For committee and screen – PART 1

NICE National Institute for Health and Care Excellence

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

Chair presentation

Chair: Amanda Adler
Technology Appraisal Committee B
Lead team: Mark Glover (clinical), Nick Latimer (cost), Tony Wootton (lay)
ERG: Kleijnen Systematic Reviews (KSR)
Technical team: Aminata Thiam, Yelan Guo, Nicole Elliott
Company: Boehringer Ingelheim
9 September 2021- 2nd meeting

Key issues

- Do protocol violations in INBUILD trial related to “restricted concurrent medicines’’ bias results? Do the “restricted” medications reflect NHS clinical practice?
- Is nintedanib’s treatment effect on decline in FVC measured by ml/year clinically meaningful?
- Does the evidence presented by company support nintedanib’s long-term treatment effect on decline in rates of FVC and of mortality?
- What uncertainties arise when assuming natural history of untreated disease is similar to PF-ILD and idiopathic pulmonary fibrosis?
- Does evidence from the trial suggest nintedanib improves survival?
  If not, is it reasonable to model a survival benefit?
- Using a Bayesian approach, which extrapolations for the overall survival in placebo arm does the committee prefer? Do the gains have face validity?

Nintedanib not recommended

Committee not presented with evidence needed to assess nintedanib's long-term effectiveness and value for money, important **uncertainties** include:

Clinical:

- Impact of concurrent NHS treatments on treatment effect
- Whether change in FVC measured in milimeters (INBUILD) reflects clinically meaningful change
- Nintedanib's treatment effect in long term

Modelling:

- Modelling and validating overall survival in placebo arm based on IPF registries, not on PF-ILD
- Independent parametric distributions fit to nintedanib and placebo arms
- Modelling of exacerbations and decline in lung function
- Modelling of stopping treatment
- Therefore, cost effectiveness estimate unknown

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FVC: forced vital capacity

Recap of clinical, economic evidence, and committee conclusions

Nintedanib (OFEV, Boehringer Ingelheim)

Marketing authorisation	"..indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF)." *recommended by NICE (TA379)* "..also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype" - current appraisal *Other indications:* - *systemic sclerosis-associated interstitial lung disease – no NICE submission planned – included within this appraisal* - *Locally advanced, metastatic or locally recurrent non-small cell adenocarcinoma lung after 1st-line chemotherapy, in combination with docetaxel – recommended by NICE (TA347)*
Administration & dose	• Oral 150 mg twice daily • 100 mg twice daily for patients with mild hepatic impairment 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)

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

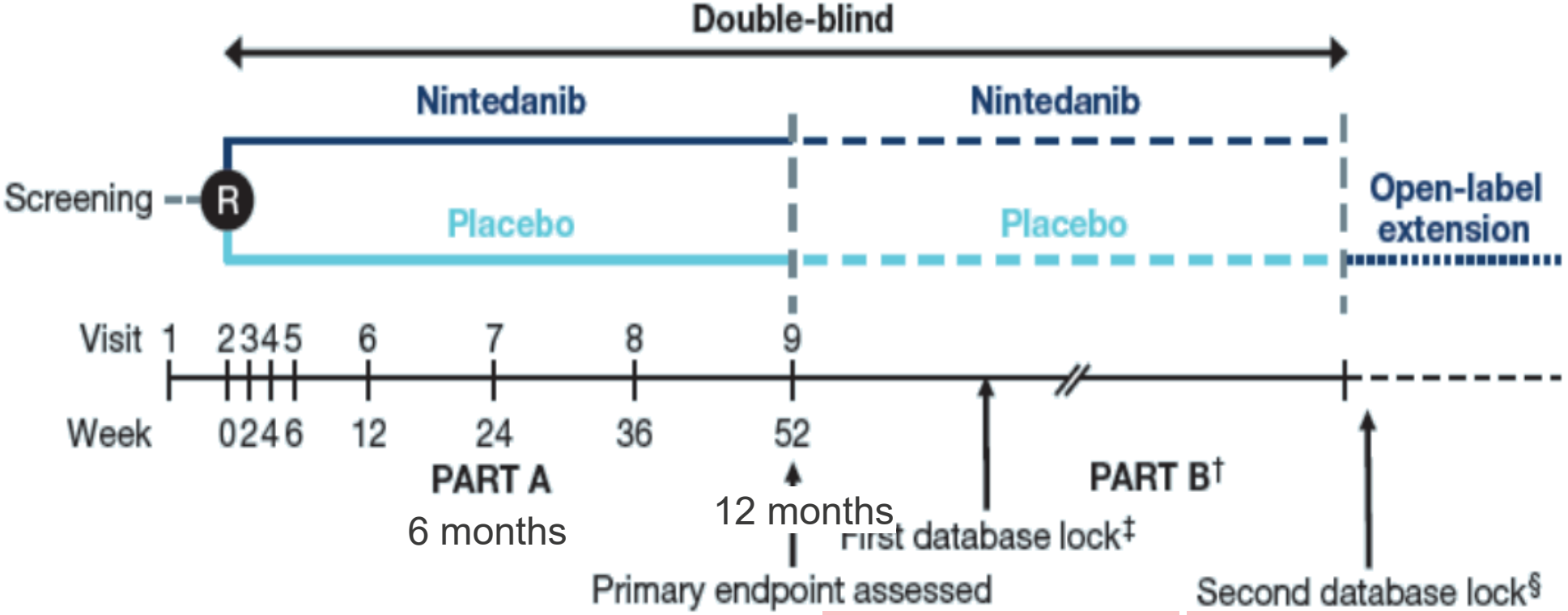
Background interstitial lung diseases - ILD

- ~ 200 diseases characterised by inflammation + fibrosis
  - includes idiopathic pulmonary fibrosis (IPF)
  - Despite treating underlying diseases some ILDs can worsen and lungs fibrose/scar = 'progressive-fibrosing' ILD (PF-ILD)
- PF-ILD
  - Symptoms: dyspnoea, worse physical performance and quality of life, may share some features of natural history with IPF
  - Mortality: Per company - similar to patients with IPF
  - Care: respiratory physicians and rheumatologists
  - Treatment depends on underlying disease:
    - corticosteroids for sarcoidosis
    - azathioprine
    - mycophenolate
    - cyclophosphamide
    - rituximab

PF-ILD: progressive fibrosing ILD; ILD: interstitial lung disease; IPF: Idiopathic pulmonary fibrosis

INBUILD trial multi-country

- P: 633 people with progressive-fibrosing ILD
- I: nintedanib without azathioprine, cyclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil and oral corticosteroids >20 mg daily
- 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 adjusted FVC decline (ml) over 52 weeks between



3 Jun 2019, n=565 patients ongoing

11 Sep 2019, all patients completed trial; median follow up ~ 19 months

Timepoint for model outcomes

†Visits occurred every 16 weeks until end of treatment. ‡After last 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; FVC: forced vital capacity; ILD: interstitial lung disease; R, randomisation

INBUILD trial Part A: protocol restricted medications

Company: Concurrent immunomodulatory treatments not allowed for 1st 6 months; after 6 months, allowed for worsening ILD and/or connective tissue disease

Baseline & 1st 6 months:

- medications ***not*** allowed include: azathioprine, cyclosporin, tacrolimus, rituximab, other disease modifying drugs for rheumatoid arthritis, cyclophosphamide, mycophenolate mofetil and oral corticosteroids >20mg/day; ~17% protocol violations
- medications for underlying rheumatoid arthritis and connective tissue disease allowed at stable doses

2nd 6 months: restricted medications ***allowed*** for worsening ILD or connective tissue disease

