An addendum to these minutes has been included at the end of the document.

6.06 NINTEDANIB, Capsule 100 mg, Capsule 150 mg, Ofev®, Boehringer Ingelheim Pty Ltd

1 Purpose of submission

1.1 The submission requested Authority Required (in writing) listing for nintedanib for the treatment of adult patients with progressive fibrosing interstitial lung disease (PF-ILD).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus placebo + BSC.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with non-IPF chronic progressive fibrosing interstitial lung disease (PF-ILD)
Intervention	Oral nintedanib 150 mg twice daily. Dose can be reduced to 100 mg twice daily if required.
Comparator	Placebo + BSC
Outcomes	Lung function (FVC decline), acute exacerbation, progression, death, quality of life and adverse events
Clinical claim	In adult patients with PF-ILD, nintedanib is superior in terms of efficacy and non-inferior in terms of safety compared to placebo + BSC.

Source: Table 1.1, p2 of the submission.
BSC = best supportive care, IPF = idiopathic pulmonary fibrosis, FVC = forced vital capacity, PF-ILD = progressive fibrosing interstitial lung disease

2 Background

Registration status

2.1 Nintedanib was registered by the Therapeutic Goods Administration (TGA) for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype on 5 January 2021.

2.2 The TGA Delegate sought advice from the Advisory Committee on Medicines (ACM) on the following issues: (a) the recognition of 'chronic fibrosing ILD with a progressive phenotype' as a clinical entity; (b) the appropriateness of FVC as a surrogate endpoint and extent of correlation with exacerbations, morbidity and death in the disease; and (c) the benefit-risk profile of nintedanib for the proposed indication. The ACM considered nintedanib to have an overall positive benefit-risk profile for "treatment of other chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive

phenotype." The ACM agreed that chronic fibrosing ILD with a progressive phenotype is a recognised clinical entity and that a decrease in FVC correlates to an increase in mortality rates and that this is an appropriate marker for surrogate endpoints.

2.3 Nintedanib is also TGA registered for the following therapeutic indications:

- In combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer of adenocarcinoma tumour histology after failure of first line chemotherapy (from 1 September 2015)
- For the treatment of idiopathic pulmonary fibrosis (IPF) (from 1 September 2015)
- For slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) (from 3 Apr 2020).

2.4 On 9 March 2020, the U.S. Food & Drug Administration (FDA) approved the addition of a new indication: treatment for chronic fibrosing interstitial lung diseases with a progressive phenotype." On 28 May 2020, the Committee for Medicinal Products for Human Use (CHMP), the European Medicines Agency's (EMA) committee responsible for human medicines, adopted a new indication for nintedanib: in adults for the treatment of other chronic fibrosing interstitial lung diseases with a progressive phenotype.

Previous PBAC consideration

2.5 There is no previous PBAC consideration of nintedanib for the proposed indication. There are however, previous PBAC considerations of nintedanib for other related therapeutic indications.

2.6 The PBAC considered nintedanib (150 mg and 100 mg capsules) for the treatment of patients with IPF in March 2015, November 2015, and November 2016. The PBAC, at its November 2016 meeting, was satisfied that nintedanib "provides, for some patients, a significant improvement in effectiveness compared with best supportive care (BSC)" and recommended the listing of nintedanib for the treatment of IPF under certain conditions (para. 7.1, Public Summary Document (PSD), nintedanib, November 2016 meeting). The PBAC also recommended a Risk Sharing Arrangement (RSA), which included a financial cap on the Government expenditure based on estimates of uptake rates in the submission and a [redacted]% rebate on any Government expenditure beyond the financial cap (para. 6.49, PSD, Nintedanib, November 2016 meeting). Nintedanib was listed on the Pharmaceutic Benefits Scheme (PBS) on 1 May 2017.

2.7 The PBAC also considered pirfenidone (267 mg capsule), an immunosuppressant, for the treatment of IPF in November 2015, March 2016, November 2016, and March 2018. In December 2016 the PBAC recommended the listing of pirfenidone for the

treatment of IPF on a cost-minimisation basis to nintedanib. Pirfenidone was to be included within a common financial cap with nintedanib (Addendum, PSD, Pirfenidone, November 2016 meeting). Pirfenidone 267 mg capsules were listed on the PBS on 1 July 2017, and pirfenidone 267 mg and 801 mg tablets were listed on 1 August 2018.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Max. Qty (packs)	№.of Rpts	Dispensed Price for Max. Qty	Available brands
NINTEDANIB				
nintedanib 100 mg capsule, 60	1	5	$1,763.61 published price $[redacted] effective price	Ofev
nintedanib 150 mg capsule, 60	1	5	$3,398.76 published price $[redacted] effective price	

Source: Table 1.5, p16 of the submission.

Category/Program:	General Schedule (Code GE)
PBS indication:	Progressive fibrosing interstitial lung disease
Treatment phase:	Initial - new patient
Restriction type:	Authority Required - In Writing

Treatment criteria:
Must be treated by a specialist physician experienced in the diagnosis and treatment of interstitial lung disease, or in consultation with such as a specialist physician.

Clinical criteria:
The condition must be diagnosed through a multidisciplinary team,
AND
Patient must have chest high resolution computed tomography (HRCT) consistent with diagnosis of progressive fibrosing interstitial lung disease within the previous 12 months including features of diffuse fibrosing lung disease of greater than 10% extent on HRCT,
AND

- Patient must have a forced vital capacity (FVC) equal to or greater than 45% predicted for age, gender and height and in the last 24 months one or more of the following that demonstrates progression:
- have had a relative decline in FVC % predicted of equal to or greater than 10% OR
- a relative decline in FVC % predicted equal to or greater than 5% and less than 10% combined with worsening of respiratory symptoms OR
- a relative decline in FVC % predicted equal to or greater than 5% and less than 10% combined with an increasing extent of fibrotic changes on HRCT,

AND
Patient must have a forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) equal to or greater than 0.7,
AND
Patient must have diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin equal to or greater than 30% and less than 80% predicted,
AND
Patient must not have interstitial lung disease due to idiopathic pulmonary fibrosis or due to drug toxicity,
AND
The treatment must be the sole PBS subsidised treatment

Population criteria: Patient must be aged 18 years and over.
Prescriber criteria: A multidisciplinary team is defined as comprising of at least a specialist experienced in the diagnosis and treatment of interstitial lung disease, a radiologist and where histological material is considered, a pathologist. If attendance is not possible because of geographical isolation, consultation with a multidisciplinary team is required for diagnosis. Interstitial lung disease includes connective tissue associated interstitial lung disease or chronic fibrosing hypersensitivity pneumonitis or idiopathic non-specific interstitial pneumonia or environmental / or occupational lung disease or sarcoidosis. Patient must not have an acute respiratory infection at the time of FVC testing. Patient must be aged equal to or greater than 18 years of age. Application for authorisation of initial treatment must be in writing and must include: a) A completed authority prescription form; and b) A completed PF-ILD Authority Application Supporting Information Form; and c) A signed patient acknowledgement.

Source: Table 1.6, pp17-19 of the submission.

Treatment phase:	Initial treatment 2 – change or re-commencement of treatment
Treatment criteria: Must be treated by a specialist physician experienced in the diagnosis and treatment of interstitial lung disease, or in consultation with such as a specialist physician. AND Patient must not have idiopathic pulmonary fibrosis.	
Clinical criteria: Patient must have previously received PBS-subsidised treatment with nintedanib for this condition, AND The treatment must be the sole PBS subsidised treatment for this condition.	
Population criteria: Patient must be aged 18 years and over.	

Source: Table 1.6, pp19-20 of the submission.

Treatment phase:	Continuing treatment
Treatment criteria: Must be treated by a specialist physician experienced in the diagnosis and treatment of interstitial lung disease, or in consultation with such as a specialist physician. AND Patient must not have idiopathic pulmonary fibrosis.	
Clinical criteria: Patient must have previously received PBS-subsidised treatment with nintedanib for this condition, AND The treatment must be the sole PBS subsidised treatment for this condition.	
Population criteria: Patient must be aged 18 years and over.	

Source: Table 1.6, pp20-21 of the submission.

Treatment phase:	Grandfather treatment
Treatment criteria: Must be treated by a specialist physician experienced in the diagnosis and treatment of interstitial lung disease, or in consultation with such as a specialist physician.	

Clinical criteria: Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [insert listing date] AND The condition must be diagnosed through a multidisciplinary team, AND Patient must have chest high resolution computed tomography (HRCT) consistent with diagnosis of progressive fibrosing interstitial lung disease within the previous 12 months including features of diffuse fibrosing lung disease of greater than 10% extent on HRCT, AND Patient must have a forced vital capacity (FVC) equal to or greater than 45% predicted for age, gender and height and in the last 24 months one or more of the following that demonstrates progression: • have had a relative decline in FVC % predicted of equal to or greater than 10% OR • a relative decline in FVC % predicted equal to or greater than 5% and less than 10% combined with worsening of respiratory symptoms OR • a relative decline in FVC % predicted equal to or greater than 5% and less than 10% combined with an increasing extent of fibrotic changes on HRCT, AND Patient must have a forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) equal to or greater than 0.7, AND Patient must have diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin equal to or greater than 30% and less than 80% predicted, AND Patient must not have interstitial lung disease due to idiopathic pulmonary fibrosis or due to drug toxicity, AND The treatment must be the sole PBS subsidised treatment for this condition.
Population criteria: Patient must be aged 18 years and over.
Prescriber Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. A multidisciplinary team is defined as comprising of at least a specialist experienced in the diagnosis and treatment of interstitial lung disease, a radiologist and where histological material is considered, a pathologist. If attendance is not possible because of geographical isolation, consultation with a multidisciplinary team is required for diagnosis. Interstitial lung disease includes connective tissue associated interstitial lung disease or chronic fibrosing hypersensitivity pneumonitis or idiopathic non-specific interstitial pneumonia or environmental / or occupational lung disease or sarcoidosis. Patient must not have an acute respiratory infection at the time of FVC testing. Patient must be aged equal to or greater than 18 years of age. Application for authorisation of initial treatment must be in writing and must include: a) A completed authority prescription form; and b) A completed PF-ILD Authority Application Supporting Information Form; and c) A signed patient acknowledgement.

Source: Table 1.6, pp21-22 of the submission.

3.1 The submission proposed a confidential Special Pricing Arrangement (SPA).

3.2 The proposed eligibility criteria were based on clinical deterioration (progressive fibrosing) rather than the diagnosis of underlying ILD, leading to the potential eligibility of patients with any type of PF-ILD, with a progressive phenotype that is not IPF.

3.3 The proposed PBS restriction requires patients to have a high resolution computed tomography (HRCT) consistent with diagnosis of PF-ILD within the previous 12 months AND evidence demonstrating progression in the last 24 months. The Pre-Sub-Committee Response (PSCR) noted that the proposed timeframe of 24 months for evidence demonstrating progression was consistent with the inclusion criteria of the INBUILD trial. The ESC considered it was appropriate to specify this timeframe in the proposed restriction.

3.4 The PBAC considered that if nintedanib was listed for PF-ILD, there may be a proportion of patients with clinical characteristics of both IPF and PF-ILD who may be eligible to receive treatment under either listing.

For more detail on PBAC's view, see section 7 PBAC outcome.

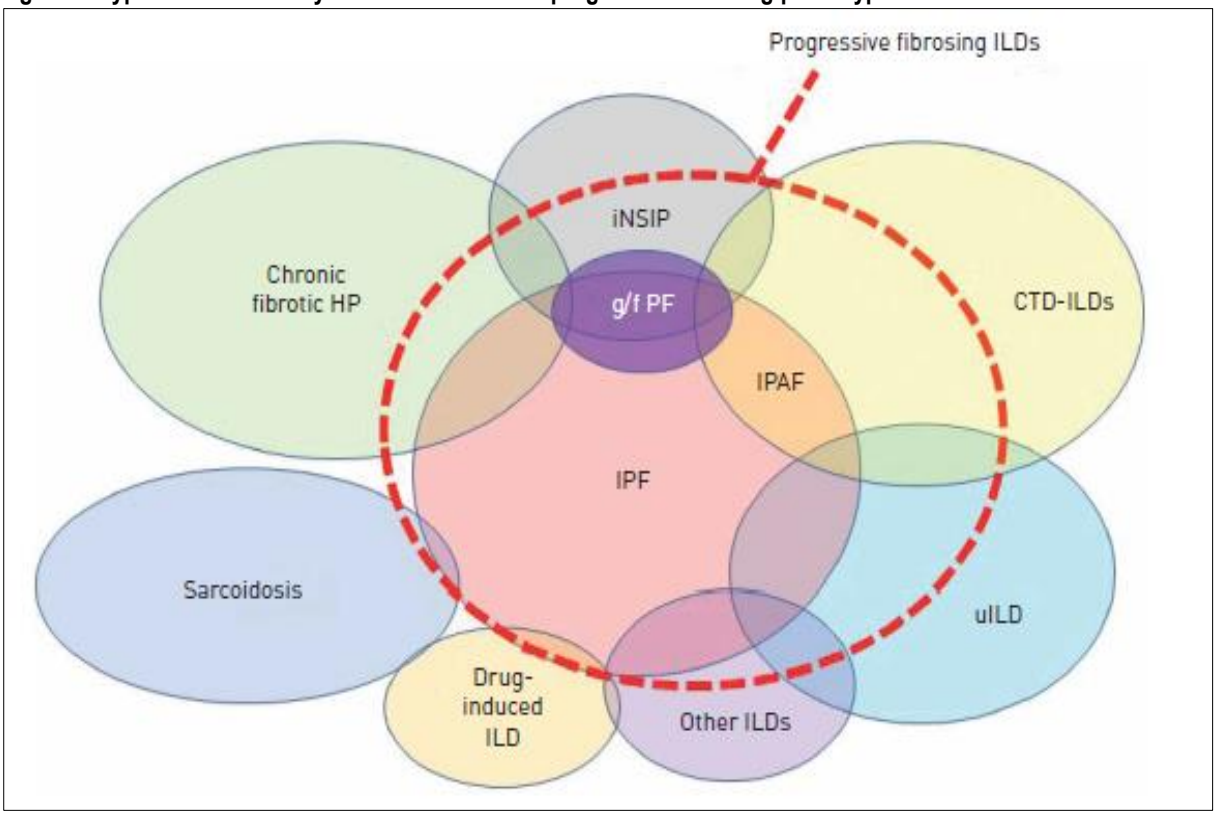
4 Population and disease

4.1 ILD refers to a large and heterogeneous group of parenchymal lung disorders,[1] characterised by diffuse inflammation and fibrosis.[2] IPF is the most common type of idiopathic ILD and represents the prototype of progressive fibrosing ILD, characterised by a decline in lung function and early mortality.[3]

4.2 PF-ILD other than IPF includes idiopathic non-specific interstitial pneumonia (iNSIP), unclassifiable idiopathic interstitial pneumonias (IIPs), connective tissue disease-related ILDs (CTD-ILDs) like rheumatoid arthritis-associated ILD, (RA-ILD) and systemic sclerosis-associated ILD (SSc-ILD), chronic sarcoidosis, chronic hypersensitivity pneumonitis (HP) and exposure-related diseases (e.g. asbestosis, silicosis) (Figure 1).

