Screen PART 1 slides

NICE National Institute for Health and Care Excellence

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

Lead team presentation

Chair: Amanda Adler
Technology Appraisal Committee B
Lead team: Mark Glover (clinical), Nick Latimer (cost), Tony Wootton (lay)
ERG: Kleijnen Systematic Reviews (KSR)
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Company: Boehringer Ingelheim
1st committee meeting 7 July 2021 virtual

Key issues: clinical

- Where in NHS treatment pathway would nintedanib fit, and what reflects standard care?
- In the trial, INBUILD:
  - Do the diagnostic criteria for progressive-fibrosing interstitial lung disease (PF-ILD) reflect NHS practice?
  - Do the “restricted” medications reflect NHS clinical practice?
  - Do protocol violations related to ‘restricted medicines’ bias results?
  - Is ‘placebo’ a relevant comparator to reflect practice?
  - Is nintedanib clinically more effective than placebo?
  - Does nintedanib prolong life?
- In NHS practice, would nintedanib be offered along with immunomodulatory therapies?

Key issues: cost effectiveness

- Does evidence from the trial suggest nintedanib improves survival? If not, is it reasonable to model a survival benefit?
- When extrapolating overall survival beyond end of the trial:
  - Appropriate to assume similar natural history between and progressive-fibrosing interstitial lung disease (PF-ILD) and idiopathic pulmonary fibrosis (IPF) including survival?
  - Which of the Bayesian and frequentist approaches is most appropriate?
  - Does heterogeneity between epidemiological data for IPF and INBUILD and IPF trials allow comparison?
- Is the model fit for purpose with respect to treatment discontinuation?

Nintedanib (OFEV, Boehringer Ingelheim)

Marketing authorisation	"..indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF)." NICE TA379 "..also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype". - TODAY's indication *Other indications:* - *systemic sclerosis associated interstitial lung disease – no NICE submission planned* - *Locally advanced, metastatic or locally recurrent non-small cell adenocarcinoma of the lung after 1st-line chemotherapy, in combination with docetaxel (VARGATEF, Nov. 2014) – recommended by NICE (TA347)*
Mechanism	Tyrosine kinase inhibitor which targets 3 growth factor receptors
Administration & dose	• Oral; 150 mg twice daily • 100 mg twice daily for patients with mild hepatic impairment (Child Pugh A), and patients who do no tolerate recommended dose;
Treatment	Administered until disease progression or unacceptable toxicity
Price	List price: £2,150 per pack of 60 capsules tablets Patient access scheme (PAS) discount in place (confidential)

Sources: CS, NICE scope and BNF NINTEDANIB | Medicinal forms | BNF content published by NICE

Background interstitial lung diseases - ILD

- Group of ~ 200 diseases characterised by inflammation + fibrosis
  - includes idiopathic pulmonary fibrosis (IPF), idiopathic interstitial pneumonias, autoimmune, hypersensitivity pneumonitis, sarcoidosis
- Some worsen despite treating underlying diseases so are 'progressive' and develop fibrotic/scarred lung, so 'progressive-fibrosing' ILD (PF-ILD)
- Diagnosis: history, serology, high resolution CT, sometimes biopsy
- Symptoms: dyspnoea, worse physical performance and quality of life
- Prevalence: Company ~ 876 patients in England;
- Cumulative incidence: Clinician 15% with ILD develop PF-ILD
- Mortality: Company similar to patients with idiopathic pulmonary fibrosis
- Care: Chest physicians and rheumatologists
- NICE guidelines for ILD but not progressive fibrosing phenotype
- Treatment : depends on underlying disease: corticosteroids for sarcoidosis; azathioprine; mycophenolate; cyclophosphamide, rituximab

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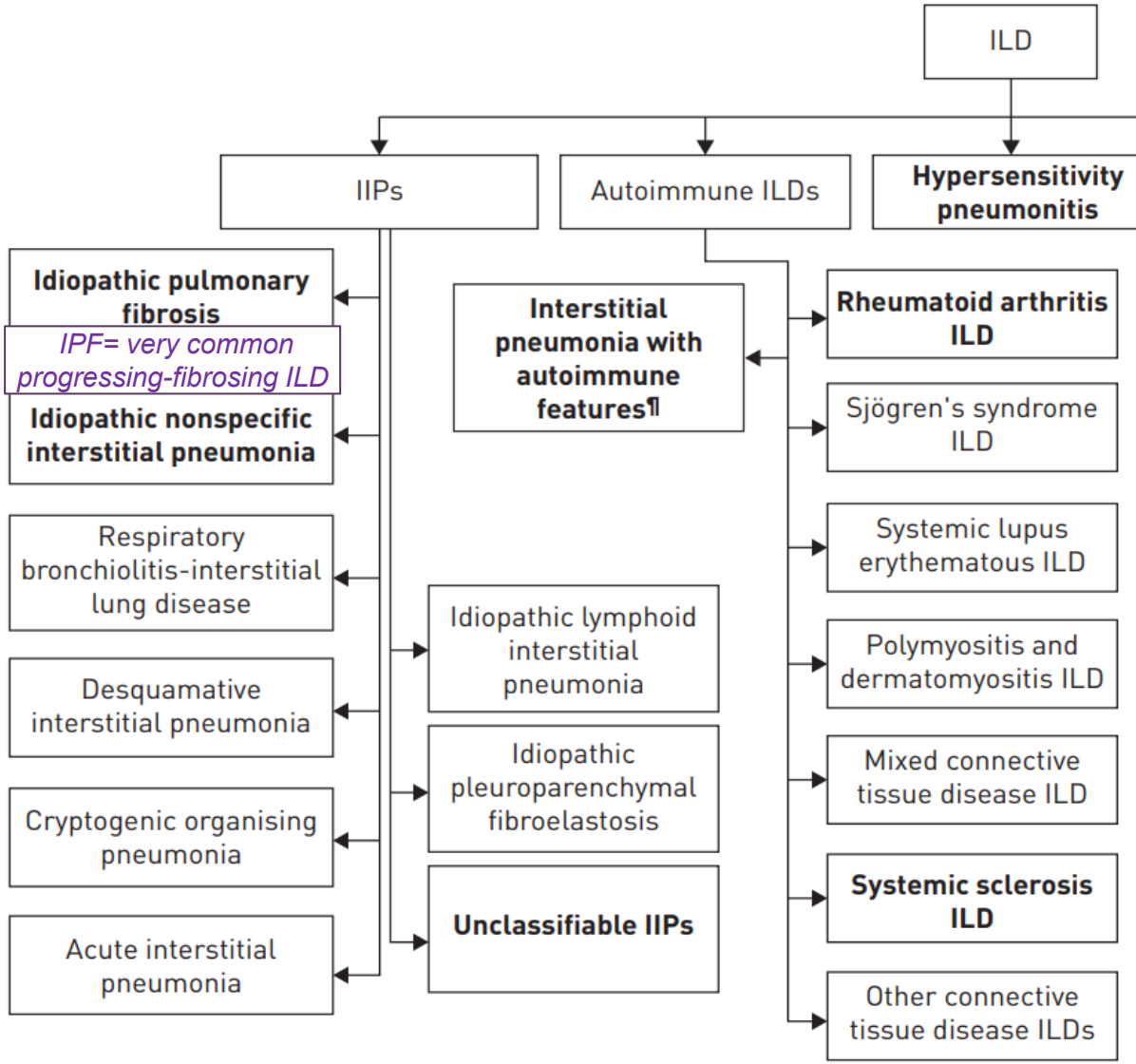
Abbreviations: CT: computed tomography; PF-ILDs: progressive fibrosing ILD; ILD: interstitial lung disease; IPF: Idiopathic pulmonary fibrosis

Interstitial lung disease most likely to have progressive fibrosing phenotype



Clinical expert:

- Treat underlying disease
- Treat inflammation not fibrosis
- Natural history: in some, inflammation predominates, and in others fibrosis
- All end up with scarred/fibrotic lung wherever they started from.

: stage IV sarcoidosis only; ¶ : not an established clinical diagnosis; + : e.g. asbestosis, silicosis

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Abbreviations: IIPs : idiopathic interstitial pneumonias; ILD: interstitial lung disease

Source: Cottin et al., 'Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases'. *Eur Respir Rev* 2018; 27: 180076

Patient perspective: Living with condition

- “When you are diagnosed with PF-ILD, you are given a death sentence. You are told that disease is incurable, only going to get worse, you have, on average, only 3-4 years to live”
- “It feels like an open prison – you can do almost everything you used to do. But, within a short time, you start to become more and more breathless”
- “At first, you find it difficult to walk up slopes/ climb stairs, without becoming severely breathless. In time, even walking on the flat becomes a challenge and you have to stop frequently to catch breath.”
- 2/3 of patients suffer from debilitating cough, some patients are so embarrassed by it that they are reluctant to see friends or family”
- “Eventually …you find yourself stuck at home and dependent on supplementary oxygen ... You need help from carer for taking a shower or getting dressed.”
- As symptoms worsen, “..you just concentrate on managing ..on getting through the day. The strain is taken by your carer, if you have one, who has to both stay strong for you and manage the home and links with family and the health care system”
- “In time, you will sadly die from respiratory failure or a related illness, like pneumonia”

Sources: Patient expert submission from Action for Pulmonary Fibrosis

Patient perspective: Nintedanib

- **New medications:** Patients desperate for new medications like nintedanib which has been a 'game changer' for people with idiopathic pulmonary fibrosis (IPF). People with progressive fibrotic ILD envy access of IPF patients with IPF to anti-fibrotics: "Why them and not me?"
- **Adverse effects:** Patients aware of adverse effects, especially diarrhoea. But most IPF patients stay on drug. Potential benefits outweigh adverse effects
- **Current standard of care:**
  - Concerned about absence of clinical trials to prove safety and efficacy of current treatments
  - Treatment with corticosteroids and other immunosuppressants have adverse effects causing patients to swap treatments many times, or give up

Sources: Patient expert and professional submissions
ILD: interstitial lung disease

Decision problem

	Final NICE scope	Company submission
Population	People with fibrosing interstitial lung disease excluding idiopathic pulmonary fibrosis that has progressed despite treatment	Same – adults only
Intervention	Nintedanib	Nintedanib
Comparators	Established clinical management without nintedanib including, but not limited to: • immunosuppressants#,* • corticosteroids* • infliximab* • rituximab* • best supportive care	Placebo: added to treatment patients received in INBUILD trial which restricted use for immunomodulatory treatments during 1st 6 months of trial

#Immunosuppressants: such as azathioprine, cyclophosphamide, mycophenolate
*Do not have currently have a marketing authorisation in the UK for this indication

◉ *Is nintedanib added to standard care or does it replace standard care? Would clinicians stop any drugs when starting nintedanib? Are the company's choice of comparators appropriate?*

Decision problem outcomes

	Final NICE scope	Company submission
Outcomes	• lung function • physical function • exacerbation rate • progression-free survival • mortality • adverse effects of treatment • health-related quality of life	• Forced vital capacity (FVC) at 52 weeks • Absolute change from baseline in total score on K-BILD questionnaire at 52 weeks • Time until acute exacerbation • Death at 52 weeks • Acute exacerbation of ILD or death up to database lock 2 • Death up to database lock 2 • Adverse events • Not reported: physical function
Subgroups to be considered	If the evidence allows - ILD type	Baseline characteristics Underlying ILD disease

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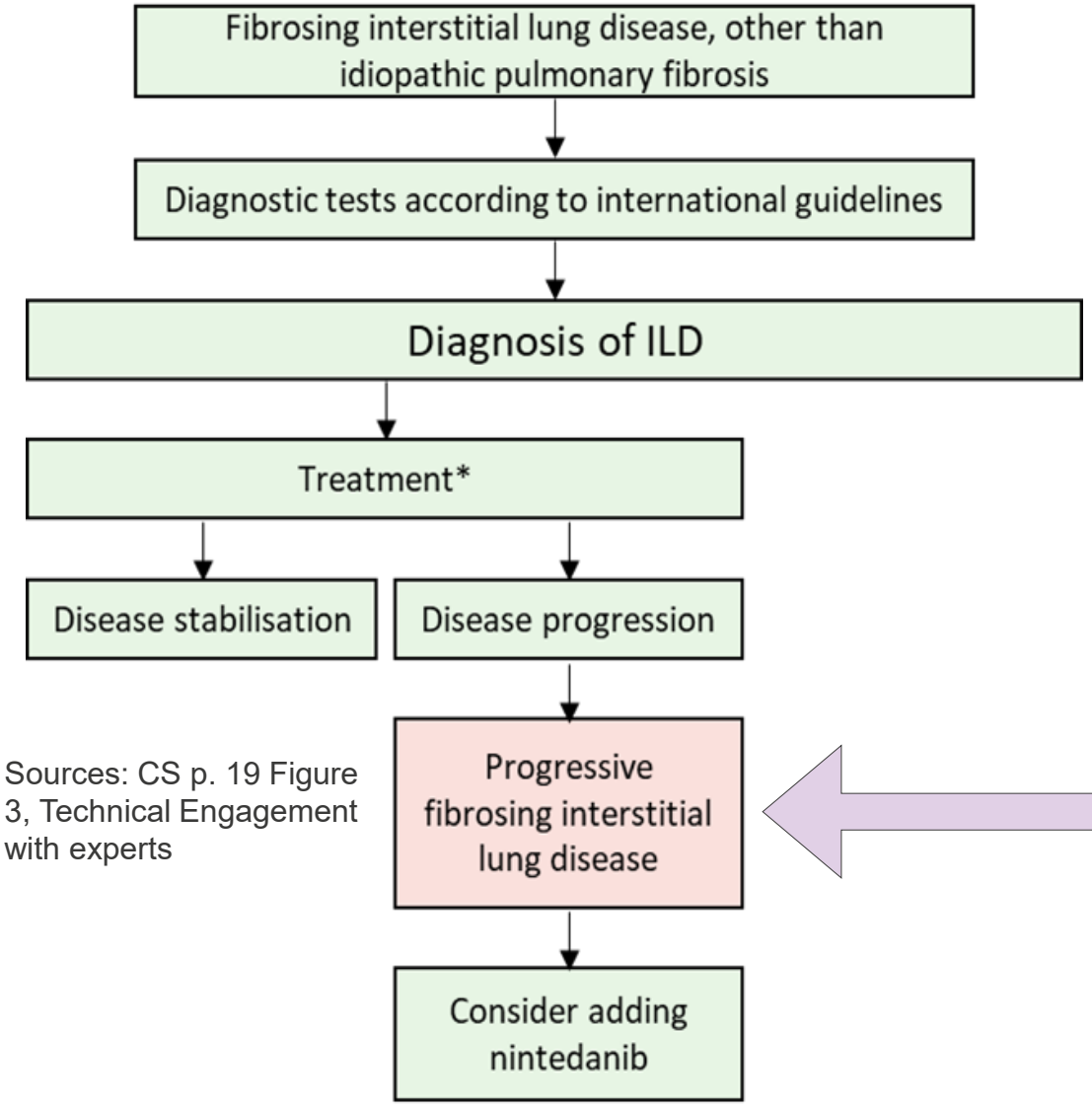
Abbreviations: AE: adverse event; DBL2: database lock 2 occurred around 3 months after the 52 weeks; FVC: forced vital capacity; HRCT, high-resolution computed tomography; ILD: interstitial lung disease; K-BILD: King's Brief Interstitial Lung Disease; UIP, usual interstitial pneumonia

Company's positioning of nintedanib



Sources: CS p. 19 Figure 3, Technical Engagement with experts

Company:

- Nintedanib will be offered to patients that have progressed despite receiving conventional treatment.

