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Nintedanib (other chronic progressive fibrosing interstitial lung diseases) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nintedanib (andere chronische progredient fibrosierende interstitielle Lungenerkrankungen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 November 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Table of contents

List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
A-IQOLS	Asthma Impact on Quality of Life Scale
ATAQ-IPF	A Tool to Assess Quality of Life in IPF
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
DL_{CO}	Diffusing Capacity of the Lung for Carbon Monoxide
EMA	European Medicines Agency
EQ-5D	European Quality of Life Questionnaire
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HRCT	high-resolution computed tomography
IPF	idiopathic pulmonary fibrosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
K-BILD	King's Brief Interstitial Lung Disease Questionnaire
L-PF	Living with Pulmonary Fibrosis
PF-ILD	progressive fibrosing interstitial lung diseases
PF-IQOLS	Pulmonary Fibrosis Impact on Quality of Life Scale
PRO	patient-reported outcome
PT	Preferred Term
QOLS	Quality of Life Scale
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
STE	surrogate threshold effect
UIP	usual interstitial pneumonia
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nintedanib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 12 August 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of nintedanib in comparison with best supportive care (BSC) as appropriate comparator therapy (ACT) in patients with other chronic progressive fibrosing interstitial lung disease (other chronic PF-ILD).

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of nintedanib

Therapeutic indication	**ACT[a]**
Adults with other chronic progressive fibrosing interstitial lung diseases (PF-ILD)[b]	BSC[c, d]

a. Presentation of the ACT specified by the G-BA.
b. With regard to the patient population, the grouping of patients with PF-ILD of different diagnoses/aetiology as well as the underlying medical rationale of this grouping is to be justified, presented and discussed – as well as, if applicable, the transferability of the results to the patients of the target population covered by the therapeutic indication who are not included in the study population.
c. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.
d. Physical therapy (in accordance with the Remedies Directive) may also be indicated in the framework of BSC. The drugs azathioprine, MMF, N-acetylcysteine, rituximab, cyclophosphamide, ciclosporin and tacrolimus are not approved for the treatment of progressive interstitial lung disease. In principle, a lung transplant is a treatment option that can be considered for patients with progressive interstitial lung disease. However, this cannot be assumed to be a regular treatment option for patients according to the present therapeutic indication (e.g. due to comorbidities or limited availability of suitable donor organs).

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; MMF: mycophenolate mofetil; PF-ILD: progressive fibrosing interstitial lung disease

The company named BSC as ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

The study INBUILD was used to assess the added benefit of nintedanib in comparison with BSC for the treatment of adults with PF-ILD.

Study design

The INBUILD study is a placebo-controlled, randomized parallel-group study on nintedanib. The study included patients with chronic PF-ILD, defined by features of diffuse fibrosing lung disease of > 10% extent on high-resolution computed tomography (HRCT). Patients had to show a deterioration in lung function and respiratory symptoms or a progression of fibrotic changes in the lungs using imaging procedures within 24 months before screening, despite patient-specific therapy.

A total of 663 patients were included and randomized in a 1:1 ratio to treatment with nintedanib (N = 332) or to the placebo group (N = 331). In the INBUILD study, treatment with nintedanib was in compliance with the approval. Patients in the comparator arm received placebo soft capsules of identical appearance at the same time points. In addition, individually indicated drugs could be used in both study arms at the discretion of the physician unless they were explicitly prohibited. The supportive therapies allowed in the INBUILD study were considered to be a sufficient implementation of the ACT BSC.

The primary outcome of the study was the annual rate of decline in forced vital capacity (FVC) (in mL/year) over 52 weeks. Patient-relevant secondary outcomes were overall survival, morbidity, and adverse events (AEs).