[1] Cottin V. Treatment of progressive fibrosing interstitial lung diseases: a milestone in the management of interstitial lung diseases. *Eur Respir Rev*. 2019 Oct 1;28(153):190109.
[2] Wong AW, Ryerson CJ, Guler SA. Progression of fibrosing interstitial lung disease. *Respir Res*. 2020 Jan 29;21(1):32.
[3] Cottin 2019, op. cit.

Figure 1: Types of ILD that may be associated with a progressive fibrosing phenotype



Source: Figure 1 in Cottin 2019b[4]
CTD-ILD=Connective tissue disease-associated ILD; g/f PF=genetic and/or familial pulmonary fibrosis; HP=hypersensitivity pneumonitis; ILD=interstitial lung disease; iNSIP=idiopathic nonspecific interstitial pneumonia; IPAF=interstitial pneumonia with autoimmune features; IPF= idiopathic pulmonary fibrosis; RA=rheumatoid arthritis; SSc-ILD=systemic sclerosis-associated ILD; uILD=unclassifiable ILD
CTD-ILDs include RA-associated ILD, SSc-associated ILD, mixed CTD-associated ILD and other autoimmune ILDs.
Other ILDs include exposure-related ILDs (asbestosis and silicosis), non-idiopathic pulmonary fibrosis (IPF), idiopathic interstitial pneumonias (desquamative interstitial pneumonia, etc.), and others.

4.3 PF-ILD is characterised by the presence of progressive pulmonary fibrosis, worsening respiratory symptoms, declining lung function, and early mortality. Patients with IPF have access to subsidised treatment with either nintedanib or pirfenidone. However, there is no PBS-listed treatment for non-IPF chronic PF-ILD. The current clinical management for patients with non-IPF chronic PF-ILD consists primarily of treatment with unlicensed anti-inflammatory or immunomodulatory agents. The proposed clinical management is for nintedanib to be used in addition to BSC in patients with PF-ILD. The ESC considered there is a high clinical need for effective treatments for PF-ILD. The ESC acknowledged that PF-ILD is associated with debilitating effects which have a significant impact on quality of life.

[4] Cottin V. Treatment of progressive fibrosing interstitial lung diseases: a milestone in the management of interstitial lung diseases. *Eur Respir Rev*. 2019 Oct 1;28(153):190109.

4.4 Nintedanib belongs to the pharmacotherapeutic group of antineoplastic agents - protein-tyrosine kinase inhibitors (ATC code: L01XE31).

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated placebo, in combination with BSC as the comparator. The submission reported that BSC may include education (individual or as patient support groups), lung function support (oxygen), pneumonia prophylaxis, pain relief, treatment of co-morbidities (e.g. gastro-oesophageal reflux disease, sleep apnoea, pulmonary hypertension), and palliative care .The main argument provided in support of this nomination was: there is currently no approved treatment for patients with PF-ILD. Current management relies on the off-label use of corticosteroids and immunomodulatory agents, none of which are approved for use in PF-ILD. The ESC considered that placebo + BSC is an appropriate comparator for nintedanib in PF-ILD.

5.2 BSC was the nominated main comparator for both nintedanib and pirfenidone in patients with IPF. The PBAC previously considered that BSC was an appropriate comparator for either treatment in IPF. Pirfenidone was also considered a relevant secondary comparator for nintedanib (para. 7.5, PSD, Nintedanib, November 2016 meeting), and vice versa (para. 7.5, PSD, Pirfenidone, November 2016 meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician considered that the availability of nintedanib has extended survival and reduced the number of fatal exacerbations of patients with IPF. The clinician considered that the distinction between IPF and PF-ILDs was largely arbitrary given these diseases are fundamentally fibrosing and patients undergo a similar disease course. The clinician noted that the results of the INBUILD trial reflected the available efficacy evidence for nintedanib for the treatment of IPF. The clinician indicated that FVC is a reliable surrogate for mortality in patients with PF-ILD noting it is the main criterion used in clinical practice to make decisions around timing of transplants and referral of patients to palliative care. The clinician noted that most patients with PF-ILD are diagnosed relatively late in the disease course when FVC has already decreased substantially, and that mortality is substantially higher when FVC%pred falls below 50%. In this regard, the clinician emphasised that the mean difference in reduction from baseline in FVC%pred of 3.24% between nintedanib and placebo arms of the INBUILD trial is clinically significant.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The majority of comments from individuals were from family members of patients with SSc-ILD. The comments noted that patients and their families were currently funding treatment with nintedanib on their own, and that the cost of treatment was associated with a high financial burden. The health care professional noted improvements in terms of lung function and quality of life in patients with SSc-ILD who have been able to access nintedanib.

6.3 The Australian Idiopathic Pulmonary Fibrosis Registry Steering Committee and the Australian Interstitial Lung Disease Registry, Centre of Research Excellence in Pulmonary Fibrosis and the Lung Foundation Australia strongly supported listing nintedanib on the PBS for the treatment of PF-ILD. The comments emphasised the high unmet clinical need for effective treatments for PF-ILD, which has a progressive disease course similar to IPF. The comments noted there were currently no compassionate access schemes available for nintedanib in PF-ILD and the high cost of nintedanib treatment through private script would restrict the majority of patients from access.

Clinical trials

6.4 The submission was based on one double-blind, randomised controlled trial (RCT) comparing nintedanib +BSC to placebo + BSC (n=663) (Trial 1199.247 or INBUILD).

6.5 Details of the trial presented in the submission are provided in Table 2.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trial 1199.247 (INBUILD) (NCT02999178)	Clinical Trial Report title	November 2019
	INBUILD®: A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD). (Document Number: c26471552-02)	
	Nintedanib for the Treatment of Progressive-fibrosing Interstitial Lung Disease, Technical Report (EVA-20662-00), version 1.0, 19 November 2019 (provided as Attachment 20 of the submission).	*Unpublished*
	Flaherty KR, Wells AU, Cottin V, et al.; INBUILD Trial Investigators. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases.	*NEJM* 2019; 381(18):1718-1727.
	Flaherty KR, Brown KK, Wells AU, et at. Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease.	*BMJ Open Respir Res* 2017; 4(1):e000212.
	Wells AU, Flaherty KR, Brown KK, et al.; INBUILD trial investigators. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial.	*Lancet Respir Med* 2020; pii: S2213-2600(20)30036-9.

Source: Table 2.1, p31 of the submission.

6.6 The key features of the randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Nintedanib vs. placebo						
INBUILD	663	Phase 3, R, DB, MC, MN, nintedanib vs. placebo, 52 weeks treatment	Low	Adults with PF-ILD	Annual rate of FVC decline (mL/year) (primary outcome) Absolute change from baseline to week 52 in K-BILD total score Proportion with an absolute decline >10%, >5% FVC%Pred Time to progression (≥10% absolute decline in FVC%Pred)	Not used
					Absolute change from baseline to week 52 in FVC%Pred Time to death (OS) Time to acute ILD exacerbation	Used

Source: summarised during the evaluation from pp26, 96, 99 and 104 of the submission.
DB=double blind; FVC=forced vital capacity; FVC%Pred= forced vital capacity % predicted; ILD=interstitial lung disease; K-BILD=King's Brief Interstitial Lung Disease questionnaire; MC=multi-centre; MN=multinational; N=number of trial participants; OS=overall survival; PF-ILD=progressive fibrosing interstitial lung disease; R=randomised.

6.7 The submission claimed that, as in patients with IPF, a decline in FVC was "associated with an increased risk of early mortality" and was therefore "an appropriate surrogate marker in lieu of survival and a clinically important outcome measure for patients with PF-ILD" (page iii of the submission). The ESC noted that FVC is a clinically accepted surrogate outcome for survival and that the PBAC have previously accepted FVC as a surrogate outcome for mortality in IPF (see below).

Comparative effectiveness

6.8 The PBAC previously noted that in patients with IPF, lung function loss was a more critical clinical issue than exacerbations (para. 7.7, PSD, nintedanib, November 2015 PBAC meeting). The PBAC also noted an FDA review[5] of nintedanib and pirfenidone studies that suggested that FVC is a valid surrogate for mortality in IPF (para. 7.7, PSD, nintedanib, November 2016 PBAC meeting). The FDA review provided the PBAC more confidence that the lack of statistical significance in overall survival in IPF might be an issue of lack of power in the trials (para. 7.8, PSD, nintedanib, November 2015 PBAC meeting).

6.9 The methods used to derive the MCID (minimal clinically important difference) and a trial-based analysis of MCID for FVC%Pred were presented in the November 2015 resubmission of nintedanib for IPF. The pooled mean difference in absolute change in FVC%Pred from baseline to week 52 was 3.31 (95% CI 2.46, 4.16), favouring nintedanib (Table 3, para. 6.10, PSD, nintedanib, November 2015 PBAC meeting). The PBAC previously noted that a 3.31% absolute decline in FVC was close to the MCID calculated by the anchor-based method (2.5 and 2.84%) and the distribution-based method (3.12%) (para. 7.7, PSD, nintedanib, November 2015 PBAC meeting).

6.10 The K-BILD (King's Brief Interstitial Lung Disease) questionnaire has not been considered by the PBAC in previous submissions for nintedanib or pirfenidone in IPF.

6.11 Results over 52 weeks in the INBUILD trial are provided in Table 4.

[5] Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib. *The New England Journal of Medicine*. 2015;372(13):1189-91.

Table 4: Results in the INBUILD trial (52 weeks)

	Nintedanib		Placebo+BSC		Difference (Nintedanib – Placebo)
	N	**Mean* (SD)**	**N**	**Mean* (SD)**	**Mean* (95% CI), P-value**
OVERALL POPULATION					
Annual rate^ (SD) of FVC decline, mL/year	332	-80.82 (274.59)	331	-187.78 (269.99)	106.96 (65.42, 148.50), **P<0.0001**
Absolute decline in FVC%Pred, n/N (%)~					
>10%		94/332 (28.3%)		121/331 (36.6%)	**OR#=0.68 (0.49, 0.95)**
>5%		144/332 (43.4%)		182/331 (55.0%)	**OR#=0.63 (0.46, 0.85)**
Absolute change from baseline					
FVC (mL)	332	-85.45 (-113.04, -57.86)	331	-192.20 (-219.37, -165.03)	106.75 (68.03, 145.48)
FVC%Pred	332	-2.62 (-3.44, -1.80)	331	-5.86 (-6.67, -5.05)	**3.24 (2.09, 4.40)**
K-BILD total score	332	0.55 (-0.62, 1.72)	331	-0.79 (-1.94, 0.37)	1.34 (-0.31. 2.98), p=0.1115
L-PF symptoms dyspnoea domain score	329	4.28 (2.43, 6.14)	323	7.81 (5.97, 9.66)	-3.53 (-6.14, -0.92) **P†=0.0081**
L-PF symptoms cough domain score	327	-1.84 (-4.36, 0.69)	320	4.25 (1.74, 6.76)	-6.09 (-9.65, -2.53) **P†=0.0008**
PATIENTS WITH HRCT WITH UIP-LIKE FIBROTIC PATTERN					
Annual rate of FVC decline (mL/year)	206	-82.87 (297.96)	206	-211.07 (294.09)	128.20 (70.81, 185.59), **P<0.0001**
Absolute decline in FVC%Pred, n/N (%)					
>10%		63/206 (30.6%)		85/206 (41.3%)	**OR=0.63 (0.42, 0.94)**
>5%		90/206 (43.7%)		118/206 (57.3%)	**OR=0.58 (0.39, 0.85)**
Absolute change from baseline					
FVC (mL)	206	-80.72 (-116.75, -44.68)	206	-212.55 (-248.20, -176.91)	131.84 (81.15, 182.52)
FVC%Pred	206	-2.34 (-3.41, -1.27)	206	-6.44 (-7.49, -5.38)	**4.10 (2.59, 5.60)**
K-BILD total score	206	0.75 (-0.82, 2.31)	206	-0.78 (-2.34, 0.78)	1.53 (-0.68, 3.74), p=0.1747
L-PF symptoms dyspnoea domain score	204	4.14 (1.81, 6.47)	201	8.32 (5.99, 10.66)	-4.18 (-7.48, -0.88) **P†=0.0132**
L-PF symptoms cough domain score	203	-3.20 (-6.43, 0.04)	199	4.09 (0.85, 7.32)	-7.28 (-11.86, -2.71) **P†=0.0019**

Source: Tables 2.19-2.22 and 2.24-2.25, pp74, 84, 86, 88, 90 and 92 of the submission

BSC=best supportive care; CI=confidence interval; FVC=forced vital capacity; FVC%Pred= forced vital capacity % predicted; HRCT=high-resolution computed tomography; K-BILD=King's Brief Interstitial Lung Disease; L-PF=Living with Pulmonary Fibrosis; N=number of patients analysed; OR=odds ratio; SD=standard deviation; UIP=usual interstitial pneumonia; vs=versus

***** Adjusted mean based on Mixed-Effect Model Repeated Measure (MMRM), with fixed effects for baseline, visit, treatment-by-visit interaction, baseline-by-visit interaction and random effect for patient.

