 28: Model results NDB vs. PFN, alternative mechanical ventilation cost (non-elective inpatients long stay procedure code NEI_L), NDB PAS discount price

	PFN	NDB	Incremental
Treatment costs	£60,707.68	[redacted]	[redacted]
Adverse event costs	£1,054.92	[redacted]	[redacted]
Liver panel tests	£9.31	[redacted]	[redacted]
Patient monitoring and O_2 use	£10,955.83	[redacted]	[redacted]
Acute exacerbation costs	£1,501.72	[redacted]	[redacted]
End of life costs	£13,251.74	[redacted]	[redacted]
Total costs	£87,481.20	[redacted]	[redacted]
Total QALYs	3.6249	3.6720	0.0471
LYs	4.8558	4.8593	0.0036
Exacerbation events	0.3633	0.2882	-0.0750
Net monetary benefit	£21,264.99	[redacted]	[redacted]
Cost-effectiveness	£24,133.59	[redacted]	[redacted]
ICER (per QALY)		[redacted]	[redacted]
ICER (per LY)		[redacted]	[redacted]
ICER (per exacerbation avoided)		[redacted]	[redacted]

Table 29: Model results NDB vs. BSC, alternative mechanical ventilation cost (non-elective inpatients short stay procedure code NEI_S), NDB list price

	BSC	NDB	Incremental
Treatment costs	£0.00	[redacted]	[redacted]
Adverse event costs	£625.98	[redacted]	[redacted]
Liver panel tests	£0.00	[redacted]	[redacted]
Patient monitoring and O_2 use	£9,962.58	[redacted]	[redacted]
Acute exacerbation costs	£1,336.83	[redacted]	[redacted]

	BSC	NDB	Incremental
End of life costs	£13,440.51	[redacted]	[redacted]
Total costs	£25,365.91	[redacted]	[redacted]
Total QALYs	3.2721	3.6720	0.3999
LYs	4.3602	4.8593	0.4992
Exacerbation events	0.3234	0.2882	-0.0352
Net monetary benefit	£72,796.50	[redacted]	[redacted]
Cost-effectiveness	£7,752.23	[redacted]	[redacted]
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 30: Model results NDB vs. PFN, alternative mechanical ventilation cost (non-elective inpatients short stay procedure code NEI_S), NDB list price

	PFN	NDB	Incremental
Treatment costs	£60,707.68	[redacted]	[redacted]
Adverse event costs	£1,054.92	[redacted]	[redacted]
Liver panel tests	£9.31	[redacted]	[redacted]
Patient monitoring and O_2 use	£10,961.27	[redacted]	[redacted]
Acute exacerbation costs	£1,501.72	[redacted]	[redacted]
End of life costs	£13,251.74	[redacted]	[redacted]
Total costs	£87,486.64	[redacted]	[redacted]
Total QALYs	3.6249	3.6720	0.0471
LYs	4.8558	4.8593	0.0036
Exacerbation events	0.3633	0.2882	-0.0750
Net monetary benefit	£21,259.55	[redacted]	[redacted]
Cost-effectiveness	£24,135.09	[redacted]	[redacted]
ICER (per QALY)		[redacted]	[redacted]
ICER (per LY)		[redacted]	[redacted]
ICER (per exacerbation avoided)		[redacted]	[redacted]

B6. On pages 65 and 182 of the company submission it is stated that liver enzyme elevations were assumed to be asymptomatic for patients (and therefore there was no disutility or additional costs associated with them in the model). Please provide a justification for this assumption.

It was assumed that since patients are monitored every three months, any elevation in liver enzymes would be picked up by the tests and the patient would discontinue from treatment. No further complications would occur within three months due to liver enzymes elevation and consequently, no disutility was assigned to this event. Furthermore, some of the treatment discontinuation (considered elsewhere in the model) would include patients who had to stop the treatment due to liver enzyme elevation.

Validation of models

B7. **Priority question:** The post-hoc analysis (reference 97 of the company submission) was the most frequently cited reference for the model, but the reference has not been provided. Due to this, the validity of the analyses conducted based on these data could not be fully checked. Please provide reference 97: Ingelheim B. data on file - phase III trial (trial no. 1199.32 and 1199.34) post-hoc analysis. 2014.

There were analyses performed as per protocol on TOMORROW and INPULSIS 1 and 2; data presented in the publications and in other section of the MS. The post-hoc analysis refers to additional retrospective analysis of the individual patient data (IPD) that was performed solely with the objective of obtaining model inputs for the cost-effectiveness analysis. There is no publication for the post-hoc analyses of the IPD (for the cost-effectiveness model). For your consideration additional information is provide here (and where it is requested elsewhere).

- For the analysis of time to event data (OS phase III, OS phase II + phase III, time to first acute exacerbation, overall discontinuation): please see Excel file "IPD-TTE outcomes_B7(1).xlsx" containing the clinical trial data per arm (patients at risk, number of events, number censored, Kaplan-Meier estimate per timepoint). Please note that for overall survival, two sets of data are shown: OS phase III data (INPULSIS) and OS phase II and phase III data (TOMORROW and INPULSIS pooled). The pooled data were used in the cost-effectiveness model.

  See IPD-TTE outcomes_B7(1).xlsx

- For the analysis of loss of lung function: please refer to A11ii
- For the analyses performed on baseline EQ-5D please refer to B1
- For the background health care resource use (HCRU) analysis please refer to B3
- For the analysis performed for the disutility values related to exacerbation events: please see Word file:

  See Exacerbations disutility_B7(2).docx

- For the analysis on serious GI events disutility:

  See Serious GI event calculations_B7(3).docx

B8. **Priority question:** Please explain how the exponential models were fitted in Figure 44 of the company submission (including the time-horizons that were considered). It appears that the model does not fit the data very well (it appears to be fixed to the first and last point, but not fixed to any in-between). Please provide an explanation for this.

Parametric model extrapolation using phase III (Richeldi et al. 2014) clinical data was used to derive time-to- acute-exacerbation estimates. Data were used from 1-year clinical trial follow-up. Two outcomes were explored:

Table 31: Outcomes explored for modelling time-to-acute-exacerbation

	Placebo	**Nintedanib**
Acute exacerbation based on investigator reporting	32 patients out of 426 have at least 1 exacerbation during the	31 patients out of 640 have at least 1 exacerbation during the

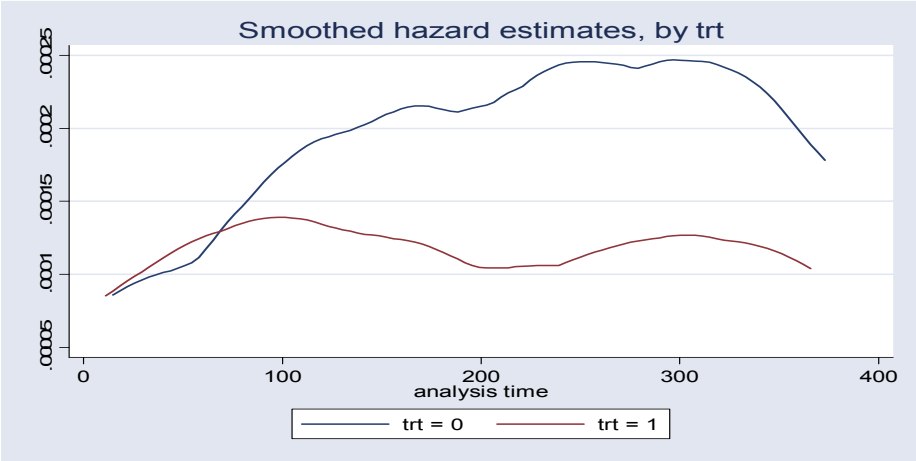
	trial period	trial period
Acute exacerbation based on adjudication committee	24 patients	12 patients

Note that the baseline risk in the model was based on analysis of the placebo arm only. Unfortunately, similar data of time-to-exacerbation do not exist in the literature to compare against our estimates (as performed in the OS analysis). Therefore, statistical criteria were relied upon. Details of the AIC values and goodness of fit are provided in the MS. Although Gompertz was the model with the lowest AIC, the exponential, loglogistic and Weibull models deserve consideration as well because these were within 1-2 points of the "best" model.

A second consideration was model parsimony and the computational complexity of introducing time-dependent probabilities for time-to-exacerbation. A simulation (rather than a cohort analysis) was considered as a more elegant solution since more than one parameter would require tracking of patient history. This would impact the required time to perform sensitivity and subgroup analysis. Given the rarity of the acute exacerbation events in the data-set and therefore, the low sensitivity of the cost-effectiveness results to this, on balance, it was considered that a constant hazard (exponential model) would be sufficient for this parameter.

Furthermore, an analysis on the observed hazard estimates (from INPULSIS) (Figure 7) supported the assumption of a constant hazard; note that the hazard is moving within a range of just under 0.0001 to 0.00015 for NDB and 0.00025 for PBO. Furthermore, note that the assumption of a constant risk for placebo is conservative in terms of the likely incremental cost-effectiveness of nintedanib vs. BSC; a time-dependent risk for placebo would, most likely, produce more exacerbation events for the BSC strategy.

Figure 7: Smoothed hazard estimates by treatment - time to exacerbation



B9. **Priority question:** In Table 169 and Figure 66 of the company submission, model projections are compared with clinical trial data for best supportive care. These comparisons are made for nintedanib in Table 170 and Figure 67. However, this has not been done for any pirfenidone trial. Please compare the model projections for

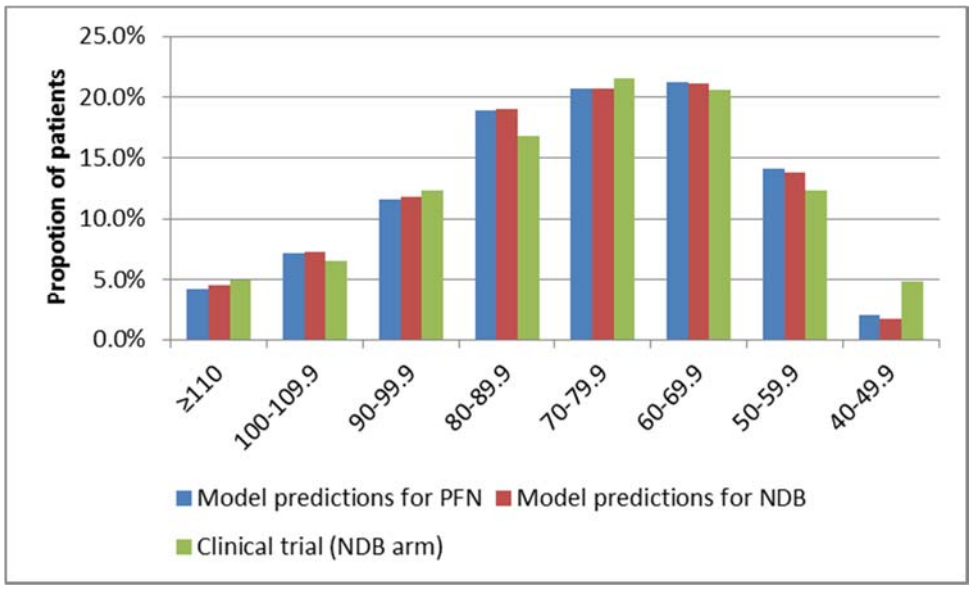
pirfenidone to pooled pirfenidone data from the CAPACITY and SP2&3 trials (replicating Tables 169–70 and Figures 66–7).

Unfortunately, Boehringer Ingelheim does not have access to the pirfenidone data to replicate the requested tables and figures using pirfenidone trials against the model predictions. For your consideration we have added the pirfenidone model estimates to relevant tables and figures.

Table 32: Proportion of patients alive and in each FVC%Pred category at the end of one year: NDB and PFN model predictions vs. NDB arm of the clinical trial

FVC%Pred category	≥110	100-109.9	90-99.9	80-89.9	70-79.9	60-69.9	50-59.9	40-49.9
Model predictions for PFN	4.2%	7.2%	11.7%	18.9%	20.7%	21.2%	14.1%	2.0%
Model predictions for NDB	4.5%	7.3%	11.8%	19.0%	20.7%	21.1%	13.9%	1.7%
Clinical trial (NDB arm)	5.0%	6.6%	12.3%	16.8%	21.6%	20.6%	12.3%	4.8%

Figure 8: Proportion of patients alive and in each FVC%Pred category at the end of one year: NDB and PFN model predictions vs. NDB arm of the clinical trial



B10. **Priority question:** Figure 65 of the company submission shows that the fit of proportional hazards model for overall survival is not as good for pirfenidone as for nintedanib (Figure 64) or best supportive care (Figure 63). The model will underestimate overall survival in the first year of treatment with pirfenidone, and this underestimation will increase in magnitude over time. As survival is one of the primary drivers of the model, please conduct an analysis where proportional hazards are not assumed for overall survival with pirfenidone. Please provide tabulated survival data for this analysis. Please also provide tabulated survival data for pirfenidone from the loglogistic, Weibull, and Gompertz models which were presented in Figure 65 of the submission.