16% started immunosuppressants during 2nd 6 months - 11% nintedanib 21% placebo

INBUILD baseline ---------- 6 months ---------- 52 weeks ->

ACD :

- Excluding concurrent treatments in INBUILD does not reflect NHS practice
- If recommended, nintedanib would be an add-on therapy to conventional treatments

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ILD: interstitial lung disease

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

Trial: 1º end point adjusted for baseline FVC imaging pattern over 52 weeks
Model: FVC% predicted beyond 52 weeks

Adjusted **rate of decline in FVC over 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 to 148.5; p<0.001)

Appraisal consultation document (ACD) ***:***

- Company primary outcome adjusted rate of decline in FVC differs from FVC% predicted, which defines disease progression in INBUILD and is an outcome in model.
- Clinical experts: 10% in FVC% predicted => FVC ~150 ml
- Unclear if difference of 107 ml/year in adjusted rate of decline in FVC over 52 weeks equals a 10% difference (relative or absolute) in FVC% predicted and indicate a clinically meaningful change in FVC
- Committee would like to see how company transformed trial data into modelled data

CI: confidence interval; 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 converge, worsen after 52 weeks – should be reflected in analyses

ACD:

- Decrease of treatment effect after 52 weeks suggests either waning effect of nintedanib in long term or treatment effect of rescue immunosuppressants.
- This decrease should be reflected in company cost-effectiveness analyses.

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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: Response to Clarification, Question A5, Figure 2, page 12; CS table 15 p.40

INBUILD 2º main outcomes

Exacerbation composite endpoint; immature mortality data
No difference in exacerbation, quality of life, mortality by treatment
EQ-5D collected used in model

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 – 12 months	26/332 (7.8)	32/331 (9.7)	Hazard ratio= 0.80 (0.48, 1.34; p=0.3948)‡
Up to database lock 2 – 19 months	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 – disease specific quality of life			
52 weeks§	0.55±0.60	−0.79±0.59	Mean difference = 1.34 (−0.31, 2.98; p=0.1115)‡
Time to death			
52 weeks	16/332 (4.8)	17/331 (5.1)	0.94 (0.47, 1.86; p=0.85)‡
Up to database lock 2	36/332 (10.8)	45/331(13.6)	0.78 (0.50 to 1.21)

ACD:

- INBUILD did not show conclusively that nintedanib prolongs life
- Immature survival data with ~90% of population alive after database lock 2

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

§ For analysis of scores on K-BILD questionnaire, 332 patients were included in nintedanib group and 330 in placebo group in overall population

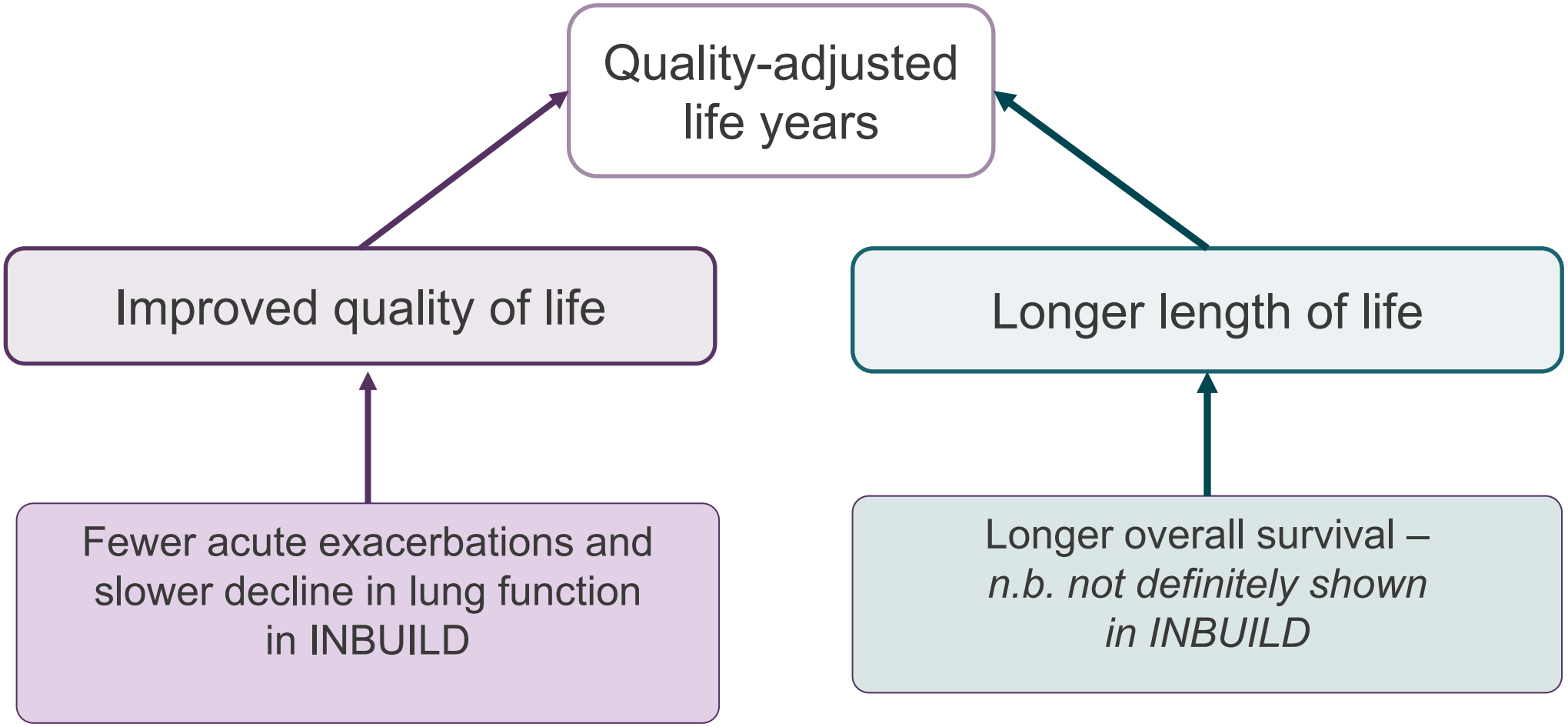
‡ Widths of confidence intervals have not been adjusted for multiple comparisons, so intervals should not be used to infer definitive treatment effect