Dates of analysis

The primary analysis of the efficacy outcomes had been planned for the time point at which all patients had been treated for 52 weeks and was conducted for all patients based on the data between baseline and week 52. After reaching 52 weeks, patients remained in the study and continued their blinded treatment until the last randomized participant had completed the planned treatment period of 52 weeks. The company presented analyses on 52 weeks of treatment and on the entire study period in its dossier. For the present benefit assessment, the longer observation period is considered appropriate in this chronic disease. For this reason, the analyses at the end of the study were primarily used, taking into account the data from the total study duration. Patient-reported outcomes (PROs) were only recorded during the first 52 weeks of treatment.

Risk of bias

The risk of bias across outcomes was rated as low. Likewise, the risk of bias for the results for all outcomes included in the benefit assessment was rated as low.

Results

Mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit for this outcome is therefore not proven.

The company presented the results of the outcome "FVC" as valid surrogate for overall survival. Although the data for surrogate validation are in principle suitable for validating FVC as surrogate for overall survival, the methodical implementation of this validation was flawed, which led to an underestimation of the surrogate threshold effect (STE). Overall, the effect on the surrogate was not large enough in the present situation to derive an effect on overall survival. In this benefit assessment, FVC was therefore not considered to be a valid surrogate for overall survival.

Morbidity

Acute exacerbation or death

A statistically significant difference in favour of nintedanib + BSC was shown between the treatment arms for the composite outcome of acute exacerbation or death. This resulted in an indication of an added benefit of nintedanib + BSC in comparison with BSC.

Symptoms (King's Brief Interstitial Lung Disease Questionnaire [K-BILD] total score)

There was no statistically significant difference between the treatment arms for the outcome "symptoms", represented by the K-BILD total score. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

Health status (European Quality of Life Questionnaire [EQ-5D] visual analogue scale [VAS])

There was no statistically significant difference between the treatment arms for the outcome "health status" recorded using the EQ-5D VAS. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

Health-related quality of life

No usable results were available for the outcome category "health-related quality of life". This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of nintedanib + BSC was shown for the outcome "discontinuation due to AEs". The extent of the effect was no more than marginal, however. This resulted in no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC for this outcome; greater or lesser harm is therefore not proven.

Gastrointestinal disorders, diarrhoea, hepatobiliary disorders

A statistically significant difference to the disadvantage of nintedanib + BSC was shown for the following outcomes: gastrointestinal disorders (System Organ Class [SOC], AEs), diarrhoea (Preferred Term [PT], severe AEs), and hepatobiliary disorders (SOC, SAEs). This resulted in an indication of greater harm from nintedanib + BSC in comparison with BSC for each of these outcomes.

Decreased appetite

A statistically significant difference to the disadvantage of nintedanib + BSC was shown for the outcome "decreased appetite (PT, AEs)". However, there was an effect modification by the characteristic "age". This resulted in an indication of greater harm from nintedanib + BSC in comparison with placebo + BSC for patients < 65 years of age. For patients ≥ 65 years of age, there was no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC; greater or lesser harm for this patient group is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug nintedanib in comparison with the ACT are assessed as follows:

Overall, there is a positive effect in the outcome category of morbidity for the outcome "acute exacerbation or death" for nintedanib in comparison with BSC, which is accompanied by negative effects regarding side effects of different severity grades. The negative effects are mainly related to outcomes of gastrointestinal side effects. One of the negative effects is limited to patients < 65 years of age.

The composite outcome "acute exacerbation or death" considers both exacerbations and mortality. An exacerbation is an acutely life-threatening event and is associated with high

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

lethality. The severe/serious side effects do not fully call into question the positive effect of nintedanib regarding the outcome “acute exacerbation or death”.

In summary, there is an indication of a minor added benefit of nintedanib in comparison with the ACT BSC for patients with chronic PF-ILD.

Table 3 shows a summary of probability and extent of the added benefit of nintedanib.