^ Based on a random coefficient regression with fixed effects for treatment, HRCT pattern (for the overall population only), and baseline FVC (mL), and including treatment-by-time and baseline-by-time interactions. Within-patient errors were modelled by an unstructured variance-covariance matrix.

~ Worst-case analysis: patients with missing data at Week 52 were considered non-responders.

Adjusted OR based on a logistic regression model with continuous covariate baseline FVC%Pred and binary covariate HRCT pattern (for the overall population only)

† Nominal p-value

p-values in **bold** indicate reaching statistical significance

OR in **bold** indicate reaching statistical significance

K−BILD: The total score ranges from 0 to 100; a higher score indicates a better health status. The minimal clinically important difference (MCID) for K-BILD has not been established, but a change of between 4 and 8 points has been suggested to represent a meaningful change in a population of patients with different ILDs (p95 in the Clinical Trial Report for INBUILD).

L-PF symptoms domain scores range from 0 to 100, the higher the score, the greater the impairment. An MCID for L-PF has not been established (p95 in the Clinical Trial Report for INBUILD).

6.12 In the overall population, the annual rate of FVC decline over 52 weeks was significantly slower in the nintedanib group than in the placebo + BSC group (adjusted mean difference = 106.96 mL/year P<0.0001). The annual rate of FVC decline over 52 weeks was also significantly slower with nintedanib in both subgroups of patients with HRCT with UIP (usual interstitial pneumonia)-like fibrotic pattern only and patients with HRCT with other fibrotic pattern. The PBAC noted that the results over 52 weeks were similar for the overall population and the subgroup of patients with HRCT with UIP-like fibrotic pattern.

6.13 The reduction from baseline to Week 52 in FVC%Pred was significantly smaller in the nintedanib group than in the placebo + BSC group, in the overall population. The adjusted mean difference was 3.24% (95% CI 2.09%, 4.40%), favouring nintedanib. The submission considered a 3.24% difference in FVC%Pred clinically meaningful. The submission reported that the mean difference of 3.24% in the overall population exceeded the MCID of 2.2% reported in Patel 2013.[6] It was also consistent with the results from "internal analysis" (2.5%-2.84% using an anchor-based method and 3.12% using a distribution-based approach) (Table 5). The ESC considered that a 3.24% difference in FVC%Pred exceeds the likely MCID.

Table 5: Determination of MCID for absolute change in FVC%Pred in the submission (anchor-based method)

Anchor-based method	**Change in FVC%Pred from baseline to week 52 Mean (95% CI)**	**Comparison vs. stable Mean (95% CI)**
K-BILD Total derived subgroups		
Stable: Decline or increase <2.2 points	−4.06 (−5.29, −2.83)	
Deterioration: ≤−2.2 points	−6.57 (−7.48, −5.65)	−2.50 (−4.04, −0.97), **p=0.0014**
Improvement: ≥+2.2 points	−1.23 (−2.14, -0.32)	2.84 (1.31, 4.37) **p=0.0003**
Distribution-based approach	**FVC%Pred at baseline, mean (SD)**	**MCID (effect size=0.2)**
Overall population (N=663):	68.99 (15.62)	3.12%
UIP-like fibrotic pattern population (N=412):	70.58 (15.89)	3.18%
Other HRCT fibrotic pattern population (N=251):	66.37 (14.82)	2.96%

Source: Tables 2.16-2.17, p70 of the submission

FVC=forced vital capacity; FVC%Pred= forced vital capacity % predicted; K-BILD=King's Brief Interstitial Lung Disease questionnaire; MCID=minimal clinically important difference

6.14 The adjusted mean difference of absolute change from baseline in K-BILD total score at Week 52 did not reach statistical significance (1.34, 95% CI -0.31 to 2.98, p=0.1115). The submission suggested that a small change in the K-BILD total score was expected from a disease characterised by progression, and as such, no change might indicate

[6] Patel AS, Siegert RJ, Keir GJ et al. The minimal important difference of the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and forced vital capacity in interstitial lung disease. *Respir Med* 2013; 107:1438-1443.

stabilisation of disease. The ESC considered that the lack of a statistically significant difference in quality of life between nintedanib and placebo + BSC arms was not entirely unexpected given the progressive nature of the disease and given the high symptom burden associated with the disease.

6.15 Results of time-to-event data over 52 weeks in the INBUILD trial are presented in Table 6.

Table 6: Results of the INBUILD trial: time-to-event data over 52 weeks

	Nintedanib		Placebo+BSC		Nintedanib vs. placebo	
	Patients with event, n/N (%)	**Obs. time (pt-yr)**	**Patients with event, n/N (%)**	**Obs. time (pt-yr)**	**Survival**	**HR (95% CI) p-value**
Overall population						**HR^ (95% CI)**
Time to death (OS) over 52 weeks	16/332 (4.8)	330.8	17/331 (5.1)	330.1	NR	0.94 (0.47, 1.86) P=0.8544
Time to first acute ILD exacerbation	16/332 (4.8)	324.8	22/331 (6.6)	319.6	NR	0.72 (0.38, 1.37) P=0.3095
Time to progression (≥10% absolute decline in FVC%Pred)	73/332 (22.0)	295.2	115/331 (34.7)	283.9	NR	**0.60 (0.45, 0.80) P~=0.0005**
Patients with HRCT with UIP-like fibrotic pattern						**HR# (95% CI)**
Time to death (OS) over 52 weeks	11/206 (5.3)	203.8	16/206 (7.8)	202.9	NR	0.68 (0.32, 1.47) P=0.3291
Time to first acute ILD exacerbation	11/206 (5.3)	NR	15/206 (7.3)	NR	0.946 vs. 0.926	0.72 (0.33, 1.58) P=NR
Time to progression (≥10% absolute decline in FVC%Pred)	49/206 (23.8)	NR	74/206 (35.9)	NR	0.757 vs. 0.640	**0.62 (0.43, 0.89)** P=NR

Source: Tables 2.28-2.29 and 2.31, pp97, 99 and 104 of the submission; Tables 36.1.1.9 and 79.1.1.1.3 in Attachment 3 provided with the submission

BSC=best supportive care; CI=confidence interval; FVC=forced vital capacity; FVC%Pred= forced vital capacity % predicted; HR=hazard ratio; HRCT=high-resolution computed tomography; ILD=interstitial lung disease; n=number of participants with event; N=total participants in group; NR=not reported; obs=observational; OS=overall survival; pt-yr=patient-year; UIP=usual interstitial pneumonia; vs=versus

^ Based on a Cox's regression model with terms for treatment and stratified by HRCT pattern

Based on a Cox's regression model with terms for treatment

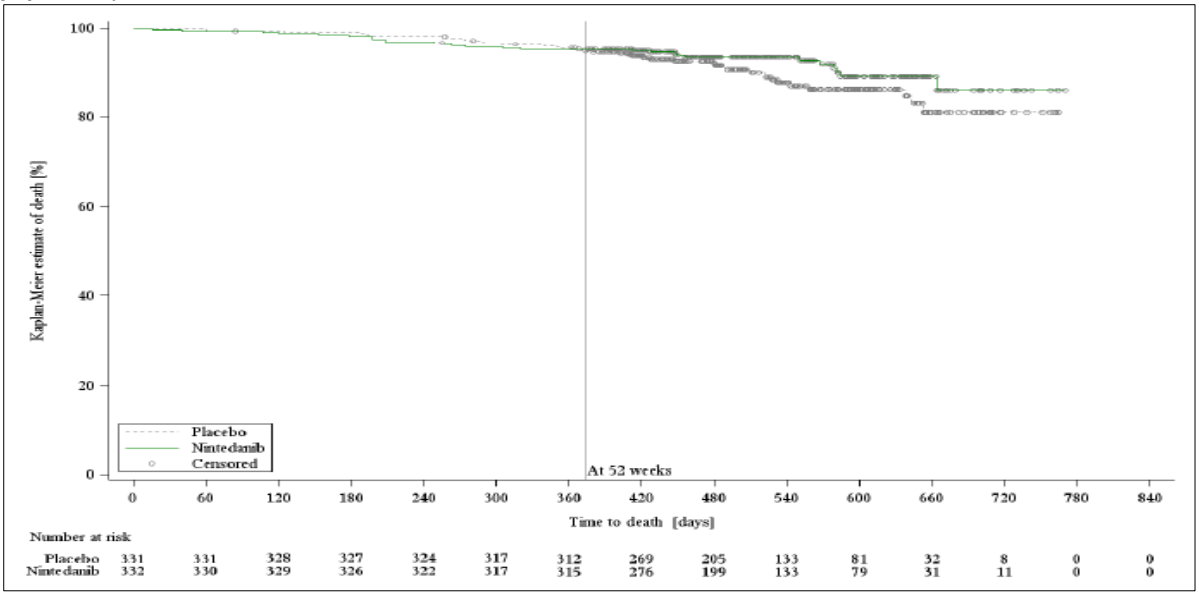
p-values in **bold** indicate reaching statistical significance

6.16 Figures 2 presents the Kaplan-Meier plot for time to death over 52 weeks and the whole trial up to database lock 1 (DBL1) for the overall population in the INBUILD trial. In the overall population, 4.8% of patients in the nintedanib group died over 52 weeks, compared to 5.1% in the placebo + BSC group. The difference was not statistically significant (P=0.8544). The submission reported that the trial was not powered to detect a statistically significant reduction in mortality. Data up to 17.2 months was used in the economic model. The Clinical Trial Report noted that the Kaplan-Meier curves for time to death over the whole trial started separating after 480 days

(approximately 68 weeks), and showed subsequent continued separation.[7] The PSCR noted there was a clear trend towards improved survival for nintedanib for the overall population and argued that this trend is biologically plausible given there is a statistically significant difference in the rate of disease progression (i.e. the rate of decline in FVC and change in FVC%Pred). The PSCR noted the divergence in the KM curves occurred during Part B of the trial, where patients and investigators remained blinded until trial completion. The PSCR considered the trend towards improved survival over the whole trial is not an artefact but rather supports the use of FVC as a surrogate marker for mortality. The ESC agreed that there was a trend to improved survival and considered that the trial follow-up period of 25-months would unlikely be sufficient to detect any survival benefit in PF-ILD. However, the ESC considered that the possibility of the divergence being due to chance cannot be excluded given the non-significance of overall survival.

6.17 While survival with nintedanib treatment over 52 weeks was also not statistically significant compared with BSC for IPF (RR=0.72 (95% CI 0.48, 1.09), which was considered by the PBAC in November 2016, there was a clearer trend towards a survival benefit for nintedanib with a lower point estimate for the HR in IPF compared with that seen for PF-ILD. The ESC considered there was more uncertainty associated with the OS results for PF-ILD than that for IPF.

Figure 2: Kaplan-Meier curve of time to death over the whole trial (Part A+B) up to DBL1 in INBUILD (overall population)

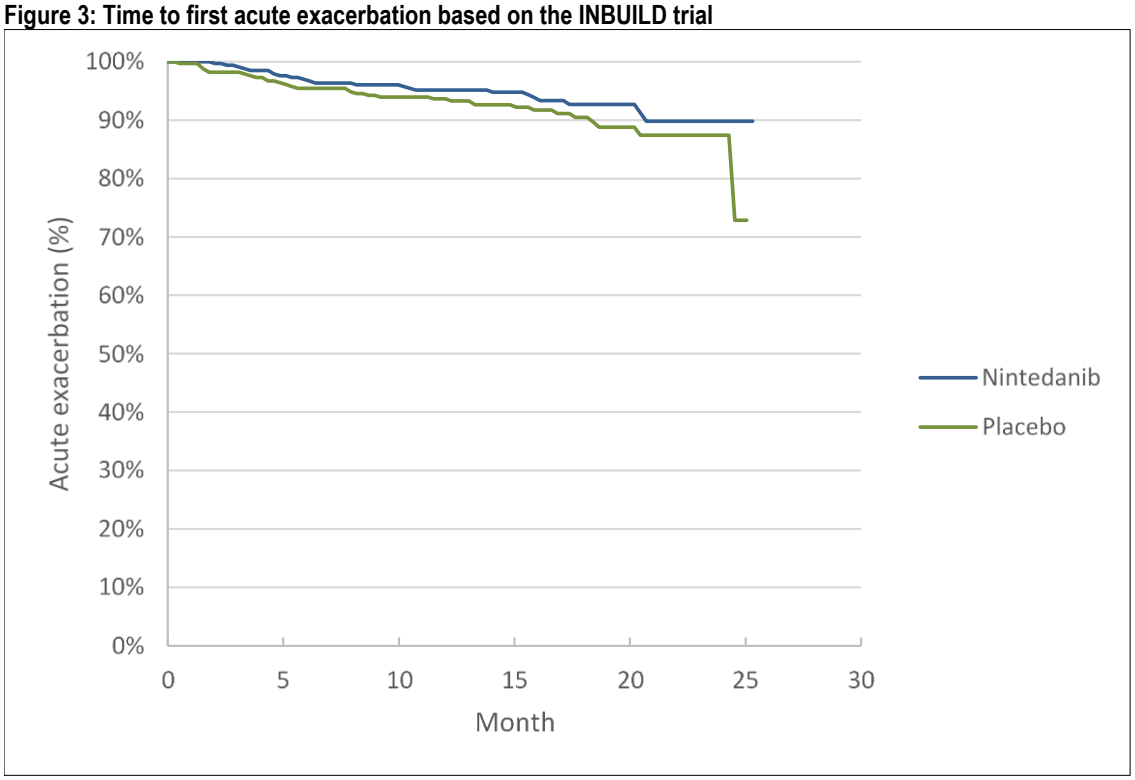


Source: Figure 11.1.3.2.2:1, p267 in the Clinical Trial Report Main analysis (Document No: c26471552-02), Trial 1199.247, November 2019.

[7] Source: p266 in the Clinical Trial Report Main analysis (Document No: c26471552-02), Trial 1199.247, November 2019.