Cost effectiveness

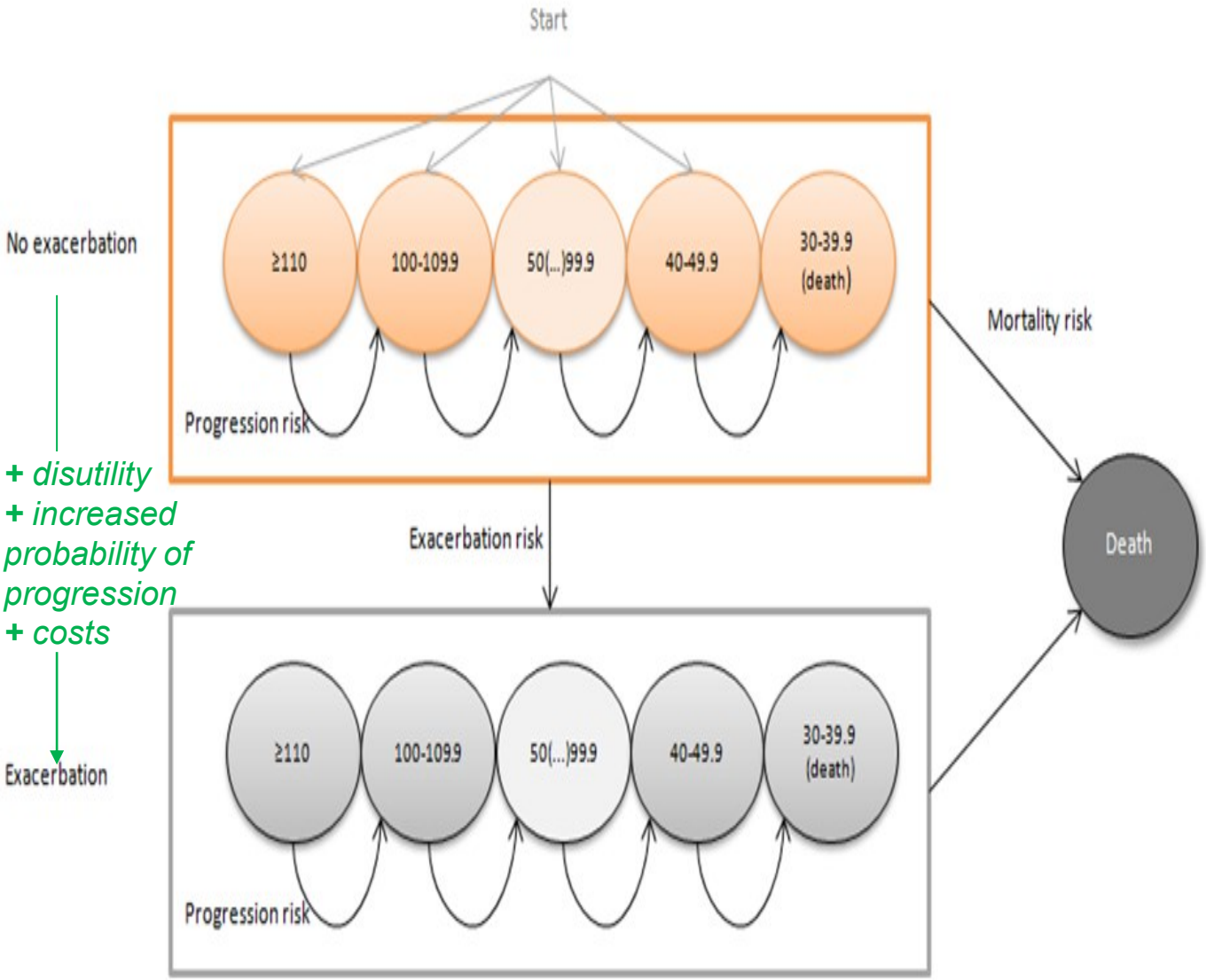
How company accrues quality-adjusted life years

Treatment with nintedanib compared to without nintedanib

Company makes claim for improving length and quality of life; trial does not show this



Company model to estimate cost effectiveness



- Markov model same as nintedanib for IPF in TA379; numbers are FVC percentage predicted (FVC%pred)
- Health states defined as absolute decline in FVC%pred = 10% predicted
- Efficacy informed by
  - lung function decline, acute exacerbation (INBUILD)
  - 2nd database lock
- Mortality informed by parametric extrapolation of overall survival
- Cycle length: 3 months
- 3.5% discounting

ACD conclusions:

- Model structure acceptable but important uncertainties in assumptions
- No link between exacerbations/lung function decline and mortality is important limitation

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

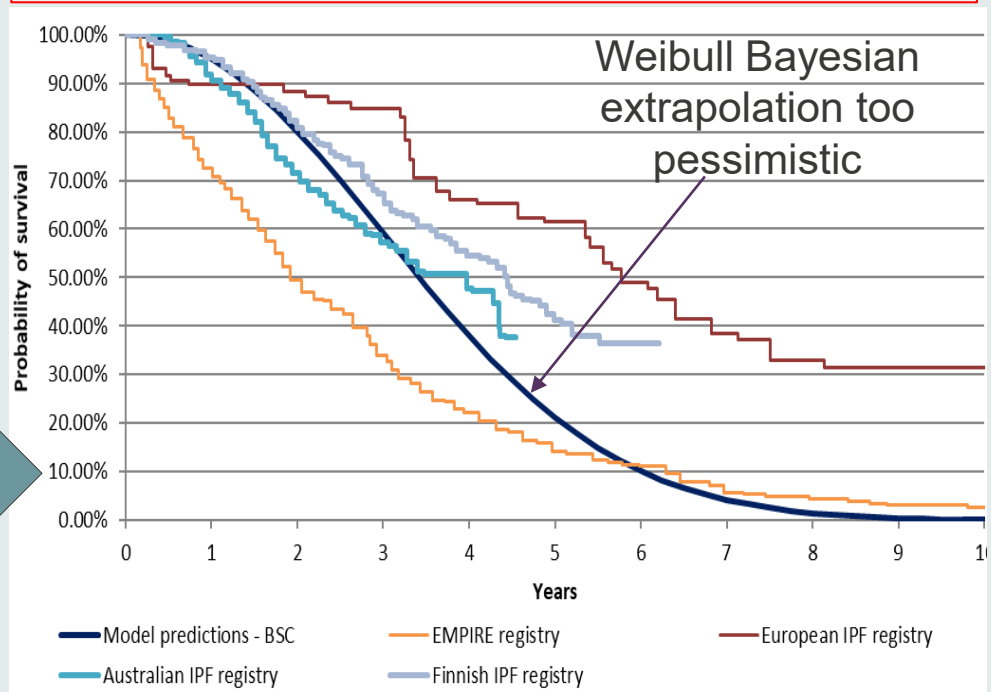
Extrapolating overall survival beyond trial
2 company approaches: frequentist + Bayesian

- 'Frequentist' : based only on (immature) PF-ILD data from INBUILD
  ERG base case: Weibull curves for both arms
- 'Bayesian': individual patient level data from IPF trial of nintedanib matched to patients with PF-ILD, fitted parametric extrapolations to matched IPF patients, shape of IPF curves (shape parameters) then used to inform the shape of parametric extrapolations fitted to data on PF-ILD from INBUID trial
  - Company chose Weibull, log-logistic and gamma distributions but large differences between distributions, treatment arms and within placebo arm
  - Company **validated** curves against IPF registries for both arms and by seeking clinician opinion, chose Weilbull for both arms

ACD conclusions:

- **Bayesian** approach to inform shape parameter reasonable **but** uncertainties when validating against IPF registries:
  - **Nintedanib**: offered to less severe IPF patients in registry countries; Weibull curve does not fit registry data well
  - **Placebo**: Weibull curve too pessimistic vs registry data and short follow-up for placebo in IPF trials so modelling survival in placebo arm likely underestimates ICER

1st committee meeting: validating overall survival extrapolation - placebo



ICER: incremental cost effectiveness ratio; IPF: idiopathic pulmonary fibrosis; PF-ILDs: progressive fibrosing interstitial lung disease Source: Figure 21 of company submission

Extrapolating overall survival beyond trial

*Company's **Bayesian** approach for nintedanib and placebo – entirely trial based*
Later attempt to validate with IPF registry data

Company's assumptions and methods:

- Company assumes IPF and PF-ILD have similar 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 placebo-controlled RCTs of IPF using nintedinib (but not pirfenidone) and from trial extensions including: TOMORROW; INPULSIS I and II; observational INPULSIS ON (long-term extension all together)
  - **Propensity score weighting to** matching patients with IPF (with longer trial follow-up) to PF-ILD for age; sex; race (Asian versus other); disease duration; % predicted diffusing capacity for carbon monoxide (DLCO) corrected for Hb; % predicted FVC at baseline; smoking
  - **Generating survival curves**: for matched IPF patients, choose parametric models
  - **Generating informative priors**: from IPF parametric models, retain shape parameters for nintedanib and placebo
  - **OS curves generated for progressive fibrosing ILD:** parametric models fit to INBUILD data, using the shape parameters from the IPF models as informative priors

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FVC: forced vital capacity; Hb: haemoglobin; IPF: idiopathic pulmonary fibrosis, OS: overall survival; PF-ILD: progressive-fibrosing ILD; RCT randomised controlled trial
Source: CS p.65

Relationship between death rate in trials of IPF and PF- ILD

Brown et al. company submission

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.