Table 3: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with other chronic progressive fibrosing interstitial lung diseases (PF-ILD)	BSC	Indication of minor added benefit[b]

a. Presentation of the respective ACT specified by the G-BA.
b. It is unclear whether the results of the INBUILD study are transferable to other underlying ILD diseases that are underrepresented or not represented in the study.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; ILD: interstitial lung disease; PF-ILD: progressive fibrosing interstitial lung disease

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of nintedanib in comparison with BSC as ACT in patients with other chronic PF-ILD.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of nintedanib

Therapeutic indication	**ACT[a]**
Adults with other chronic progressive fibrosing interstitial lung diseases (PF-ILD)[b]	BSC[c, d]

a. Presentation of the ACT specified by the G-BA.
b. With regard to the patient population, the grouping of patients with PF-ILD of different diagnoses/aetiology as well as the underlying medical rationale of this grouping is to be justified, presented and discussed – as well as, if applicable, the transferability of the results to the patients of the target population covered by the therapeutic indication who are not included in the study population.
c. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.
d. Physical therapy (in accordance with the Remedies Directive) may also be indicated in the framework of BSC. The drugs azathioprine, MMF, N-acetylcysteine, rituximab, cyclophosphamide, ciclosporin and tacrolimus are not approved for the treatment of progressive interstitial lung disease. In principle, a lung transplant is a treatment option that can be considered for patients with progressive interstitial lung disease. However, this cannot be assumed to be a regular treatment option for patients according to the present therapeutic indication (e.g. due to comorbidities or limited availability of suitable donor organs).

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; MMF: mycophenolate mofetil; PF-ILD: progressive fibrosing interstitial lung disease

The company named BSC as ACT and thus followed the G-BA's specification.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on nintedanib (status: 9 June 2020)
- bibliographical literature search on nintedanib (last search on 2 June 2020)
- search in trial registries/trial results databases for studies on nintedanib (last search on 2 June 2020)
- search on the G-BA website for nintedanib (last search on 2 June 2020)

To check the completeness of the study pool:

- search in trial registries for studies on nintedanib (last search on 21 August 2020)

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Study 1199.247 (INBUILD[c])	Yes	Yes	No	No[d]	Yes [3-5]	Yes [6]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

BSC: best supportive care; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; vs.: versus

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
INBUILD	RCT, double-blind, parallel	Adult patients with chronic PF-ILD[b] defined by ▪ features of diffuse fibrosing lung disease of > 10% extent on HRCT ▪ DL_{CO} 30–80% predicted[c, d] ▪ FVC ≥ 45% predicted[d]	Nintedanib (N = 332) placebo (N = 331)	Screening: up to 12 weeks Treatment: at least 52 weeks[e] Follow-up observation: 28 days[f]	153 centres in Argentina, Belgium, Canada, Chile, China, France, Germany, Italy, Japan, Poland, Russia, South Korea, Spain, United Kingdom, USA 2/2017–8/2019	Primary: annual rate of decline in FVC over 52 weeks Secondary: overall survival, morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. PF-ILD was diagnosed by meeting one of the following criteria within 24 months prior to screening: FVC decline of ≥ 10% predicted, FVC decline of ≥ 5–< 10% predicted combined with worsening of respiratory symptoms, FVC decline of ≥ 5–< 10% predicted combined with increasing extent of fibrotic changes on chest imaging, worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging. Diagnosis of IPF led to exclusion.
c. Corrected for haemoglobin.
d. Values at randomization.
e. The primary efficacy analysis was planned after 52 weeks. After reaching 52 weeks, patients remained in the study on their blinded treatment until the last randomized participant had completed the planned treatment period of 52 weeks.
f. Efficacy outcomes were recorded up to week 52. AEs, acute ILD exacerbations and lung function parameters were observed for up to 28 days after the end of treatment if patients did not switch to the open-label extension study INBUILD-ON.