Clinical expert:

- Company's choice of positioning clinically sensible and appropriate

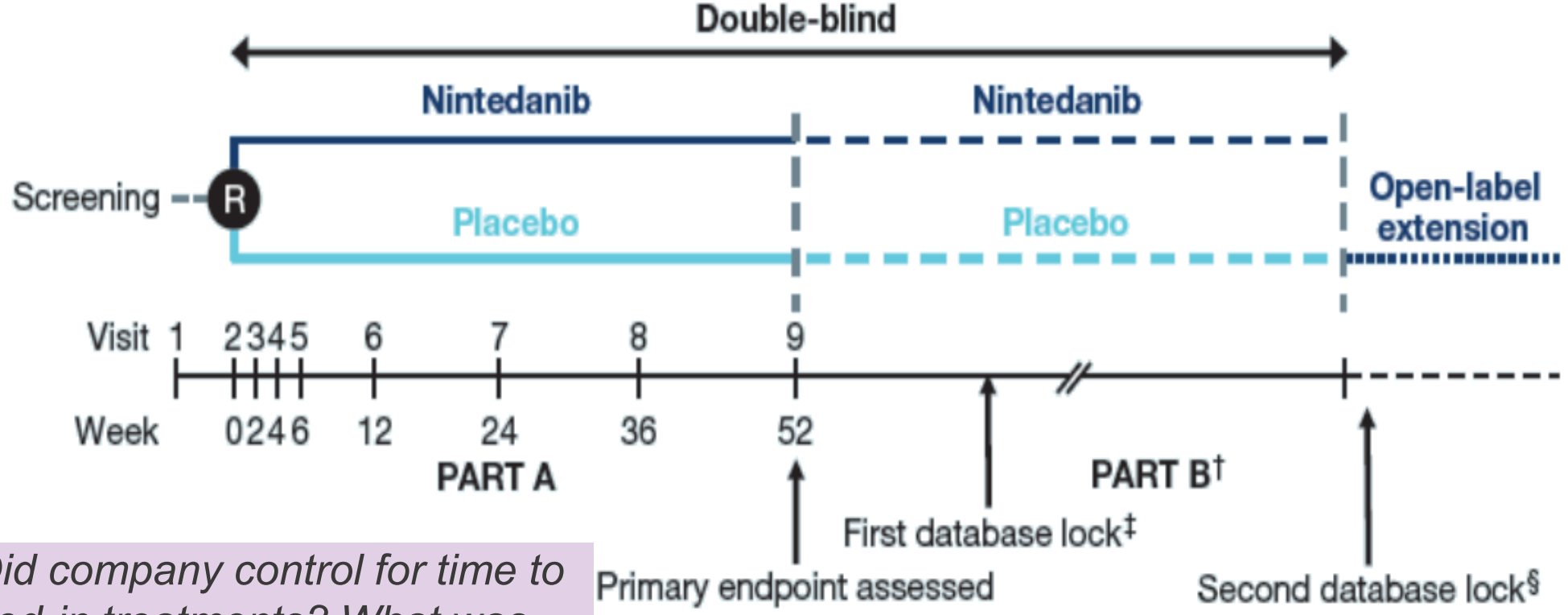
*Conventional treatments based on the specific interstitial lung disease, including, but not limited to, corticosteroids, mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, rituximab.

◉ *Where would nintedanib be used in NHS practice? What is standard care? Would drugs be stopped when adding nintedanib?*

Clinical effectiveness

INBUILD trial multi-country

- P: 633 people with progressive fibrosing ILD
- I: nintedanib **without** azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids
- C: placebo **without** azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids
- Design: 52-week initial period (PART A) then (PART B), where patients continued PART A
- O: 1◦ endpoint FVC at 52 weeks at end of Part A – FVC between groups at 52 weeks



◉ *Did company control for time to added-in treatments? What was median follow-up for 2nd data base lock?*

3 Jun 2019, n=565 patients ongoing

11 Sept 2019, all patients completing trial

Timepoint for outcomes in model

t subject had completed week 52 visit. §After all patients had completed follow-up visit or entered open-label extension study. Abbreviations: EOT, end of trial; ILD: interstitial lung disease R, randomisation

INBUILD outcomes

Company used few outcomes from INBUILD in model

INBUILD, N=663 (nintedanib n=332; placebo n=331)	In model
1º outcome: • Annual rate of decline in FVC	✓
2º outcomes†: • Change from baseline K-BILD questionnaire total score = quality of life	✗
• Time until 1st acute exacerbation or death	✓
• Time until death	✗
Other 2º endpoints • Time to death due to respiratory cause • Time to progression (≥10% absolute decline in FVC % predicted) or death • Proportion of patients with relative decline in FVC % predicted of >10% vs. baseline • Proportion of patients with relative decline in FVC % predicted of >5% vs. baseline • Change from baseline symptoms, dyspnoea domain score • Change from baseline symptoms, cough domain score	✗
Other model-relevant endpoints • EQ-5D	✓
Safety • Adverse events; physical examination; vital signs; bodyweight	✓ ✗

◉ *Are these the relevant endpoints? If FVC a relevant endpoint? Are exacerbations relevant?*

Abbreviations: FVC, forced vital capacity; HRQoL, health-related quality of life; ILD, interstitial lung disease; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; L-PF, living with pulmonary fibrosis. † Main secondary endpoints were not powered to show statistical significance; Source: CS table 8 p. 28

INBUILD inclusion vs NHS diagnostic criteria

INBUILD inclusion criteria

Progressive disease defined as: ≥ 1 following criteria within past 24 months

- a relative decline of ≥10% in forced vital capacity (FVC) % predicted;
- a relative decline of 5% to <10% in FVC% predicted, with worsening respiratory symptoms or, increasing fibrotic changes on chest imaging;
- worsening respiratory symptoms and increasing fibrotic changes on chest imaging

NHS

- No defined criteria
- Clinical experts classify a patient if:
  - patient receive conventional treatment for underlying ILD
  - lung function worsen despite treatments
  - fibrosis on CT scans

Clinical and patient experts:
INBUILD criteria reasonable

◉ *Are the diagnostic criteria for PF-ILD in INBUILD generalisable to NHS practice?*
Are the aetiologies in NHS practice reflected in this trial?
If nintedanib were recommended, would clinicians expect these criteria to be specified in the guidance?

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Abbreviations: FVC: forced vital capacity; ILD: interstitial lung disease; PF-ILD: progressive-fibrosing ILD
Source: Technical Engagement with experts

INBUILD trial: baseline characteristics

	Nintedanib (n=332)	Placebo (n=331)
Male – no. (%)	179 (54)	177 (54)
Age – years	65 ±10	66 ±10
Former or current smoker – no. (%)	169 (51)	169 (51)
Criteria for disease progression in 24 months before screening (grouped) – no. (%)		
Relative decline in FVC ≥10% predicted	160 (48)	172 (52)
Relative decline in FVC ≥5–<10% predicted combined with worsening of respiratory symptoms and/or increased extent of fibrosis on HRCT	110 (33)	97 (29)
Worsened respiratory symptoms and increased extent of fibrosis on HRCT only	62 (19)	61 (18)
FVC		
Mean value – mL	2,340±740	2,321±728
% of predicted value	68±16	69±15

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Abbreviations: FVC = forced vital capacity, K-BILD = King's Brief Interstitial Lung Disease, Plus–minus values are means ± SD. HRCT = high-resolution computed tomography;

INBUILD trial Part A: restricted medications

Company: Concomitant immunomodulatory treatments not allowed during first 6 months; but after 6 months, allowed for patients with worsening ILD and/or connective tissue disease

1st 6 months: ***not*** allowed, including: azathioprine, cyclosporin, tacrolimus, rituximab, other disease modifying drugs for RA, cyclophosphamide, mycophenolate mofetil and oral corticosteroids >20mg/day; small % of protocol violations (~17%)

Baseline and 1st 6 months: medications for underlying rheumatoid arthritis and connective tissue disease allowed at stable doses not "*restricted medications*"

After 6 months: restricted medications OK –

Over 52 weeks: 16% started them from beginning of trial– more in placebo group

◉ *Does this trial address the clinical decision problem? Would clinicians offer any of the 'restricted' medications along side nintedanib? Would clinicians stop treatments before starting nintedanib?*

Abbreviations: CTD: connective tissue disease; ILD: interstitial lung disease; RA: rheumatoid arthritis;

Comparator in INBUILD – company and ERG

ERG doubts control arm reflects clinical care without nintedanib

Company:

- Population in scope progresses despite treatment so won't be benefiting from conventional therapies, and currently no other anti-fibrotic therapy licensed for progressive disease - justifies placebo
- Clinical experts consensus agreed immunomodulatory treatments may be used to treat inflammatory component, extrapulmonary aspects of underlying disease; immunomodulatory treatments may not treat fibrosis *per se*
- No randomised controlled trials suggest unlicensed treatments delay fibrosis
- Some immunosuppressants allowed in 1st 6 months of trial, provided stable doses

ERG:

- Doubtful control arm represents current best practice or best supportive care
- Therapies restricted/not allowed during 1st 6 months actually used in NHS practice
- Company should have included other relevant comparators in scope
- Given lack of evidence for most comparators, ERG has no suggestions for an approach
- Effectiveness of current treatments in clinical practice might be underestimated

Comparator in INBUILD – clinicians

Stakeholders agree placebo arm represents standard care

Clinical experts

- No evidence immunosuppressants play significant role once disease develops
- In practice, if patients progress on immunosuppressant treatments they may be stopped

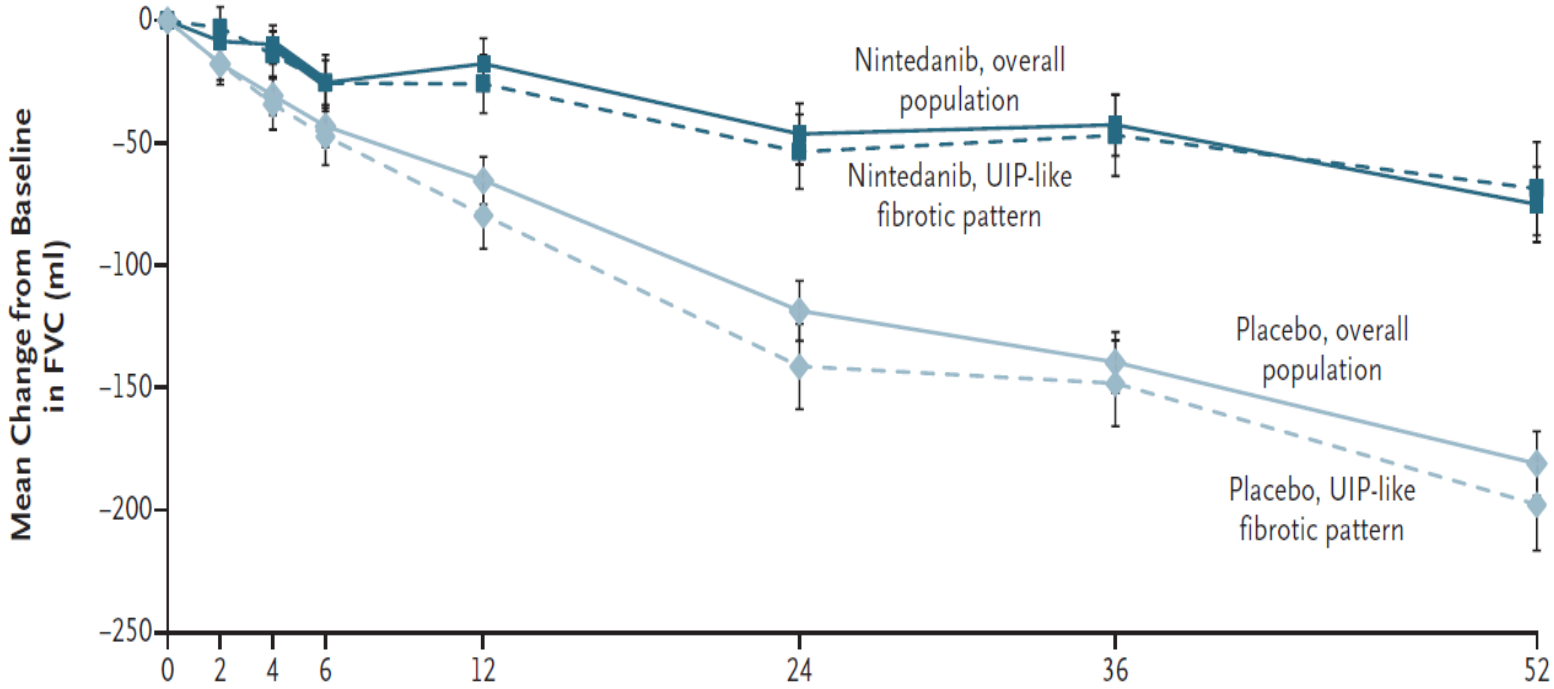
British Thoracic Society

- Common to reduce or stop immunosuppression because lack of effectiveness – considered treatment failure
- Acceptable that for 1st 6 months of trial, patients not on 2nd line immunosuppressants
- Conventional therapy includes non-evidence-based therapies, such as:
  - best supportive care when immunosuppression not suitable because of risk of infections, consistent with placebo arm in INBUILD
  - glucocorticoid only, consistent with placebo arm - 69% of patients had glucocorticoids at baseline or over 52-weeks
  - combination therapy with glucocorticoid & 2nd line immunosuppression with mycophenolate or azathioprine (n.b. 'restricted'), consistent with placebo arm - 40% of patients had non steroid anti-rheumatic or anti-inflammatory therapies at baseline or over 52 weeks