Please note that Boehringer Ingelheim do not have access to the CAPACITY or ASCEND data to accurately reflect the mortality risk with pirfenidone. Figure 65 of the MS is a product of data extraction of the KM curve from the publication figures and as such it already contains imprecisions from the extraction process. A comparison of the model projections with the extracted KM from a figure of the publication is not a solid assessment of the goodness-of-fit of the constant hazard ratio assumption.
Furthermore, given the weakness of the evidence for pirfenidone, a survival analysis on the digitised KM output was not performed, but assigned the NMA OR to the baseline risk model to derive the survival curve for pirfenidone (details in the MS). Therefore, it is not possible to derive the AIC or other goodness-of-fit parameters for pirfenidone from the MS base-case analysis.

For the ERG's consideration the data have been re-analysed (TOMORROW, INPULSIS, and CAPACITY) using the method of fractional polynomials. Details of the method are presented elsewhere (Jansen 2011 (see below)). *With this approach the treatment effects are presented with multiple parameters rather than a single parameter or outcome* (…) with the advantage that a number of possible shapes of the survival distribution can be modelled

(Jansen 2011). Furthermore, by modelling the hazard function with fractional polynomials (1st and/or 2nd order) the constant hazard ratio assumption is no longer relied upon.

See Jansen_2011_B10.pdf

Methods:
IPD was used for TOMORROW and INPULSIS. For CAPACITY the KM curve from a figure off the publication was digitised, adjusting for censoring using the Hoyle and Henley (2011) (see below for ref) method. All data were adjusted to 1-month intervals for input to the model.
Both 1st and 2nd order fractional polynomial fixed effects models were used with powers chosen from the following set: -2.0, -1.0, -0.5, 0.0, 0.5, 1.0, 2.0, 3.0.
Given the small number of studies (3), and the fact that there was only one study for pirfenidone vs. placebo, only the fixed effects model was run; from experience after running the fixed effects models it was predicted that the estimates would be very imprecise from the random effects model.

Non-informative priors were set to follow a normal distribution with mean 0 and variance 10,000 (precision 0.0001). The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the WinBUGS software package (Spiegelhalter et al. 2003). The WinBUGS sampler, using two chains, was run for 30,000 iterations discarded as “burn in”. Then the model was run for a further 50,000 iterations to produce the analysis results. The two chains had different initial values, and a thinning of 50 was applied to reduce autocorrelations. Convergence of the chains was confirmed by visual inspection (history plots and posterior densities).

The Deviance Information Criterion (DIC) was used to compare the goodness-of-fit of different models with 1st and 2nd order fractional polynomials with different powers. The model with the lowest DIC is the model providing the “best” fit to the data.

See Hoyle and Henley_2011_B10.pdf

Results:
The model fit statistics for the different models are presented in Table 33. In all instances where a positive 1, 2, or 3 powers were explored for P2, the model did not converge to the same posterior with two independent chains. The same occurred for P1 when powers of positive 2 or 3 were tested. This is a limitation of the data; there are a small number of studies and a large number of incomplete survival data. It follows that there is insufficient data to inform the tails of the distribution (most likely dependent on the P2 powers). Note that in other occasions where this method was implemented the scanned survival curves were more complete. For example in Jansen (2011) at the end of the observed data period almost 80% of patients were dead. In the data used in this analysis there are around 80-90% still alive. Different initial values were investigated and attempt to reduce the width of the priors (make them less vague) was made to resolve this issue. Since the models did not converge, those runs were ignored and only the DICs for the remaining cases were included.

The best model in terms of goodness-of-fit was the 1st order with power P1=1. The second best was P1=0.5). It was also noted that the best model from the 2nd order fractional

polynomials was the one with P1=-2, and P2=0.5 (highlighted in bold). Table 34 presents the parameter estimates for the abovementioned models.

Table 33: Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2

Power P1	Power P2	DIC	comment on simulation
-2	-	456.9	
-1	-	449.7	
-0.5	-	443.6	
0	-	437.3	
0.5	**-**	**431.9**	
1	**-**	**428.5**	
2	-	-	unsatisfactory
3	-	-	unsatisfactory
-2	-2	451.0	
-2	-1	446.0	
-2	-0.5	442.9	
-2	0	439.2	
-2	**0.5**	**436.0**	
-2	1	-	unsatisfactory
-2	2	-	unsatisfactory
-2	3	-	unsatisfactory
-1	-1	443.6	
-1	-0.5	441.2	
-1	0	439.4	
-1	0.5	437.3	
-1	1	-	unsatisfactory
-1	2	-	unsatisfactory
-1	3	-	unsatisfactory
-0.5	-0.5	440.2	
-0.5	0	439.0	
-0.5	0.5	437.7	
-0.5	1	-	unsatisfactory
-0.5	2	-	unsatisfactory
-0.5	3	-	unsatisfactory
0	0	438.9	
0	0.5	437.9	
0	1	-	unsatisfactory
0	2	-	unsatisfactory
0	3	-	unsatisfactory
0.5	0.5	437.9	
0.5	1	-	unsatisfactory
0.5	2	-	unsatisfactory
0.5	3	-	unsatisfactory
1	1	-	unsatisfactory

Power P1	Power P2	DIC	comment on simulation
1	2	-	unsatisfactory
1	3	-	unsatisfactory
2	2	-	unsatisfactory
2	3	-	unsatisfactory
3	3	-	unsatisfactory

Table 34: Model parameter estimates for different fractional polynomial NMA models

	Median	**95% CrI**	**Median**	**95% CrI**	**Median**	**95% CrI**
	Best fit FP model		**Second best fit FP model**		**Best fit 2nd order FP model**	
P1	1		0.5		-2	
P2	-		-		0.5	
Placebo						
pbo beta0	-6.2	-6.897, -5.574	-7.274	-8.517, -6.175	-6.539	-8.232, -4.834
pbo beta1	0.152	0.086, 0.222	0.834	0.46, 1.237	-4.367	-11.76, -0.228
pbo beta2	-	-	-	-	0.625	0.083, 1.159
Nintedanib						
effect0 vs. pbo	-0.371	-1.477, 0.724	-0.346	-2.24, 1.536	-0.417	-2.956, 2.118
effect1 vs. pbo	0.02	-0.091, 0.134	0.052	-0.57, 0.686	0.105	-3.51, 3.865
effect2 vs. pbo	-	-	-	-	0.077	-0.734, 0.893
ntd beta0	-6.571	-7.49, -5.734	-7.617	-9.188, -6.209	-6.942	-9.097, -4.87
ntd beta1	0.173	0.085, 0.263	0.887	0.412, 1.396	-4.278	-11.89, 0.246
ntd beta2	-	-	-	-	0.698	0.037, 1.378
Pirfenidone						
effect0 vs. pbo	-0.857	-2.024, 0.245	-1.282	-3.207, 0.537	-2.279	-5.083, 0.437
effect1 vs. pbo	0.051	-0.033, 0.138	0.31	-0.222, 0.863	4.467	-8.041, 18.63
effect2 vs. pbo	-	-	-		0.58	-0.182, 1.365
pfn beta0	-7.063	-8.33, -5.885	-8.568	-10.7, -6.582	-8.821	-11.81, -5.898
pfn beta1	0.203	0.103, 0.307	1.147	0.535, 1.781	0.122	-12.98, 12.02
pfn beta2	-	-	-	-	1.206	0.35, 2.075

Figure 9, Figure 10, and Figure 11 present the estimated difference in the hazard for each treatment vs. placebo. The hazard ratio for both treatments is increasing; considerably faster for pirfenidone treatment.

Figure 9: Hazard ratio (vs. placebo) based on best-fit model P1=1

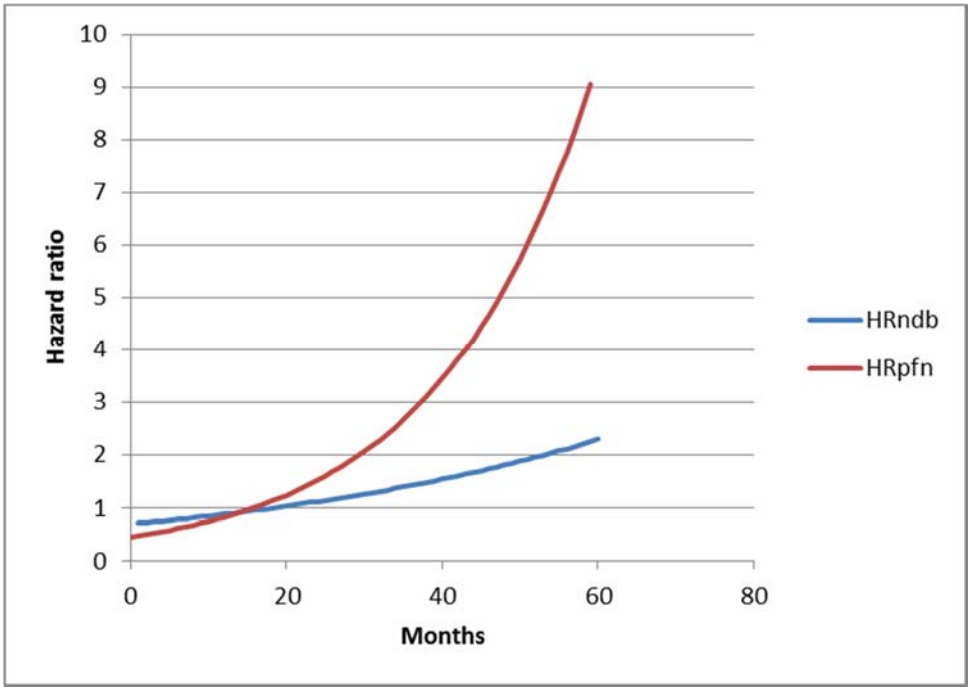


Figure 10: Hazard ratio (vs. placebo) based on best-fit model P1=0.5

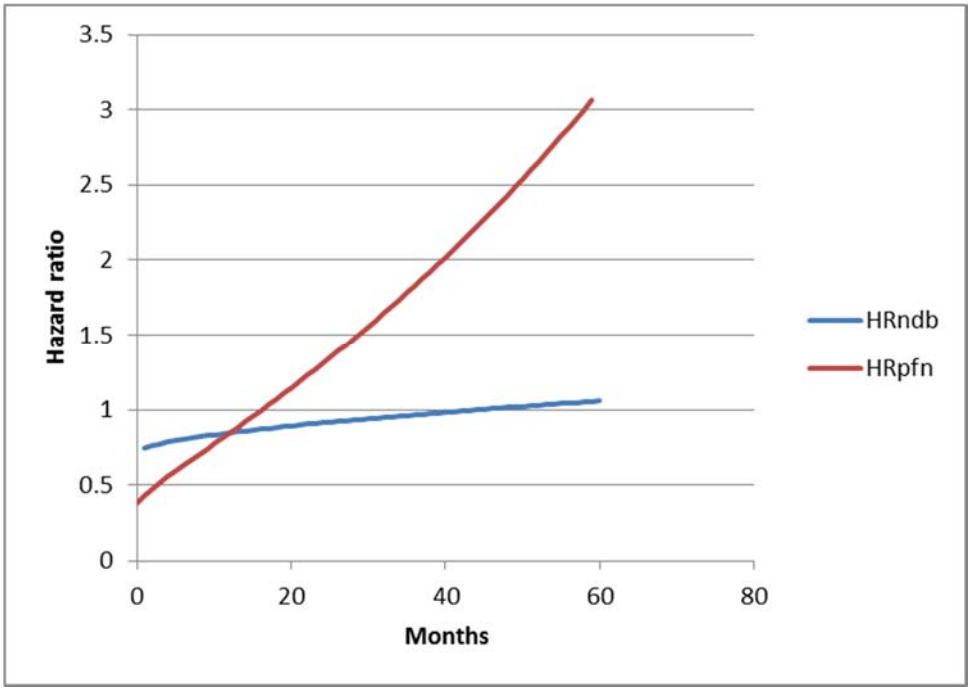
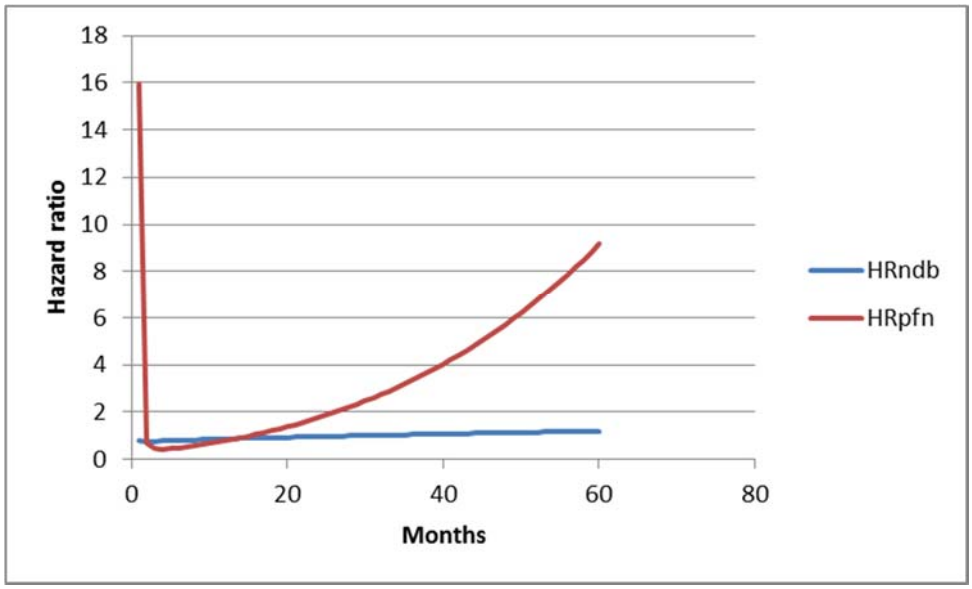