AE: adverse event; BSC: best supportive care; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; FVC: forced vital capacity; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; N: number of randomized patients; PF-ILD: progressive fibrosing ILD; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study	Intervention	Comparison
INBUILD	Nintedanib 150 mg twice daily[a], orally + BSC	Placebo, twice daily[a], orally + BSC
	Dose adjustments due to AEs ▪ in case of treatment-related AEs: ▫ dose reduction to 100 mg twice daily or treatment interruption ≤ 4 weeks with re-initiation at a reduced dose (100 mg twice daily) allowed ▫ re-escalation to 150 mg within ≤ 4 weeks after reduction or re-initiation at a reduced dose possible ▪ in case of AEs not related to treatment, and acute exacerbations: ▫ interruption ≤ 8 weeks allowed ▫ re-initiation of treatment at a full dose possible ▪ discontinuation of therapy in case of major toxicity or if the reduced dose was not tolerated	
	Permitted concomitant treatment ▪ individually indicated drugs could be used at the discretion of the physician unless they were explicitly prohibited ▪ diarrhoea always had to be managed as early as possible with standard treatment (e.g. loperamide) ▪ in case of acute exacerbations: any treatment option at the physician's discretion ▪ for the treatment of collagenosis-associated ILD: DMARD (e.g. MTX or TNF inhibitors) and other approved medications, unless they were explicitly prohibited (see below)	
	Prohibited prior and concomitant treatment ▪ nintedanib before study start ▪ pirfenidone ▪ immunomodulators such as azathioprine, ciclosporin, tacrolimus, MMF, OCS (> 20 mg per day) and the combination of OCS + azathioprine + N-acetylcysteine (all from 4 weeks prior to randomization)[b] ▪ rituximab (from 6 months prior to randomization)[b] ▪ cyclophosphamide (from 8 weeks prior to randomization)[b] ▪ full-dose anticoagulants, high-dose platelet aggregation inhibitors	

a. If possible after meals at 12-hour intervals.
b. Allowed if there is a clinically significant worsening of the ILD (e.g. relative FVC decline of > 10% from baseline) ≥ 6 months after study start; patients with collagenosis-associated ILD whose disease is treated with these drugs were not to be included in the study.

AE: adverse event; BSC: best supportive care; DMARD: disease-modifying antirheumatic drug; FVC: forced vital capacity; ILD: interstitial lung disease; MMF: mycophenolate mofetil; MTX: methotrexate; OCS: oral corticosteroid; RCT: randomized controlled trial; TNF: tumour necrosis factor; vs.: versus

The INBUILD study is a placebo-controlled, randomized parallel-group study on nintedanib. The study included patients with chronic PF-ILD, defined by features of diffuse fibrosing lung disease of > 10% extent on HRCT. Patients had to show a deterioration in lung function and respiratory symptoms or a progression of fibrotic changes in the lungs using imaging procedures within 24 months before screening, despite patient-specific therapy. These criteria were defined as FVC decline of ≥ 10% predicted, or FVC decline of ≥ 5 to < 10% predicted combined with worsening of respiratory symptoms, or FVC decline of ≥ 5 to < 10% predicted

combined with increasing extent of fibrotic changes on chest imaging, or worsening of respiratory symptoms as well as increasing extent of fibrotic changes on chest imaging. Further inclusion criteria were a Diffusing Capacity of the Lung for Carbon Monoxide (DL_{CO}) of 30 to 80% predicted and an FVC of ≥ 45% predicted. Patients diagnosed with idiopathic pulmonary fibrosis (IPF) were not included in the studies.

A total of 663 patients were included and randomized in a 1:1 ratio to treatment with nintedanib (N = 332) or to the placebo group (N = 331). Randomization was stratified according to HRCT pattern (usual interstitial pneumonia [UIP]-like fibrotic pattern/other fibrotic pattern). All patients who were treated with the study medication up to the end of the study could receive continued treatment with nintedanib in the single-arm, open-label extension study INBUILD-ON [7] (N = 431).

In the INBUILD study, treatment with nintedanib was in compliance with the approval [8]. Patients in the comparator arm received placebo soft capsules of identical appearance at the same time points. In addition, individually indicated drugs could be used in both study arms at the discretion of the physician unless they were explicitly prohibited.