Appraisal consultation document (ACD) conclusions + company response (1)

No change to base-case modelling or price

Issues	Committee conclusion	Company **response** new evidence?
FVC (ml) versus FVC% predicted	Unclear how company transformed trial data adjusted FVC into percent predicted FVC modelled data (ACD 3.3)	✔ - provided equation
Nintedanib's positioning	If recommended, nintedanib would be an add-on therapy to conventional treatments (ACD 3.4)	✖
Concurrent treatments	INBUILD trial population generalisable to NHS except absence of concurrent treatments (ACD 3.5)	✔ - provided post-hoc analysis
Clinically meaningful FVC change	Unclear if FVC over 52 weeks reflects a clinically meaningful change when measured by FVC% predicted (ACD 3.7-8)	✔ - literature
Clinical effectiveness	• Nintedanib's treatment effect may decrease in long term; suggests either waning of nintedanib or treatment effect of rescue immunosuppressants (ACD 3.7) • Cost-effectiveness analyses should reflect this	✔ 2º endpoints post-52 weeks
	• Nintedanib's treatment effect on mortality is uncertain (ACD 3.8) – data immature	✖

FVC: forced vital capacity

Appraisal consultation document (ACD) conclusions + company response (2)

Issues	Committee conclusion	Company response new evidence?
Model structure	Acceptable, but uncertainties on why exacerbation rates and decline in lung function not linked to mortality (ACD 3.10-12, 3.19-20)	✔
Overall survival extrapolation	Bayesian approach reasonable but uncertainties on modelling and validating placebo with IPF registries: placebo curves higher death rates than registry; European best registry for validation (ACD 3.14, 3.16-17)	✔ - alternative curves for placebo with more optimistic survival
Proportional vs. non-proportional hazard assumptions	Proportional hazard not assessed. Fitting independent parametric survival distributions to both arms may cause bias of cost effectiveness estimates in favour of nintedanib (ACD 3.18)	✔ - alternative curves
Stopping nintedanib	Company's modelling of time-to-stopping nintedanib treatment may have underestimated costs of nintedanib (ACD 3.23)	✔
Cost-effectiveness	Unknown (ACD 3.26)	✔ Price unchanged

Other factors

ACD:

- End of life criteria – not met
- Innovation – not met
- Equalities – no equality issues

Summary of responses to appraisal consultation document

ACD consultation responses

Company

- Boehringer Ingelheim
  - No revised base case
  - Evidence from INBUILD trial

Web comments

- 9 web comments

Clinical expert

- Dr Lisa Spencer

Patients & Professionals

- Action for Pulmonary Fibrosis (APF)
- Association of Respiratory Nurse Specialists (ARNS)
- British Society for Rheumatology (BSR)
- British Thoracic Society (BTS)
- Sarcoidosis UK
- Scleroderma and Raynaud's UK (SRUK)
- UK Clinical Pharmacy Association

Company provides alternative scenarios to address committee concerns:

- modelling and validating overall survival in placebo arm
- fitting independent curves not having assessed proportionality of hazards

Price of nintedanib unchanged

Topics

Patients/Professionals/Clinicians/ Web

1. General comments
2. Comparators and nintedanib as an ‘add on’
3. Generalisability of trial which limited concurrent treatments
4. Systemic-sclerosis ILD
   - Separate marketing authorisation

Company

1. Long term treatment
   - Waning
2. How to transform FVC (ml/year) into FVC % predicted
3. minimum clinically important difference and change in FVC% predicted
4. Generalisability of trial which limited concurrent treatments
5. Extrapolating overall survival for people who do **not** receive nintedanib
6. Applying proportional hazard assumption
7. Other issues in modelling
   - exacerbations
   - decline in lung function
   - stopping treatment
8. Innovation

Patient and clinical organisation comments

General comments

- 'Action for Pulmonary Fibrosis calls on NICE and the company to …do all they can to find a flexible and pragmatic way to bridge the gap between their two positions'
- 'PF/ILD patients will feel a heightened sense of injustice compared to IPF patients ..'
- 'Inequity - those living in Scotland who can already access this essential treatment'
- Want treatment options that do not immunosuppress patients
- Innovative Medicines Fund as a way to ensure access to nintedanib? (APF)

Web comments:

- "No treatment" = correct comparator for cost effectiveness analysis of nintedanib
- 'Robust definition and assessment of response should be incorporated in treatment algorithm. Could allow a subgroup of patients to receive nintedanib. For example, patients with autoimmune PF-ILD whose FVC stabilises
- Model should link mortality with decline in lung function
- Nintedanib is approved for IPF, but not for sarcoidosis fibrosis for which it potentially has better outcomes.
- Discriminatory to differentiate different fibrosing lung diseases including IPF for treatment but not other fibrotic lung diseases.
- If not approved, should undertake further research because INBUILD suggests decline of lung function is slowed

Patient and clinical organisation comments

Nintedanib as an add-on

- **Clinical expert and BTS**:
  - Immunosuppressants not established treatment for all causes of PF-ILD
  - Nintedanib given instead of immunosuppressants when disease has progressed despite being on immunosuppressants – nintedanib would not be 'added in'
    - *N.b. 'add-on' implies no direct comparison - could be clearer?*
  - 'Decline in FVC despite management is associated with a much higher mortality'
    - *Nb. not modelled by company*

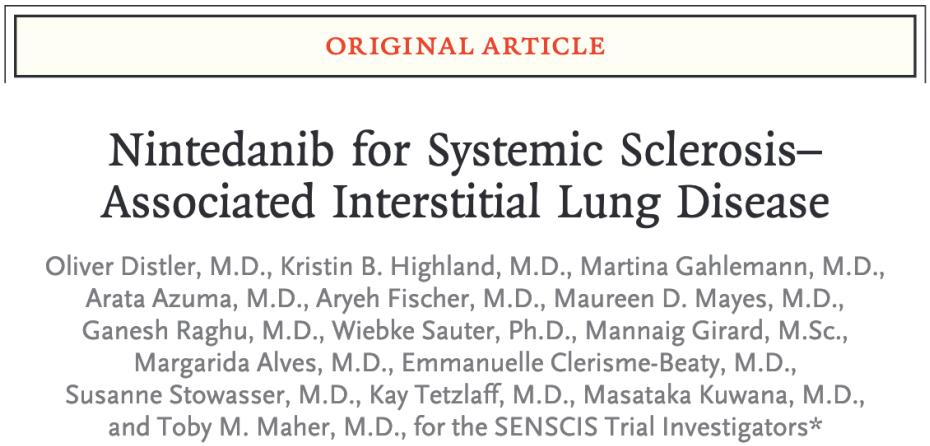
Concurrent treatments and rescue immunosuppressants

- **ACD**: "fewer patients randomised to nintedanib than placebo needed immunosuppressants… 'a substantial proportion of participants needed the treatments that the protocol restricted earlier in the trial"
- **Clinical expert**: 'INBUILD study does reflect current NHS care'
- **BTS**: 'Statement that "the committee interpreted this to show that fewer patients randomised to nintedanib than placebo needed immunosuppressants" is an incorrect conclusion' finding could have occurred by chance; only 16% of patients received immunosuppressants after 6 months which means a significant greater proportion 84% DID NOT require immunosuppression after 6 months. Factually incorrect'
- **UKDPA**: 'We believe the INBUILD trial design .. not .. dissimilar' to NHS practice