Figure 11: Hazard ratio (vs. placebo) based on best-fit 2nd order model



Based on the parameters from Table 34 please see below the hazard over time and the survival function for the three strategies and using the best fit model, the second-best and the best fit from the 2nd order runs.

Figure 12: Hazard over time for each treatment using the best fit model (P1=1)

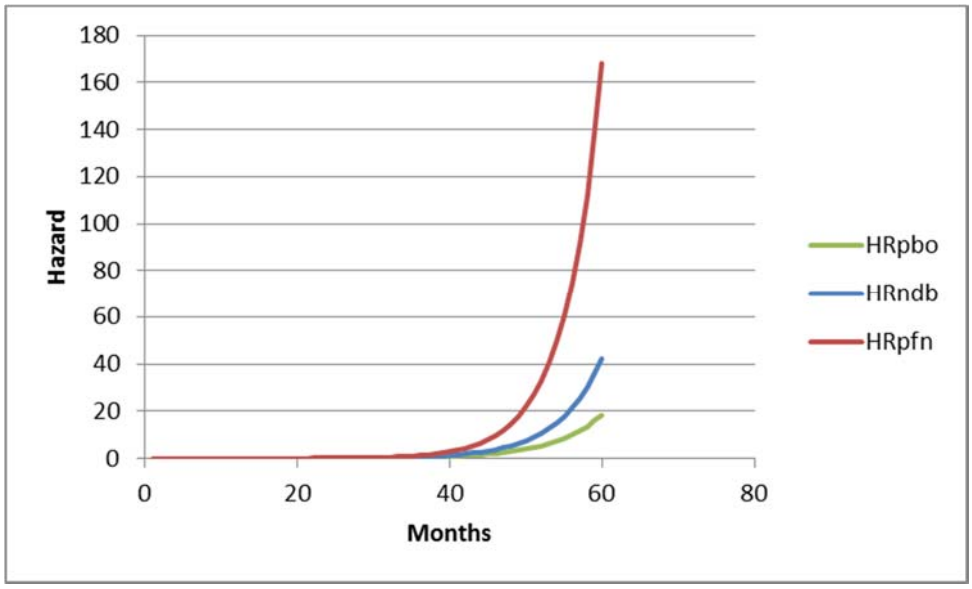


Figure 13: Survival over time for each treatment using the best fit model (P1=1)

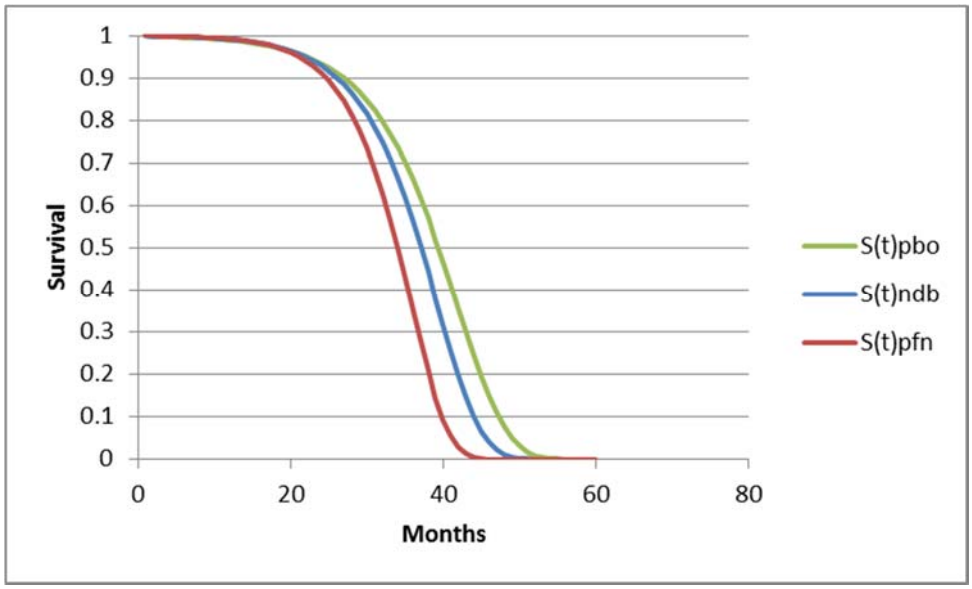


Figure 14: Hazard over time for each treatment using the second-best fit model (P1=0.5)

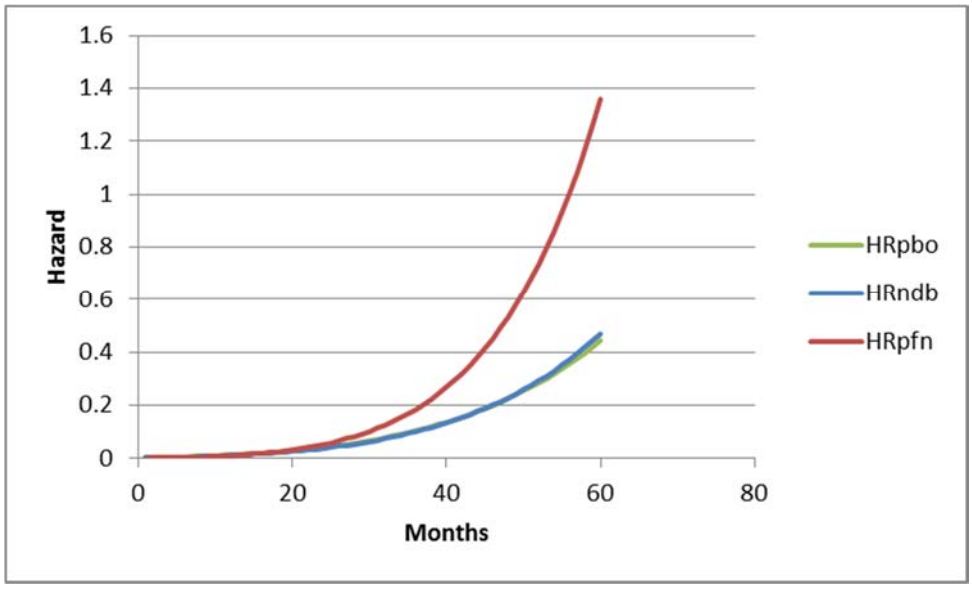


Figure 15: Survival over time for each treatment using the second-best fit model (P1=0.5)

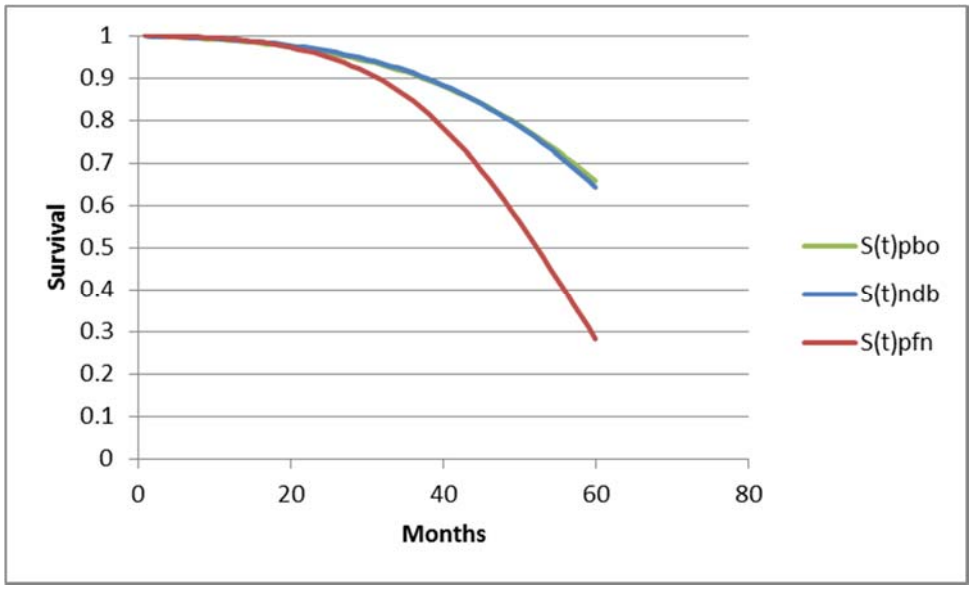


Figure 16: Hazard over time for each treatment using the 2nd order best fit model (P1=-2, P2=0.5)

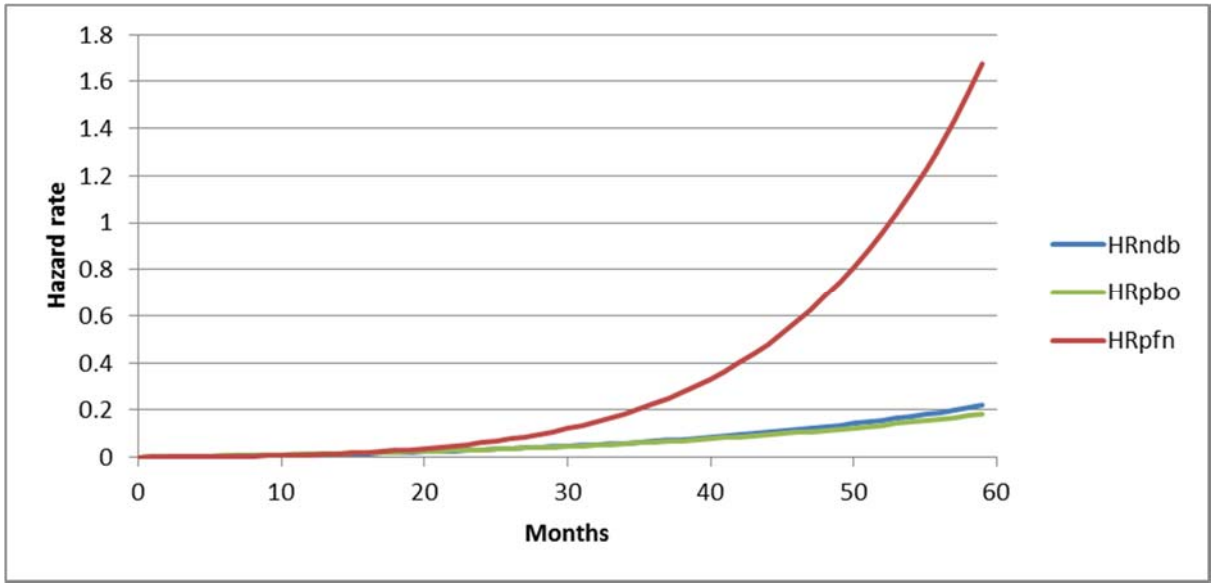
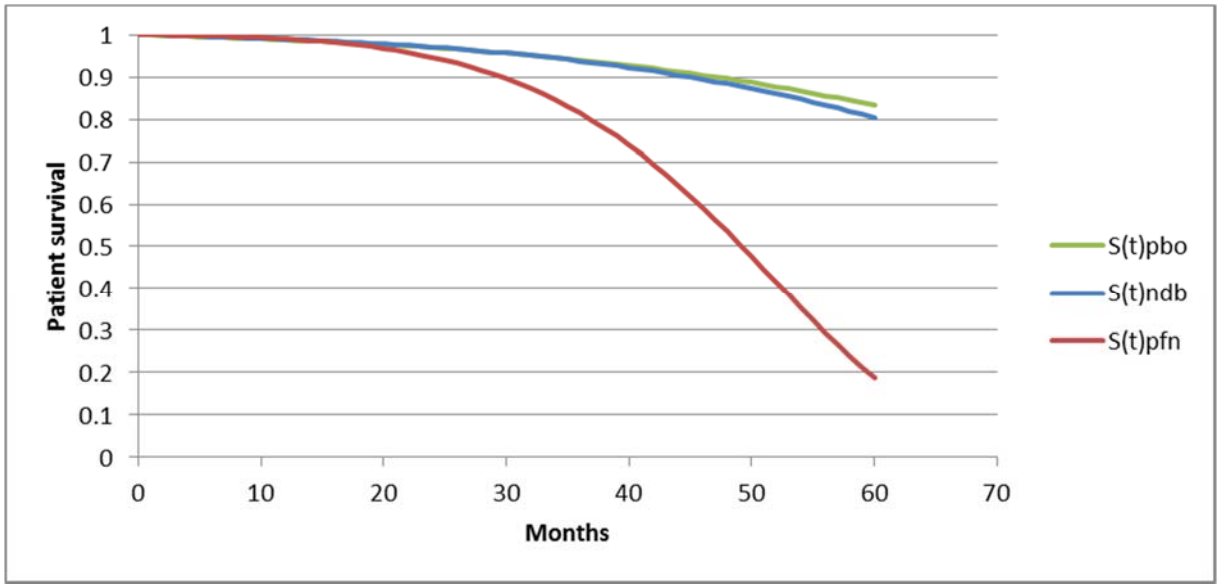