6.18 Fewer patients in the nintedanib group (5.3%) experienced acute ILD exacerbation over 52 weeks, when compared to placebo + BSC (7.3%), but this was not statistically significant (P=0.3095). Figure 3 presents the distribution of acute observations in the INBUILD trial. Approximately 90% of patients treated with nintedanib and 73% treated with placebo +BSC remained free of acute exacerbations at the end of the INBUILD trial follow-up period of 25 months. Data up to 17.2 months was used in the economic model.

Figure 3: Time to first acute exacerbation based on the INBUILD trial



Source: Figure 3.7, p177 of the submission

Comparative harms

6.19 Significantly more patients in the nintedanib group experienced acute respiratory failure SAE, drug-induced liver injury SAE, investigator-defined drug-related AEs, and gastrointestinal disorders (diarrhoea, nausea, abdominal pain) over 52 weeks when compared to placebo + BSC in the INBUILD trial (Table 7).

6.20 The TGA Delegate's Overview noted that the pattern of nintedanib toxicity observed in the INBUILD trial was consistent with that previously documented for the drug.

Table 7: Summary of key adverse events the INBUILD trial over 52 weeks (overall population)

	Nintedanib N=332 n (%=n/N)	Placebo + BSC N=331 n (%=n/N)	Nintedanib vs. placebo	
			RR (95% CI)	RD (95% CI)
AEs resulting in death	11 (3.3)	17 (5.1)	0.65 (0.31, 1.36)	−0.02 (−0.05, 0.01)
Any SAE	107 (32.2)	110 (33.2)	0.97 (0.78, 1.21)	−0.01 (−0.08, 0.06)
Respiratory, thoracic and mediastinal disorders[a]	44 (13.3)	64 (19.3)	**0.69 (0.48, 0.97)**	**-0.06 (-0.12, -0.00)**
ILD[a]	11 (3.3)	31 (9.4)	**0.35 (0.18, 0.69)**	**-0.06 (-0.10, -0.02)**
Acute respiratory failure[a]	10 (3.0)	2 (0.6)	**4.98 (1.10, 22.58)**	**0.02 (0.00, 0.04)**
Hepatobiliary disorders[a]	11 (3.3)	3 (0.9)	**3.66 (1.03, 12.98)**	**0.02 (0.00, 0.05)**
Drug-induced liver injury[a]	6 (1.8)	0 (0)	–	**0.02 (0.00, 0.03)**
Any AE	317 (95.5)	296 (89.4)	**1.07 (1.02, 1.12)**	**0.06 (0.02, 0.10)**
AEs leading to premature and permanent discontinuation of trial medication	65 (19.6)	34 (10.3)	**1.91 (1.30, 2.80)**	**0.09 (0.04, 0.15)**
Investigator-defined drug-related AEs[a]	262 (78.9)	126 (38.1)	**2.07 (1.79, 2.40)**	**0.41 (0.34, 0.48)**
AESIs^	16 (4.8)	5 (1.5)	**3.19 (1.18, 8.61)**	**0.03 (0.01, 0.06)**
Other significant AEs#[a]	131 (39.5)	19 (5.7)	**6.87 (4.35, 10.85)**	**0.34 (0.28, 0.40)**
Gastrointestinal disorders[a]	268 (80.7)	149 (45.0)	**1.79 (1.57, 2.04)**	**0.36 (0.29, 0.43)**
Diarrhoea[a]	222 (66.9)	79 (23.9)	**2.80 (2.28, 3.45)**	**0.43 (0.36, 0.50)**
Nausea[a]	96 (28.9)	31 (9.4)	**3.09 (2.12, 4.49)**	**0.20 (0.14, 0.25)**
Abdominal pain[a]	30 (9.0)	6 (1.8)	**4.98 (2.10, 11.82)**	**0.07 (0.04, 0.11)**
Investigations[a]	114 (34.3)	56 (16.9)	**2.03 (1.53, 2.69)**	**0.17 (0.11, 0.24)**
ALT increased[a]	43 (13.0)	12 (3.6)	**3.57 (1.92, 6.65)**	**0.09 (0.05, 0.13)**
AST increased[a]	38 (11.4)	12 (3.6)	**3.16 (1.68, 5.93)**	**0.08 (0.04, 0.12)**
Metabolism and nutrition disorders[a]	69 (20.8)	38 (11.5)	**1.81 (1.26, 2.61)**	**0.09 (0.04, 0.15)**
Decreased appetite[a]	48 (14.5)	17 (5.1)	**2.82 (1.65, 4.79)**	**0.09 (0.05, 0.14)**
Hepatobiliary disorders[a]	38 (11.4)	10 (3.0)	**3.79 (1.92, 7.48)**	**0.08 (0.05, 0.12)**
Hepatic function abnormal[a]	19 (5.7)	3 (0.9)	**6.31 (1.89, 21.13)**	**0.05 (0.02, 0.08)**

Source: Table 2.43, p134 of the submission; Table 12.1.2.1:1, p311 in the Clinical Trial Report Main analysis (Document No: c26471552-02), Trial 1199.247, November 2019.

AESI=adverse event of special interest; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSC=best supportive care; CI=confidence interval; HRCT=high-resolution computed tomography; n=number of participants with event; N=total participants in group; RD=risk difference; RR=relative risk; SAE=serious adverse event

^ AESI relates to any specific AE identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial. Protocol-specified AESIs included gastrointestinal perforation and hepatic injury.

Non-serious AEs that led to dose reduction or premature discontinuation of trial medication.

Bold indicates statistically significant results.

[a] Not reported in the submission but extracted from the Clinical Trial Report during the evaluation. Data for these values were prepared during the evaluation using raw data reported in the Clinical Trial Report.

Benefits/harms

6.21 A summary of the comparative benefits and harms for nintedanib versus placebo + BSC is presented in Table 8.

Table 8: Summary of comparative benefits and harms for nintedanib and PBO + BSC in INBUILD (52 weeks, overall population)

Trial	Nintedanib % (n/N)	PBO + BSC % (n/N)	Adjusted OR† (95% CI)	Event rate/100 patients[a]		RD[a] (95% CI)
				Nintedanib	PBO+BSC	
Benefits						
Proportion of patients with an absolute decline from baseline in FVC%Pred at week 52 (adjusted OR)						
Decline >10%	28.3 (94/332)	36.6 (121/331)	**0.68 (0.49, 0.95)**	*28.3*	*36.3*	***−8.2 (−15.3, −1.1)***
Decline >5%	43.4 (144/332)	55.0 (182/331)	**0.63 (0.46, 0.85)**	*43.4*	*55.0*	***−11.6 (−19.2, −4.1)***

Annual rate of FVC decline over 52 weeks (mL/year)							
	Nintedanib			**PBO + BSC**			**Mean difference*: Nintedanib vs. PBO + BSC (95% CI)**
	N	**Mean Δ baseline**	**SD**	**N**	**Mean Δ baseline**	**SD**	
Over 52 weeks	332	-80.82	274.59	331	-187.78	269.99	106.96 (65.42, 148.50), **P<0.0001**

Absolute change from baseline to week 52 for FVC and K-BILD score							
	Nintedanib			**PBO + BSC**			**Mean difference*: Nintedanib vs. PBO + BSC (95% CI)**
	N	**Mean Δ baseline**	**(95% CI)**	**N**	**Mean Δ baseline**	**(95% CI)**	
FVC (mL)	332	-85.45	(-113.04, -57.86)	331	-192.20	(-219.37, -165.03)	**106.75 (68.03, 145.48)**
FVC%Pred	332	-2.62	(-3.44, -1.80)	331	-5.86	(-6.67, -5.05)	**3.24 (2.09, 4.40)**
K-BILD total score	332	0.55	(-0.62, 1.72)	331	-0.79	(-1.94, 0.37)	1.34 (-0.31. 2.98), p=0.1115

	Nintedanib	**PBO + BSC**	**Absolute Difference[a]**	**HR (95% CI)**
Event	% (n/N), Obs. Time (pt-yr)	% (n/N), Obs. Time (pt-yr)		
Deaths (Overall survival)				
Over 52 weeks	4.8 (16/332), 330.8	5.1 (17/331), 330.1	*−0.3 (−3.6, 3.0)*	0.94 (0.47, 1.86) P=0.8544
Over the whole trial (Part A+B) up to DBL1	8.1 (27/332), 466.3	11.5 (38/331), 465.2	*−3.3 (−7.9, 1.2)*	0.70 (0.43, 1.15) P=0.1620
First acute ILD exacerbation				
Over 52 weeks	4.8 (16/332), 324.8	6.6 (22/331), 319.6	*−1.8 (−5.4, 1.7)*	0.72 (0.38, 1.37) P=0.3095
Over the whole trial (Part A+B) up to DBL1	6.9 (23/332), 456.4	9.7 (32/331), 447.2	*−2.7 (−6.9, 1.5)*	0.71 (0.41, 1.21)
Progression (≥10% absolute decline in FVC%Pred)				
Over 52 weeks	22.0 (73/332)	34.7 (115/331)	***−12.8 (−19.5, −6.0)***	**0.60 (0.45, 0.80) P~=0.0005**
Over the whole trial (Part A+B) up to DBL1	30.4 (101/332)	42.9 (142/331)	***−12.5 (−19.8, −5.2)***	**0.65 (0.50, 0.84)**

Harms (over 52 weeks)						
	Nintedanib n/N	**PBO + BSC n/N**	**RR[a] (95% CI)**	**Event rate/100 patients**		**RD[a] % (95% CI)**
				Nintedanib	**PBO + BSC**	
Serious adverse event						
Acute respiratory failure	10/332	2/331	***4.98 (1.10, 22.58)***	3.0	0.6	***2.4 (0.4, 4.4)***
Drug-induced liver injury	6/332	0/331	−	1.8	0.0	***1.8 (0.4, 3.2)***
Adverse event (AE)						

Harms (over 52 weeks)						
	Nintedanib n/N	**PBO + BSC n/N**	**RR[a] (95% CI)**	**Event rate/100 patients**		**RD[a] % (95% CI)**
				Nintedanib	**PBO + BSC**	
Any AE	317/332	296/331	**1.07 (1.02, 1.12)**	95.5	89.4	***6.1 (2.1, 10.1)***
Investigator-defined drug-related AEs	262/332	126/331	***2.07 (1.79, 2.40)***	78.9	38.1	***40.8 (34.0, 47.7)***
AEs leading to premature and permanent discontinuation of trial medication	65/332	34/331	**1.91 (1.30, 2.80)**	19.6	10.3	***9.3 (3.9, 14.7)***
AESIs^	16/332	5/331	***3.19 (1.18, 8.61)***	4.8	1.5	***3.3 (0.7, 6.0)***
Other significant AEs#	131/332	19/331	***6.87 (4.35, 10.85)***	39.5	5.7	***33.7 (27.9, 39.5)***
Gastrointestinal disorders	268/332	149/331	***1.79 (1.57, 2.04)***	80.7	45.0	***35.7 (28.9, 42.5)***
Diarrhoea	222/332	79/23.9	***2.80 (2.28, 3.45)***	66.9	23.9	***43.0 (36.2, 49.8)***
Nausea	96/332	31/331	***3.09 (2.12, 4.49)***	28.9	9.4	***19.6 (13.8, 25.3)***
Abdominal pain	30/332	6/331	***4.98 (2.10, 11.82)***	9.0	1.8	***7.2 (3.8, 10.6)***
Investigations	114/332	56/331	***2.03 (1.53, 2.69)***	34.3	16.9	***17.4 (10.9, 23.9)***
ALT increased	43/332	12/331	***3.57 (1.92, 6.65)***	13.0	3.6	***9.3 (5.2, 13.5)***
AST increased	38/332	12/331	***3.16 (1.68, 5.93)***	11.4	3.6	***7.8 (3.8, 11.8)***
Decreased appetite	48/332	17 (5.1)	***2.82 (1.65, 4.79)***	14.5	5.1	***9.3 (4.9, 13.8)***
Hepatobiliary disorders	38 (11.4)	10 (3.0)	***3.79 (1.92, 7.48)***	11.4	3.0	***8.4 (4.5, 12.3)***
Hepatic function abnormal	19 (5.7)	3 (0.9)	***6.31 (1.89, 21.13)***	5.7	0.9	***4.8 (2.1, 7.5)***

Source: Table 12.1.2.1:1, p311 in the Clinical Trial Report Main analysis (Document No: c26471552-02), Trial 1199.247, November 2019.
AE=adverse event; AESI=adverse event of special interest; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSC=best supportive care; FVC=forced vital capacity; FVC%Pred= forced vital capacity % predicted; HR=hazard ratio; OR=odds ratio; PBO=placebo; pt-yr=patient-year; RD=risk difference; RR=risk ratio

***** Based on a random coefficient regression with fixed effects for treatment, HRCT pattern (for the overall population only), and baseline FVC (mL), and including treatment-by-time and baseline-by-time interactions. The within-patient errors were modelled by an unstructured variance-covariance matrix.

† Based on a logistic regression model with continuous covariate baseline FVC%Pred and binary covariate HRCT pattern (for the overall population only).

^ AESI relates to any specific AE identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial. Protocol-specified AESIs included gastrointestinal perforation and hepatic injury.

Non-serious AEs that led to dose reduction or premature discontinuation of trial medication.

Data in **bold** indicate reaching statistical significance.

[a] data prepared during the evaluation. Comparative data were not provided in the submission.

6.22 On the basis of the direct evidence presented by the submission, treatment with nintedanib compared with placebo + BSC resulted in:

- An approximate 107 mL/year reduction in the rate of decline in forced vital capacity (FVC, measure of lung function) over 52 weeks of treatment exposure.

6.23 On the basis of the direct evidence presented by the submission, for every 100 patients treated with nintedanib in comparison with placebo + BSC over 52 weeks of exposure:

- Approximately 11 fewer patients would have declined by 5% or more in the predicted value of forced vital capacity. A change of 3.12% was considered clinically meaningful by the submission.