CTD: Connective Tissue Disease; ILD: interstitial lung disease; PF-ILD: progressive fibrosing interstitial lung disease; SSc-ILD: systemic sclerosis ILD

Systemic sclerosis-associated ILD

BSR, Scleroderma and Raynaud's UK
NICE appraisal for SSc-ILD suspended – included within this
SENSCIS an 'important trial' – results not included by company
Nintedanib less effective in this trial than INPULSIS



ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Oliver Distler, M.D., Kristin B. Highland, M.D., Martina Gahlemann, M.D., Arata Azuma, M.D., Aryeh Fischer, M.D., Maureen D. Mayes, M.D., Ganesh Raghu, M.D., Wiebke Sauter, Ph.D., Mannaig Girard, M.Sc., Margarida Alves, M.D., Emmanuelle Clerisme-Beaty, M.D., Susanne Stowasser, M.D., Kay Tetzlaff, M.D., Masataka Kuwana, M.D., and Toby M. Maher, M.D., for the SENSCIS Trial Investigators*

◉ *Reasonable to include systemic sclerosis associated ILD in this appraisal? What is committee's view on excluding key trial for systemic sclerosis PF-ILD?*

'People with SSc-ILD are overlooked (~1,200 would benefit from nintedanib)'

- n.b. company estimates only '876' for all PF-ILD

SENSCIS trial

- Randomised placebo-controlled trial
- P: ILD associated with systemic sclerosis only some with progressing fibrosing phenotype
- O: FVC declines at 52 weeks
- Results: Difference between groups: 41.0 ml; 95% CI, 2.9 to 79.0
- Half on mycophenalate – effective but less improvement than no-mycophenalate

Modelling

- 'Confirmed' relationship lung function decline to mortality 'important surrogate'
  - N.b. company model does not link FVC to mortality

Company comments

Nintedanib's long term effect (1)

Company: Not reasonable to conclude insufficient survival evidence and waning

ACD: Nintedanib is associated with a slower decline of lung function compared with placebo, but its long-term treatment effect is uncertain

Company: INBUILD not designed to assess data >52 weeks; important methodological limitations

- **INBUILD post-52 week objective** – 'to collect supportive, longer-term efficacy and safety data'
- **Annual rate of decline in FVC post-52 weeks** – not pre-specified in protocol/ statistical analysis plan; added as post-hoc exploratory analysis
- **Methodological limitations of analysis post-52 weeks**
  - different follow-up times
  - fewer patients
  - 'healthy survivor bias' underestimates treatment effect of nintedanib
  - linearity assumption in statistical models might be violated
- **Unpublished time-to-event endpoints should be considered** up to database lock 2
  - ILD 'progression' (decline in FVC ≥10% predicted) or died: HR nintedanib vs placebo 0.66 (95% CI: 0.53, 0.83; p=0.0003)
  - Acute exacerbation or died: HR= 0.67 (95% CI: 0.46, 0.98; p=0.04)
  - IPF data show consistent treatment effect over time
    - Long-term INPULSIS-ON: decline in FVC over 192 weeks -135.1 mL (IPF) comparable to over 52 weeks (PF-ILD; -113.6 mL) for nintedanib: Δ 22mL not clinically meaningful
      - *N.b. does not address treatment difference – no comparator*
    - Greek registry show FVC % predicted stable at 3 years for nintedanib patients

ACD: appraisal consultation document; FVC: forced vital capacity

Nintedanib's long term effect (2)

ERG critique

ERG:

- Post-52 weeks data should be considered even if not in protocol
- If company says treatment effect of nintedanib vs. comparator is best not estimated by assuming a single linear trend over entire follow-up period then company should change statistical model to better fit data post 52 weeks.
- Cannot understand comment on impact of higher treatment intercept post vs within 52 weeks
- For IPF data from INPUSIS-ON, no placebo data at 140 weeks so cannot compare
- Greek registry seems to show change in FVC%pred remains relatively stable over 3 years on nintedanib, however, it appears to be weak evidence of a trend downwards

◉ Has the committee seen evidence to change its conclusion that treatment effect beyond end of trial is uncertain?

FVC: forced vital capacity; HR: hazard ratio; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; PF-ILD: progressive fibrosing interstitial lung disease

Company: how to transform trial data into modelled data

Company:

FVC % predicted calculated according to Global Lung Initiative (GLI) equation which varies depending on individual patients' race, age, gender and height. Described by Quanjer et al 2012 and Kubota et al. 2014:

$$Predicted\ value = e^{a} \times H^{b} \times A^{c} \times e^{d \times group} \times e^{spline}$$

a=intercept, H=height (cm), b=exponent for height, A=age (years), c=exponent for age, spline= contribution from age spline. Group= Caucasian, African-American, South or North East Asian and value of 1 or 0 depending on group.

ERG:

- Confirm they were able to replicate the results
- Confirm this is exponential of equation used by Quanjer et al 2012:

log(Y) = a + b*log(H) + c*log(A) + age-spline + d*group

ACD: appraisal consultation document; FVC: forced vital capacity

Company & professionals: minimum clinically important difference (1)

Company: nintedanib's effect on change in FVC% predicted is clinically meaningful

ACD: Trials results 'adjusted FVC'; literature for clinically meaningful change FVC% predicted

Company: evidence from INBUILD showed change in FVC% predicted is clinically meaningful

- Adjusted absolute change in FVC% predicted from baseline to week 52:
  - Nintedanib: -2.6%; Placebo: -5.9%;
- Adjusted mean difference between groups from baseline: 3.2% (95%CI: 2.1 to 4.4)
  –

Minimum clinically important difference (MCID):

- du Bois et al. 2011: MCID for % predicted FVC is 2-6% in IPF patients
- meta-analysis of trials for IPF/ PF-ILD/ SSc-ILD showed strong association between annual rate of change in FVC % predicted & risk of death (2021 American Thoracic Society Conference, Maher et al. 2021)
- difference in FVC reported in INBUILD measure in both mL and % predicted similar to that reported in INPULSIS. Clinical experts and patients agree nintedanib effect on IPF meaningful
- 258 patients started 'Named Patient Supply' to access nintedanib in exceptional, life-threatening cases of PF-ILD (2018 to 2021; 19 ILD specialist centres).

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ACD: appraisal consultation document; CI: confidence interval; FVC: forced vital capacity; ILD: interstitial lung disease; MCID: minimum clinically important difference; PF-ILD: progressive fibrosing interstitial lung disease; SSc-ILD: systemic sclerosis ILD

Company & professionals: minimum clinically important difference (2)

Stakeholders and ERG critique

BTS: "A 107ml difference in FVC is significant in clinical practice whether reaches 10% or not", "established in IPF as a significant difference"

Clinical expert: patients on nintedanib on average have 107 ml more of lung left at end of study. Falling FVC ultimately leads to death so preventing that fall is significant. No need to hit 10% reduction in FVC to prolong life. A healthy person loses 30 ml of lung volume/ year. PF-ILD patients are losing lung at significantly accelerated rate and leads to premature death.