The primary outcome of the study was the annual rate of decline in FVC (in mL/year) over 52 weeks. Patient-relevant secondary outcomes were overall survival, morbidity, and AEs.

Implementation of the appropriate comparator therapy BSC

The G-BA defined BSC as ACT. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. The company followed the G-BA's specification, and considered the ACT as implemented in the placebo-controlled INBUILD study.

In principle, the physicians participating in the study could use individually indicated drugs in both study arms at their own discretion, unless they were explicitly excluded according to the study protocol (see Table 7). Concrete information on the extent to which and how often supportive measures in the sense of a BSC were used in the study was not available in Module 4 A.

The INBUILD study excluded the use of high-dose oral corticosteroids (> 20 mg/day) and certain immunomodulators (azathioprine, ciclosporin, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil). Corticosteroids are approved for the treatment of ILD also at higher doses, such as prednisolone and prednisone (40 to 80 mg/day) [9,10]. However, there is not sufficient evidence that corticosteroids should also be used in PF-ILD [11]. The exclusion of this treatment option is therefore without further consequence.

One of the most common underlying diseases of patients with chronic PF-ILD in the INBUILD study were autoimmune diseases, including rheumatoid arthritis, for example (see Table 8). Patients with rheumatoid arthritis in particular are sometimes treated in everyday clinical

practice with the immunomodulators not permitted in the INBUILD study. According to the inclusion criteria, however, patients treated with these drugs could not participate in the study. It was therefore not assumed that the restriction of immunomodulators in the study led to worse treatment of patients with rheumatoid arthritis. Patients with chronic PF-ILD whose underlying disease can be treated well with immunomodulators are thus not represented in the INBUILD study, however.

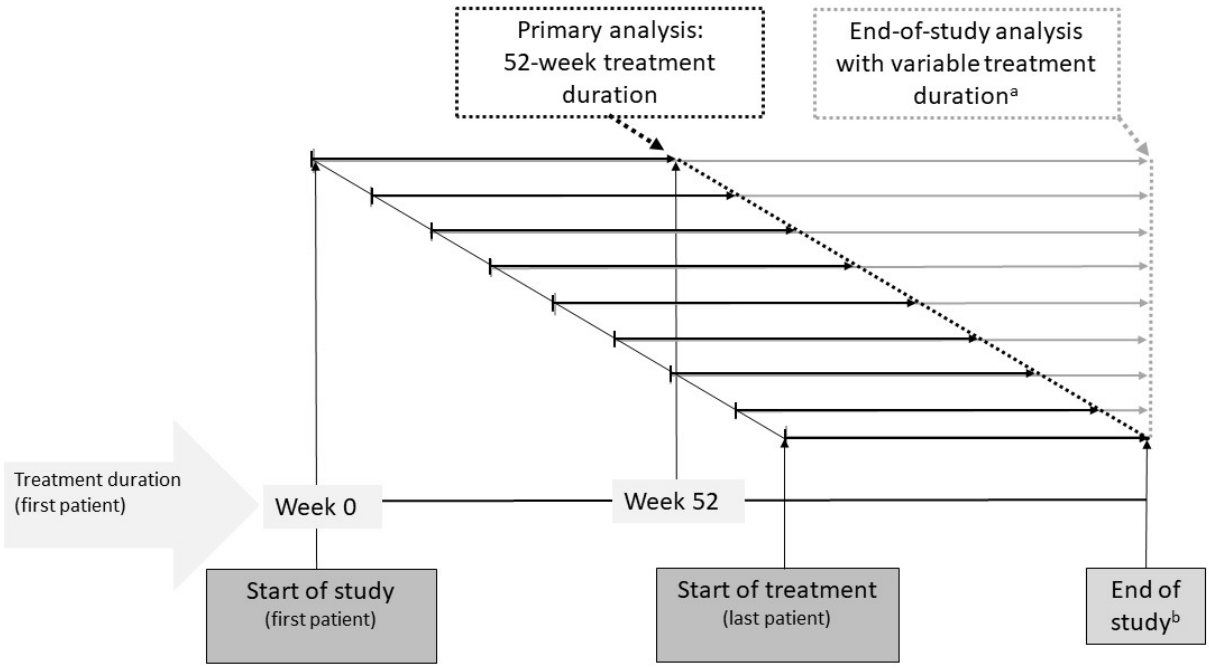
Overall, the supportive therapies allowed in the INBUILD study were considered to be a sufficient implementation of the ACT BSC.