◉ *Does placebo arm of INBUILD represent best supportive care of NHS practice?*

Results INBUILD 1º outcome rate of decline in forced vital capacity (FVC) at 52 weeks

Solid line relevant population



Adjusted rate of decline in FVC at 52 weeks (mL/year)	Nintedanib (N = 332)	Placebo (N = 331)	Difference vs. placebo (95% CI; p-value)
Overall population	−80.8±15.1	−187.8±14.8	107.0 (65.4, 148.5; p<0.001)

◉ *What is declined 'adjusted' for? Do units in figure reflect units in analysis?*

Abbreviations: FVC, forced vital capacity; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; Source: CS Figure 6 p 41, table 15 p.40.

INBUILD 1º outcome to 24 months end Part B

Curves start converging and worsen after 52 weeks

Company: "*over whole trial analysis should be interpreted with caution. Trial design allowed variable duration in Part B, many had missing FVC assessment values after week 52*"

Adjusted annual rate of decline in FVC (mL/ year) up 2nd data base lock (rounded)	Nintedanib (N = 332)	Placebo (N = 331)	Difference vs. placebo (95% CI)
Overall population	−118 ±11	−176±11	58 (26–89)

Abbreviations: DBL2, database lock 2 occurred approximately 3 months after the 52 weeks; FVC, forced vital capacity; UIP, usual interstitial pneumonia
Source: Response to Clarification, Question A5, Figure 2, page 12; CS table 15 p.40

◉*Does the evidence suggest nintedanib has a long-term effect or wanes? Company encourages 'caution' but uses whole trial analysis for modelling?*

INBUILD 2º main outcomes

Nintedanib associated with lower risk of 1st acute exacerbation or death at end of Part B

Timepoint	Nintedanib (N = 332)	Placebo (N = 331)	Difference vs. placebo (95% CI; p-value)
Time to 1st acute exacerbation or death (no. with event/total no. [%])			
52 weeks	26/332 (7.8)	32/331 (9.7)	Hazard ratio= 0.80 (0.48, 1.34; p=0.3948)‡
up to 2nd data base lock	46/332 (13.9)	65/331 (19.6)	Hazard ratio = 0.67 (0.46 to 0.98)
Absolute change from baseline in total score on K-BILD			
52 weeks§	0.55±0.60	−0.79±0.59	Mean difference = 1.34 (−0.31, 2.98; p=0.1115)‡

§ For analysis of scores on K-BILD questionnaire, 332 patients were included in nintedanib group and 330 in placebo group in overall population
‡ Widths of confidence intervals have not been adjusted for multiple comparisons, so intervals should not be used to infer definitive treatment effect

Abbreviations: DBL2, database lock 2 occurred approximately 3 months after the 52 weeks; FVC, forced vital capacity; ILD, interstitial lung disease; K-BILD, King's Brief Interstitial Lung Disease Questionnaire; NR, not reported; UIP, usual interstitial pneumonia. Source: CS Figure 6 p 41

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◉ *How did the company model exacerbations?*

INBUILD 2º outcome death

Timepoint	Nintedanib (N = 332)	Placebo (N = 331)	Hazard ratio (95% CI; p-value)
Time to death (no. with event/total no. [%])			
52 weeks	16/332 (4.8)	17/331 (5.1)	0.94 (0.47, 1.86; p=0.85)‡
up to 2nd data base lock	36/332 (10.8)	45/331 (13.6)	0.78 (0.50 to 1.21)

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

◉ *Is nintedanib clinically more effective than placebo? Does the evidence suggest nintedanib reduces death?*

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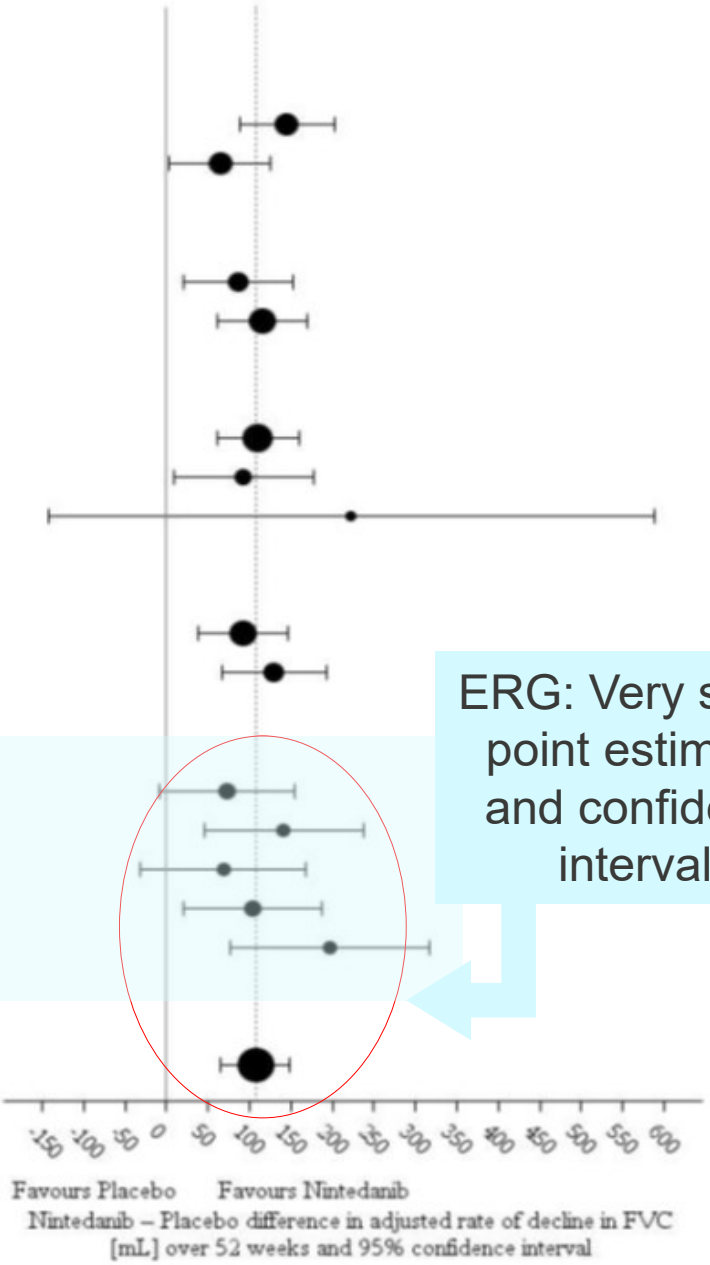
Abbreviations: DBL2, database lock 2 occurred approximately 3 months after the 52 weeks; FVC, forced vital capacity; UIP, usual interstitial pneumonia
Source: CS Figure 6 p 41

Subgroup analyses

Treatment effect not driven by a type of disease

	N analysed Placebo	N analysed Nintedanib	Estimate [95% CI]	Treatment-by-subgroup-by-time interaction p-value
Gender				0.0553
Male	177	179	145.20 [88.47; 201.93]	
Female	154	153	64.21 [3.87; 124.55]	
Age group				0.5123
<65 years	121	139	86.87 [21.53; 152.21]	
>=65 years	210	193	115.13 [61.41; 168.84]	
Race				0.7736
White	246	242	110.59 [61.97; 159.20]	
Asian	80	84	92.98 [9.30; 176.67]	
Black or African American	5	5	222.48 [-143.09; 588.05]	
Baseline FVC % predicted				0.3695
<=70%	193	196	91.68 [37.36; 145.99]	
>70%	138	136	129.98 [66.22; 193.73]	
Underlying ILD Diagnosis in Groups				0.4139
Hypersensitivity pneumonitis	89	84	73.12 [-8.57; 154.81]	
Idiopathic nonspecific interstitial pneumonia	61	64	141.61 [46.04; 237.17]	
Unclassifiable idiopathic interstitial pneumonia	50	64	68.33 [-31.43; 168.10]	
Autoimmune ILDs	88	82	104.02 [21.11; 186.92]	
Other ILDs	43	38	197.13 [77.57; 316.70]	
ALL	331	332	106.96 [65.42; 148.50]	



ERG: Very similar point estimates and confidence intervals

◉ *Statistical test for interaction?*

Abbreviations: ILD: interstitial lung disease
Source: CS, Appendix E

INBUILD safety profile at 52 weeks

Gastrointestinal adverse effects more common with nintedanib

AE	Nintedanib	Placebo
Any (n [%])	317 (95.5)	296 (89.4)
Any except for progression of ILD	317 (95.5)	295 (89.1)
Most frequent AEs		
Diarrhoea	222 (66.9)	79 (23.9)
Nausea	96 (28.9)	31 (9.4)
Bronchitis	41 (12.3)	47 (14.2)
Nasopharyngitis	44 (13.3)	40 (12.1)
Dyspnoea	36 (10.8)	44 (13.3)
Vomiting	61 (18.4)	17 (5.1)
Cough	33 (9.9)	44 (13.3)
Decreased appetite	48 (14.5)	17 (5.1)
Headache	35 (10.5)	23 (6.9)
ALAT increased	43 (13.0)	12 (3.6)
Progression of ILD	16 (4.8)	39 (11.8)
Weight loss	41 (12.3)	11 (3.3)
ASAT increased	38 (11.4)	12 (3.6)
Abdominal pain	34 (10.2)	8 (2.4)
Severe AEs	60 (18.1)	73 (22.1)
Serious AEs	107 (32.2)	110 (33.2)
Fatal AE		
Any	11 (3.3)	17 (5.1)
Any except progression of ILD	10 (3.0)	14 (4.2)
AE leading to discontinuation	65 (19.6)	34 (10.3)
AE leading to permanent dose reduction	110 (33.1)	14 (4.2)

- Diarrhoea most common adverse event on nintedanib
- Increased frequency of indicators of hepatic injury
- **Clinical experts**:
  - ~25 -30% of patients may not tolerate nintedanib in longer term.
  - No risk of infection compared with immunosuppressants.

Company did not include other comparators

Company: indirect treatment comparison not feasible:

- Only 1 study including pirfenidone suitable but 24 weeks follow-up
- Comparison immature as PF-ILD chronic condition

ERG: agreed no identified studies suitable for indirect comparison

- Pirfenidone not a relevant comparator in scope
- Company has not included any comparators from scope