- Approximately eight fewer patients would have declined by 10% in the predicted value of forced vital capacity.
- Approximately two additional patients would experience acute respiratory failure as a serious adverse event.
- Approximately two additional patients would experience drug-induced liver injury as a serious adverse event.
- Approximately six additional patients would experience any adverse event.
- Approximately 40 additional patients would experience drug-related adverse events.
- Approximately three additional patients would experience adverse events of particular concern for prospective safety monitoring and safety assessment including gastrointestinal perforation and hepatic injury.
- Approximately 35 additional patients would experience gastrointestinal disorders. In particular, diarrhoea, roughly nausea, and abdominal pain.

Clinical claim

6.24 The submission described nintedanib as superior in terms of effectiveness compared to placebo + BSC. The claim of superior comparative effectiveness was based on a statistically significant slower decline in FVC (p<0.0001), and a statistically significantly lower risk of progression (≥10% absolute decline in FVC%Pred) (p=0.0005) for nintedanib over 52 weeks when compared to placebo + BSC. However, there was no statistically significant difference in overall survival or quality of life (K-BILD total score, p=0.1115) between nintedanib and placebo + BSC over 52 weeks (p=0.8544). The ESC considered that the claim of superior comparative effectiveness was reasonable based on decline in FVC and FVC%Pred.

6.25 The submission did not formally consider the requirements outlined in the PBAC guidelines for linking proposed surrogate measures to target clinical outcomes. The ACM considered that a decrease in FVC correlates to an increase in mortality rates and that this is an appropriate marker for surrogate endpoints. The economic model used overall survival Kapan-Meier data from the INBUILD trial, which was subsequently extrapolated despite not being statistically significant. The economic model also predicted utilities using data from the INBUILD trial, including FVC%Pred and acute ILD exacerbation.

6.26 The submission described nintedanib as non-inferior in terms of safety compared to placebo + BSC. This claim was not adequately supported. Significantly more patients on nintedanib than placebo + BSC experienced acute respiratory failure SAE, drug-induced liver injury SAE, investigator-defined drug-related AEs, and gastrointestinal

disorders (diarrhoea, nausea, abdominal pain). The PSCR noted that the rate of acute respiratory failure and drug-induced liver injury was low in both treatment arms and the difference in rates of drug-induced liver injury was not statistically significant between arms. The PSCR acknowledged that the risk of gastrointestinal disorders was higher with nintedanib treatment, however noted these are known adverse effects and, for most patients, diarrhoea was of mild to moderate intensity and resolved without permanent dose reduction or premature discontinuation of trial medication. The PSCR noted that analysis of post-market authorisation data suggest that rates of diarrhoea appear lower in clinical practice with most cases reported to be non-serious of mild to moderate severity. The PSCR considered that overall, the safety profile of nintedanib in PF-ILD patients comprised risks that were manageable or occurred at a low frequency. The ESC considered that while AEs associated with nintedanib were generally manageable, the claim of non-inferior safety compared to placebo + BSC was not supported given the higher incidence of AEs in the nintedanib arm.

6.27 The previous submissions of nintedanib for IPF claimed that nintedanib was inferior in safety compared with placebo + BSC.

6.28 The PBAC considered that the claim of superior comparative effectiveness was adequately supported in terms of decline in FVC and FVC%Pred over 52 weeks.

6.29 The PBAC considered that the claim of non-inferior safety was not adequately supported, noting that significantly more patients in the nintedanib arm had investigator-defined drug-related AEs (78.9% vs. 38.1%) than the placebo + BSC arm of the INBUILD trial. The PBAC also noted that gastrointestinal adverse events and some SAEs were significantly higher in the nintedanib arm compared to the placebo + BSC arm. The PBAC considered that the substantial rate of discontinuation in the nintedanib arm compared to the placebo + BSC arm at 52 weeks (19.6% vs. 10.3%) would largely be due to gastrointestinal adverse events.

Economic analysis

6.30 The submission presented a stepped economic evaluation based on a direct randomised trial (INBUILD) and implemented a modelled economic evaluation using microsimulation. Table 9 summarises the key components of the economic evaluation.

6.31 Overall survival was modelled separately from acute ILD exacerbations and FVC. Kaplan-Meier overall survival data and acute ILD exacerbations data were used, which was then extrapolated. FVC%Pred was modelled using a separate (independent) linear mixed-effect regression model, which was based on a post-hoc analysis of the individual patient data from the INBUILD trial and using several parameters, including acute ILD exacerbation. The ESC noted that acute exacerbations are known to result in death or reduction in FVC, which would likely reduce survival overall. The PBAC

noted the model indirectly links acute exacerbations to mortality in the model via FVC%Pred in that acute exacerbations reduces FVC%Pred, which then results in mortality if the lung function declines to an unsustainable level (i.e. FVC%Pred ≤ 40%).

Table 9: Summary of model structure and rationale

Component	Summary
Type of analysis	Stepped economic evaluation Steps 1 to 3: Cost-effectiveness analysis (LYG as the outcome) Step 4: Cost-utility analysis (QALYs gained as the outcome)
Time horizon	15 years in the base case analysis; 25 months for within-trial economic evaluation (step 1) At the end of trial follow-up 90% of patients treated with nintedanib and 73% treated with placebo + BSC remained free of acute exacerbations; 86% of patients treated with nintedanib and 81% treated with placebo + BSC still survived; and 66% of patients treated with nintedanib and 71% treated with placebo + BSC continued treatment. The ICER was sensitive to time horizons less than 10 years. The submission for IPF considered by the PBAC in 2016 applied a 10-year time horizon.
Methods used to generate results	Microsimulation The use of a microsimulation is reasonable, given the availability of patient-level data from the INBUILD trial and the impact of the past number of acute exacerbations experienced on FVC%Pred and mortality (thus needing a Markov model to have memory). For each patient, a random value for each baseline characteristic[8] from "a normal distribution with a mean and standard deviation that corresponds to that observed in INBUILD" was drawn. Assuming normal distribution may not be appropriate for all parameters, including for utility, which is likely to have a highly negatively skewed distribution. If the patient experienced an acute exacerbation, they were assumed to experience a permanent drop in FVC%pred and a temporary (1 cycle) drop in utility values regardless of the treatment.
Health states	1. Alive with or without acute exacerbation 2. Alive with or without lung transplantation 3. Dead The selection of these health states is reasonable. The selected health states were similar to the previous submission for pirfenidone for the treatment of patients with IPF. In that submission, the selected health states were: 'PFS', 'progression', 'lung transplant' and 'death' (paragraph 6.27, pirfenidone, PSD, November 2015 PBAC meeting).
Cycle length	1 month
Transition probabilities	Transition probabilities for all modelled events, except lung transplantation, were derived from a post-hoc analysis of the individual patient data from the INBUILD trial. A separate (independent) linear mixed-effects regression model was used to model FVC%Pred using several parameters, including acute ILD exacerbation.

[8] Including age, gender, FVC%Pred, utility value, usual interstitial pneumonia (UIP)-like pattern, grouped criteria for progressive interstitial lung disease (PGGR- marginal and worsening) and time since trial initial diagnosis (TSTIDIA).

Component	Summary
	Kaplan-Meier overall survival data and acute ILD exacerbations data were used up to 17.2 months, which was then extrapolated. The submission fitted parametric functions to the following parameters: -Acute exacerbations: Exponential -OS: Independent Weibull -Time to treatment discontinuation: Exponential The choice of extrapolation functions was reasonable. The ICER was not sensitive to the choice of extrapolation function for acute exacerbations or time to treatment discontinuation, but was sensitive to the choice of extrapolation function for OS. Discontinuation rates in the INBUILD trial, especially in the nintedanib treatment arm, were substantial. The long-term benefit in terms of OS and acute exacerbations from nintedanib and placebo + BSC may converge in the long run given high discontinuation rates. The ICER was sensitive to OS curves converging. AEs (diarrhoea, nausea and vomiting) were based on the proportions observed over 52 weeks in the INBUILD trial. The PBAC previously noted these AEs were associated with nintedanib treatment in its previous consideration of nintedanib for IPF. Nintedanib treatment was associated with a greater risk of acute respiratory failure SAE (3.0% versus 0.6%, RR = 4.98, 95% CI 1.10, 22.58) and drug-induced liver injury SAE (1.8% versus 0%, RD=0.02, 95% CI 0.00, 0.03) in the INBUILD trial, when compared to placebo + BSC. The submission did not consider these SAEs in the economic model. The impact of these omissions is not clear. Background mortality was not considered. *This is not appropriate*.
Utilities	Utilities associated health state and acute exacerbation event (dis)utilities: Post-hoc regression analysis of the individual EQ-5D (converted to EQ-5D-3L) data from the INBUILD trial. Parameters were selected adopting backwards stepwise regression with a p-value cut-off of 0.05. Parameters included FVC%Pred and acute ILD exacerbation. The use of trial-based (dis)utilities is appropriate. However, the methodology adopted to select the covariates for the regression analysis was not reasonable. For example, the diarrhoeal status could have been retained in the final regression model even though p-value exceeded 0.05, given its high prevalence for a more extended period and its likely negative impact on utilities. Disutilities associated with AEs: Disutilities associated with gastrointestinal AEs from nintedanib for the treatment of IPF were used as a proxy for that experienced by nintedanib treated patients with PF-ILD. This is reasonable, given the similar mechanism for IPF and PF-ILD. Sensitivity analysis conducted during the evaluation found that the ICER was not sensitive to the disutility value assumed in the model.

Source: Table 3.1, p140 of the submission and Table 3.1 of the commentary
AE= Adverse Event, FVC= Forced Vital Capacity, FVC%Pred= Forced Vital Capacity % Predicted, IPF= Idiopathic Pulmonary Fibrosis, LYG= Life years gained, OS= Overall Survival, PFS= Progression-free Survival, PF-ILD= Progressive Fibrosing Interstitial Lung Disease, QALY= Quality Adjusted Life Year, SAE: Serious Adverse Event

6.32 Table 10 presents the key drivers of the economic model.

Table 10: Key drivers of the model

Description	***Method/Value***	***Impact***
Time horizon	15 years in the base case. The ICER was sensitive to time horizons less than 10 years.	High
Extrapolation of non-significant OS	There was no statistically significant difference in overall survival (OS) (p=0.8544) between nintedanib and placebo + BSC over 52 weeks in the INBUILD trial.	High
Extrapolation	OS was extrapolated using a Weibull function in the base case. The ICER was sensitive to the choice of extrapolation functions.	High
Regression function used to model FVC%Pred	A separate (independent) linear mixed effects regression model in the base case. Using a single (dependent) regression model for both nintedanib and placebo + BSC reduced the ICER. The base case used an independent linear mixed effects model as the assumption of a constant relative benefit versus placebo + BSC may not be reasonable.	Low
OS hazard convergence	No convergence of OS benefit in the base case. Assumed convergence to start at 25 months with full convergence reached at 180 months increased the ICER.	High

Source: compiled during the evaluation
FVC= Forced Volume Capacity, ICER= Incremental cost-effectiveness ratio, OS= Overall survival, QALY= Quality-adjusted life year

6.33 Table 11 shows the results of the stepped analysis.

Table 11: Results of the stepped economic evaluation

Step and component	**Nintedanib**	**Placebo + BSC**	**Increment**
Step 1: trial-based costs and outcomes, time horizon = 25 months			
Costs	$[redacted]	$0	$[redacted]
LY	1.82	1.74	0.08
Incremental cost/extra LY gained (ICER)			$[redacted][1]
Step 2: parametric extrapolation from 17 months over lifetime horizon (15 years)			
Costs	$[redacted]	$0	$[redacted]
LY	3.74	2.63	1.11
Incremental cost/extra LY gained			$[redacted][2]
Step 3 (Step 2 + costs associated with acute exacerbations, disease monitoring and follow-up, management of treatment-related adverse and end of life use of health care resources)			
Costs	$[redacted]	$48,113	$[redacted]
LY	3.74	2.63	1.11
Incremental cost/extra LY gained			$[redacted][3]
Step 4 (LYs in Step 3 converted to QALYs)			
Costs	$[redacted]	$48,113	$[redacted]
QALY	2.41	1.64	0.77
Incremental cost/extra QALY gained (base case)			**$**[redacted][4]

Source: Based on Table 3.23, p209 of the submission
LY= Life Years, QALY= Quality-adjusted Life Year
The redacted values correspond to the following ranges:
[1] *$255,000 to < $355,000*
[2] *$35,000 to < $45,000*
[3] *$45,000 to < $55,000*
[4] *$55,000 to < $75,000*

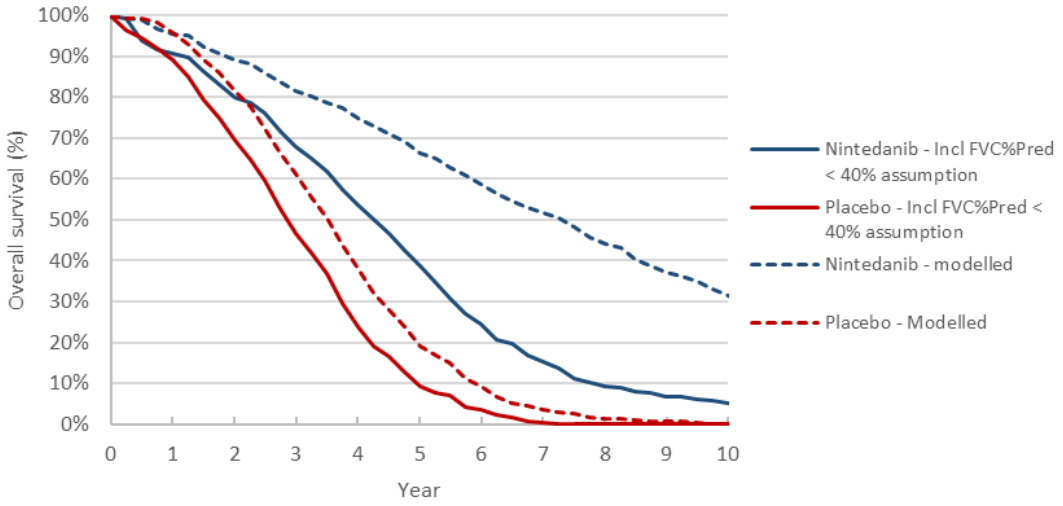
6.34 In Step 2-4, the model included the Kaplan-Meier data (up to 25 months), which were extrapolated to a lifetime time horizon (15 years). This significantly impacted the ICER as the extrapolation increased the incremental life years gained (LYG) from 0.08 to 1.11 years. The PSCR noted that the overall survival of patients treated with nintedanib and/or pirfenidone at 10 years is between 10% and 20% while the maximum observed survival is approximately 20 years (Guenther et al., 2018). On this basis, the PSCR considered that a time horizon of 15 years is reasonable. The ESC considered that the main issue around the time horizon was the extrapolation of a non-significant overall survival benefit over its duration, which adds substantial uncertainty to the model. The PBAC noted that the ICER was not sensitive to changes in the time horizon to between 10 and 20 years (see Table 12).