Dates of analysis

The INBUILD study is a completed study. Analyses were planned at 2 points in time:

- analysis date: 52 weeks
- analysis date: total study duration (= end of study)

Figure 1 shows a schematic representation of the study design and the resulting 2 dates of analysis.



a. On a patient-individual basis for longer than 52 weeks until the end of the study.
b. The end of the study was defined as the time point when the last randomized patient had completed the treatment period of 52 weeks planned according to the protocol.

Figure 1: Study design and dates of analysis of the INBUILD study

The primary analysis of the efficacy outcomes had been planned for the time point at which all patients had been treated for 52 weeks and was conducted for all patients based on the data between baseline and week 52.

After reaching 52 weeks, patients remained in the study and continued their blinded treatment until the last randomized participant had completed the planned treatment period of 52 weeks. The fact that the study ended at the time point when the last randomized patient was treated for 52 weeks means that the length of treatment duration and observation period varied between the individual patients, depending on the start of the study. The company presented analyses on 52 weeks of treatment and on the entire study period in its dossier.

For the present benefit assessment, the longer observation period is considered appropriate in this chronic disease. If available, the analyses at the end of the study were therefore used, taking into account the data from the total study duration. PROs were only recorded during the first 52 weeks of treatment.

Table 8 shows the characteristics of the patients in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study Characteristic Category	Nintedanib + BSC N[a] = 332	Placebo + BSC N[a] = 331
INBUILD		
Age [years], mean (SD)	65 (10)	66 (10)
Sex [F/M], %	46/54	47/54
Region		
Europe	154 (46)	147 (44)
Canada and USA	67 (20)	69 (21)
Asia	79 (24)	76 (23)
Other	32 (10)	39 (12)
Time since ILD diagnosis [years], mean (SD)	3.7 (3.8)	3.9 (3.7)
ILD diagnosis, n (%)		
Allergic alveolitis	84 (25)	89 (27)
Idiopathic non-specific interstitial pneumonia	64 (19)	61 (18)
Unclassifiable idiopathic interstitial pneumonia	64 (19)	50 (15)
Autoimmune ILD[b]	82 (25)	88 (27)
Other ILD[c]	38 (11)	43 (13)
FVC [mL], mean (SD)	2340 (740)	2321 (728)
FVC [% predicted], mean (SD)	68.7 (16.0)	69.3 (15.2)
DL_{CO} [% predicted], mean (SD)	44.4 (11.9)	47.9 (15.0)
Treatment discontinuation, n (%)		
52 weeks	80 (24)	49 (15)
Total study duration	114 (34)	100 (30)
Study discontinuation, n (%)		
52 weeks	18 (5)	20 (6)
Total study duration	68 (20)	71 (21)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Includes RA-ILD (13%), MCTD-ILD (3%), SSc-ILD (6%) and other autoimmune fibrosing ILDs (3%).
c. Includes sarcoidosis (2%), exposure-related ILD (6%) and other fibrosing ILDs (5%).