◉ *Has the company addressed the decision problem?*

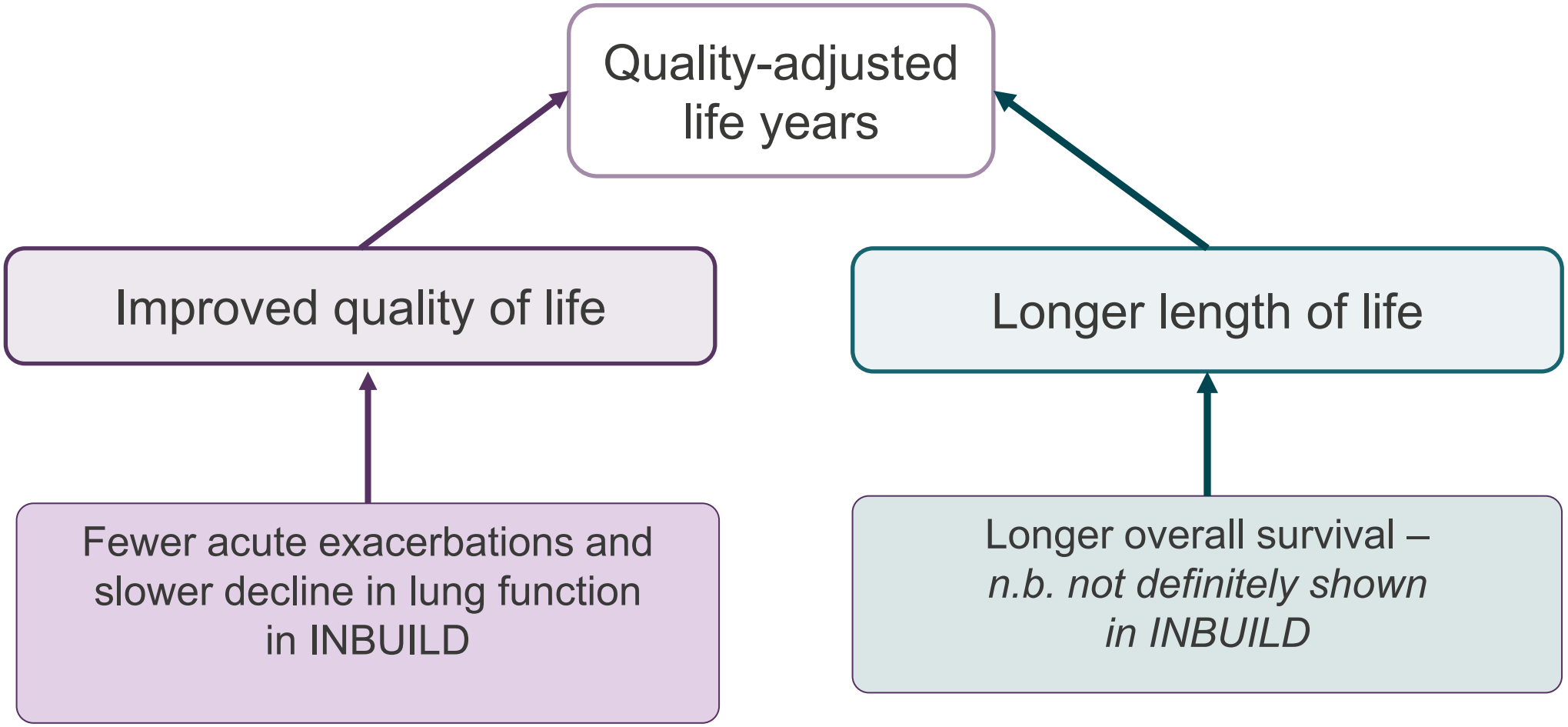
Cost effectiveness

Key issues: cost effectiveness

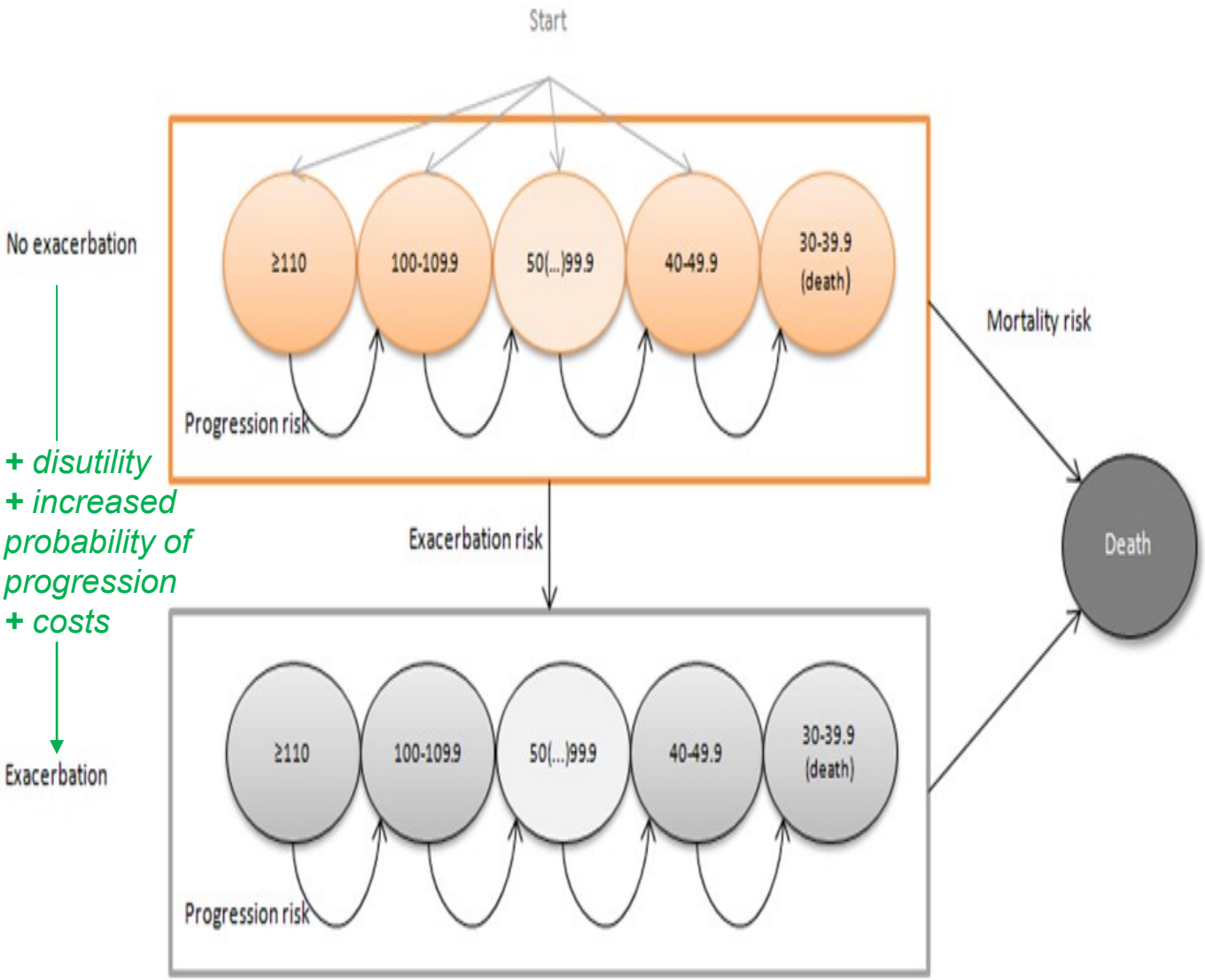
- Extrapolating overall survival :
  - Appropriate to assume same natural history between idiopathic pulmonary fibrosis (IPF) and progressive-fibrosing ILD including for survival?
  - If so, how to extrapolate? Bayesian or frequentist? Of the 2 Weibull curves selected by clinicians which, if either, does committee prefer?
  - Do differences between epidemiological/trial data for IPF and trial data INBUILD for progressive fibrosing ILD allow a meaningful comparison?
  - Does evidence from the trial suggest nintedanib has a long-term survival benefit?
  - Is company's modelling of stopping treatment appropriate?

How company accrues quality-adjusted life years

Treatment with nintedanib instead of without



Company model to estimate cost effectiveness



- Markov model same as nintedanib for IPF in TA379; numbers refer to FVC percentage predicted (FVC%pred)
- Efficacy informed by decline in lung function and acute exacerbation from INBUILD
- Efficacy data based on 2nd database lock of INBUILD
- Mortality risk informed by parametric extrapolation of overall survival, applied irrespective of health state
- Cycle length: 3 months
- 3.5% discounting
- Lifetime horizon
- NHS and Personal Social Services (PSS) perspective

◉ *Does the company provide sufficient evidence to estimate transition probabilities ?*

Abbreviations: FVC%Pred : FVC percentage predicted; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; OS: overall survival

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Extrapolating overall survival is key driver

FVC over time - 1º trial outcome and health states based on this - may also impact cost effectiveness

Model inputs	Impact on ICER	ERG and company assumptions
Overall survival		☒ • **Company**: Bayesian Weibull distribution • **ERG**: frequentist Weibull distribution
Time to 1st acute exacerbation		☑ **Company & ERG**: exponential distribution
Recurrent exacerbation		☑ **Company & ERG**: included recurrent exacerbation
Loss of lung function		☑ **Company & ERG:** estimated from odds ratio
Health related quality of life		☒ • **Company**: lower utility for 80-89 • **ERG**: adjusted utility assuming linear decline

 Represent size of impact

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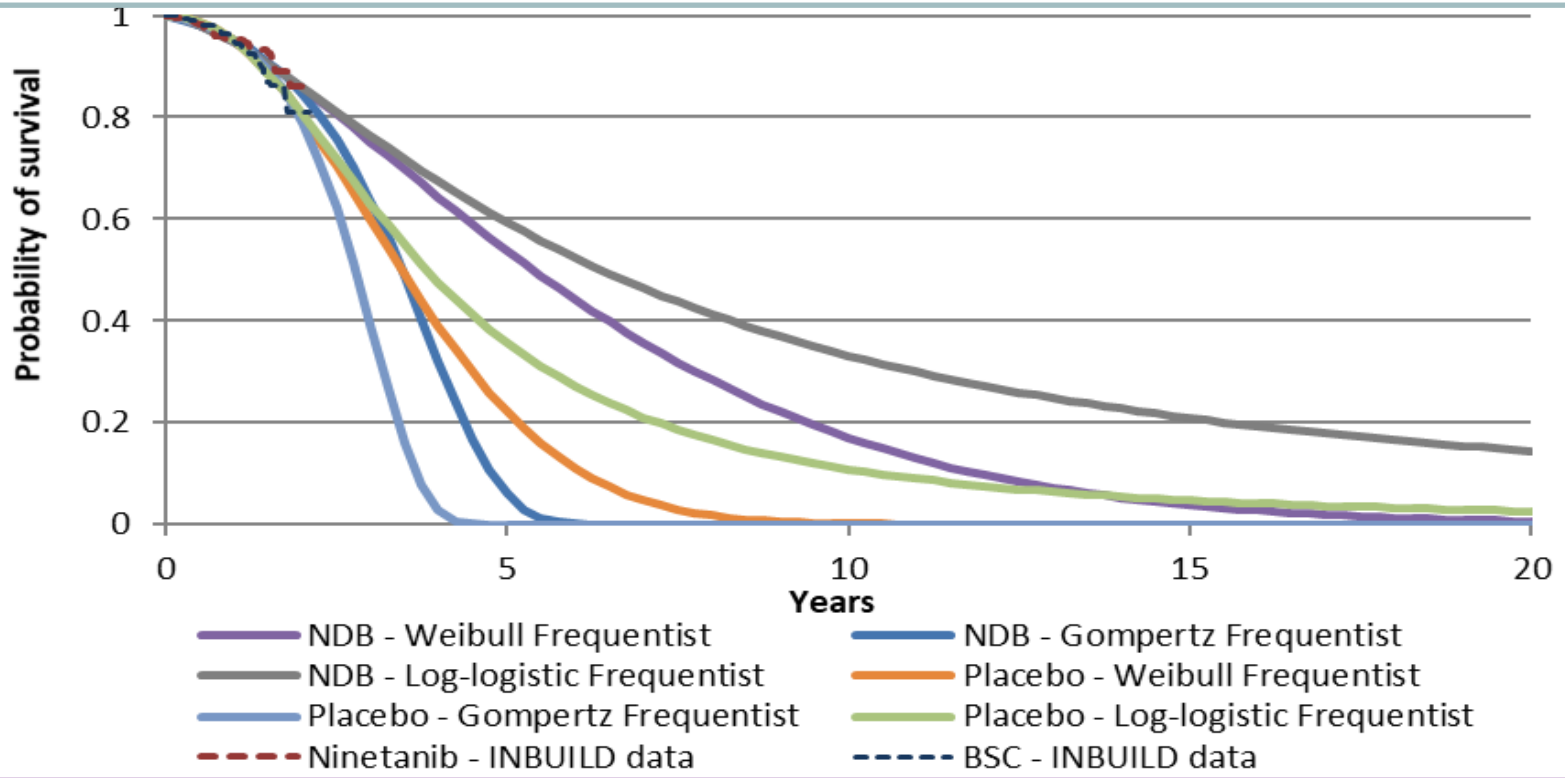
Extrapolating overall survival beyond trial
2 approaches: frequentist + Bayesian

*Company's **frequentist** approach – large differences in survival*

- **Frequentist based only on progressive fibrosis ILD data from trial**: standard parametric overall survival distributions fitted **independently** to each arm
- Company assessed goodness of fit using AIC/BIC; it considered models OK if within 3 points of parametric model with lowest AIC or BIC; included loglogistic, Gompertz and Weibull

Overall survival frequentist Weibull, log-logistic and Gompertz in both arms



◉ *Are the modelled results plausible, given trial results? Can committee choose a 'best' curve with information presented?*

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; FVC%Pred: forced vital capacity % predicted; OS: overall survival
Source: Figure 1 from ERG Response to additional questions

Extrapolating overall survival beyond trial

*Company's **Bayesian** approach*

Company's assumptions and methods:

- Company assumes IPF and progressive fibrosing ILD have same natural history including survival
  - Brown et al 2020 showed PF-ILD and IPF patients who don't receive antifibrotic treatment have similar disease trajectories
- Company used IPF trial data to generate 'informative prior' for progressive fibrosing ILD by:
  - **Obtaining data:** from RCTs of IPF and from extensions of trials, including: TOMORROW (phase II); INPULSIS I and II (phase III); and INPULSIS ON (long-term extension all together)
  - **Propensity score weighting**: matching patients with IPF and progressive fibrosing ILD for characteristics including age, sex, race (Asian versus other), disease duration; % predicted diffusing capacity for carbon monoxide (DLCO) corrected for haemoglobin; % predicted forced vital capacity at baseline; smoking
  - **Generating survival curves**: for matched and weighted IPF patients, and parametric models were fitted
  - **Generating informative priors**: from those IPF parametric models, the shape parameters were retained for nintedanib and placebo
  - **OS curves generated for progressive fibrosing ILD:** parametric models were fit to the INBUILD data, using the shape parameters from the IPF models as informative priors

◉ *Is company's approach methodologically sound? Is it appropriate to assume similar natural history between IPF and PF-ILD including survival? Has committee been presented with evidence? What other evidence from other treatments for IPF could inform modelling?*

Abbreviations: IPF: idiopathic pulmonary fibrosis, PF-ILD: progressive-fibrosing ILD; RCT randomised controlled trial; Source: CS p.65

Brown et al. 2020 suggests lower not equal death rates for placebo groups in PF-ILD (INBUILD) vs. IPF (INPULSIS)

TABLE 2 Proportion of subjects who died over 52 weeks in the placebo groups of the INBUILD and INPULSIS trials

	INBUILD trial			INPULSIS trials (n=423)
	Overall population (n=331)	UIP-like fibrotic pattern on HRCT (n=206)	Other fibrotic patterns on HRCT (n=125)	
Deaths over 52 weeks	17 (5.1)	16 (7.8)	1 (0.8)	33 (7.8)
Hazard ratio *versus* INPULSIS trials[#]	0.63 (0.35–1.13)	0.97 (0.53–1.76)	0.10 (0.01–0.70)	
Nominal p-value[¶]	0.12	0.92	0.004	

Data are presented as n (%) or hazard ratio (95% CI), unless otherwise stated. UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; CI: confidence interval. [#]: based on a Cox regression model with terms for patient population (idiopathic pulmonary fibrosis (IPF) *versus* non-IPF); [¶]: based on a log-rank test.