Figure 17: Survival over time for each treatment using the 2nd order best fit model (P1=-2, P2=0.5)



The 2nd order fractional polynomial model produced unrealistically high survival rates for placebo and nintedanib, while showing a rapid decline for pirfenidone (Figure 16 and Figure 17). A similar distinction across the three treatments from the second-best 1st order model (Figure 14 and Figure 15) was obtained. On the other hand the best fit model (Figure 12 and Figure 13) described a difference in survival function that is not supported by any other data in the literature (placebo has the best survival, nintedanib second best and pirfenidone has the worst).

Furthermore, the estimated (INPULSIS) and scanned (CAPACITY) KM curves were used for a comparison of the model fit in the first two years. Figure 18 and Figure 19 show that although the fractional polynomial estimates are projecting a better survival for both treatments they do not fit better than the base-case analysis model (constant hazard ratio assumption – loglogistic model).

Figure 18: Comparison of nintedanib estimates, KM curve, base-case analysis and fractional polynomials

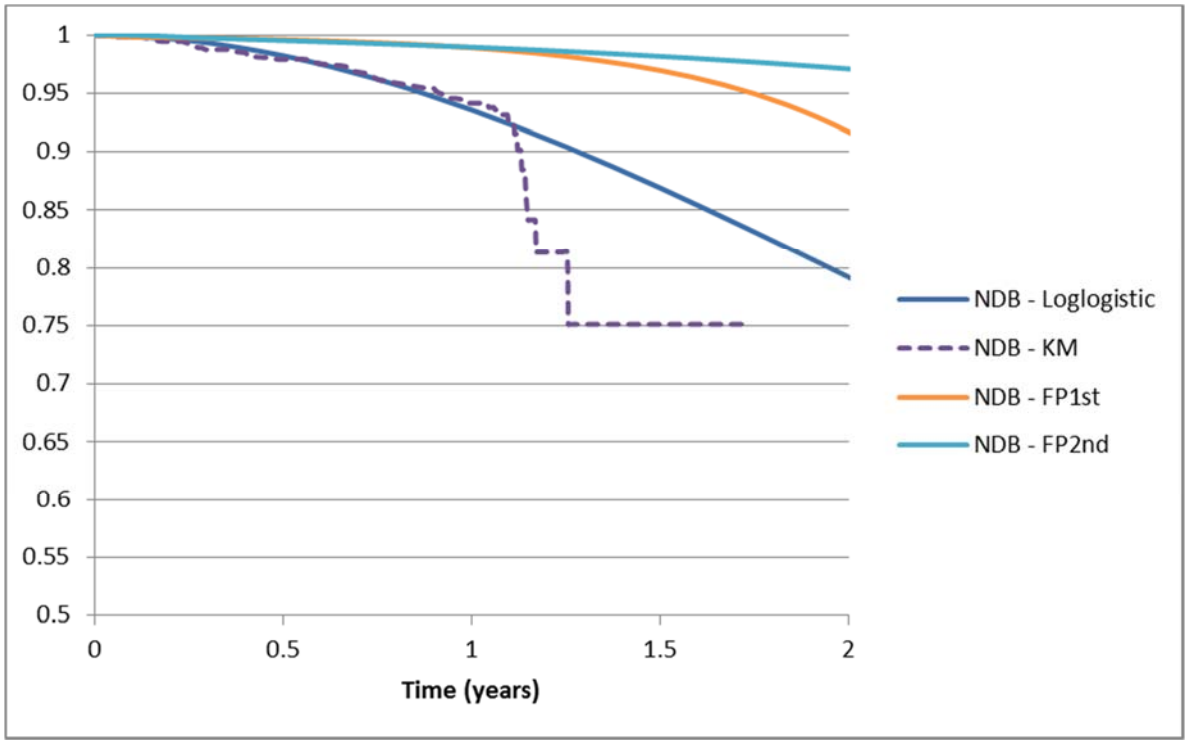
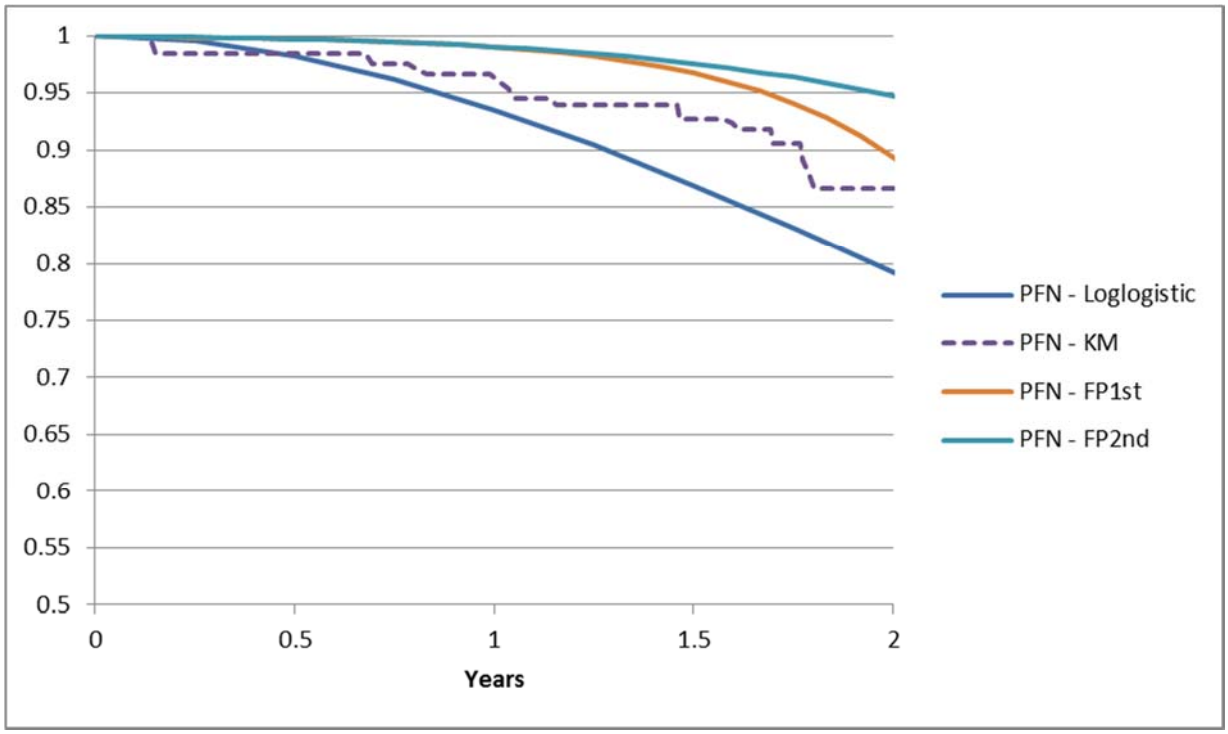


Figure 19: Comparison of pirfenidone estimates, KM curve, base-case analysis and fractional polynomials



Discussion:

An alternative way that does not rely on the constant hazard ratio assumption was used to indirectly compare the survival of patients under the three strategies; placebo, nintedanib

and pirfenidone. The objective was to obtain three sets of survival curves with different shapes (contrary to the MS base-case analysis).
It appears that the evidence available is insufficient to support such an analysis. The observed data is limited; there are only three studies (one for pirfenidone) and at the end of the observed follow-up period there are only 10-20% deaths. Using the fractional polynomial models was not successful in a number of cases tested (positive values for 2nd order P2=1, 2, and 3 did not converge). Furthermore, for the cases that the models did converge to a common posterior, the obtained survival functions were not following a logical pattern supported by the literature.

An additional method of revised modelling was also considered: a comparison of

- either the KM curve for pirfenidone or the best-fit model from the fractional polynomials against
- the MS base-case analysis estimates (loglogistic for placebo and constant hazard ratio for nintedanib [based on NMA])

Although this method would appear to respect the trajectory of the KM curves, it would be a naïve comparison and insufficient to infer on the likely relative risk of mortality across the tree treatments.

Conclusion:
There is insufficient data to infer on the validity of the proportional hazards assumption (constant hazard ratio). An alternative analysis of the indirect treatment effect on mortality did not produce reliable results.

B11. Please describe how the proportional hazards assumptions were checked for validity in each of the various survival models used for the economic model.

Visual inspection of the model estimates against the KM trajectories was performed, with the caveat that for pirfenidone the KM curve is extracted from the publication and not produced based on IPD. Please refer also to response B10.

Clarifications and additional analyses

B12. The loglogistic curve for nintedanib is missing from Figure 42 of the company submission (although it is listed in the figure legend). Please provide an updated Figure 42.

The curves for nintedanib and pirfenidone are one on top of the other. This is explained with a footnote on figure 42 of the MS.

B13. Figures 41 and 42 of the company submission present overall survival extrapolations for placebo, nintedanib and pirfenidone. The figures compare these models with data from the study by Kondoh et al. (where data from Kondoh et al. is broken into 2 patient cohorts: ‘with exacerbations’ and ‘without exacerbations’).

i. Please provide tables and graphs of the overall survival data with best supportive care from the INPULSIS trials, broken down by exacerbation status ('with exacerbations' and 'without exacerbations'). Please compare these (in the same tables and graphs) with the Kondoh et al. survival data presented in Figure 41 and Figure 42 of the submission.

Two retrospective subgroups were analysed from the placebo arms of the INPULSIS trials, as requested:

- Without exacerbation
- With exacerbation (investigator reported)

The KM curves are presented in Table 35, Figure 20 and Figure 21. A clear split can be seen in the survival between the two subgroups of the INPULSIS trials, mirroring the split seen in Kondoh et al. (2010). It can also be observed that in the first 12 months patients without exacerbation follow closely the trend of the Kondoh et al. (2010) subgroup. After that point the INPULSIS patients have worse survival to the Kondoh et al. (2010) patients. In the subgroup with exacerbation, the INPULSIS patients have a much worse survival trajectory to those in the Kondoh et al. (2010) group throughout the whole trial follow up period. One of the factors that could explain the increased mortality risk in the INPULSIS subgroup with exacerbation may be the management of the disease in the Kondoh et al. (2010) study: Patients were treated with varied regimens, including no therapy, prednisone with or without immunosuppressants (cyclophosphamide, azatioprine, or cyclosporin), and experimental protocols.