ERG:

- Confirmed evidence from INBUILD trial reported in CSR or CS;
- Noted that clear direct relationship between FVC% predicted difference and HR for mortality as reported in paper by Maher et al. 2021
- Data from Maher et al. 2021 include very little information, only from nintedanib trials up to 52 weeks

◉ *Given new information, is difference 'clinically significant' over duration of trial?*

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ACD: appraisal consultation document; FVC: forced vital capacity; ILD: interstitial lung disease; MCID: minimum clinically important difference; PF-ILD: progressive fibrosing interstitial lung disease; SSc-ILD: systemic sclerosis ILD

Company & professionals: restricted concurrent NHS treatments

Company: restricted treatments did not impact treatment effect or reduce trial's relevance

- Company submitted post-hoc analyses**:** exclude patients who take restricted medication (Cottin et al. 2021) but compared subgroup to whole group to conclude little difference
- Post-hoc subgroup taking glucocorticoids at baseline vs do not take: effect of nintedanib on reducing FVC decline not influenced by use of glucocorticoids at baseline (interaction p = 0.18)
- Clinical consensus statement *"… extrapulmonary manifestations … may require treatment with corticosteroids and/or immunosuppressants, but these are not to treat the ILD, and they do not have any meaningful impact on the ILD"*
- **Clinical expert:** INBUILD absolutely reflects clinical practice:~ 70% had drug suppressing immune system i.e. prednisolone

ERG: Post-hoc analyses do not support that restricted treatments have no effect: -187.8 and -80.8 vs -157.2 and -49.4 respectively. Clinical consensus contradicts findings: *"… no meaningful impact on ILD"*

◉ *Given new information, is magnitude of trial results generalizable to NHS care?*

Source: company response to ACD table 5; ACD: appraisal consultation document; FVC: forced vital capacity; ILD: interstitial lung disease; PF-ILD: progressive fibrosing interstitial lung disease; SE: standard error

Company: modelling & validation for overall survival in placebo arm (1)

Registry data mixes antifibrotic treatments and best supportive care

ACD: Uncertainties on modelling and validating placebo with IPF registries: placebo curves higher death rates than registry; European best registry for validation

Data source	Mean age	Male	Smoker	UIP	FVC	DC	HR treated/ no treated
INBUILD trial	66	54%	51%	62%	69%	46%	Nintedanib only 0.94 (0.47 to 1.86) at 52 weeks; 0.78 (0.50,1.21) at database lock 2
European IPF registry	68	73%	65%	64%	68%	42%	Anti-fibrotic (83% pirfenidone; 17% nintedanib) NR p=0.001
EMPIRE registry	67	68%	NR	68%	77%	NR	Nintedanib only NR
Australian registry	71	68%	71%	NR	81%	48%	Anti-fibrotic (23% pirfenidone or nintedanib) 0.38, (0.24 to 0.59), p<0.001
Greek IPF registry	72	79%	78%	NR	73%	43%	Nintedanib only NR
Finnish IPF registry	73	65%	55%	NR	80%	56%	Anti-fibrotic (26% pirfenidone or nintedanib) NR; p=0.035

◉ *Is validating against **these** registry data appropriate? What uncertainties exist?*

Source: table 35 company submission; Rounded to nearest integer. Abbrev: DC, diffusing capacity; ; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia

Company: modelling + validating survival in placebo arm using registry data for IPF not PF-ILD (2)

Company explores Australian registry with more favourable death rates

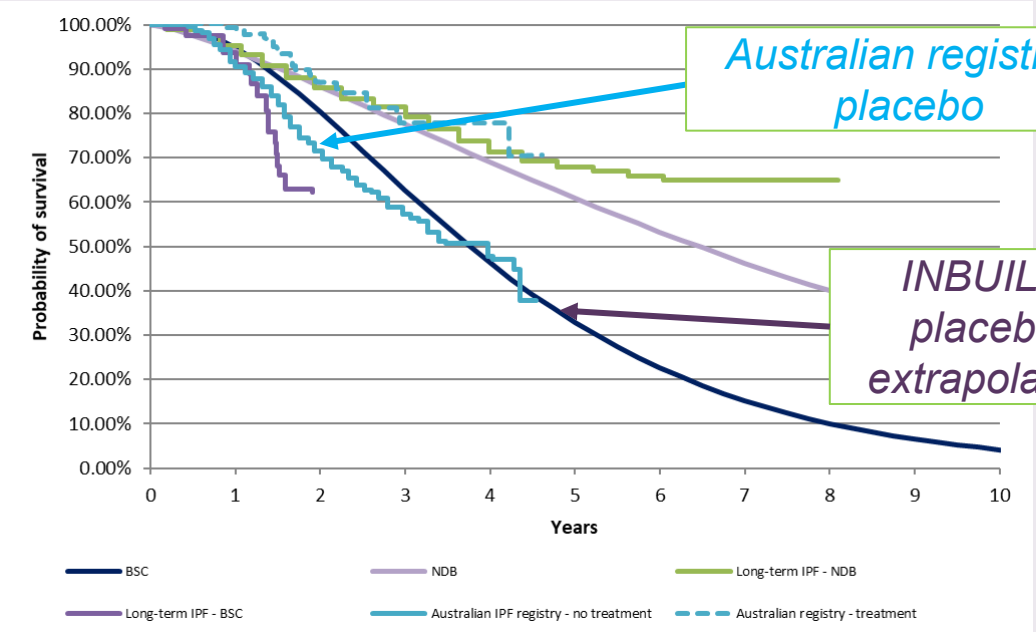
Trial data not shown – 5% died during trial

Bayesian gamma and Bayesian log logistic provide good visual match to Australian registry

Advisory board clinical experts considered most appropriate similarities with UK practice