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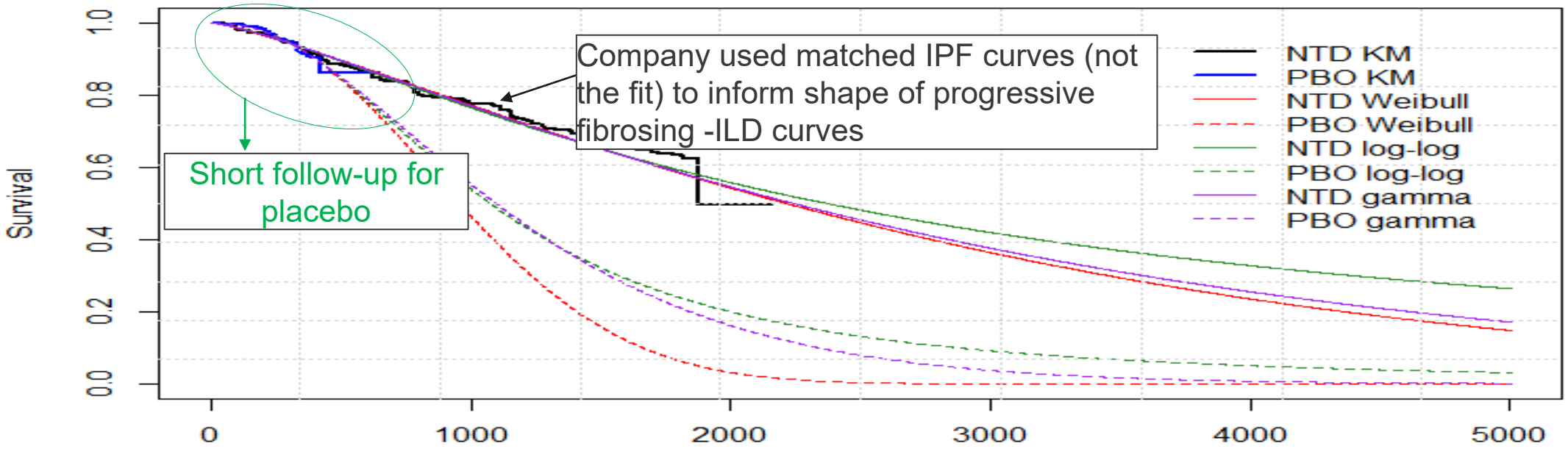
Abbreviations: IPF: idiopathic pulmonary fibrosis, PF-ILD: progressive-fibrosing ILD;

Extrapolating overall survival beyond trial

Company's Bayesian approach: IPF survival models used to generate prior

- Weibull, log-logistic and gamma distributions of IPF survival models produced lowest overall AICs/BICs across nintedanib and placebo
- Small differences in fit between models, therefore company used all of them to inform ***shape parameter prior*** of progressive fibrosing ILD for both nintedanib and placebo.
- For each IPF model, company used same survival model applied to progressive fibrosing ILD

Matched Kaplan-Meier curves for IPF placebo and nintedanib for 3 'best' survival models



◉ *Are the IPF data combined appropriately?*

Source: Figure 12 of CS. Abbrev: IPF = idiopathic pulmonary fibrosis; KM = Kaplan-Meier; log-log = log-logistic; NTD = nintedanib; PBO = placebo.

Extrapolating overall survival beyond trial

Company's Bayesian approach results in differences between models, and predicts large differences in life expectancy between nintedanib treatment and placebo

Overall survival estimates produced by Bayesian survival models: curves fitted to ILD data with informative priors

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

◉ *Are the modelled results plausible, given trial results?*

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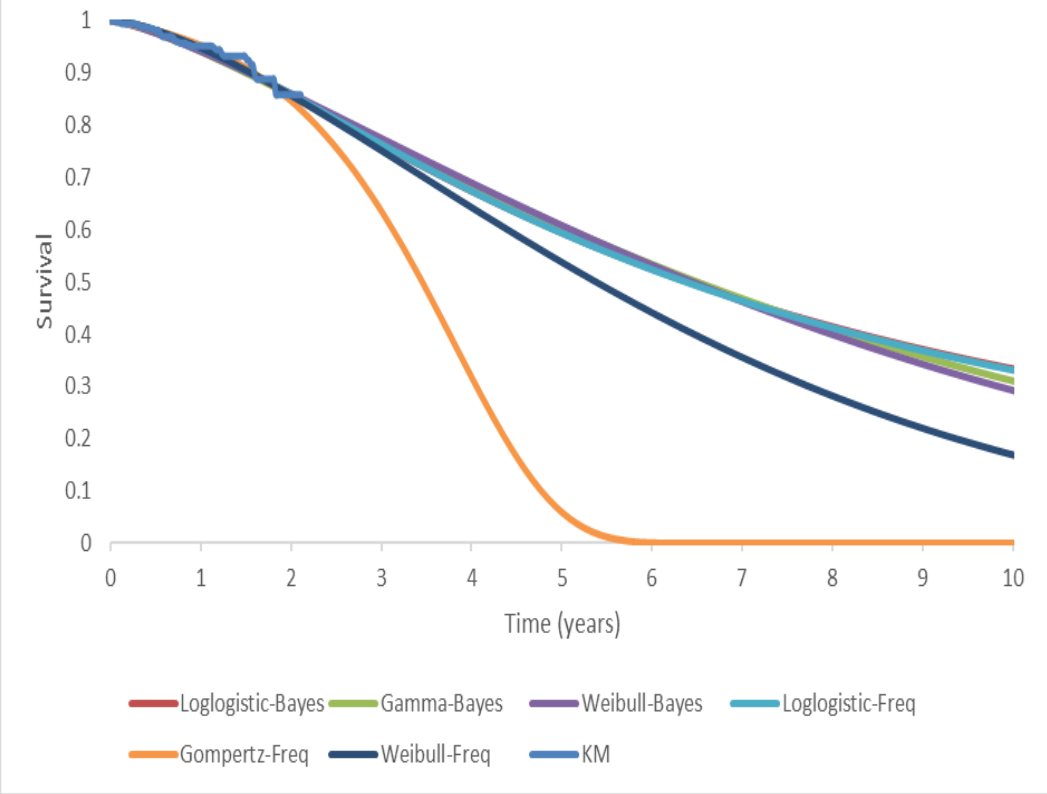
Source: Table 29, CS. Abbreviation: OS = overall survival.

Extrapolating overall survival beyond trial

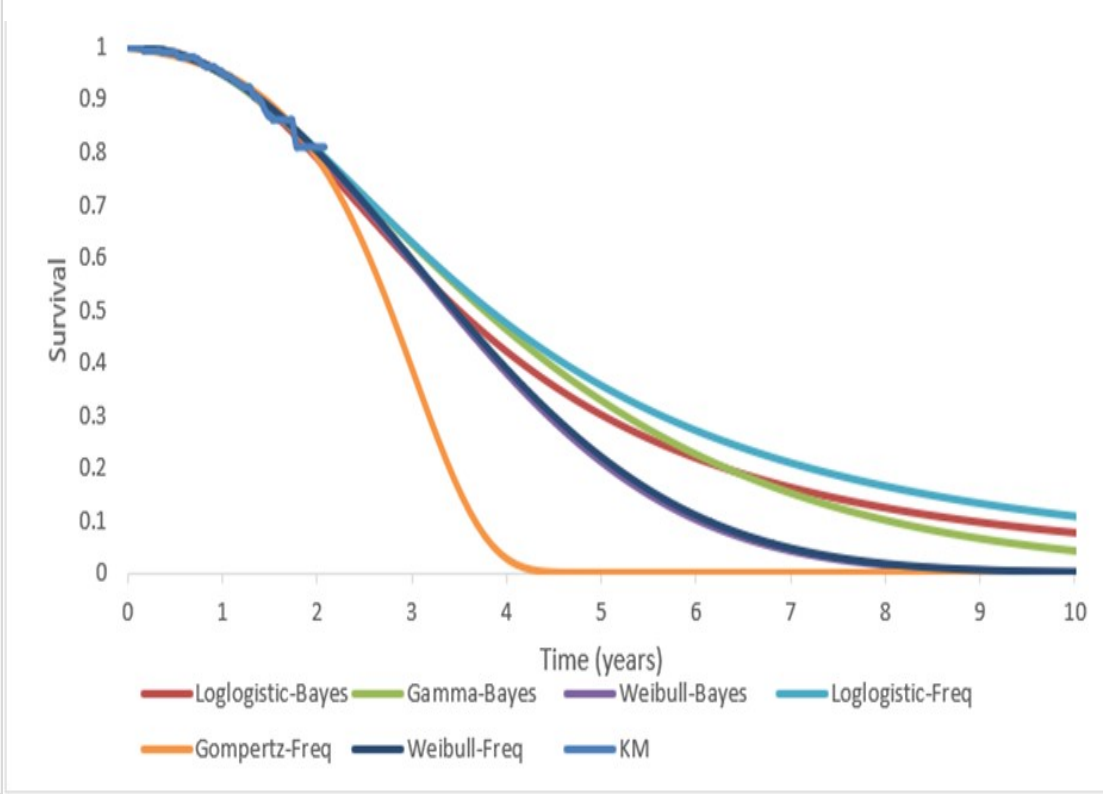
Summary: 6 distributions considered, 3 frequentist (based on PF-ILD data alone) and 3 Bayesian survival models (PF-ILD informed by IPF)

Overall survival model fits vs. INBUILD trial Kaplan-Meier

Nintedanib



Placebo



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Source: Figures 16 and 17 of CS; Bayes = Bayesian; Freq = frequentist; KM = Kaplan-Meier; OS = overall survival.

Validating extrapolation of overall survival

Company's 'external validation' (1/2): Company consulted clinicians who consider Weibull curve frequentist or Bayesian plausible for standard care without nintedanib

Company hired 5-member advisory board Nov 2020:

- **Curves for standard care without nintedanib:**
  - **Weibull (frequentist or Bayesian)** curves plausible
  - Excluded
    - frequentist Gompertz curve, likely underestimates survival
    - log logistic curves frequentist or Bayesian, likely overestimates survival
- **Nintedanib curves:**
  - 'Limited knowledge' on long-term impact of nintedanib

Company used Weibull Bayesian for both arms in its base case– it considered Bayesian analysis 'more robust' estimates of long-term survival because the analysis include 'longer-term' data from IPF to support use of immature data for current indication – progressive fibrosing ILD

◉ *What is the committee's view on this validation?*

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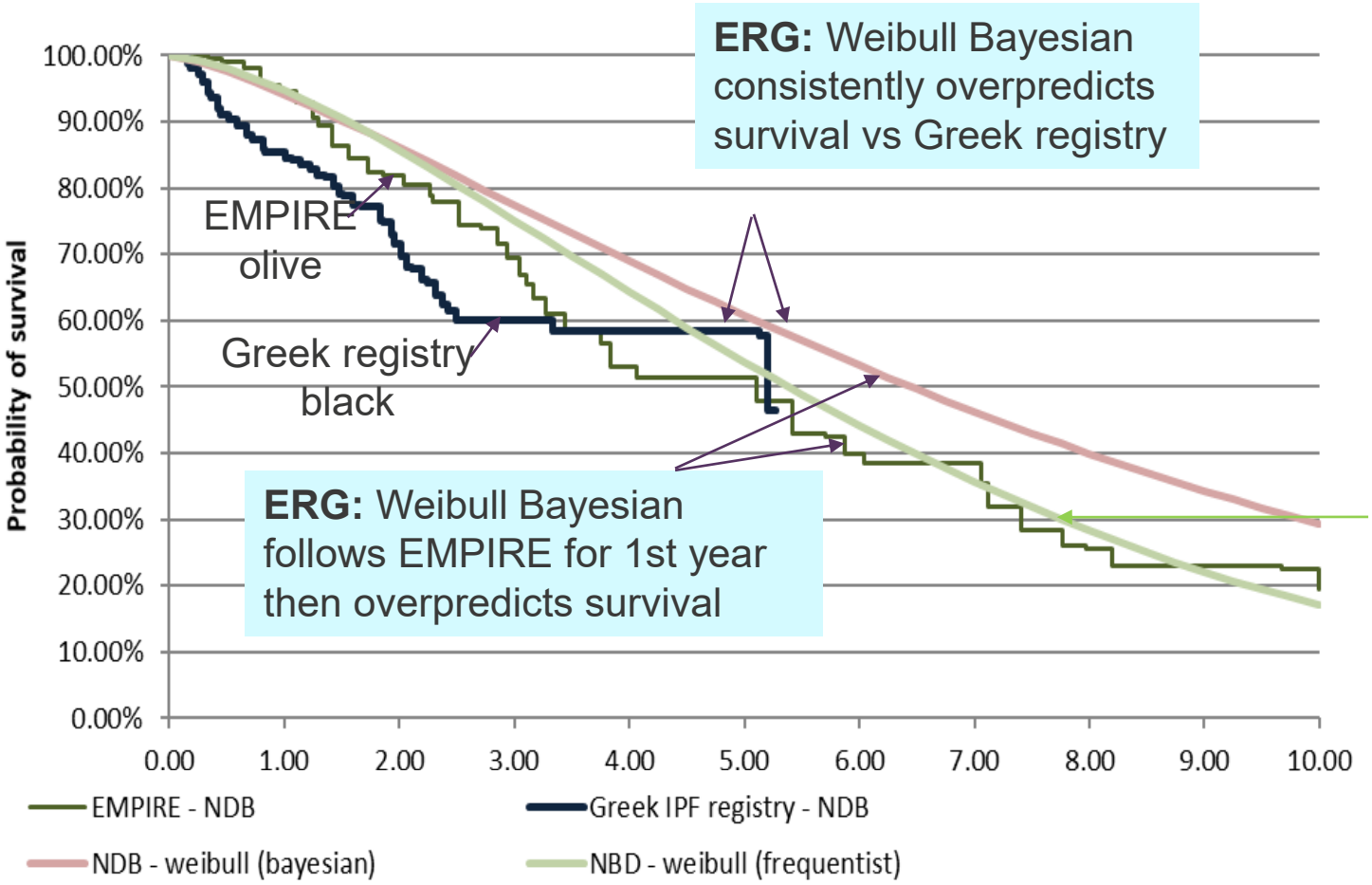
Abbreviations: BSC: best supportive care; IPF: idiopathic pulmonary fibrosis, PF-ILD: progressive-fibrosing ILD