Table 35: KM curve of the two subgroups

Days	PBO - Pts with exacerbation	days	PBO - Pts without exacerbation
0	1.0000	0	1.0000
22	0.9688	1	1.0000
48	0.9375	33	0.9975
128	0.9063	75	0.9949
161	0.875	87	0.9949
181	0.8438	123	0.9924
192	0.8125	161	0.9898
196	0.7813	169	0.9873
224	0.75	187	0.9873
257	0.7188	198	0.9847
317	0.6875	207	0.9821
319	0.6563	233	0.9796
326	0.6563	240	0.977
330	0.6234	252	0.9745
336	0.5906	284	0.9719
342	0.5906	291	0.9694
354	0.5559	294	0.9668
361	0.5211	312	0.9642
365	0.5211	314	0.9642
370	0.4811	324	0.9617
372	0.4811	346	0.9591
381	0.4373	358	0.9591
386	0.3936	363	0.9591
392	0.3936	364	0.9591
397	0.3936	365	0.9591

399	0.3936	366	0.9591
400	0.3936	368	0.9591
412	0.3936	369	0.9591
414	0.3936	370	0.9564
461	0.3936	371	0.9537
536	0.3936	372	0.9537
		374	0.9537
		375	0.9537
		378	0.9537
		380	0.9537
		384	0.9537
		385	0.9537
		386	0.9537
		387	0.9537
		388	0.9507
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		406	0.9507
		407	0.9507
		408	0.9507
		409	0.9507
		410	0.9507
		411	0.9507
		413	0.9507
		414	0.9507
		417	0.9507
		422	0.9054
		423	0.8551
		427	0.8551
		430	0.8551
		432	0.8551
		438	0.8551
		439	0.8551
		445	0.8551
		446	0.8551
		449	0.8551
		453	0.8551
		466	0.733
		477	0.733
		493	0.733
		571	0.733
		645	0.733

Figure 20: KM curves of the two subgroups compared with Kondoh 2010

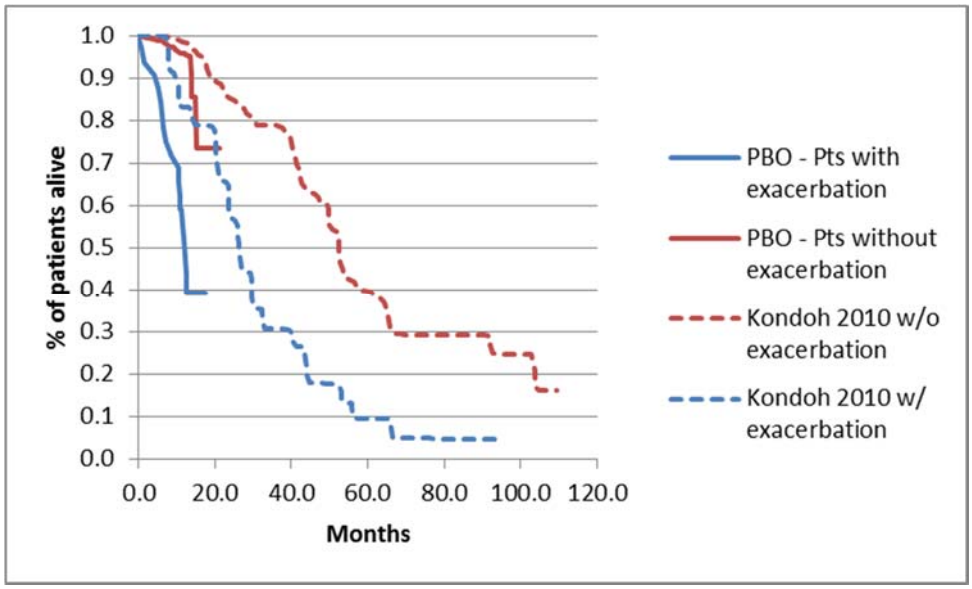
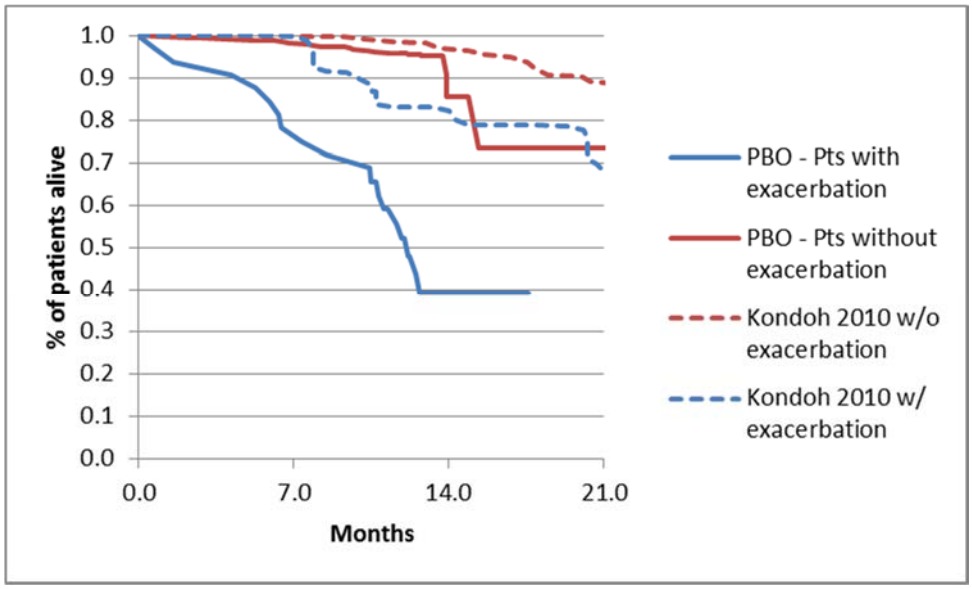


Figure 21: KM curves of the two subgroups compared with Kondoh 2010 – first 21 months (INPULSIS available evidence)



ii. Please provide a sensitivity analysis using pooled survival data from Kondoh (that is, combining the 'with' and 'without exacerbations' cohorts) as an alternative to overall survival data from the INPULSIS trials (if this is possible based on the data available in the Kondoh publication). Please present full cost-effectiveness results for this alternative analysis.

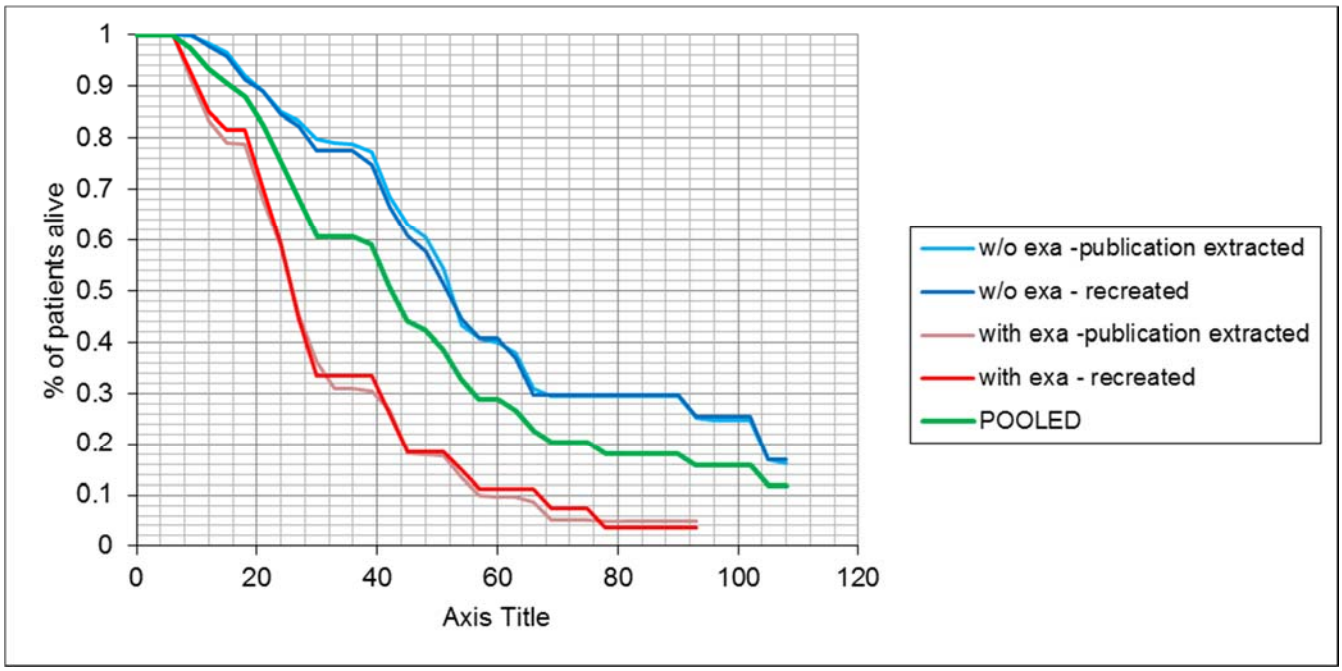
Figure 2 from the Kondoh et al. (2010) publication was digitised and the KM curve data was adjusted for censoring using the Parmar et al. (1998) study. Note that Kondoh et al. 2010 did not provide with the KM curve a corresponding table of patients at risk, to allow the use of a superior method of adjusting for censoring such as Guyot et al in (2012) or Hoyle and

Henley (2011). Furthermore, note that Parmar's assumption of informative censoring throughout the study follow up is problematic in the case of the Kondoh et al. 2010; there are a small number of patients and a relatively high proportion of events. When using the Parmar method of adjustment it was necessary to recreate some of the patient survival to match the published KM curves. Figure 22 presents the originally extracted KM curves, the recreated and the KM after pooling the two subgroups.

See Parmar_1998_B13ii(1).pdf

See Guyot_2012_B13ii(2).pdf

Figure 22: Kondoh et al. adjustments and pooled data



Parametric model extrapolation using the pooled Kondoh 2010 data was used to derive overall survival parameters for the BSC arm. The goodness-of-fit for the five parametric models for overall survival is presented in Table 36.

Table 36: Goodness-of-fit - overall survival of Kondon 2010

Model	Exponential	Weibull	Gompertz	**lognormal**	**log logistic**
AIC	174.07	159.78	169.66	**151.41**	**152.52**

The lowest AIC value was reported for the lognormal model. However, the loglogistic model also deserves consideration as its AIC value is only 1 point higher.
The coefficients of the Kondoh 2010 loglogistic model are compared with those of the INPULSIS trial in Table 37. The coefficients (and CI) are not very different from those of the INPULSIS trial model estimates.

Table 37: Coefficients of parametric models - overall survival

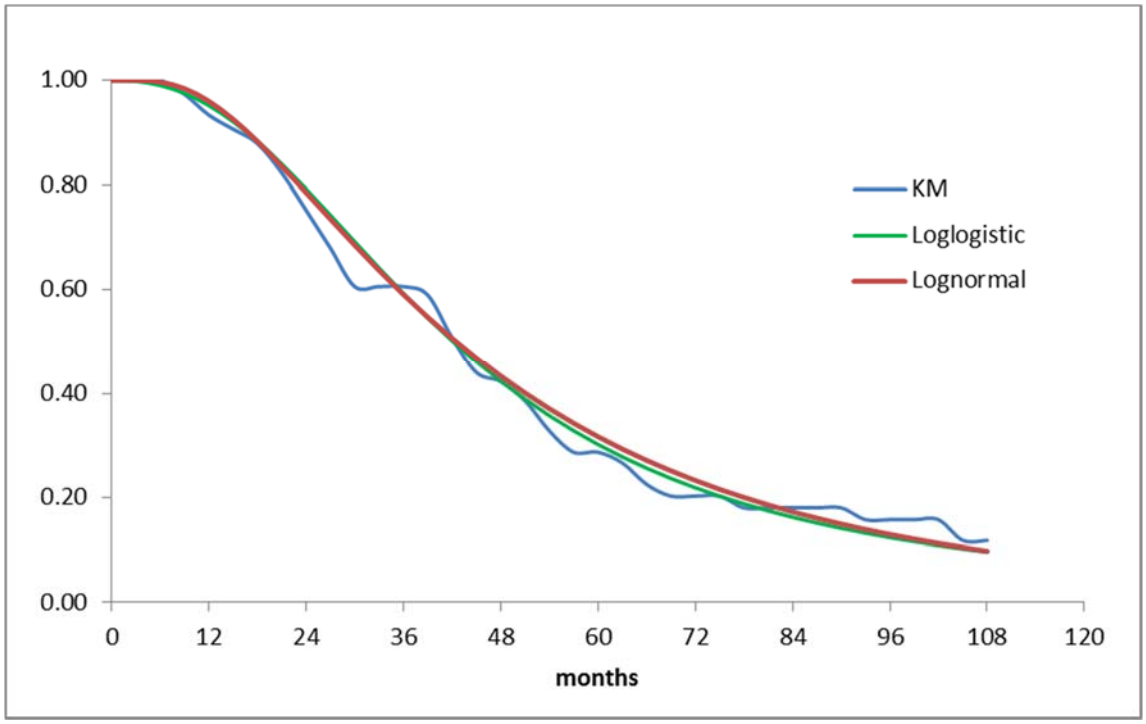
Model	**Variable**	**Coefficient**	**Std. Err.**	**Z**	**P>z**	**95% Conf. Interval**

Model	Variable	Coefficient	Std. Err.	Z	P>z	95% Conf. Interval	
Lognormal Kondoh	*constant*	7.165	0.090	79.37	<0.001	6.988	7.342
	ln_sigma	-0.326	0.099	-3.28	0.001	-0.520	-0.131
Loglogistic Kondoh	*constant*	7.156	0.090	79.9	<0.001	6.981	7.332
	ln_gamma	-0.866	0.112	-7.72	<0.001	-1.085	-0.646
Loglogistic INPULSIS*	*constant*	7.164	0.187	38.4	<0.001	6.799	7.530
	ln_gamma	-0.633	0.139	-4.56	<0.001	-0.905	-0.361

*Cost-effectiveness base-case analysis

The 10-year extrapolation is depicted in Figure 23 below. The two alternatives with the best fit are very close in terms of their shape and patient survival estimates.