6.35 The submission claimed that the slope of the modelled survival curve is virtually identical to that observed in Jo et al. (2017), which supported the selection of the Weibull distribution to extrapolate OS. Jo et al. (2017) used the Australian IPF registry (AIPFR) data consisting of patients using anti-fibrotics (n = 146) and no anti-fibrotics (n= 501). The study included a median follow-up of two years (range 6 months to 4.5 years). At 4.5 years, the OS for no anti-fibrotics was nearly 45% in Jo et al (2017). The ESC noted that in contrast, the estimated OS for placebo + BSC in the submission was 10%. The ESC noted the AIC and BIC statistics between different parametric extrapolations were similar and considered that the most suitable extrapolation function for OS was not entirely clear. Overall, the ESC considered it was uncertain whether long term survival is accurately estimated by the economic model. The pre-PBAC Response argued that the modelled OS was comparable with the survival estimates for nintedanib and placebo in the published literature.

6.36 The submission performed scenario and univariate sensitivity analyses and the results are summarised in Table 12 and Figure 5. Overall, the ICER was most sensitive to the assumptions related to OS convergence, the choice of extrapolation function for OS, and the regression method used to model lung function decline (FVC%Pred).

6.37 The modelled OS estimates for both nintedanib and placebo + BSC included additional mortality resulting from the assumption of deaths occurring when a patient's FVC%Pred declined to 40% or less (Figure 4). This assumption lowered the survival of the modelled OS estimates. The submission claimed that incorporating the assumption into the model improved the external validity of the modelled OS estimates. As less than 10% of the nintedanib patients survive at 10 years, the assumption of OS convergence at 180 months (15 years) did not have a substantial impact on the ICER.

Figure 4: Overall survival modelled with and without FVC%Pred < 40% mortality.



Source: Figure 3.17, p205 of the submission
FVC%Pred= forced vital capacity % predicted

6.38 Sensitivity analyses conducted during the evaluation found that the ICER was sensitive to the choice of extrapolation functions, reflecting the short duration that overall survival Kaplan-Meir data was available for the trial. Applying exponential, Gompertz, log-logistic and lognormal independent functions for both nintedanib and placebo + BSC increased the ICER to $115,000 to < $135,000, $55,000 to < $75,000, $55,000 to < $75,000 and $75,000 to < $95,000 per QALY gained, respectively.

6.39 The ESC considered the base case ICER of $55,000 to < $75,000/QALY was uncertain and this uncertainty was largely driven by the uncertainty around the extrapolation of survival outlined above.

6.40 The PSCR provided a sensitivity analysis of the convergence of the acute exacerbations hazard which assumed convergence starts at 25 months and full convergence is reached at 180 months. The PSCR noted that when these changes are made to the economic model, the ICER increases marginally to $55,000 to < $75,000/QALY gained. The PBAC noted convergence of the OS curves over the same period increased the ICER to $55,000 to < $75,000/QALY gained.

6.41 The PBAC considered that convergence of the OS curves was appropriate given the high discontinuation rates among patients treated with nintedanib and given nintedanib does not stop disease progression.

6.42 Results of the scenario and sensitivity analyses are presented in Table 12.

Table 12: Results of scenario and univariate sensitivity analyses

	Incremental cost	Incremental QALY	ICER
Base case	**$** [redacted]	**0.77**	**$** [redacted][1]
Regression models			
Utilities: Fixed effect model	$ [redacted]	0.77	$ [redacted][1]
Progression (lung function decline): Dependent model	$ [redacted]	1.51	$ [redacted][2]
Parametric functions – Nintedanib			
OS: Convergence (25 - 180 months)	$ [redacted]	0.65	$ [redacted][1]
OS: Lognormal - full parametric	$ [redacted]	0.97	$ [redacted][1]
OS: Log-logistic - full parametric	$ [redacted]	0.84	$ [redacted][1]
Parametric functions – Placebo + BSC			
OS: Log-logistic - full parametric	$ [redacted]	0.63	$ [redacted][3]
OS: Gompertz - full parametric	$ [redacted]	1.05	$ [redacted][4]
Time horizon (years)			
10	$ [redacted]	0.74	$ [redacted][1]
20	$ [redacted]	0.77	$ [redacted][1]
Sensitivity analyses conducted during evaluation			
Extrapolation functions- OS (independent model)[a]			
Exponential (both nintedanib and placebo + BSC)			$ [redacted][5]
Gompertz (both nintedanib and placebo + BSC			$ [redacted][1]
Log-logistic (both nintedanib and placebo + BSC)			$ [redacted][1]
Lognormal (both nintedanib and placebo + BSC)			$ [redacted][3]
Weibull (base case) (both nintedanib and placebo + BSC)			$ [redacted][1]
Weibull_BSA (both nintedanib and placebo + BSC)			$ [redacted][1]
Time horizon (years)			
2			$ [redacted][6]
3			$ [redacted][5]
5			$ [redacted][3]

[a] The baseline ICER was based on assumption that FVC%Pred≤40% would lead to death.

BSA= Bayesian Survival Analysis, FVC%Pred= forced vital capacity % predicted; GI= Gastrointestinal, ICER= Incremental Cost-effectiveness Ratio, MBS= Medical Benefits Schedule, OS= Overall Survival, TTD: Time to Discontinuation, QALY= Quality-adjusted Life Year

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

[2] *$25,000 to < $35,000*

[3] *$75,000 to < $95,000*

[4] *$45,000 to < $55,000*

[5] *$115,000 to < $135,000*

[6] *$155,000 to < $255,000*

Drug cost/patient/year

6.43 The drug cost per patient per year is presented in Table 13. The proposed price for nintedanib is $[redacted] per day or $[redacted] per 30 days, resulting in a cost of $[redacted] per patient per year. The patients start treatment with 150 mg twice/day, but this may be reduced to 100 mg twice/day or interrupted temporarily to manage adverse events.

Table 13: Drug cost per patient for nintedanib

	Nintedanib Trial dose and duration	Nintedanib Model	Nintedanib Financial estimates
Mean dose	138.81 mg bid/day[a]	138.81 mg bd/day	138.81 mg bid/day
Mean duration	1 year	1 year	1 year
Cost/patient/month (cycle)	$[redacted][b]	$[redacted]	$[redacted]
Cost/patient/year	$[redacted][c]	$[redacted]	$[redacted]

Source: Table 3.14, p194 of the submission; p208 of the submission.
[a]150 mg x 77.62% + 100 mg x 22.38%; The proportions (77.62% and 22.38% for 150 mg and 100mg respectively) were estimated based on the INBUILD trial.
[b]$[redacted] x 77.62% + $[redacted] x 22.38%; where $[redacted] and $[redacted] were DPMQs (effective prices).
[c]22.38% x $[redacted] + 77.62% x $[redacted]; where $[redacted] = $[redacted] x [365.25/(60/2)] and $[redacted] = $[redacted] x [365.25/(60/2)]; Number of capsules =60.

Estimated PBS usage & financial implications

6.44 The submission was considered by DUSC.

6.45 The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the requested PBS listing of nintedanib for PF-ILD.

6.46 Table 14 outlines the sources of data used to calculate the financial impact as described in the submission.

Table 14: Key inputs for financial estimates

Data	Value	Comment
Prevalence of disease	9.08 per 100,000	A systematic review was performed in the submission. It yielded 23 articles. Six studies were used to estimate prevalence (Coultas et al. (1994), Duchemann et al. (2017), Karakatsani et al. (2009), Thomeer et al. (2001), Nasser et al. (2020) (unpublished), Gouder et al. (2012)). In addition, an unpublished systematic review was identified (Olson et al. 2018). Olson et al. (2018) provided estimates of PF-ILD from four studies (Coultas et al. (1994), Duchemann et al. (2017), Karakatsani et al. (2009), Thomeer et al. (2001)). Prevalence of PF-ILD was estimated multiplying the reported prevalence of ILD with fibrosing phenotype by the by the proportion of patients with progressive phenotype estimated through an expert survey. All studies in Olson et al. (2018) were identified in the submission's review. Estimates from Olson et al. (2018) and the highest estimate from Nasser et al. (2020) (unpublished) were combined using a simple mean for the base case prevalence.
Uptake rate	Yr 1: 48.0% Yr 2: 65.0% Yr 3: 75.0% Yr 4: 83.0% Yr 5: 90.0% Yr 6: 95.0%	Uptake rates were based on assumption.
Proportion of patients on each dose	150mg: 77.62% 100mg: 22.38%	This proportion may overestimate the financial impact as poorer compliance in clinical practice due to gastrointestinal adverse events might increase the use of the 100 mg dose.
Adverse events	Affected patients over a year: Diarrhoea: 41.2% Nausea: 18.1% Vomiting: 10.2%	
Adverse events duration	Diarrhoea: 136 days Nausea: 7 days Vomiting: 7 days	This is likely to be underestimated. The submission assumed seven days duration for nausea and vomiting with no rationale given. This duration is unlikely, as diarrhoea, which was directly measured, lasted on average 136 days in the INBUILD trial.
Liver function tests	Frequency: 1 every 4 months	

Source: Table 4.1, p217, 218; Table 4.4, p228; Table 4.5, p229; Table 4.6, p230; Table 4.8, p231; Table 4.9, p231; Table 4.10, p232 of the submission.

COVID-19 = coronavirus disease, DUSC = drug utilisation sub committee, IPF = idiopathic progressive fibrosing interstitial lung disease, mg = milligram, PF-ILD = progressive fibrosing interstitial lung disease, Yr = year.

6.47 The estimated extent of use and financial implications, as estimated in the submission are provided in Table 15 below.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]
Estimated financial implications of nintedanib						
Cost to PBS/RPBS	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]
Copayments	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Cost to PBS/RPBS less copayments	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]
Estimated financial implications for loperamide and metoclopramide						
Cost to PBS/RPBS less copayments	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]
Net cost to MBS	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Net cost to {PBS/RPBS/MBS/DHS}	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]

[a] Assuming 11.8 scripts per year as estimated by the submission.
Source: Table 4.9, Table 4.10, Table 4.15, Table 4.20, Table 4.21, Table 4.27 of the submission.
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] 10,000 to < 20,000
[3] 20,000 to < 30,000
[4] $10 million to < $20 million
[5] $20 million to < $30 million
[6] $30 million to < $40 million
[7] $0 to < $10 million

6.48 The total cost to the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS) of listing nintedanib was estimated to be $30 million to < $40 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing.

6.49 DUSC considered the estimates presented in the submission to be overestimated. The main issues identified were:

- The financial estimates are most sensitive to the prevalence assumptions. There is a lack of epidemiological data to estimate the prevalence of PF-ILD in the Australian population. The prevalence figure used in the base case (9.08 per 100,000) of the submission is uncertain as it was calculated instead of being measured directly. In the absence of more reliable data on the true prevalence of PF-ILD, the ESC considered that a prevalence estimate derived from the five studies used for the submission's base case using an inverse weighted variance method may be more appropriate.
- The submission assumed an uptake rate of 48% in Year 1, increasing to 95% in Year 6. The uptake of nintedanib is uncertain. The treatment uptake may be underestimated during the early years of listing as it would be the first PBS-listed treatment for PF-ILD and overestimated over time due to the cumulative experience

of gastrointestinal adverse effects associated with treatment, such as diarrhoea; greater utility of other pharmacological treatments; and clinicians becoming familiar with the limitations of therapy.

- No discontinuation criteria or risk sharing arrangement was proposed in the submission, in contrast to the IPF submission.

6.50 The submission conducted a systematic literature review to identify studies that estimated the prevalence of PF-ILD. Among them, five relevant published studies were found plus the unpublished study of Nasser et al. (2020a) based on French national data which the submission claimed was relevant because it was the only one that directly estimated the prevalence of PF-ILD. Minimal data from this study was available, as only the abstract could be obtained. The prevalence estimates varied from 6.6 to 19.4, with 46% of those with fibrosing interstitial lung disease having PF-ILD. These estimates were based on three successive steps based on clinical ICD-10 coding, which DUSC commented were unlikely to match the rigor of the INBUILD trial criteria. DUSC commented the estimates from the Nasser study (2020a) considered by the submission may be overestimated, or it could be due to the increased recognition of the PF-ILD and the introduction of anti-fibrotics.

6.51 Prevalence of PF-ILD was estimated from multiplying the reported prevalence of ILD with fibrosing phenotype by the proportion of patients with progressive phenotype estimated through an expert survey. DUSC considered the prevalence should have been measured directly instead of being calculated. DUSC noted the demographic differences of the studies and questioned their applicability to the Australian population. DUSC noted there may be a higher prevalence in the United States as sarcoidosis is more common in African Americans. Further, smoking is more prevalent in France compared to Australia, which may further influence estimates of fibrosing interstitial lung disease. Estimates from Olson et al. (2018) and the highest estimate from Nasser et al. (2020) were combined using a simple mean for the base case prevalence. The PSCR stated, "plotting the prevalence rates against the time at which the study was conducted shows a clear and increasing trend which broadly coincides with the start of the clinical development program… the initiation of clinical development programs resulted in increased awareness of the disease, increased accuracy and hence the number of diagnoses… resulting in further increases in the number of patients diagnosed with ILD." DUSC considered that an inverse weighted variance would be more appropriate instead of using a simple mean and sensitivity analyses should have been conducted. DUSC commented the base case estimates excluded the Nasser 2010 study. The current prevalence may be underestimated due to the increase observed in studies over time. Overall, DUSC considered that there was a lack of epidemiological data to address the uncertainty of prevalence estimates.