Validating extrapolation of overall survival - nintedanib

*Company's 'external validation' (2/2): used 2 sources of registry data for nintedanib-treated IPF to validate Weibull Bayesian curve for **nintedanib** in progressive-fibrosing ILD*



- **EMPIRE study**: 10 years follow-up in 637 **IPF** patients taking nintedanib
- Antoniou et al, 2020: 5 years follow-up in 244 **Greek IPF** patients taking nintedanib

Company: frequentist curve is pessimistic, not in line with IPF trials

ERG: data from IPF population so cannot be sure it is pessimistic; long term effect might differ for IPF and PF-ILD

ERG:

- Weibull frequentist provides a better fit to registry data; included **Weibull frequentist curves for best supportive care and nintedanib** in base case
- Estimating survival using PF-ILD data available better than using survival data of another population viz. IPF

Abbreviations: IPF: idiopathic pulmonary fibrosis; PF-ILD: progressive-fibrosing ILD; Source: Figure 11 of the Clarification Response

Validating extrapolation of overall survival - nintedanib

Differences in risk factors for death between IPF registry and trials

Company: acknowledges differences between registries and clinical trials

- **EMPIRE – IPF Registry** vs clinical trial:
  - Different time when clock starts ticking to death - from diagnosis vs time from treatment
  - Included countries have very different standard care compared with UK Austria, Bulgaria, Croatia, Czech Republic, Hungary, Israel, North Macedonia, Poland, Serbia, Slovakia, Turkey
  - Treat severe disease unlike UK where antifibrotic allowed to start is moderate disease
- **Greek registry IPF** vs clinical trial:
  - Differences in time on treatment: patients spent less time on nintedanib than unmatched IPF long-term clinical trial patients (mean 23.6±15.0 vs 27.7 months; SD: 20.5)
  - Differences in baseline characteristics: patients older compared with INBUILD (mean age: 72 vs. 66 years), and smokers (78% vs. 51%)
  - Differences could lead to decreased survival Greek registry patients vs. INBUILD (PF-ILD)/IPF trial

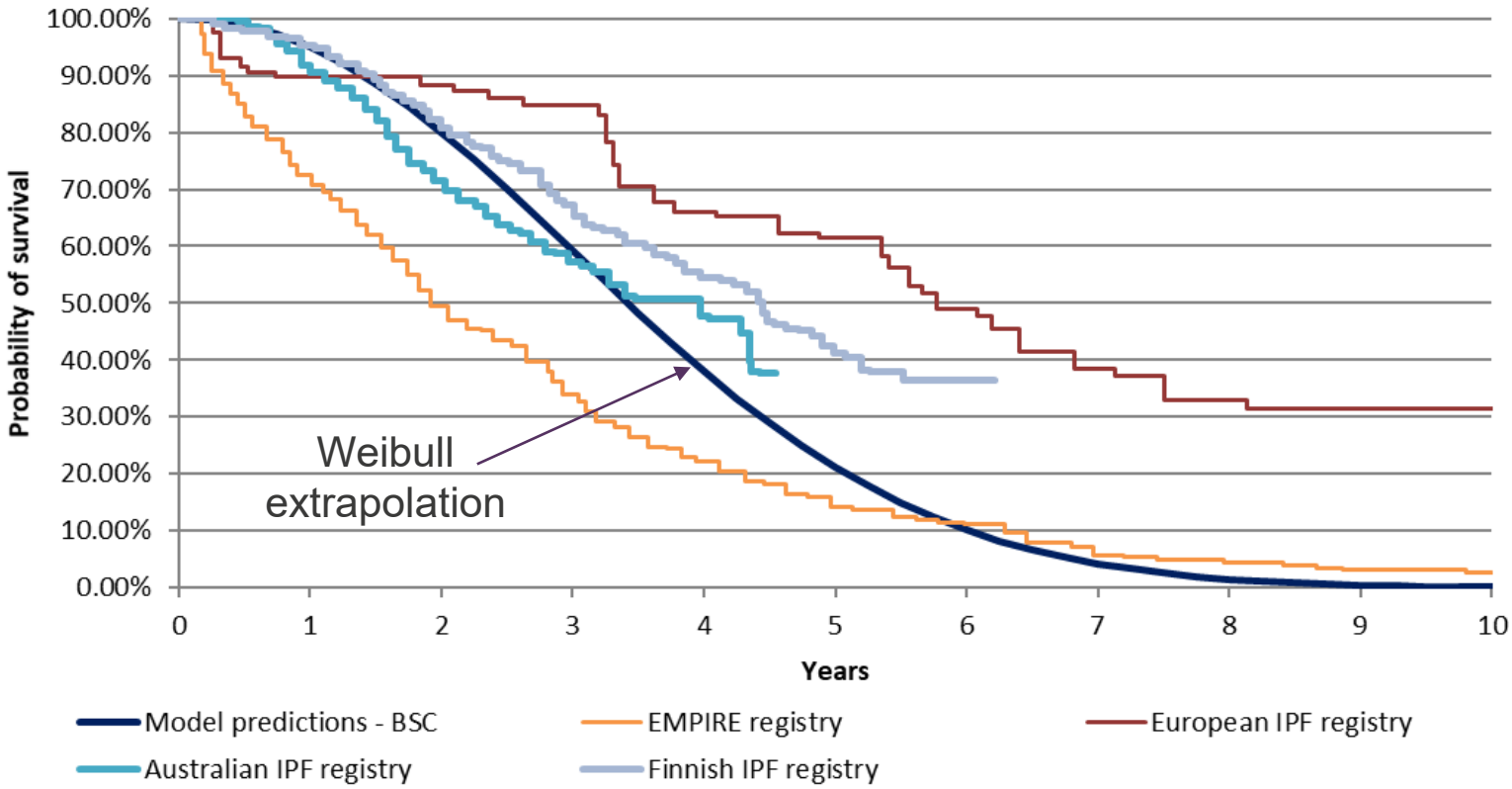
ERG: Company considers registry a poor source of external validation but had no problem using them to validate Weibull Bayesian.

◉ *What are the committee's view on using observational data unadjusted for differences in risk factors for death from one disease to 'validate' data from trials for another disease?*

Abbreviations: FVC%: forced vital capacity %; IPF: idiopathic pulmonary fibrosis, PF-ILD: progressive-fibrosing ILD
Sources: Company Technical Engagement response, ERG critique to TE response

Validating extrapolation of overall survival - placebo

Company's 'external validation' (3/3): used several IPF registry data for no-anti fibrotic treatment to validate Weibull distribution for best supportive care



Company: lack of consistency in survival between these registries
Clinicians considered the Australian registry most appropriate due to similarities between UK and Australian clinical practice

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Abbreviations: IPF: idiopathic pulmonary fibrosis; PF-ILD: progressive-fibrosing ILD; Source: Figure 21 of company submission

Extrapolating overall survival beyond trial

Company chose Bayesian Weibull; ERG believes Bayesian uncertain

ERG:

- Bayesian analysis may provide more precise estimates, but in this case data that drives them from a different disease (IPF); not necessarily accurate for population of interest
- Unclear if benefits of having longer-term data from IPF outweigh additional uncertainty when using Bayesian methods
- If company values clinical plausibility and fit to long-term data, it should have chosen frequentist Weibull for both arms because it provided better fit to long-term data

Company*:*

- Lack long term progressive fibrosing-ILD data; using long-term IPF data best alternative; evidence supported equivalent survival between IPF and PF-ILD patients:
  - Simpson et al 2020 (showed consistent survival for IPF and PF-ILD patients in the UK (hazard ratio= 1.06; 95% confidence interval, 0.84 –1.35; p = 0.6; measured up to approximately 2.5 years)

◉ Which, if either, of the Bayesian and frequentist approach is most appropriate? Which curve, if any, does committee prefer?

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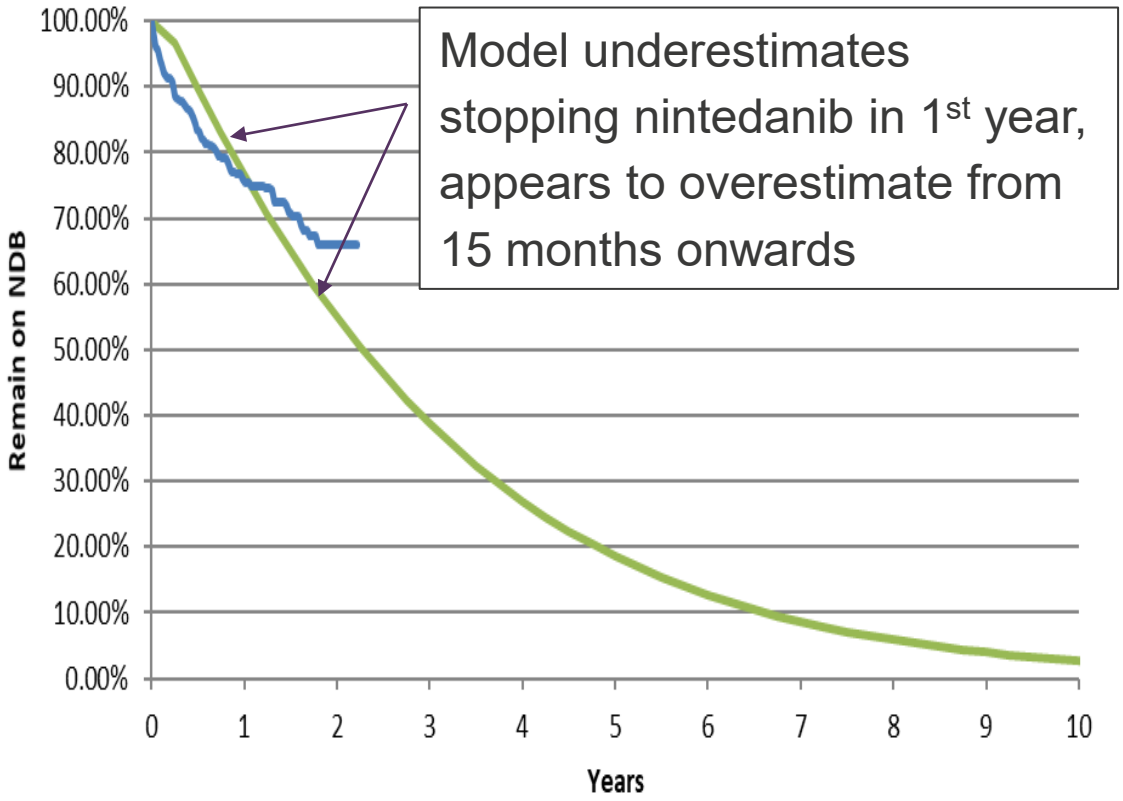
Stopping treatment beyond end of trial 1/3

Company says exponential model may underestimate true discontinuation

- **Company** extrapolating time to discontinuation using an exponential model (constant hazard so fixed ate of stopping) as in TA379 - for nintedanib = 6% per month



Company:

- Because exponential model did not fit KM data well, company validated with external data Lancaster et al. 2019 but from IPF population:
  - median exposure to nintedanib: 22.5 months (Lancaster) vs 27-28 months (INBUILD);
  - maximum: 93.1 months (Lancaster) vs > 96 months (INBUILD)
- Exponential model may underestimate true rate of stopping nintedanib
- Applied higher rates in scenario analyses

ERG : requested a model which better represents data from INBUILD trial

◉ *Why did company choose a model it acknowledges doesn't fit data? Is it appropriate to generalise from one disease to a different disease?*

Abbreviations: KM: Kaplan-Meier. Source: CS figure 27 p.100

Stopping treatment beyond end of trial 2/3

ERG notes implausible results with company's modelling of discontinuation

- **Company** modelled overall survival independently from lung function decline and acute exacerbations, a major cause of mortality, to avoid double counting of death
- **ERG:** model generated implausible results: increasing discontinuation rate has zero impact on life years and minimal impact on QALYs. This may be because of 2 modelling aspects:

1. High number (34% at 2nd data base lock) of patients who stopped nintedanib continued to be represented by survival analysis post-discontinuation, as most discontinued patients included in trial survival analysis

2. Company does not link rate of exacerbation to mortality; so, increased risk of exacerbations after stopping treatment does not translate into any difference in life years; this results in a lifetime treatment effect on OS in the model