BSC: best supportive care; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; F: female; FVC: forced vital capacity; ILD: interstitial lung disease; M: male; MCTD: mixed connective tissue disease; n: number of patients in the category; N: number of randomized (or included) patients, RA-ILD: rheumatoid arthritis-associated ILD; RCT: randomized controlled trial; SD: standard deviation; SSc-ILD: systemic sclerosis-associated ILD; vs.: versus

Patient characteristics were sufficiently balanced between the treatment arms. The mean age of the patients was 66 years; most of them were male (54%) and of European family origin. The majority of the patients with chronic PF-ILD included showed allergic alveolitis (approx. 26%) or an entity from the group of autoimmune-associated ILDs (approx. 26%), with patients with

rheumatoid arthritis-associated ILD (13% of the total population) representing the largest group.

Patients with PF-ILD of other underlying diseases

The company described that the evidence of the present study population could be transferred to patients with other underlying PF-ILD diseases, as all underlying diseases are based on common pathophysiological processes underlying the development and perpetuation of the progressive fibrosing phenotype. The company did not make any further statements on the extent to which a grouping of patients with PF-ILD of different diagnoses/aetiology is medically justified and to what extent the results of the INBUILD study can be transferred to patients with PF-ILD of other underlying diseases not represented in the study.

In the framework of the approval process of nintedanib, an ad hoc expert group on this issue was convened by the European Medicines Agency (EMA). This expert group saw the transferability as a pragmatic solution, especially due to the similar pathomechanisms and the rarity of the individual underlying diseases [12].

In summary, these assessments of the company and the EMA were based on pathophysiological considerations and are not supported by data. The characteristic "underlying ILD diagnosis" (allergic alveolitis; non-specific interstitial pneumonia; unclassifiable interstitial pneumonia; autoimmune ILD; other ILD) was investigated in the study in the framework of subgroup analyses. These did not find any consistent effect modifications with regard to the individual ILD diagnoses. However, the INBUILD study was not designed to demonstrate such effect modifications. Overall, it remains unclear whether the results of the INBUILD study are transferable to other underlying ILD diseases that are underrepresented or not represented in the study.

Treatment duration and observation period

Table 9 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 9: Information on the course of the study – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study **Duration of the study phase** **Outcome category**	**Nintedanib + BSC** **N = 332**	**Placebo + BSC** **N = 331**
INBUILD		
Treatment duration [months]		
Until week 52		
Mean (SD)	10.3 (3.8)	11.2 (2.6)
Median [min; max]	12.2 [0.0; 12.2]	12.2 [0.3; 12.2]
Total study		
Mean (SD)	15.6 (7.2)	16.8 (5.8)
Median [min; max]	17.4 [0.0; 27.7]	17.4 [0.3; 26.6]
Observation period [months]		
Until week 52		
Mean (SD)	11.9 (1.4)	12.0 (1.3)
Median [min; max]	12.2 [0.5; 12.7]	12.2 [2.0; 12.9]
Total study		
Mean (SD)	18.7 (4.3)	18.6 (4.2)
Median [min; max]	18.6 [0.5; 27.8]	18.4 [2.0; 27.0]

BSC: best supportive care; max: maximum; min: minimum; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Both the treatment duration and the observation period are comparable between the 2 study arms. The median treatment duration in both study arms was 12.2 months up to week 52 and 17.4 months over the total study duration. The median observation period in both study arms was 12.2 months at week 52 and 18.6 months (nintedanib + BSC) or 18.4 months (placebo + BSC) over the total study duration.

Data on the observation period for the individual outcomes were not available. However, as most of the outcomes were to be observed over the entire study period, it can be assumed that the observation period for the individual outcomes was approximately the same as the observation period for the total study. The results based on relative risk (RR) were therefore used for the analysis of AEs, since comparable median observation periods were assumed due to the study design. In such cases, the RR is regarded as interpretable despite patient-specific differences in the observation period, since the individually different observation periods are not due to informative reasons (e.g. different rates of progression) and it can be assumed that the observation periods are similarly distributed in the treatment groups.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
INBUILD	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes for the INBUILD study was rated as low. This concurs with the company's assessment.