Figure 23: Fit of OS parametric models on pooled Kondoh 2010 data



A full incremental cost-effectiveness analysis using the pooled Kondoh 2010 data (both loglogistic and lognormal) was performed as a sensitivity analysis. The tables below present the pairwise comparisons (against placebo and pirfenidone) and a full incremental analysis for the two scenarios using the list price and the PAS for nintedanib.
The ICER for nintedanib vs. BSC increases by £40-50,000 with the list price and around £20,000 with the PAS. The result of the incremental cost-effectiveness against pirfenidone is the same with the base-case analysis (NDB dominates).

NDB list price, Kondoh loglogistic parametric model for OS

Table 38: Model results NDB vs. BSC, using the Kondoh loglogistic parametric model for OS, NDB list price

	BSC	NDB	Incremental
Treatment costs	£0.00	£59,122.64	£59,122.64
Adverse event costs	£581.43	£721.68	£140.25
Liver panel tests	£0.00	£9.06	£9.06
Patient monitoring and O_2 use	£8,994.62	£9,604.33	£609.71
Acute exacerbation costs	£1,235.24	£1,053.53	-£181.70
End of life costs	£13,882.54	£13,717.48	-£165.06
Total costs	£24,693.81	£84,228.72	£59,534.90
Total QALYs	3.0625	3.3803	0.3178
LYs	4.0498	4.4386	0.3888
Exacerbation events	0.2988	0.2549	-0.0440
Net monetary benefit	£67,179.97	£17,179.38	
Cost-effectiveness	£8,063.39	£24,917.75	
ICER (per QALY)			£187,328.36
ICER (per LY)			£153,136.54
ICER (per exacerbation avoided)			£1,354,354.95

Table 39: Model results NDB vs. PFN, using the Kondoh loglogistic parametric model for OS, NDB list price

	PFN	NDB	Incremental
Treatment costs	£60,717.90	£59,122.64	-£1,595.26
Adverse event costs	£995.20	£721.68	-£273.53
Liver panel tests	£9.31	£9.06	-£0.24
Patient monitoring and O_2 use	£9,730.17	£9,604.33	-£125.84
Acute exacerbation costs	£1,365.63	£1,053.53	-£312.10
End of life costs	£13,720.77	£13,717.48	-£3.29
Total costs	£86,538.98	£84,228.72	-£2,310.27
Total QALYs	3.3389	3.3803	0.0413
LYs	4.4394	4.4386	-0.0008
Exacerbation events	0.3304	0.2549	-0.0755
Net monetary benefit	£13,628.74	£17,179.38	
Cost-effectiveness	£25,918.22	£24,917.75	
ICER (per QALY)			NDB dominates
ICER (per LY)			NDB dominates
ICER (per exacerbation avoided)			NDB dominates

Table 40: Full incremental cost-effectiveness analysis results, using the Kondoh loglogistic parametric model for OS, NDB list price

Treatment	Total costs	Total QALYs	ICER
BSC	£24,693.81	3.0625	
PFN	£86,538.98	3.3389	Dominated by NDB
NDB	£84,228.72	3.3803	£187,328 per QALY gained

NDB list price, Kondoh lognormal parametric model for OS

Table 41: Model results NDB vs. BSC, using the Kondoh lognormal parametric model for OS, NDB list price

	BSC	NDB	Incremental
Treatment costs	£0.00	£59,366.03	£59,366.03
Adverse event costs	£581.79	£720.09	£138.30
Liver panel tests	£0.00	£9.10	£9.10
Patient monitoring and O_2 use	£8,966.56	£9,523.98	£557.42
Acute exacerbation costs	£1,235.93	£1,047.55	-£188.38
End of life costs	£13,979.42	£13,843.30	-£136.11
Total costs	£24,763.69	£84,510.06	£59,746.37
Total QALYs	3.0675	3.3747	0.3072
LYs	4.0523	4.4251	0.3728
Exacerbation events	0.2990	0.2534	-0.0456
Net monetary benefit	£67,260.31	£16,731.20	
Cost-effectiveness	£8,073.01	£25,042.18	
ICER (per QALY)			£194,460.34
ICER (per LY)			£160,283.70
ICER (per exacerbation avoided)			£1,311,021.20

Table 42: Model results NDB vs. PFN, using the Kondoh lognormal parametric model for OS, NDB list price

	PFN	NDB	Incremental
Treatment costs	£60,974.66	£59,366.03	-£1,608.62
Adverse event costs	£994.87	£720.09	-£274.78
Liver panel tests	£9.35	£9.10	-£0.25
Patient monitoring and O_2 use	£9,652.01	£9,523.98	-£128.03
Acute exacerbation costs	£1,361.30	£1,047.55	-£313.75
End of life costs	£13,844.17	£13,843.30	-£0.87
Total costs	£86,836.35	£84,510.06	-£2,326.29
Total QALYs	3.3337	3.3747	0.0410
LYs	4.4265	4.4251	-0.0015
Exacerbation events	0.3293	0.2534	-0.0759
Net monetary benefit	£13,173.57	£16,731.20	
Cost-effectiveness	£26,048.32	£25,042.18	
ICER (per QALY)			NDB dominates
ICER (per LY)			NDB dominates
ICER (per exacerbation avoided)			NDB dominates

Table 43: Full incremental cost-effectiveness analysis results, using the Kondoh lognormal parametric model for OS, NDB list price

Treatment	Total costs	Total QALYs	ICER
BSC	£24,763.69	3.0675	
PFN	£86,836.35	3.3337	Dominated by NDB
NDB	£84,510.06	3.3747	£194,460 per QALY gained

NDB PAS discount price, Kondoh loglogistic parametric model for OS

Table 44: Model results NDB vs. BSC, using the Kondoh loglogistic parametric model for OS, NDB PAS discount price

	BSC	NDB	Incremental
Treatment costs	£0.00	[redacted]	[redacted]
Adverse event costs	£581.43	[redacted]	[redacted]
Liver panel tests	£0.00	[redacted]	[redacted]
Patient monitoring and O_2 use	£8,994.62	[redacted]	[redacted]
Acute exacerbation costs	£1,235.24	[redacted]	[redacted]
End of life costs	£13,882.54	[redacted]	[redacted]
Total costs	£24,693.81	[redacted]	[redacted]
Total QALYs	3.0625	3.3803	0.3178
LYs	4.0498	4.4386	0.3888
Exacerbation events	0.2988	0.2549	-0.0440
Net monetary benefit	£67,179.97	[redacted]	[redacted]
Cost-effectiveness	£8,063.39	[redacted]	[redacted]
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 45: Model results NDB vs. PFN, using the Kondoh loglogistic parametric model for OS, NDB PAS discount price

	PFN	NDB	Incremental
Treatment costs	£60,717.90	[redacted]	[redacted]
Adverse event costs	£995.20	[redacted]	[redacted]
Liver panel tests	£9.31	[redacted]	[redacted]
Patient monitoring and O_2 use	£9,730.17	[redacted]	[redacted]
Acute exacerbation costs	£1,365.63	[redacted]	[redacted]
End of life costs	£13,720.77	[redacted]	[redacted]
Total costs	£86,538.98	[redacted]	[redacted]
Total QALYs	3.3389	3.3803	0.0413
LYs	4.4394	4.4386	-0.0008
Exacerbation events	0.3304	0.2549	-0.0755
Net monetary benefit	£13,628.74	[redacted]	[redacted]
Cost-effectiveness	£25,918.22	[redacted]	[redacted]
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 46: Full incremental cost-effectiveness analysis results, using the Kondoh loglogistic parametric model for OS, NDB PAS discount price

Treatment	Total costs	Total QALYs	ICER
BSC	£24,693.81	3.0625	
PFN	[redacted]	3.3389	[redacted]
NDB	[redacted]	3.3803	[redacted]

NDB PAS discount price, Kondoh lognormal parametric model for OS

Table 47: Model results NDB vs. BSC, using the Kondoh lognormal parametric model for OS, NDB PAS discount price

	BSC	NDB	Incremental
Treatment costs	£0.00	[redacted]	[redacted]
Adverse event costs	£581.79	[redacted]	[redacted]
Liver panel tests	£0.00	[redacted]	[redacted]
Patient monitoring and O_2 use	£8,966.56	[redacted]	[redacted]
Acute exacerbation costs	£1,235.93	[redacted]	[redacted]
End of life costs	£13,979.42	[redacted]	[redacted]
Total costs	£24,763.69	[redacted]	[redacted]
Total QALYs	3.0675	3.3747	0.3072
LYs	4.0523	4.4251	0.3728
Exacerbation events	0.2990	0.2534	-0.0456
Net monetary benefit	£67,260.31	[redacted]	[redacted]
Cost-effectiveness	£8,073.01	[redacted]	[redacted]
ICER (per QALY)		[redacted]	[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 48: Model results NDB vs. PFN, using the Kondoh lognormal parametric model for OS, NDB PAS discount price

	PFN	NDB	Incremental
Treatment costs	£60,974.66	[redacted]	[redacted]
Adverse event costs	£994.87	[redacted]	[redacted]
Liver panel tests	£9.35	[redacted]	[redacted]
Patient monitoring and O_2 use	£9,652.01	[redacted]	[redacted]
Acute exacerbation costs	£1,361.30	[redacted]	[redacted]
End of life costs	£13,844.17	[redacted]	[redacted]
Total costs	£86,836.35	[redacted]	[redacted]
Total QALYs	3.3337	3.3747	0.0410
LYs	4.4265	4.4251	-0.0015
Exacerbation events	0.3293	0.2534	-0.0759
Net monetary benefit	£13,173.57	[redacted]	[redacted]
Cost-effectiveness	£26,048.32	[redacted]	[redacted]
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 49: Full incremental cost-effectiveness analysis results, using the Kondoh lognormal parametric model for OS, NDB PAS discount price

Treatment	Total costs	Total QALYs	ICER
BSC	£24,763.69	3.0675	
PFN	[redacted]	3.3337	[redacted]
NDB	[redacted]	3.3747	[redacted]

B14. Please update hospitalisation costs (£303.73; Tables 141, 158 and 159 of the company submission) to 2012-13 NHS Reference costs and provide details of what data were used to calculate the average cost per day on treatment. Please provide updated model results based on the revised hospitalisation costs.

The hospitalisation cost was updated to 20212-13 NHS Reference Costs values using the non-elective inpatient short stay (NEI_S), and non-elective inpatient long stay value (NEI_L), and the impact of the revised values was explored in sensitivity analysis. The model results were not affected significantly in either scenario.