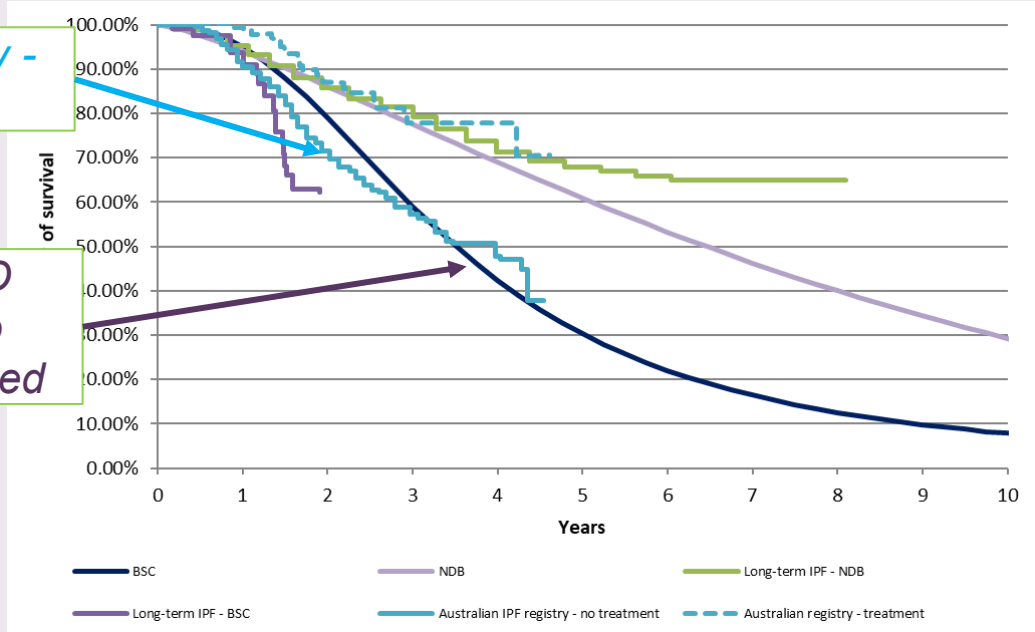
Placebo curve: Bayesian gamma

Nintedanib: Bayesian Weibull



Placebo curve: Bayesian log-logistic

Nintedanib: Bayesian Weibull

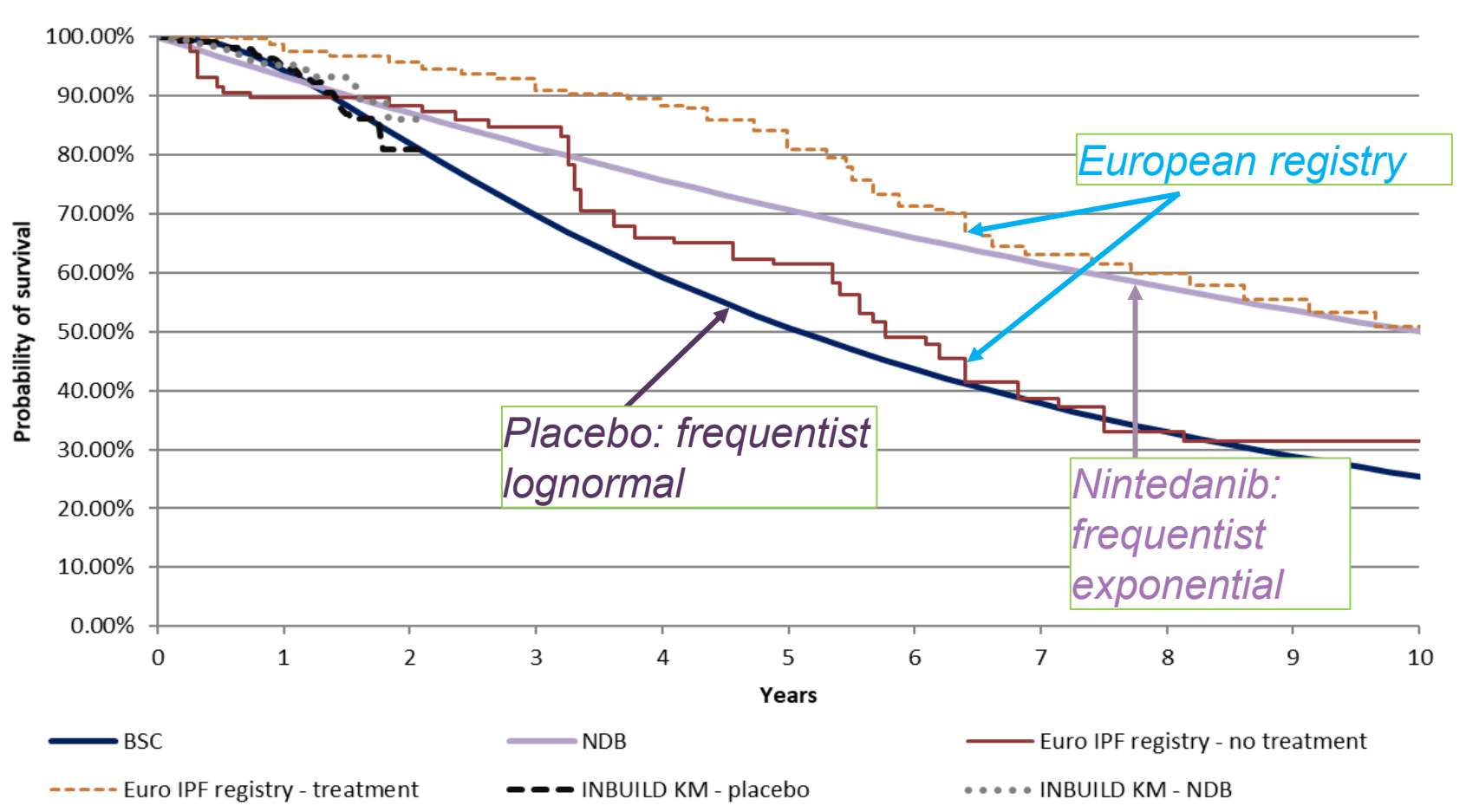


Source: figure 11 and 12, company response to appraisal consultation document; ACD: appraisal consultation document; ICER: incremental cost effectiveness ratio; QALY: quality adjusted life year

Company: modelling + validating survival in placebo arm using registry data for IPF not PF-ILD (3)

Company explores European registry using survival benefit of nintedanib + pirfenidone in IPF

Company selected BOTH placebo and nintedanib curves to match European registry to avoid underestimate nintedanib survival

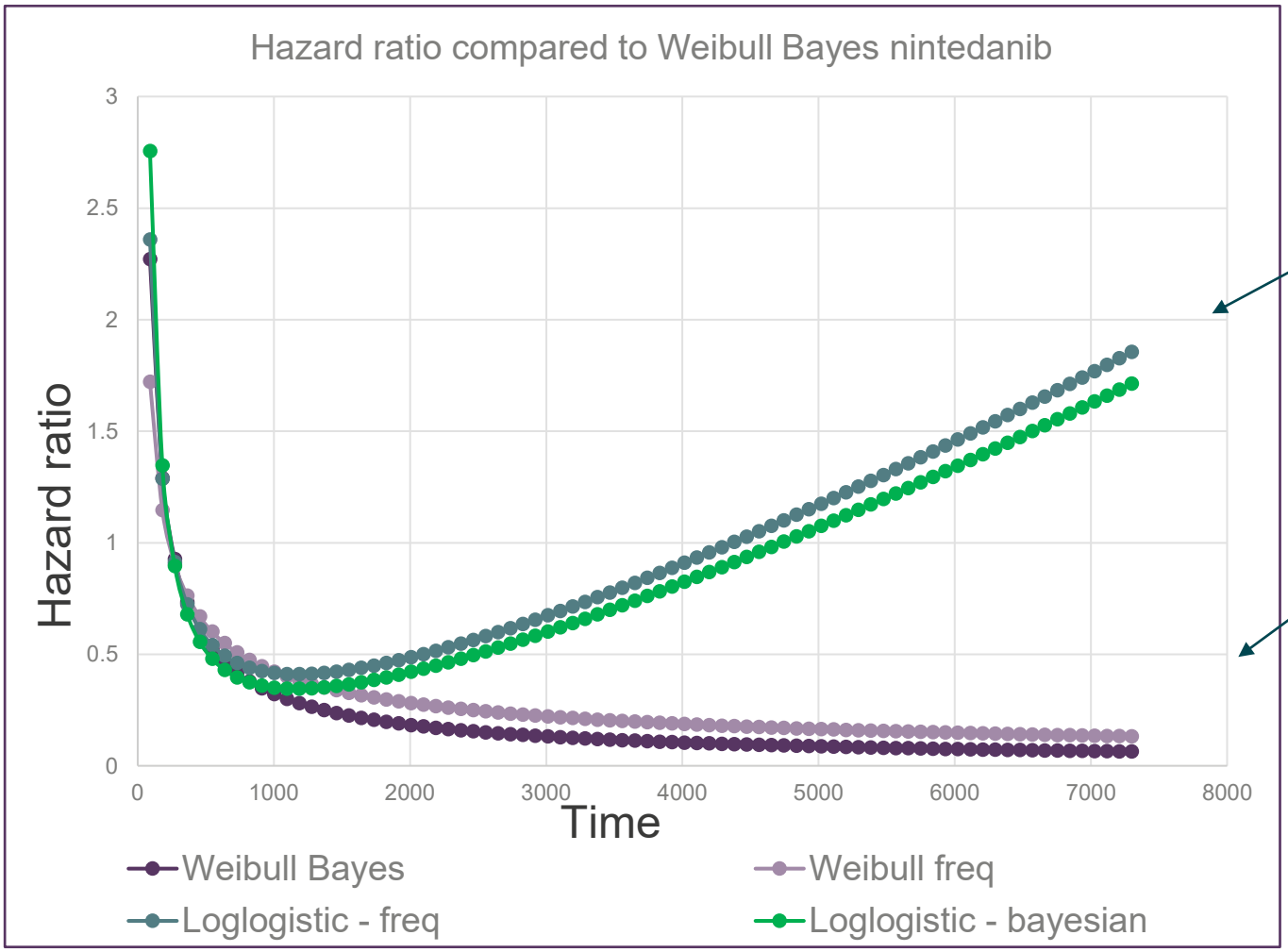


◉ *What is committee view on choice of IPF registry to validate the extrapolation of placebo?*