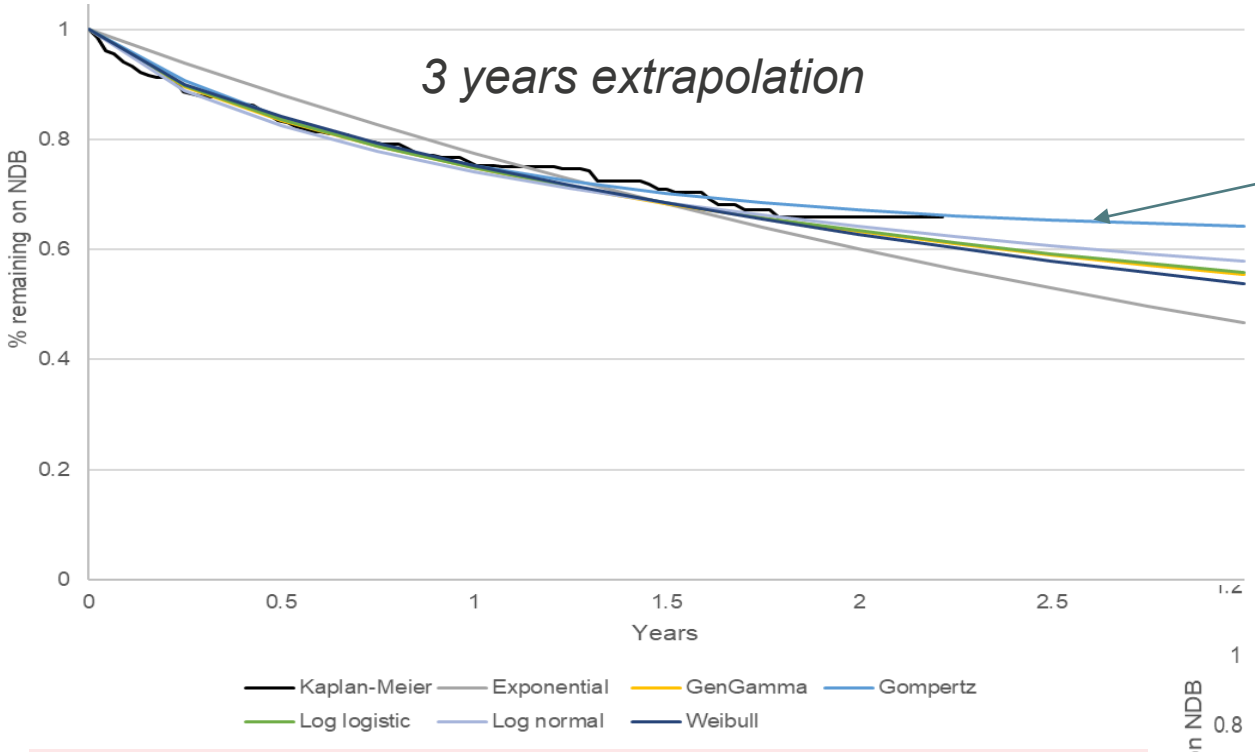
- **ERG:**
  - OS likely reflect weighted efficacy on and off-treatment over observed period;
  - However, long-term impact on efficacy uncertain as unclear whether trial follow-up sufficiently long to fully capture the impact of discontinuation on OS
  - Impossible to assess impact of changes in discontinuation rate on ICER given how discontinuation is incorporated into survival analysis, as a new OS curve would be needed.

◉ *Does evidence from trial suggest nintedanib has a long-term treatment effect on OS? Is it plausible that frequency of exacerbation not a risk factor for death? Does committee consider company's modelling of discontinuation appropriate?*

Abbreviations: DBL2, database lock 2; ICER: incremental cost effectiveness ratio; ILD: interstitial lung disease; OS: overall survival; QALY: quality adjusted life year. Source: ERG report section 4.2.6.5

Stopping treatment beyond end of trial 3/3

Company instead provided alternative extrapolations for discontinuation:
3 years vs full time horizon (base case: exponential) – no impact on QALYs

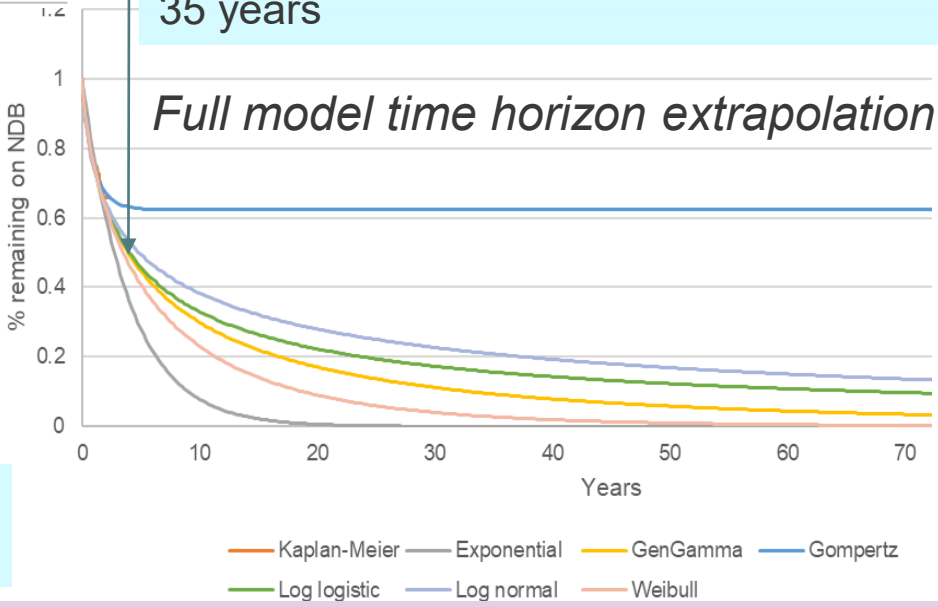


Company: Gompertz curve closest to INBUILD data over 3 years but, over long term, produces unrealistically optimistic rates of stopping nintedanib; generalised gamma, log logistic, log normal or Weibull curves give more realistic estimates of discontinuation.

ERG: Weibull model probably more realistic INBUILD mean age of 65years and likely most patients do **not** remain on treatment for 35 years

Company: choice of distribution does not impact QALYs; once a patient stops treatment they revert to transition probabilities for best supportive care and transition faster through FVC states. Transition probabilities for lung function decline not key driver

ERG: exploratory analyses do not provide correct ICERs but give an idea of impact of changing the curve



◉ *Do these results have face validity? What is the best way to model how many people stop nintedanib and when for progressive fibrosing ILD rather than for IPF?*

Exacerbations

In company's model, little impact on cost effectiveness

Input	Company's model	ERG critique	Impact on ICER
Time to 1st acute exacerbation	Company extrapolated beyond trial using exponential curve base case)	• ERG - overpredicts risk • Small impact on ICER is likely due to mortality not directly linked to the occurrence of acute exacerbation in the model • ERG explores impact of overprediction in both arms and potential overestimation of the difference between arms	Company scenario analyses indicate that varying from 1.12% to 20% per cycle only resulted in increase of 3,000 per QALY
Recurrent exacerbations	Assumed patients could experience recurrent exacerbations based on INBUILD data	In company's model, impact of recurrent exacerbations is limited to utility and costs; does not further increase the probability of loss of lung function beyond 1st exacerbation.	Limited impact of <£100 on ICER for recurrent exacerbations of 1.5% and 1.2% for placebo and nintedanib, converted to 3-month probabilities

◉ *Do these results have face validity? Is it plausible that these would have little impact on cost effectiveness?*

Abbreviations: ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

Losing lung function

In company's model, little impact on cost effectiveness

Input	Company	ERG critique	Impact on ICER
Losing lung function	• Used 2 different methods to calculate losing lung function on standard care (multivariate logistic regression) and on nintedanib (odds ratio applied to baseline placebo risk). • ERG asked company to use regression analysis for both treatments which company did	• Very different probabilities between original and new regression models after 1st exacerbations, • Small impact on results likely because relative differences between pre- and post-exacerbation and between nintedanib and placebo do not differ much between old and new models, while absolute values differ substantially. • In both models, the coefficient for treatment not statistically significant, and confidence intervals crossing 1 • ERG would have preferred that impact of treatment on probability of progression **was included in full model**, but given minimal impact on ICER, no change was made. • Both models assume lifetime treatment effect while on nintedanib	Minimal (<£20)

◉ *Do these results have face validity? Is it plausible that these would have little impact on cost effectiveness? How should company amend model, if at all? Has the committee seen evidence of a 'lifetime treatment' effect?*

Health-related quality of life for health states and adverse events

In company's model, little impact on cost effectiveness

- INBUILD collect EQ-5D-5L; mean utilities for different lung function states i.e., FVC%Pred Health state
  - **ERG:** implausible that patients with lower FVC%Pred have higher utility in the 80-89 FVC%Pred category, ERG applied a utility of **0.7265** for this category in its base case (instead of 0.7333), which equates to a linear decline in utility from 90-99 and 70-79 health states
  - **Company**: change of utility little impact on cost effectiveness
- **Company** assumed disutility for **all** gastrointestinal events estimated as 50% of value of **serious** gastrointestinal events in TA379 (-0.068)
- **ERG**: unclear why company chose 50% but not a key issue driver of cost effectiveness; company base case disutility for acute exacerbation: -0.167, identified 2 other sources disutility from TA379

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

◉ *Do these results have face validity? Is it plausible that these would have little impact on cost effectiveness?*

Source: Table 46 of the CS; Abbrev: EQ-5D: European Quality of Life-5 Dimensions; FVC%Pred: forced vital capacity % predicted; NA: not applicable; SD: standard deviation; TA: technology appraisal

Cost effectiveness results

- Include confidential patient access scheme for nintedanib
- Discussed in PART 2

End of life

- NICE ‘end of life’ criteria is satisfied when
  - treatment is indicated for patients with a short life expectancy, normally less than 24 months
  - treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment

- Company: nintedanib not expected to meet end-of-life criteria
  - *“it is expected that patients with PF-ILD who are not receiving an anti-fibrotic therapy would have a median post-diagnosis survival of 2 to 5 years”.* Therefore, treatment is not indicated for patients with a short life expectancy (normally less than 24 months)

Innovation

- **Company**: until the recent approval of nintedanib for SSc-ILD and PF-ILD, there were no licensed treatments for patients with PF-ILD other than IPF. Nintedanib is the first pharmacological treatment to show clinical evidence of slowing disease progression in patients with PF-ILD
- **Clinical expert**: nintedanib will make a significant impact in PF-ILD care; PF-ILD patients currently have no disease modifying therapies on offer to them to treat the fibrotic component of their disease

◉ *Is nintedanib a step-change and does it offer benefits not captured in modelling for PF-ILD?*

Abbreviations: PF-ILD: progressive fibrosing interstitial lung disease; SSc-ILD: systemic sclerosis associated interstitial lung disease

Equalities issues

- **Patient expert**:
  - Inequality because IPF patients can access nintedanib
  - Patients with progressive fibrosing ILD are generally younger than patients with IPF and more ethnically diverse (i.e., include more people of south Asian and Afro-Caribbean heritage)
  - Inequality because most cancer patients have a life expectancy better than PF-ILD patients

◉ *Is it an equalities issues as defined that a treatment would be available to one disease but not another? What is the committee's consideration on other equality issues raised by stakeholders?*

Back-up slides

INBUILD trial: underlying clinical ILD diagnosis

*Table 10: **Underlying** clinical ILD diagnosis*

	Placebo		Nintedanib 150 mg bid		Total	
Number of patients (N, %)	331	100.0	332	100.0	663	100.0
Time since first diagnosis of ILD based on imaging [years] (mean, SD)	3.90	3.69	3.65	3.80	3.77	3.75
Time since ILD diagnosis based on imaging in categories [years] (N, %)						
≤1	67	20.2	67	20.2	134	20.2
>1 to ≤3	112	33.8	115	34.6	227	34.2
>3 to ≤5	57	17.2	74	22.3	131	19.8
>5	95	28.7	75	22.6	170	25.6
Missing	0	0	1	0.3	1	0.2
Diagnosis of ILD confirmed by surgical biopsy (N, %)						
Yes	102	30.8	87	26.2	189	28.5
No	222	67.1	234	70.5	456	68.8
Missing	7	2.1	11	3.3	18	2.7
Diagnosis of ILD confirmed by transbronchial biopsy (N, %)						
Yes	55	16.6	48	14.5	103	15.5
No	263	79.5	265	79.8	528	79.6
Missing	13	3.9	19	5.7	32	4.8
Underlying clinical ILD diagnosis, eCRF categories (N, %)						
Idiopathic non-specific interstitial pneumonia	61	18.4	64	19.3	125	18.9
Unclassifiable idiopathic interstitial pneumonia	50	15.1	64	19.3	114	17.2
Hypersensitivity pneumonitis	89	26.9	84	25.3	173	26.1
Rheumatoid Arthritis-associated ILD	47	14.2	42	12.7	89	13.4
Mixed connective tissue disease	12	3.6	7	2.1	19	2.9
Systemic sclerosis-associated ILD	16	4.8	23	6.9	39	5.9
Exposure-related ILD	18	5.4	21	6.3	39	5.9
Sarcoidosis	8	2.4	4	1.2	12	1.8
Other fibrosing ILD	30	9.1	23	6.9	53	8.0
Underlying ILD diagnosis in groups (N, %)						
Hypersensitivity pneumonitis	89	26.9	84	25.3	173	26.1
Idiopathic non-specific interstitial pneumonia	61	18.4	64	19.3	125	18.9
Unclassifiable idiopathic interstitial pneumonia	50	15.1	64	19.3	114	17.2
Autoimmune ILDs[1]	88	26.6	82	24.7	170	25.6
Other ILDs[3]	43	13.0	38	11.4	81	12.2