Table 50: Calculation of the hospitalisation unit cost – non-elective inpatients short stay procedure (NEI_S) (National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts, Non-Elective Inpatients Short Stay)

Currency Code	Currency Description	Service Code	Service Description	FCEs	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Data Submissions
DZ27H	Respiratory Failure without Intubation, with CC Score 12+	340	Respiratory Medicine	78	£826	£353	£721	37
DZ27J	Respiratory Failure without Intubation, with CC Score 8-11	340	Respiratory Medicine	239	£518	£353	£622	68
DZ27J	Respiratory Failure without Intubation, with CC Score 8-11	341	Respiratory Physiology	1	£753	£753	£753	1
DZ27K	Respiratory Failure without Intubation, with CC Score 4-7	340	Respiratory Medicine	551	£477	£353	£564	91
DZ27L	Respiratory Failure without Intubation, with CC Score 0-3	340	Respiratory Medicine	345	£521	£338	£547	75
DZ27L	Respiratory Failure without Intubation, with CC Score 0-3	341	Respiratory Physiology	1	£420	£420	£420	1
Weighted average*					**£520.12**			

* Weights: FCE values (finished consultant episodes)

Table 51: Calculation of the hospitalisation unit cost – non-elective inpatients long stay procedure code (NEI_L) (National Schedule of Reference Costs - Year 2012-13 - NHS trusts and NHS foundation trusts, Non-Elective Inpatients Long Stay)

Currency Code	Currency Description	Service Code	Service Description	FCEs	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average Length of Stay - Days	Unit cost per day	Data submissions
DZ27H	Respiratory Failure without Intubation, with CC Score 12+	340	Respiratory Medicine	418	£4,049	£2,346	£4,992	11.66	£347.21	80
DZ27J	Respiratory Failure without Intubation, with CC Score 8-11	340	Respiratory Medicine	1,110	£3,123	£2,195	£3,721	8.83	£353.64	109
DZ27J	Respiratory Failure without Intubation, with CC Score 8-11	341	Respiratory Physiology	2	£2,935	£831	£5,039	11.50	£255.24	2
DZ27K	Respiratory Failure without Intubation, with CC Score 4-7	340	Respiratory Medicine	1,794	£2,227	£1,788	£2,543	6.28	£354.45	109
DZ27L	Respiratory Failure without Intubation, with CC Score 0-3	340	Respiratory Medicine	714	£1,696	£1,324	£2,088	4.40	£385.66	95
DZ27L	Respiratory Failure without Intubation, with CC Score 0-3	341	Respiratory Physiology	2	£4,791	£1,224	£8,358	6.00	£798.44	2
Weighted average*					**£359.17**					

*Weights: FCE values (finished consultant episodes)

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NDB list price model results

Table 52: Model results NDB vs. BSC, alternative hospitalisation cost (non-elective inpatients short stay procedure code NEI_S), NDB list price

	BSC	NDB	Incremental
Treatment costs	£0.00	£59,037.76	£59,037.76
Adverse event costs	£625.98	£781.97	£155.98
Liver panel tests	£0.00	£9.05	£9.05
[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	£2,278.34	£2,030.66	-£247.68
End of life costs	£13,440.51	£13,242.07	-£198.44
Total costs	£28,459.72	£88,269.47	£59,809.75
Total QALYs	3.2721	3.6720	0.3999
LYs	4.3602	4.8593	0.4992
Exacerbation events	0.3234	0.2882	-0.0352
Net monetary benefit	£69,702.69	£21,889.73	
Cost-effectiveness	£8,697.75	£24,038.70	
ICER (per QALY)			£149,564.31
ICER (per LY)			£119,819.43
ICER (per exacerbation avoided)			£1,701,154.38

Table 53: Model results NDB vs. PFN, alternative hospitalisation cost (non-elective inpatients short stay procedure code NEI_S), NDB list price

	PFN	NDB	Incremental
Treatment costs	£60,707.68	£59,037.76	-£1,669.92
Adverse event costs	£1,054.92	£781.97	-£272.95
Liver panel tests	£9.31	£9.05	-£0.26
[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	£2,559.36	£2,030.66	-£528.70
End of life costs	£13,251.74	£13,242.07	-£9.67
Total costs	£90,909.92	£88,269.47	-£2,640.44
Total QALYs	3.6249	3.6720	0.0471
LYs	4.8558	4.8593	0.0036
Exacerbation events	0.3633	0.2882	-0.0750
Net monetary benefit	£17,836.27	£21,889.73	
Cost-effectiveness	£25,079.48	£24,038.70	
ICER (per QALY)			NDB dominates
ICER (per LY)			NDB dominates
ICER (per exacerbation avoided)			NDB dominates

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Table 54: Model results NDB vs. BSC, alternative hospitalisation cost (non-elective inpatients long stay procedure code NEI_L), NDB list price

	BSC	NDB	Incremental
Treatment costs	£0.00	£59,037.76	£59,037.76
Adverse event costs	£625.98	£781.97	£155.98
Liver panel tests	£0.00	£9.05	£9.05
[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	£1,578.03	£1,406.48	-£171.55
End of life costs	£13,440.51	£13,242.07	-£198.44
Total costs	£26,153.43	£85,902.67	£59,749.24
Total QALYs	3.2721	3.6720	0.3999
LYs	4.3602	4.8593	0.4992
Exacerbation events	0.3234	0.2882	-0.0352
Net monetary benefit	£72,008.98	£24,256.53	
Cost-effectiveness	£7,992.91	£23,394.14	
ICER (per QALY)			£149,412.99
ICER (per LY)			£119,698.21
ICER (per exacerbation avoided)			£1,699,433.34

Table 55: Model results NDB vs. PFN, alternative hospitalisation cost (non-elective inpatients long stay procedure code NEI_L), NDB list price

	PFN	NDB	Incremental
Treatment costs	£60,707.68	£59,037.76	-£1,669.92
Adverse event costs	£1,054.92	£781.97	-£272.95
Liver panel tests	£9.31	£9.05	-£0.26
[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	£1,772.67	£1,406.48	-£366.19
End of life costs	£13,251.74	£13,242.07	-£9.67
Total costs	£88,358.06	£85,902.67	-£2,455.39
Total QALYs	3.6249	3.6720	0.0471
LYs	4.8558	4.8593	0.0036
Exacerbation events	0.3633	0.2882	-0.0750
Net monetary benefit	£20,388.13	£24,256.53	
Cost-effectiveness	£24,375.49	£23,394.14	
ICER (per QALY)			NDB dominates
ICER (per LY)			NDB dominates
ICER (per exacerbation avoided)			NDB dominates

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NDB PAS discount price model results:

Table 56: Model results NDB vs. BSC, alternative hospitalisation cost (non-elective inpatients short stay procedure code NEI_S), NDB PAS discount price

	BSC	NDB	Incremental
Treatment costs	£0.00	[redacted]	[redacted]
Adverse event costs	£625.98	[redacted]	[redacted]
Liver panel tests	£0.00	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	£2,278.34	[redacted]	[redacted]
End of life costs	£13,440.51	[redacted]	[redacted]
Total costs	£28,459.72	[redacted]	[redacted]
Total QALYs	3.2721	3.6720	0.3999
LYs	4.3602	4.8593	0.4992
Exacerbation events	0.3234	0.2882	-0.0352
Net monetary benefit	£69,702.69	[redacted]	
Cost-effectiveness	£8,697.75	[redacted]	
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 57: Model results NDB vs. PFN, alternative hospitalisation cost (non-elective inpatients short stay procedure code NEI_S), NDB PAS discount price

	PFN	NDB	Incremental
Treatment costs	£60,707.68	[redacted]	[redacted]
Adverse event costs	£1,054.92	[redacted]	[redacted]
Liver panel tests	£9.31	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	£2,559.36	[redacted]	[redacted]
End of life costs	£13,251.74	[redacted]	[redacted]
Total costs	£90,909.92	[redacted]	[redacted]
Total QALYs	3.6249	3.6720	0.0471
LYs	4.8558	4.8593	0.0036
Exacerbation events	0.3633	0.2882	-0.0750
Net monetary benefit	£17,836.27	[redacted]	
Cost-effectiveness	£25,079.48	[redacted]	
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

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Table 58: Model results NDB vs. BSC, alternative hospitalisation cost (non-elective inpatients long stay procedure code NEI_L), NDB PAS discount price

	BSC	NDB	Incremental
Treatment costs	£0.00	[redacted]	[redacted]
Adverse event costs	£625.98	[redacted]	[redacted]
Liver panel tests	£0.00	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	£1,578.03	[redacted]	[redacted]
End of life costs	£13,440.51	[redacted]	[redacted]
Total costs	£26,153.43	[redacted]	[redacted]
Total QALYs	3.2721	3.6720	0.3999
LYs	4.3602	4.8593	0.4992
Exacerbation events	0.3234	0.2882	-0.0352
Net monetary benefit	£72,008.98	[redacted]	
Cost-effectiveness	£7,992.91	[redacted]	
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Table 59: Model results NDB vs. PFN, alternative hospitalisation cost (non-elective inpatients long stay procedure code NEI_L), NDB PAS discount price

	PFN	NDB	Incremental
Treatment costs	£60,707.68	[redacted]	[redacted]
Adverse event costs	£1,054.92	[redacted]	[redacted]
Liver panel tests	£9.31	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	£1,772.67	[redacted]	[redacted]
End of life costs	£13,251.74	[redacted]	[redacted]
Total costs	£88,358.06	[redacted]	[redacted]
Total QALYs	3.6249	3.6720	0.0471
LYs	4.8558	4.8593	0.0036
Exacerbation events	0.3633	0.2882	-0.0750
Net monetary benefit	£20,388.13	[redacted]	
Cost-effectiveness	£24,375.49	[redacted]	
ICER (per QALY)			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

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B15. In scenario 46 of the company's exploratory analyses, a 'stopping rule' is applied to people receiving pirfenidone (page 288 and 291 of the company submission). This explored the effect of patients discontinuing and losing treatment effect when they observe a decline of forced vital capacity percent predicted (FVC%Pred) of 10% or more. Please provide the results of an additional scenario analysis in which the 'stopping rule' is also applied to the nintedanib arm.

The results of the sensitivity analysis requested are presented below for the both comparators, with the nintedanib list price (Table 60, Table 61) and with the PAS (Table 62, Table 63).

The results for the comparison against BSC strategy are similar to the base-case analysis. Overall, the nintedanib strategy has lower incremental costs and QALYs that lead to an increase in the ICER.

In the comparison with pirfenidone, nintedanib dominates when the PAS is considered. When the list price is considered the ICER is £17,000 per QALY.

Table 60: Model results for NDB vs. BSC, stopping rule applied to NDB, NDB list price

	BSC	NDB	Incremental
Treatment costs	£0.00	£47,098.37	£47,098.37
Adverse event costs	£625.98	£745.67	£119.68
Liver panel tests	£0.00	£7.22	£7.22
Patient monitoring and O_2 use	£9,955.76	£10,525.55	£569.79
Acute exacerbation costs	£1,336.83	£1,209.62	-£127.22
End of life costs	£13,440.51	£13,310.76	-£129.76
Total costs	£25,359.09	£72,897.18	£47,538.09
Total QALYs	3.2721	3.5695	0.2974
Lys	4.3602	4.7253	0.3651
Exacerbation events	0.3234	0.2926	-0.0308
Net monetary benefit	£72,803.32	£34,188.18	
Cost-effectiveness	£7,750.14	£20,422.17	
ICER (per QALY)			£159,828.60
Dominance			positive ICER
ICER (per LY)			£130,199.71
ICER (per exacerbation avoided)			£1,544,637.30

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Table 61: Model results for NDB vs. PFN, stopping rule applied to NDB and PFN, NDB list price

	PFN	NDB	Incremental
Treatment costs	£45,634.43	£47,098.37	£1,463.94
Adverse event costs	£943.08	£745.67	-£197.41
Liver panel tests	£7.00	£7.22	£0.22
Patient monitoring and O_2 use	£10,568.30	£10,525.55	-£42.75
Acute exacerbation costs	£1,448.70	£1,209.62	-£239.08
End of life costs	£13,330.59	£13,310.76	-£19.83
Total costs	£71,932.09	£72,897.18	£965.09
Total QALYs	3.5131	3.5695	0.0565
LYs	4.6955	4.7253	0.0297
Exacerbation events	0.3505	0.2926	-0.0578
Net monetary benefit	£33,459.77	£34,188.18	
Cost-effectiveness	£20,475.61	£20,422.17	
ICER (per QALY)			£17,096.38
Dominance			positive ICER
ICER (per LY)			£32,440.86
ICER (per exacerbation avoided)			£16,685.87

Table 62: Model results for NDB vs. BSC, stopping rule applied to NDB, NDB PAS discount price

	PFN	NDB	Incremental
Treatment costs	£0.00	[redacted]	[redacted]
Adverse event costs	£625.98	[redacted]	[redacted]
Liver panel tests	£0.00	[redacted]	[redacted]
Patient monitoring and O_2 use	£9,955.76	[redacted]	[redacted]
Acute exacerbation costs	£1,336.83	[redacted]	[redacted]
End of life costs	£13,440.51	[redacted]	[redacted]
Total costs	£25,359.09	[redacted]	[redacted]
Total QALYs	3.2721	3.5695	0.2974
LYs	4.3602	4.7253	0.3651
Exacerbation events	0.3234	0.2926	-0.0308
Net monetary benefit	£72,803.32	[redacted]	
Cost-effectiveness	£7,750.14	[redacted]	
ICER (per QALY)			[redacted]
Dominance			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

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Table 63: Model results for NDB vs. PFN, stopping rule applied to NDB and PFN, NDB PAS discount price

	PFN	NDB	Incremental
Treatment costs	£45,634.43	[redacted]	[redacted]
Adverse event costs	£943.08	[redacted]	[redacted]
Liver panel tests	£7.00	[redacted]	[redacted]
Patient monitoring and O_2 use	£10,568.30	[redacted]	[redacted]
Acute exacerbation costs	£1,448.70	[redacted]	[redacted]
End of life costs	£13,330.59	[redacted]	[redacted]
Total costs	£71,932.09	[redacted]	[redacted]
Total QALYs	3.5131	3.5695	0.0565
LYs	4.6955	4.7253	0.0297
Exacerbation events	0.3505	0.2926	-0.0578
Net monetary benefit	£33,459.77	[redacted]	[redacted]
Cost-effectiveness	£20,475.61	[redacted]	[redacted]
ICER (per QALY)			[redacted]
Dominance			[redacted]
ICER (per LY)			[redacted]
ICER (per exacerbation avoided)			[redacted]

Section C: Textual clarifications and additional points

C1. On page 20 of the company submission (under the heading "2. Base-case deterministic analysis for nintedanib vs. BSC"), it is stated that the incremental cost of nintedanib (using the PAS price) compared with best supportive care is a negative number. Please confirm that this should be a positive number.