6.52 The submission estimated the proportion of scripts for the 150 mg and 100 mg dose, using the average dose of nintedanib sourced from the INBUILD trial. Using the average dose, it was assumed that 77.62% and 22.38% of patients were treated with 150 mg bid and 100 mg bid, respectively. DUSC considered that the estimated proportion of patients treated with the 150 mg dose is likely overestimated. There is a decreasing proportion of patients treated with 150 mg for IPF (2018: 73.1%, 2019: 70.5%, 2020: 67%). This may be due to patients being unable to tolerate the gastrointestinal adverse events, patients only initiating on the 100 mg dose and not escalating to 150 mg and practice change.

Quality Use of Medicines

6.53 DUSC considered that a consumer education program and a health professional education program would be appropriate for nintedanib listing. Patients' compliance is expected to be lower in a real-life context given the high gastrointestinal adverse effect rates. In addition, training health professionals to diagnose PF-ILD and consequently to assess nintedanib eligibility would be useful as this is a disease that does not have current treatment. The PSCR confirmed that a similar quality use of medicines program to IPF is being planned for the potential PBS listing for PF-ILD, for both prescribers and patients. The PSCR stated that for prescribers, a series of educational activities including webinars, congresses and forums will be implemented to provide training on the diagnosis and management of PF-ILD. The PSCR stated that the sponsor will engage with patient organisations to promote disease awareness as well as provide extensive patient information and educational resources to assist with patient compliance and management of known adverse events such as diarrhoea.

Financial Management – Risk Sharing Arrangements

6.54 No RSA was proposed by the submission. The ESC considered there was a potential for nintedanib to be used outside the requested and existing restriction in other types of ILD which also have limited treatment options. The ESC noted that the financial caps for the existing IPF RSA which includes both nintedanib and pirfenidone have been exceeded in Years 2 and 3 of the Deed. The ESC considered that an RSA with caps based on estimates of treated patients with [redacted]% rebate for any expenditure beyond the caps may be required to manage the risk of use outside the requested restriction. The ESC considered it may be appropriate to take into account any overlap between the IPF and PF-ILD populations in determining the expenditure caps for PF-ILD. The pre-PBAC Response argued that an RSA for the use of nintedanib in PF-ILD was not required as there is minimal risk of use outside the restriction given prescribers are required to obtain written authority approval. The pre-PBAC Response also considered the use above the caps of the existing IPF RSA are within the IPF population given the written Authority Required listing and specific clinical criteria around diagnosis of IPF within the listing.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of nintedanib for the treatment of patients with progressive fibrosing interstitial lung disease (PF-ILD). The PBAC considered that the available data indicated a benefit in terms of slowing decline in lung function compared with best supportive care (BSC), however, the PBAC considered that although an overall survival benefit was plausible, the magnitude of any such benefit was uncertain. The PBAC considered the incremental cost-effectiveness ratio (ICER) was uncertain and likely underestimated, primarily due to the uncertainty around the modelled overall survival benefit. The PBAC advised that a price reduction would be required to address this uncertainty and to achieve an acceptable ICER. The PBAC considered the financial impact was overestimated in the submission due to the prevalence of PF-ILD used, the assumed uptake rates and underestimating the extent of dose reductions.

7.2 The PBAC acknowledged the high clinical need for an effective treatment for PF-ILD, noting the disease has debilitating effects on quality of life and a progressive course similar to IPF.

7.3 The PBAC considered that best supportive care (BSC) with placebo was the appropriate main comparator. The PBAC noted that patients with PF-ILD were currently managed with off-label use of corticosteroids, immunosuppressants and immunomodulators.

7.4 The PBAC noted the submission was based on the INBUILD trial, a head-to-head randomised controlled trial comparing nintedanib + BSC to placebo + BSC. The PBAC noted that treatment with nintedanib was associated with a 3.24% (95% CI: 2.09%, 4.40%) mean difference in absolute decline in forced vital capacity percent predicted (FVC%Pred) from baseline to 52 weeks, compared to placebo + BSC. The PBAC considered that the observed 3.24% difference was likely to have clinical relevance, as it exceeded the MCID reported in Patel 2013 and MCID values calculated using the anchor and distribution based methods (see paragraph 6.13).

7.5 The PBAC noted the trial was not powered to detect a statistically significant reduction in mortality and the 25-month duration of follow-up in the trial was likely not sufficient to detect any overall survival benefit in PF-ILD. While the PBAC considered there was a biologically plausible link between a lower FVC and a higher risk of mortality, in the absence of longer-term survival data, the PBAC considered that the magnitude of any survival benefit was uncertain.

7.6 The PBAC considered that the lack of a statistically significant difference in quality of life between nintedanib and placebo + BSC arms may have been because nintedanib slows the rate of FVC decline but does not stop or reverse disease progression.

7.7 The PBAC noted that nintedanib was associated with a greater risk of adverse events and a higher proportion of adverse events leading to premature treatment discontinuation compared to placebo + BSC. The PBAC considered that the substantial rate of treatment discontinuation in the nintedanib arm of the trial was likely due to the high rates of gastrointestinal disorders including diarrhoea, nausea and abdominal pain outweighing the perceived benefit for many patients.

7.8 The PBAC considered that the base case ICER of $55,000 to < $75,000 per QALY gained was uncertain and likely underestimated, primarily due to the uncertainty around the overall survival benefit. The PBAC noted that the majority of life years and QALYs gained were due to the extrapolation of overall survival and that the ICER was sensitive to the choice of the extrapolation function for overall survival and the convergence of the overall survival curves. The PBAC recalled that the submission for IPF applied a time horizon of 10 years. While the PBAC considered that a 10 year time horizon may have been more appropriate, it noted that changing the time horizon from 15 to 10 years did not have a material impact on the ICER.

7.9 The PBAC noted the model scenario in which the overall survival curves were converged over the period 25 to 180 months resulted in an ICER of $55,000 to < $75,000 per QALY gained. The PBAC considered nintedanib would be cost-effective if the price was reduced such that the ICER for this scenario decreased to less than $45,000 to < $55,000 per QALY gained.

7.10 The PBAC noted that DUSC considered the financial estimates to be overestimated due to assumptions around the prevalence of PF-ILD, uptake of nintedanib and relatively high use of the 150 mg strength (see paragraphs 6.49 and 6.52).

7.11 The PBAC noted that the prevalence estimate (9.08 per 100,000) was based on the mean of estimates from five studies. The PBAC noted there was a paucity of data on the prevalence of PF-ILD in Australia and agreed with DUSC that in the absence of more reliable data, a prevalence estimate derived from the five studies used for the submission's base case using an inverse weighted variance method may be more appropriate.

7.12 The PBAC agreed with DUSC that the uptake of nintedanib would likely be higher than estimated in the submission in the initial years of PBS-listing given there are no other available treatments for PF-ILD, however would likely be lower than estimated in the later years due to lower persistence because of the gastrointestinal intestinal adverse events associated with treatment. The PBAC considered an uptake rate of 60% to be

reasonable for year 1 of listing, and that the uptake should be no more than a maximum of 80% in year 6.

7.13 The PBAC noted the financial estimates assumed that 77.62% and 22.38% of patients were treated with 150 mg bid and 100 mg bid, respectively, and agreed with DUSC that the estimated proportion of patients treated with the 150 mg dose is likely overestimated. The PBAC considered, consistent with use in IPF, that it would be reasonable to assume 67% and 33% of patients are treated with 150 mg bid and 100 mg bid, respectively.

7.14 The PBAC agreed with ESC that there was a potential for nintedanib to be used outside the requested and existing restrictions in other types of ILD which also have limited treatment options and considered that an RSA with expenditure caps would be required to manage this risk. The PBAC considered that if nintedanib was listed for PF-ILD, there may be a proportion of patients with clinical characteristics of both IPF and PF-ILD who may be eligible to receive treatment under either listing, and that this should be appropriately accounted for in the expenditure caps for PF-ILD.

7.15 The PBAC considered the outstanding issues may be addressed in a simple resubmission for nintedanib if the following changes were made, without any additional amendments to the economic evaluation or financial implications:

- A price reduction which results in an ICER of less than $45,000 to < $55,000 per QALY for the model scenario in which the overall survival curves are converged as detailed in paragraph 7.9.
- Revised financial estimates which account for a reduced nintedanib price, a revised prevalence estimate for PF-ILD (paragraph 7.11), revised uptake rates (paragraph 7.12) and revised use of the 150 mg versus 100 mg dose (paragraph 7.13).
- An appropriate risk sharing arrangement to address the uncertainties around utilisation as outlined in paragraph 7.14.

7.16 The PBAC also considered nintedanib addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy/reduction of toxicity, over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable if the resubmission addressed each of the points in the above paragraph with no further adjustment. The resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If any of these terms are not acceptable to the sponsor, a standard re-entry pathway is available.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

Addendum to the March 2021 PBAC Minutes:

7.01 NINTEDANIB, Capsule 100 mg, Capsule 150 mg, Ofev®, Boehringer Ingelheim Pty Ltd

8 Background

8.1 An early resolution resubmission was provided, which sought to address the PBAC's concerns from its March 2021 meeting, at which the Committee did not recommend nintedanib for the treatment of patients with progressive fibrosing interstitial lung disease (PF-ILD).

9 Consideration of the evidence

9.1 At its March 2021 meeting the PBAC considered the outstanding issues may be addressed in a simple resubmission for nintedanib if the following changes were made, without any additional amendments to the economic evaluation or financial implications:

- A price reduction which results in an ICER of less than $45,000 to < $55,000 per QALY for the model scenario in which the overall survival curves are converged as detailed in paragraph 7.9.
- Revised financial estimates which account for a reduced nintedanib price, a revised prevalence estimate for PF-ILD (paragraph 7.11), revised uptake rates (paragraph 7.12) and revised use of the 150 mg versus 100 mg dose (paragraph 7.13).
- An appropriate risk sharing arrangement to address the uncertainties around utilisation as outlined in paragraph 7.14 (paragraph 7.15, nintedanib Public Summary Document (PSD), March 2021 PBAC meeting).

9.2 The table below summarises how each of these issues were addressed in the resubmission.

Table 16: Summary of key matters and how they were addressed in the current resubmission

Outstanding issue (paragraph 7.15)	How the resubmission addressed this
A price reduction which results in an ICER of less than $[redacted][1] per QALY for the model scenario in which the overall survival curves are converged.	The AEMPs were reduced by [redacted]%: • $[redacted] to $[redacted] (100 mg) • $[redacted] to $[redacted] (150 mg) The overall survival curves in the model were converged over the period 25 to 180 months as requested. The reduced AEMPs and model changes result in an ICER of $[redacted][2] per QALY.
Revised financial estimates which account for a reduced nintedanib price, a revised prevalence estimate for PF-ILD, revised uptake rates and revised use of the 150 mg versus 100 mg dose.	The following are incorporated into the revised financial estimates: • Lower cost of nintedanib. • Revised prevalence estimate of 9.276 per 100,000 calculated from the five studies used in the previous submission's base case using an inverse weighted variance method, as requested. Previous prevalence estimate was 9.08 per 100,000. • Previous uptake of [redacted]% in year 1 increasing to [redacted]% in year 6 revised to [redacted]% in year 1 increasing to [redacted]% in year 6 of listing, as requested. • Proportion of patients on the 150 mg and 100 mg doses revised from [redacted]% and [redacted]% respectively, to [redacted]% and [redacted]% respectively, as requested. The total cost to the PBS/RPBS was estimated to be $[redacted][3] over 6 years, compared with $[redacted][3] over 6 years in the previous submission.
An appropriate risk sharing arrangement to address the uncertainties around utilisation.	Proposed an RSA with caps based on estimated financial implications and a rebate of [redacted]% for use above these caps.

Source: Compiled during preparation of the Minutes
The redacted values correspond to the following ranges
[1]*$45,000 to < $55,000*
[2]*$55,000 to < $75,000*
[3]*$100 million to < $200 million*

9.3 The two key differences between the PBAC's requested changes for an early resolution pathway versus the approach taken in the resubmission, are the following:

- The resubmission's proposed price reduction and changes to the economic model resulted in an ICER of $55,000 to < $75,000 per QALY, which is higher than the ICER specified by the PBAC of less than $45,000 to < $55,000 per QALY.
- The revised financial estimates and consequently, the RSA do not account for overlap between IPF and PF-ILD. The PBAC considered that if nintedanib was listed for PF-ILD, there may be a proportion of patients with clinical

characteristics of both IPF and PF-ILD who may be eligible to receive treatment under either listing, and that this should be appropriately accounted for in the expenditure caps for PF-ILD (paragraph 7.14, nintedanib PSD, March 2021 PBAC meeting).

9.4 Though not requested in paragraph 7.15 of the previous PSD, the resubmission's revised economic model incorporates the revised dose weightings of [redacted]% for the 150 mg twice daily dose and [redacted]% for the 100 mg twice daily dose, which was only requested for the financial estimates. However, the impact of this additional change on the ICER was minor.

9.5 The average prevalence of PF-ILD in the previous submission included the prevalence rate reported in Nasser et al., 2020 (i.e., 19.4 per 100,000), which was at the time unpublished. As the full text publication (Nasser et al., 2021), which reports prevalence rates for each year from 2010 to 2016, had become available, the resubmission's revised prevalence rate (9.276 per 100,00) was estimated using all prevalence rates for years 2010 to 2016 reported in Nasser et al., 2021 along with those from the other studies used to calculate the previous submission's base case prevalence rate (Coultas et al., 1994, Thomeer et al., 2001, Karakatsani et al., 2009 and Ducheman et al., 2017).

10 PBAC Outcome

10.1 The PBAC recommended the listing of nintedanib for the treatment of patients with progressive fibrosing interstitial lung disease (PF-ILD). The PBAC was satisfied that nintedanib provides, for some patients, a significant improvement in effectiveness compared with best supportive care (BSC). The PBAC noted that at the updated proposed price, the revised economic model resulted in an incremental cost effectiveness ratio (ICER) higher than the Committee's previously specified threshold of $45,000 to < $55,000 per QALY. The PBAC considered that the remaining uncertainty around the cost-effectiveness of nintedanib would be adequately managed by a price reduction to achieve an ICER within the range of $55,000 to < $75,000 per QALY to $55,000 to < $75,000 per QALY. The PBAC was satisfied that the proposed Risk Sharing Arrangement (RSA) would manage the financial risk of utilisation outside the eligible patient population. The PBAC also considered that the revised estimated utilisation and financial estimates were reasonable.