- About 16% of enrolled patients with underlying RA (13.4%)/CTD (2.9) at baseline
- Eligibility for CTD: "stable" CTD defined as no initiation or withdrawal of therapy for CTD within 6 weeks prior to screen
- All approved RA/CTD medications allowed at stable doses at baseline and during trial, ***except*** *those less frequently used:*
  - azathioprine, cyclosporin, tacrolimus, high dose steroids, rituximab;
  - cyclophosphamide, mycophenolate not allowed in study

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Source: Table 10, EMA assessment report: Ofev, INN-nintedanib (europa.eu)

All on-treatment restricted concomitant therapies up to DBL2

ATC3 category	Placebo		Nintedanib		Total	
	N	%	N	%	N	%
Number of patients	331	100.0	332	100.0	663	100.0
Number of patients with ≥1 therapy	329	99.4	330	99.4	659	99.4
Adrenergics for systemic use	80	24.2	58	17.5	138	20.8
Adrenergics, inhalants	115	34.7	89	26.8	204	30.8
Agents for treatment of haemorrhoids and anal fissures for topical use	150	45.3	155	46.7	305	46.0
All other therapeutic products	113	34.1	104	31.3	217	32.7
Angiotensin II receptor blockers (ARBS), plain	63	19.0	78	23.5	141	21.3
Anti-acne preparations for topical use	122	36.9	103	31.0	225	33.9
Antibiotics for topical use	71	21.5	69	20.8	140	21.1
Antihistamines for systemic use	87	26.3	72	21.7	159	24.0
Anti-infectives	144	43.5	130	39.2	274	41.3
Anti-infectives and antiseptics, excl. combinations with corticosteroids	72	21.8	60	18.1	132	19.9
Anti-inflammatory agents	248	74.9	243	73.2	491	74.1
Anti-inflammatory and anti-rheumatic products, non-steroids	143	43.2	146	44.0	289	43.6
Anti-propulsives	40	12.1	155	46.7	195	29.4
Antithrombotic agents	128	38.7	120	36.1	248	37.4
Anxiolytics	92	27.8	66	19.9	158	23.8
Beta blocking agents	66	19.9	71	21.4	137	20.7
Beta-lactam antibacterials, penicillins	89	26.9	89	26.8	178	26.8
Blood glucose lowering drugs, excl. insulins	63	19.0	69	20.8	132	19.9
Calcium	79	23.9	78	23.5	157	23.7
Corticosteroids	110	33.2	108	32.5	218	32.9
Corticosteroids for systemic use, plain	248	74.9	236	71.1	484	73.0
Corticosteroids, plain	191	57.7	175	52.7	366	55.2
Cough suppressants, excl. combinations with expectorants	85	25.7	81	24.4	166	25.0
Decongestants and other nasal preparations for topical use	201	60.7	192	57.8	393	59.3
Drugs for constipation	86	26.0	69	20.8	155	23.4
Drugs for peptic ulcer and gastrooesophageal reflux disease (GORD)	216	65.3	251	75.6	467	70.4
Expectorants, excl. combinations with cough suppressants	113	34.1	110	33.1	223	33.6
IV solution additives	74	22.4	60	18.1	134	20.2
IV solutions	77	23.3	59	17.8	136	20.5
Immunosuppressants	78	23.6	52	15.7	130	19.6
Intestinal anti-inflammatory agents	212	64.0	206	62.0	418	63.0
Lipid modifying agents, plain	127	38.4	133	40.1	260	39.2
Macrolides, lincosamides and streptogramins	70	21.1	84	25.3	154	23.2
Opioids	105	31.7	91	27.4	196	29.6
Other analgesics and antipyretics	203	61.3	182	54.8	385	58.1
Other beta-lactam antibacterials	68	20.5	78	23.5	146	22.0
Other cardiac preparations	61	18.4	79	23.8	140	21.1
Other dermatological preparations	134	40.5	108	32.5	242	36.5
Other drugs for obstructive airway diseases, inhalants	126	38.1	102	30.7	228	34.4
Other gynecologicals	97	29.3	94	28.3	191	28.8
Other ophthalmologicals	143	43.2	121	36.4	264	39.8
Other respiratory system products	71	21.5	75	22.6	146	22.0
Quinolone antibacterials	88	26.6	69	20.8	157	23.7
Selective calcium channel blockers with mainly vascular effects	51	15.4	71	21.4	122	18.4
Stomatological preparations	217	65.6	219	66.0	436	65.8
Throat preparations	116	35.0	114	34.3	230	34.7
Topical products for joint and muscular pain	177	53.5	174	52.4	351	52.9
Vitamin A and D, incl. combinations of the two	102	30.8	81	24.4	183	27.6

All on-treatment restricted concomitant therapies up to DBL2 by customised drug grouping (CDG)

ATC3 category	Placebo		Nintedanib		Total	
	N	%	N	%	N	%
Number of patients	331	100.0	332	100.0	663	100.0
Number of patients with ≥1 restricted therapy	329	99.4	330	99.4	659	99.4
Biologic DMARDs	2	0.6	3	0.9	5	0.8
Rituximab	2	0.6	3	0.9	5	0.8
Corticosteroids[1]	90	27.2	55	16.6	145	21.9
Prednisone	36	10.9	30	9.0	66	10.0
Prednisolone	27	8.2	13	3.9	40	6.0
Methylprednisolone sodium succinate	27	8.2	9	2.7	36	5.4
Methylprenisolone	13	3.9	10	3.0	23	3.5
Hydrocortisone	5	1.5	2	0.6	7	1.1
Steroids	2	0.6	3	0.9	5	0.8
Dexamethasone sodium phosphate	2	0.6	1	0.3	3	0.5
Dexamethasone	1	0.3	1	0.3	2	0.3
Meprednisone	1	0.3	1	0.3	2	0.3
Betamethasone sodium phiosphate	0	0	1	0.3	1	0.2
Carisoprodol; dexamethasone;hydroxocobalamin; piroxicam; pyridoxine hydrochloride	1	0.3	0	0	1	0.2
Deflazacort	0	0	1	0.3	1	0.2
Methylprednisolone; succinate sodium	1	0.3	0	0	1	0.2
Prednisolone sodium phosphate	0	0	1	0.3	1	0.2

Immunomodulatory medications for ILD	35	10.6	15	4.5	50	7.5
Mycophenolate mofetil	12	3.6	5	1.5	17	2.6
Azathioprine	9	2.7	1	0.3	10	1.5
Tacrolimus	7	2.1	3	0.9	10	1.5
Cyclophosphamide	4	1.2	3	0.9	7	1.1
Ciclosporin	5	1.5	0	0	5	0.8
Rituximab	2	0.6	3	0.9	5	0.8
Non-biologic DMARDs	33	10.0	12	3.6	45	6.8
Mycophenolate mofetil	12	3.6	5	1.5	17	2.6
Azathioprine	9	2.7	1	0.3	10	1.5
Tacrolimus	7	2.1	3	0.9	10	1.5
Cyclophosphamide	4	1.2	3	0.9	7	1.1
Ciclosporin	5	1.5	0	0	5	0.8

Company Bayesian approach (1)

1. **Study linking and data cleaning**: assumed equivalent survival trajectory between IPF and PF-ILD patients. Long-term IPF data were merged to support use of immature PF-ILD data from INUILD(n=663 patients with PF-ILD; 332 patients treated with nintedanib and 331 with placebo)
    - TOMORROW (phase II) : included IPF patients on nintedanib, excluded patients on placebo
    - INPULSIS 1 and 2 (phase III): included nintedanib and placebo patients with IPF
    - INPULSIS-ON (open-label extension [OLE] from phase II and III): included IFP patients previously on nintedanib who continue treatment; patients on placebo who received nintedanib in the OLE were censored on initiation of nintedanib. N=1,239 IPF patients included in global dataset; 726 patients treated with nintedanib and 513 with placebo.

2. **Propensity score matching**: IPF patients (in trials listed above) were matched to PF-ILD patients (INBUILD), baseline characteristics used for matching included: age, gender, race, time since IPF or PF-ILD diagnosis, FVC % pred at baseline, smoking status

3. **Generating survival data**: analysis only included IPF patients who received nintedanib in both trials and (optionally) an open-label extension (see trials listed above)

Abbreviations: FVC % pred, forced vital capacity % predicted IPF: idiopathic pulmonary fibrosis, PF-ILD: progressive-fibrosing ILD
Source: CS p.65

Company Bayesian approach (2)

4. <u>Generating informative priors from matched IPF data</u>:

- Standard frequentist survival models fitted to the matched, weighted IPF data, **models with lowest AIC/BIC (loglogistic, Gompertz and Weibull)** used to generate informative priors ('IPF-informed prior') for shape parameter of the Bayesian PF-ILD model and followed a gamma (α,β) distribution (Soikkeli et al. 2019 method)

5. <u>OS estimates informing Bayesian priors/Generating the PF-ILD parameter estimate</u>:

- **Weibull, log-logistic and gamma distributions** of IPF survival models produced lowest overall AICs/BICs across nintedanib and placebo cohorts. Given small differences in fit between models, all were used to inform the shape parameter prior in the Bayesian analysis of PF-ILD data for both nintedanib and placebo . For each IPF model, the same survival model was fit to the PF-ILD data.

Abbreviations: IPF: idiopathic pulmonary fibrosis, PF-ILD: progressive-fibrosing ILD
Source: CS p.65

Extrapolating overall survival beyond trial

Bayesian approach – method

- Alternative approach to standard parametric models
- Allows to flexibly model evidence from a variety of data sources, to formally incorporate expert/clinical subjective prior beliefs, and to capture all forms of uncertainty (➔ shape parameter & model/structural)
- Limited practical application, little use in previous HTA
- Company used Bayesian approach “to improve accuracy and precision of extrapolated estimates”

Source: NICE DSU TSD21:Flexible Methods for Survival Analysis: NICE-DSU-Flex-Surv-TSD-21_Final_alt_text.pdf (nicedsu.org.uk)

Utility values from patients with IPF in INPULSIS, used in company scenario analysis

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

Abbreviations: FVC%Pred = forced vital capacity percentage predicted; SD = standard deviation.
Source: Table 64 in the CS.

Info: comparison with TA379

	TA379: trial, committee conclusion/ consideration	ID1599 company submission + Technical engagement
Trial	INPULSIS 1 and INPULSIS 2 (phase III RCTs):TOMORROW (phase IIb dose-ranging RCT); Nintedanib vs. placebo for treating IPF Follow-up: 52 weeks	INBUILD: phase III RCT; Nintedanib vs. placebo for treating PF-ILD Follow-up: • Part A: 52 weeks • Part B: variable treatment periods
Network meta-analysis (NMA)	NMA of nintedanib, pirfenidone and best supportive care (BSC)	No NMA performed
Comparator in model	• people with %predFVC of 50–80%: pirfenidone or BSC • people with %predFVC > 80%: BSC	placebo
Model structure	• Markov model with health states describing patient condition as a combination of both lung function (FVC%Pred) and exacerbation • 3-month cycle length • OS modelled independently from lung function decline & acute exacerbations: • Committee concerned results not sensitive to changes in rate of exacerbations	Same as TA379

Info: comparison with TA379

	TA379 committee conclusion/ consideration	ID1599 company submission + Technical engagement
OS extrapolation	Log logistic although uncertain, but little impact on ICER because company assumed equal survival between nintedanib and pirfenidone	Bayesian Weibull curve
Estimate probability of exacerbation	Exponential model	Same as TA379
Predict loss of function	Loglogistic	Same as TA379
Quality of life	EQ-5D collected from INPULSIS + disutilities for exacerbations and treatment-related adverse event: • Committee concern no inclusion disutility for diarrhoea, a common adverse event with nintedanib considered would worsen quality of life	EQ-5D collected from INBUILD + disutilities for exacerbations and treatment-related adverse event, including gastrointestinal event disutilities from TA379 (assume half of -0.068= -0.034; validated against disutility for diarrhoea (-0.042) in recurrent non-small cell lung cancer

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Info: comparison with TA379

	TA379 committee conclusion/ consideration	ID1599 company submission
Discontinuation risk	Exponential model assumes a constant hazard therefore a fixed discontinuation rate	Same as TA379; discontinuation based on rates observed within investigation trials (5.97%/month). Company explored 2 other sources in scenario analyses (Lancaster 7.67% and INBUILD 3.97%)
ICER	• people with %predFVC of 50–80%: Nintedanib dominates pirfenidone • people with %predFVC > 80%: ICER (vs BSC) substantially higher than threshold	Nintedanib vs placebo: £XXXX

Extrapolating overall survival beyond trial using 2 approaches: Frequentist and Bayesian

Frequentist approach

- **Frequentist approach (based on PF-ILD data alone)**: standard parametric overall survival (OS) distributions fitted independently to each arm
- Goodness of fit was assessed using AIC/BIC; models considered suitable if within 3 points of parametric model with lowest AIC or BIC
- Non-excluded models (loglogistic, Gompertz and Weibull) adopted for frequentist approach

FVC%Pred Health state	Distribution	AIC	BIC	Decision
Placebo	Exponential	842.1154	845.9175	Excluded
	Weibull	822.3554	829.9597	Non-excluded
	Lognormal	825.7844	833.3886	Excluded
	Loglogistic	822.5821	830.1864	Non-excluded
	Gompertz	823.3835	830.9878	Non-excluded
	Generalised gamma	824.2238	835.6302	Excluded
Nintedanib	Exponential	690.9068	694.712	Excluded
	Weibull	687.0584	694.6687	Non-excluded
	Lognormal	690.5765	698.1868	Excluded
	Loglogistic	687.4335	695.0438	Non-excluded
	Gompertz	685.4074	693.0177	Non-excluded
	Generalised gamma	688.7022	700.1176	Excluded

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Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; FVC%Pred: forced vital capacity % predicted; OS: overall survival
Source: CS Table 25