Correct - this should be a positive number.

C2. In Table 18 of the company submission the units for 'Annual Rate of Decline in FVC' are reported in the first column as 'ml/year'. Please confirm whether the units are L/year?

Correct - this should be L/year.

C3. In Table 24 of the company submission, under the column headed 'SpO2,% (SD)', please confirm if the data from Noble et al. 2011 (CAPACITY) trials are 'Use of supplemental oxygen' not Sp02.

As the reviewer suggests, Table 24 incorrectly lists use of supplemental oxygen under the column headed SpO2, % (SD). The correct table entry should be "NR".

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C4. In Table 25 of the company submission, under the column headed 'change from FVC from baseline, L – mean (SD)', please confirm if the data from Noble et al. 2011 (CAPACITY) trials are not mean values, rather they are the number of patients with the categorical change in FVC ≥10%.

As the reviewer suggests, in Table 25, values reported for the CAPACITY trials indeed represent the numbers of patients with a categorical change in FVC ≥10% and not volume changes in L.

C5. Table 118 of the company submission presents the incidence and risk of gastrointestinal perforation events. Please confirm if the column headings are the wrong way around (for nintedanib and placebo).

Correct – the column headings are the wrong way around.

C6. On page 294 of the company submission, it is stated in the text that Table 189 uses the patient access scheme (PAS) price for nintedanib. The title for Table 189 states that the list price for nintedanib was used:

i. Please clarify which price was used.

The price of nintedanib used for generating these results is list price (£2151.10 per month). This table is replicated, but using the discounted nintedanib price, in the PAS document (Table 22).

ii. Please replicate Table 189 using the PAS price for nintedanib, if appropriate.

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Table 64: Impact of pirfenidone discount rate on ICER; nintedanib with PAS ([redacted]% discount)

	Discount Applied to Pirfenidone Drug Cost						
Pirfenidone	**Base-case (0% discount)**	**5%**	**10%**	**15%**	**20%**	**25%**	**30%**
Cost per pack	£2,151.10	£2043.55	£1935.99	£1828.44	£1720.88	£1613.33	£1505.77
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pirfenidone	**35%**	**40%**	**45%**	**50%**	**55%**	**60%**	**65%**
Cost per pack	£1398.22	£1290.66	£1183.11	£1075.55	£968.00	£860.44	£752.89
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pirfenidone	**70%**	**75%**	**80%**	**85%**	**90%**	**95%**	
Cost per pack	£645.33	£537.78	£430.22	£322.67	£215.11	£107.56	
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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iii. Please add the total and incremental costs (including the cost breakdown) to Table 189 (replicating Tables 161–164 from the base case analysis).

Table 65: Impact of pirfenidone discount rate on the ICER, nintedanib at list price

Discount on pirfenidone list price	Cost per pack pirfenidone	Costs			Incremental cost	Total QALY		Incremental QALY	ICER
		Type of costs	Nintedanib	Pirfenidone		Nintedanib	Pirfenidone		
0%	**£2151.10**	Treatment:	£59,037.76	£60,707.68	-£1,669.92	3.67	3.62	0.05	**-£50,777.45 (NDB dominates)**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£87,479.15**	**-£2,391.65**				
5%	**£2043.55**	Treatment:	£59,037.76	£57,672.47	£1,365.29	3.67	3.62	0.05	**£13,663.45**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£84,443.94**	**£643.56**				
10%	**£1935.99**	Treatment:	£59,037.76	£54,637.07	£4,400.69	3.67	3.62	0.05	**£78,108.24**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£81,408.54**	**£3,678.95**				

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15%	**£1828.44**	Treatment:	£59,037.76	£51,601.68	£7,436.08	3.67	3.62	0.05	**£142,553.03**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£78,373.15**	**£6,714.34**				
20%	**£1720.88**	Treatment:	£59,037.76	£48,566.29	£10,471.47	3.67	3.62	0.05	**£206,997.81**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£75,337.76**	**£9,749.74**				
25%	**£1613.33**	Treatment:	£59,037.76	£45,530.89	£13,506.86	3.67	3.62	0.05	**£271,442.60**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£72,302.36**	**£12,785.13**				
30%	**£1505.77**	Treatment:	£59,037.76	£42,495.50	£16,542.26	3.67	3.62	0.05	**£335,887.39**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£69,266.97**	**£15,820.52**				
35%	**£1398.22**	Treatment:	£59,037.76	£39,460.11	£19,577.65	3.67	3.62	0.05	**£400,332.17**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				

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		Patient monitoring and O2 use: Acute exacerbation: End of life: **Total costs:**	£10,825.15 £1,191.50 £13,242.07 £**85,087.49**	£10,953.78 £1,501.72 £13,251.74 **£66,231.58**	-£128.64 -£310.22 -£9.67 **£18,855.92**				
40%	**£1290.66**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: **Total costs:**	£59,037.76 £781.97 £9.05 £10,825.15 £1,191.50 £13,242.07 £**85,087.49**	£36,424.72 £1,054.92 £9.31 £10,953.78 £1,501.72 £13,251.74 **£63,196.18**	£22,613.04 -£272.95 -£0.26 -£128.64 -£310.22 -£9.67 **£21,891.31**	3.67	3.62	0.05	**£464,776.96**
45%	**£1183.11**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: **Total costs:**	£59,037.76 £781.97 £9.05 £10,825.15 £1,191.50 £13,242.07 £**85,087.49**	£33,389.32 £1,054.92 £9.31 £10,953.78 £1,501.72 £13,251.74 **£60,160.79**	£25,648.44 -£272.95 -£0.26 -£128.64 -£310.22 -£9.67 **£24,926.70**	3.67	3.62	0.05	**£529,221.75**
50%	**£1075.55**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: **Total costs:**	£59,037.76 £781.97 £9.05 £10,825.15 £1,191.50 £13,242.07 £**85,087.49**	£30,353.93 £1,054.92 £9.31 £10,953.78 £1,501.72 £13,251.74 **£57,125.40**	£28,683.83 -£272.95 -£0.26 -£128.64 -£310.22 -£9.67 **£27,962.09**	3.67	3.62	0.05	**£593,666.54**
55%	**£968.00**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation:	£59,037.76 £781.97 £9.05 £10,825.15 £1,191.50	£27,318.54 £1,054.92 £9.31 £10,953.78 £1,501.72	£31,719.22 -£272.95 -£0.26 -£128.64 -£310.22	3.67	3.62	0.05	**£658,111.32**

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		End of life: Total costs:	£13,242.07 **£85,087.49**	£13,251.74 **£54,090.01**	-£9.67 **£30,997.49**				
60%	**£860.44**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: **Total costs:**	£59,037.76 £781.97 £9.05 £10,825.15 £1,191.50 £13,242.07 **£85,087.49**	£24,283.14 £1,054.92 £9.31 £10,953.78 £1,501.72 £13,251.74 **£51,054.61**	£34,754.62 -£272.95 -£0.26 -£128.64 -£310.22 -£9.67 **£34,032.88**	3.67	3.62	0.05	**£722,556.11**
65%	**£752.89**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: **Total costs:**	£59,037.76 £781.97 £9.05 £10,825.15 £1,191.50 £13,242.07 **£85,087.49**	£21,247.75 £1,054.92 £9.31 £10,953.78 £1,501.72 £13,251.74 **£48,019.22**	£37,790.01 -£272.95 -£0.26 -£128.64 -£310.22 -£9.67 **£37,068.27**	3.67	3.62	0.05	**£787,000.90**
70%	**£645.33**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: **Total costs:**	£59,037.76 £781.97 £9.05 £10,825.15 £1,191.50 £13,242.07 **£85,087.49**	£18,212.36 £1,054.92 £9.31 £10,953.78 £1,501.72 £13,251.74 **£44,983.83**	£40,825.40 -£272.95 -£0.26 -£128.64 -£310.22 -£9.67 **£40,103.67**	3.67	3.62	0.05	**£851,445.68**
75%	**£537.78**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: **Total costs:**	£59,037.76 £781.97 £9.05 £10,825.15 £1,191.50 £13,242.07 **£85,087.49**	£15,176.96 £1,054.92 £9.31 £10,953.78 £1,501.72 £13,251.74 **£41,948.43**	£43,860.79 -£272.95 -£0.26 -£128.64 -£310.22 -£9.67 **£43,139.06**	3.67	3.62	0.05	**£915,890.47**
80%	**£430.22**	Treatment:	£59,037.76	£12,141.57	£46,896.19	3.67	3.62	0.05	**£980,335.26**

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		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£38,913.04**	**£46,174.45**				
85%	**£322.67**	Treatment:	£59,037.76	£9,106.18	£49,931.58	3.67	3.62	0.05	**£1,044,780.04**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£35,877.65**	**£49,209.85**				
90%	**£215.11**	Treatment:	£59,037.76	£6,070.79	£52,966.97	3.67	3.62	0.05	**£1,109,224.83**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£32,842.25**	**£52,245.24**				
95%	**£107.56**	Treatment:	£59,037.76	£3,035.39	£56,002.37	3.67	3.62	0.05	**£1,173,669.62**
		Adverse events:	£781.97	£1,054.92	-£272.95				
		Liver panel tests:	£9.05	£9.31	-£0.26				
		Patient monitoring and O2 use:	£10,825.15	£10,953.78	-£128.64				
		Acute exacerbation:	£1,191.50	£1,501.72	-£310.22				
		End of life:	£13,242.07	£13,251.74	-£9.67				
		Total costs:	**£85,087.49**	**£29,806.86**	**£55,280.63**				

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Table 66: Impact of pirfenidone discount rate on the ICER, nintedanib with PAS (▇% discount)

Discount on pirfenidone list price	Cost per pack pirfenidone	Costs			Incremental cost	Total QALY		Incremental QALY	ICER
		Type of costs	Nintedanib	Pirfenidone		Nintedanib	Pirfenidone		
0%	**£2151.10**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	▇	▇	▇	3.67	3.62	0.05	▇
5%	**£2043.55**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	▇	▇	▇	3.67	3.62	0.05	▇
10%	**£1935.99**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	▇	▇	▇	3.67	3.62	0.05	▇
15%	**£1828.44**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation:	▇	▇	▇	3.67	3.62	0.05	▇

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		End of life: Total costs:							
20%	**£1720.88**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
25%	**£1613.33**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
30%	**£1505.77**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
35%	**£1398.22**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
40%	**£1290.66**	Treatment:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]

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		Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:							
45%	**£1183.11**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
50%	**£1075.55**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
55%	**£968.00**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
60%	**£860.44**	Treatment: Adverse events: Liver panel tests: Patient monitoring and	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]

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		O2 use: Acute exacerbation: End of life: Total costs:							
65%	**£752.89**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
70%	**£645.33**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
75%	**£537.78**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
80%	**£430.22**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]

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		Total costs:							
85%	**£322.67**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
90%	**£215.11**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]
95%	**£107.56**	Treatment: Adverse events: Liver panel tests: Patient monitoring and O2 use: Acute exacerbation: End of life: Total costs:	[redacted]	[redacted]	[redacted]	3.67	3.62	0.05	[redacted]