10.2 The PBAC noted the resubmission provided a price reduction resulting in an ICER of $55,000 to < $75,000 per QALY for the model scenario in which the overall survival curves are converged over the period 25 to 180 months. The PBAC recalled that in March 2021 it had advised that a resubmission should include a price reduction which results in an ICER of less than $45,000 to < $55,000 per QALY for the model scenario in which the overall survival curves are converged. The PBAC recalled it previously

considered the estimated ICER for nintedanib to be uncertain and likely underestimated, noting that the majority of life years and QALYs gained were due to the extrapolation of overall survival and that the ICER was sensitive to the choice of the extrapolation function for overall survival and the convergence of the overall survival curves. The PBAC considered there was remaining uncertainty around the cost-effectiveness of nintedanib at the resubmission's proposed price. However, the PBAC considered that in the context of the high unmet need for effective treatments for PF-ILD, the cost-effectiveness nintedanib would be acceptable with a further price reduction which achieves an ICER within the range of $55,000 to < $75,000 per QALY to $55,000 to < $75,000 per QALY, as the proposed RSA provided some certainty that expenditure would not exceed beyond that considered cost-effective.

10.3 The PBAC noted the resubmission provided financial estimates which included revised uptake rates, a revised prevalence rate for PF-ILD and amended dose weightings for the 150 mg versus 100 mg dose. The PBAC considered the revised financial estimates resulted in a more reasonable estimate of utilisation and largely addressed the concerns raised by the Committee in March 2021. The PBAC considered that while the revised financial estimates and RSA did not account for potential overlap between ILD and PF-ILD, the proposed RSA would be adequate to mitigate the risk of expenditure associated with use outside the eligible population. The PBAC advised that a rebate of at least [redacted]% above the RSA caps should apply. The PBAC considered that the requirement for diagnosis by a multidisciplinary team, and the clinical criterion specifying that the patient must not have ILD due to IPF within the restriction should reduce the risk of IPF patients accessing nintedanib through the listing for PF-ILD.

10.4 The PBAC noted that the previous submission indicated that some respiratory physicians intended to prescribe nintedanib for the treatment of PF-ILD post TGA approval through the private market. The PBAC considered a grandfather restriction was appropriate to allow patients being treated with non-PBS subsidised nintedanib to transition to PBS-subsidised treatment, but that such patients would be required to essentially meet the same PBS eligibility criteria as a nintedanib-naïve patient. The PBAC recommended that the grandfathering listing could be removed after 12 months.

10.5 The PBAC noted that the previous submission requested an Authority Required (in writing only) restriction type for all treatment phases. The PBAC considered that an Authority Required (in writing only) listing for initial treatment and an Authority Required (telephone/online) listing for continuing treatment would be appropriate, noting this was consistent with the current listing for IPF. The PBAC recalled that at its July 2021 meeting, it did not recommend an amendment to the authority requirements for nintedanib or pirfenidone, given the immaturity of the IPF market, the risk of leakage, the high cost of these medicines and the financial implications to the government (PBAC Meeting Outcomes July 2021 PBAC meeting).

10.6 The PBAC considered it was appropriate to include criteria in the restriction to specify that PBS subsidy must not occur simultaneously, and, sequentially, under the existing and the new listing. The PBAC advised that these criteria should be flowed on to the current nintedanib listing.

10.7 The PBAC noted that principles of digitalisation would be applied to the initial authority required application process, whereby data capture by Services Australia would be limited to responses, expressed in either figures (numerals) or words, but not images (e.g. signatures), written phrases, or copies of diagnostic results.

10.8 The PBAC noted the current nintedanib and pirfenidone listings contain a requirement for 'a signed patient acknowledgement' that the prescriber has explained to the patient/guardian the circumstances governing PBS access and that the patient/guardian has understood the explanation. The PBAC noted this requirement could be alternatively be expressed as a restriction criterion eliciting a 'yes/no' response from the prescriber to make the overall authority application more amenable to electronic processing.

10.9 The PBAC noted that although the current nintedanib and pirfenidone listings do not specify which clinical values should be captured in the initial authority application form, the initial authority application form is currently capturing exact figures for: (i) FVC, (ii) FEV_1/FVC ratio and (iii) diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin. The PBAC noted that the Continuing treatment restrictions for these listings do not require any improvements on these measurements to be captured. The PBAC considered that any revision to the existing PBS authority application form could omit such data capture, and that a new form for this new indication could be made consistent with such requirements.

10.10 The PBAC considered that the listing should be silent on age restriction, consistent with the current listing.

10.11 The PBAC considered it would be appropriate to include a list of common ILDs in the restriction however, it considered providing a complete, exhaustive list of all possible ILDs was impractical in the listing as there are several pulmonary conditions which result in PF-ILD.

10.12 PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for nintedanib:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over standard of care;
b) The treatment is expected to address a high and urgent unmet clinical need as there are currently no medicines for this patient population; and

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

10.13 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:
Recommended

11 Recommended listing

11.1 Add new listing (Progressive fibrosing interstitial lung disease) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
NINTEDANIB					
nintedanib 100 mg capsule, 60	NEW	1	60	5	Ofev
nintedanib 150 mg capsule, 60	NEW	1	60	5	Ofev
Restriction Summary / Treatment of Concept: [new 1]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (in-writing only via post/HPOS upload)				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Episodicity: [blank]				
	Severity: [blank]				
	Condition: Progressive fibrosing interstitial lung disease				
	Indication: Progressive fibrosing interstitial lung disease				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	The condition must be diagnosed through a multidisciplinary team				
	AND				
	Clinical criteria:				
	The condition must have chest imaging through high resolution computed tomography (HRCT) that is no older than 52 weeks, to support the diagnosis of the PBS-indication – retain the imaging on the patient's medical records only				
	AND				
	Clinical criteria:				
	The condition must display, through HRCT, an affected area of no less than 10% (after rounding to the nearest multiple of 5)				

	AND
	Clinical criteria:
	Patient must have a current (no older than 2 years) forced vital capacity (FVC) measurement of no less than 45% predicted, adjusted for each of: (i) age, (ii) gender, (iii) height; document these measurements in the patient's medical records only
	AND
	Clinical criteria:
	The condition must be of a progressive nature, observed by, in the 24 months leading up to this authority application, any of: (i) a worsening in relative FVC% predicted measurement of no less than 10%, (ii) a worsening in relative FVC% predicted measurement in the range 5 – 10%, combined with worsening of respiratory symptoms, (iii) a worsening in relative FVC% predicted measurement in the range 5 – 10%, combined with increases in fibrosis observed on high resolution computed tomography; document the at least of one of (i) to (iii) in the patient's medical records only
	AND
	Clinical criteria:
	Patient must have a forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) greater than 0.7
	AND
	Clinical criteria:
	Patient must have diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin that is both: (i) at least 30% predicted, (ii) less than 80% predicted; document the % value in the patient's medical records only
	AND
	Clinical criteria:
	The condition must not be interstitial lung disease due to idiopathic pulmonary fibrosis (apply under the correct PBS listing if it is)
	AND
	Clinical criteria:
	The condition must not be due to reversible causes (e.g. drug toxicity)
	Treatment criteria:
	Must be treated by a respiratory physician or specialist physician, or in consultation with a respiratory physician or specialist physician
	AND
	Treatment criteria:
	Patient must not be undergoing treatment with this drug simultaneously through the following PBS-indications: (i) progressive fibrosing interstitial disease, (ii) idiopathic pulmonary fibrosis
	AND
	Treatment criteria:
	Patient must not be undergoing treatment with this drug sequentially through the following PBS-indications: (i) progressive fibrosing interstitial disease, (ii) idiopathic pulmonary fibrosis
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this pharmaceutical benefit only where the prescriber has explained to the patient/patient's guardian the following: (i) that certain diagnostic criteria must be met to be eligible to initiate treatment, (ii) continuing treatment is not based on quantified improvements in diagnostic measurements, but will be determined by clinician judgement
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and

	(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: A multidisciplinary team is defined as comprising of at least a specialist respiratory physician, a radiologist and where histological material is considered, a pathologist. If attendance is not possible because of geographical isolation, consultation with a multidisciplinary team is required for diagnosis.
	Prescribing Instructions: Patient must not have an acute respiratory infection at the time of FVC testing.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	Administrative advice: Interstitial lung disease includes, but is not limited to: (i) connective tissue associated interstitial lung disease; (ii) chronic fibrosing hypersensitivity pneumonitis; (iii) idiopathic non-specific interstitial pneumonia; (iv) pulmonary sarcoidosis
Restriction Summary / Treatment of Concept: [new 2]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction Type : ☒Authority Required (telephone/online PBS authorities system)
	Indication: Progressive fibrosing interstitial lung disease
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	Treatment criteria:
	Must be treated by a respiratory physician or specialist physician, or in consultation with a respiratory physician or specialist physician
	AND
	Treatment criteria:
	Patient must not be undergoing treatment with this drug simultaneously through the following PBS-indications: (i) mild to moderate progressive fibrosing interstitial disease, (ii) idiopathic pulmonary fibrosis
	AND
	Treatment criteria:
	Patient must not be undergoing treatment with this drug sequentially through the following PBS-indications: (i) mild to moderate progressive fibrosing interstitial disease, (ii) idiopathic pulmonary fibrosis

	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Restriction Summary / Treatment of Concept: [new 3]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☐ ☒Medical Practitioners
	Restriction Type: ☒Authority Required (in-writing only via post/ HPOS upload)
	Indication: Progressive fibrosing interstitial lung disease
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'Grandfather' arrangements
	Clinical criteria:
	Patient must have received non-PBS subsidised treatment with this drug for this indication of 'progressive fibrosing interstitial lung disease' (not 'idiopathic pulmonary fibrosis') prior to [insert listing date]
	AND
	Clinical criteria:
	The condition must be diagnosed through a multidisciplinary team
	AND
	Clinical criteria:
	The condition must have chest imaging through high resolution computed tomography (HRCT) that was no older than 52 weeks at the time non-PBS supply was initiated, to support the diagnosis of the PBS-indication – retain the imaging on the patient's medical records only
	AND
	Clinical criteria:
	The condition must have displayed, through HRCT, an affected area of no less than 10% (after rounding to the nearest multiple of 5) at the time non-PBS supply was initiated
	AND
	Clinical criteria:
	Patient must have had a forced vital capacity (FVC) measurement no less than 45% predicted, prior to initiating non-PBS supply treatment with this drug for this indication, that was no older than 2 years at the time of non-PBS subsidised treatment initiation, in addition to being adjusted for each of: (i) age, (ii) gender, (iii) height
	AND
	Clinical criteria:
	The condition must have been of a progressive nature prior to initiating non-PBS subsidised treatment, observed by, in any time period leading up to the initiation of non-PBS subsidised supply, any of: (i) a worsening in relative FVC% predicted measurement of no less than 10%, (ii) a worsening in relative FVC% predicted measurement in the range 5 – 10%, combined with worsening of respiratory symptoms, (iii) a worsening in relative FVC% predicted measurement in the range 5 – 10%, combined with increases in fibrosis observed on high-resolution computed tomography
	AND
	Clinical criteria:
	Patient must have had a forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) of at least 0.7 at the time of initiating non-PBS subsidised supply
	AND
	Clinical criteria:
	Patient must have had, prior to initiating non-PBS subsidised supply, a diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin that was both: (i) greater than at least 30% predicted, (ii) less than 80% predicted

	AND
	Clinical criteria:
	The condition must not be interstitial lung disease due to idiopathic pulmonary fibrosis (apply under the correct PBS listing if it is)
	AND
	Clinical criteria:
	The condition must not be due to reversible causes (e.g. drug toxicity)
	Treatment criteria:
	Patient must not be undergoing treatment with this drug simultaneously through the following PBS-indications: (i) progressive fibrosing interstitial disease, (ii) idiopathic pulmonary fibrosis
	AND
	Treatment criteria:
	Patient must not be undergoing treatment with this drug sequentially through the following PBS-indications: (i) progressive fibrosing interstitial disease, (ii) idiopathic pulmonary fibrosis
	AND
	Treatment criteria:
	Must be treated by a respiratory physician or specialist physician, or in consultation with a respiratory physician or specialist physician
	AND
	Treatment criteria:
	Patient must be undergoing treatment with this pharmaceutical benefit only where the prescriber has explained to the patient/patient's guardian the following: (i) that certain diagnostic criteria must be met to be eligible to initiate treatment, (ii) continuing treatment is not based on quantified improvements in diagnostic measurements, but will be determined by clinician judgement
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: A multidisciplinary team is defined as comprising of at least a specialist respiratory physician, a radiologist and where histological material is considered, a pathologist. If attendance is not possible because of geographical isolation, consultation with a multidisciplinary team is required for diagnosis.
	Prescribing Instructions: Patient must not have had an acute respiratory infection at the time of FVC testing.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs

	Reply Paid 9826 HOBART TAS 7001
	Administrative advice: Interstitial lung disease includes, but is not limited to: (i) connective tissue associated interstitial lung disease; (ii) chronic fibrosing hypersensitivity pneumonitis; (iii) idiopathic non-specific interstitial pneumonia; (iv) pulmonary sarcoidosis

Flow-on changes:

11.2 Add New TC1 and New TC2 to nintedanib listing for IPF.

11.3 Remove the existing requirement for 'a signed patient acknowledgement' in current nintedanib and pirfenidone listings for IPF. Insert New TC3 as a substitute.

11.4 Services Australia to revise current PBS Authority Application form (PB208) to also remove specific data capture of exact values for: (i) FVC, (ii) FEV1/FVC ratio and (iii) diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin.

These restrictions may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

12 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

13 Sponsor's Comment

The sponsor had no comment.