Source: figure 15, company response to appraisal consultation document; ACD: appraisal consultation document; AU: Australian; BSC, best supportive care; EU: European; FVC: forced vital capacity; ICER: incremental cost effectiveness ratio; IPF: idiopathic pulmonary fibrosis; QALY: quality adjusted life year

Company: modelling + validating survival in placebo arm using registry data for IPF not PF-ILD (3)

ERG calculated hazard ratios of selected curves for placebo (Bayesian Weibull, frequentist Weibull, frequentist loglogistic, Bayesian loglogistic) with nintedanib curve Weibull Bayesian



ERG:

- loglogistic curves - green and grey - unrealistic because assume placebo is better than nintedanib over time;
- Weibull - dark and light purple - also unrealistic because nintedanib gets better and better over time, with very low HRs while trial showed very little difference (HR of 0.7 at best).

Company: proportionality of hazards (PH) in overall survival data

Committee questioned why company modelled consistent with non-PH

Company: open to explore ways to address remaining material uncertainty

Company: PH assumption tested for overall survival, time to discontinuation, and time to first acute exacerbation => PH assumption not met for time to discontinuation so used independent models for consistency across outcomes

Company did not assess PH for Bayesian approach because survival curves crossed not meaningful and because of short term placebo duration

EMPIRE and European registry show statistically significant survival benefit for nintedanib/antifibrotic vs non-antifibrotic & maintained over time:

Source	Difference nintedanib vs non-antifibrotic
Company base case	LYs gained: XXXX years
AU registry *(BSC: **Bayesian gamma**, nintedanib: Bayesian Weibull)*	LYs gained: XXXX years
AU registry *(BSC: **Bayesian loglogistic**, nintedanib: Bayesian Weibull)*	LYs gained: XXXX years
EU registry *(BSC: **frequentist lognormal**, nintedanib: frequentist exponential)*	LYs gained: XXXX years
EMPIRE registry	Median survival: 2.91 years (p<0.001)
European registry	Median survival: 4.6 years (p=0.001)

ERG :

- Company has not changed modelling approaches, nor compared hazard over time and predicted hazard for modelled curves.

ACD: appraisal consultation document; AU: Australian; BSC, best supportive care; EU: European; ICER: incremental cost effectiveness ratio; IPF, idiopathic pulmonary fibrosis; LYs, life years

Modelling IPF and PF-ILD

Pooled results from INPULSIS IPF trials:
Comparable FVC decline but more favourable estimate for death compared
QALY gains in NICE's IPF appraisal much smaller than in this appraisal

INPUSIS pooled analysis	Annual rate of FVC decline (mL/yr)	FVC responders[a]	≥1 acute exacerbation/ year	Death
Nintedanib (n=640)	−113.6	70.1%	4.9%	5.5%
Placebo (n=426)	−223.5	60.5%	7.6%	7.8%
Difference (95% CI) p value	**109.9** ml (75.9, 114.0) p<0.0001	OR: 1.58 (1.21, 2.05) p=0.0007	HR: 0.64 (0.39, 1.05) p=0.08	HR: 0.70 (0.43, 1.12) p=0.70

[a] people with absolute decline in percent predicted FVC <10% at 52 weeks

Model results:

- IPF - OS benefit ~ 0.5 LYs (= 0.4 QALYs) – source: FAD NICE TA379 (IPF)
- PF-ILD - OS benefit: [redacted] LYs (= [redacted] QALYs) – source: ACD company response

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◉ *Do the committee believe the gains have face validity?*

Company: other uncertainties; ERG: no new evidence so no comment

Exacerbations, decline in lung function, stopping treatment, innovation

ACD: Lack of link between exacerbations/ loss of lung function and mortality is an important model limitation (ACD 3.19 and 3.20)

Company: when changed model structure and apply a separate risk of death for each health state, produced increased and unrealistic life years for both placebo and nintedanib

- 'ACD reports modelling of exacerbations and decline in lung function is acceptable and main driver is survival analysis, so limitations unlikely impact economic case for nintedanib.'

ACD: Model of time-to-stopping treatment with nintedanib is uncertain and may have underestimated nintedanib cost (ACD 3.23)

Company Changing distribution not a key driver of cost-effectiveness

ACD: Cannot determine if nintedanib reflects a 'step change' given shortcomings model (ACD 3.28)

Company: clinical experts and patient groups agree nintedanib is a step change

Web comment: nintedanib slows rate of deterioration lung function and reflect a 'step change'

NICE

ACD: appraisal consultation document; FVC: forced vital capacity; ICER: incremental cost effectiveness ratio; PF-ILD: progressive fibrosing interstitial lung disease

Back-up slides

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

NICE

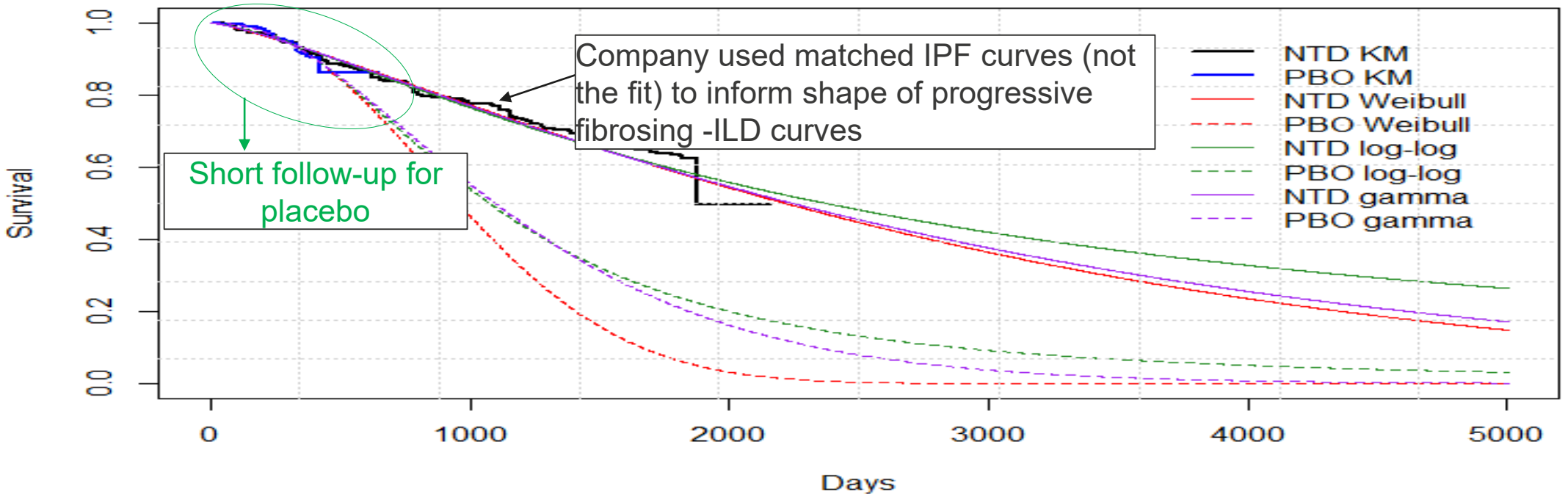
FVC: forced vital capacity

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



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

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

NICE

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