Transferability to the German health care context

The company explained that PF-ILD combines different underlying diseases, the common feature of which is the occurrence of ILD with a progressive fibrosing phenotype, and provided the PF-ILD entities included in the study. According to the company, due to the high number and rarity of possible underlying diseases, there is hardly any evidence regarding the frequency of the individual underlying diseases. It considered it therefore hardly possible to conduct a meaningful comparison of the distribution of the different underlying diseases in everyday German health care with the study population of the INBUILD study. According to the company, it can also be assumed that not all the underlying diseases for chronic PF-ILD occurring in Germany are completely represented in the study population. The company described that the evidence can be transferred to the Germany health care context despite other underlying diseases, however, as the pathophysiological processes underlying the development and perpetuation of a progressive fibrosing phenotype are similar between the different underlying diseases.

The company did not present any further information on the transferability of study results to the German healthcare context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- morbidity

- acute exacerbation or death
- symptoms (K-BILD total score)
- health status (EQ-5D VAS)

- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - gastrointestinal disorders (SOC, AEs)
  - diarrhoea (PT, sever AEs; based on the operationalization of the Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A). For explanations on the outcome "FVC" as a surrogate outcome for overall survival, see Appendix D of the full dossier assessment.

Outcome category "side effects"

Diarrhoea (PT, severe AEs): According to the study protocol, severe diarrhoea was also recorded in addition to diarrhoea (as PT, AE). The operationalization was to be in accordance with the CTCAE classification (Version 4 [13]) and to include all CTCAE grade ≥ 3 diarrhoea. The study protocol defined grade 3 as an increase of ≥ 7 stools per day over baseline or stool incontinence; grade 4 included diarrhoea with life-threatening consequences; and grade 5 included diarrhoea leading to death. However, this definition differs from the version of the CTCAE classification cited by the company, which for grade 3 diarrhoea includes other possible operationalizations in addition to those mentioned (e.g. diarrhoea leading to hospitalization). Despite the differences in comparison with the CTCAE classification (Version 4), the operationalization presented and a priori defined by the company was used as a sufficient approximation for representing severe diarrhoea.

Table 11 shows for which outcomes data were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: nintedanib + BSC versus placebo + BSC

Study	Outcomes									
	Overall survival	Acute exacerbation or death	Symptoms (K-BILD)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AEs)	Diarrhoea (PT, severe AEs[a])	Further specific AEs[b]
INBUILD	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes

a. Based on the operationalization of CTCAE grade ≥ 3 (Version 4 [13])
b. The following events (MedDRA coding) are considered: "hepatobiliary disorders (SOC, SAEs)", "decreased appetite (PT, AEs)".
c. The instruments L-PF and PF-IQOLS were used in the INBUILD study. The validity of both instruments could not be sufficiently assessed.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; K-BILD: King's Brief Interstitial Lung Disease Questionnaire; L-PF: Living with Pulmonary Fibrosis; MedDRA: Medical Dictionary for Regulatory Activities; PF-IQOLS: Pulmonary Fibrosis Impact on Quality of Life Scale; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Acute exacerbation or death

In the INBUILD study, both the composite outcome "acute exacerbation or death" and its component "acute exacerbation" as separate outcome were analysed. For the present benefit assessment, the composite outcome "acute exacerbation and death" was primarily considered.

A precondition for using a composite outcome is that the individual components are of sufficiently similar severity. As acute exacerbation is a potentially life-threatening event, the 2 components (exacerbation, death) are considered sufficiently similar in terms of severity.

Patient-reported outcomes

The company presented results on the PROs Living with Pulmonary Fibrosis (L-PF) and the Pulmonary Fibrosis Impact on Quality of Life Scale (PF-IQOLS) for the outcome categories of morbidity and health-related quality of life. Neither of the 2 questionnaires was used for the present benefit assessment. This is justified below.

PF-IQOLS

The PF-IQOLS is a generic questionnaire that can record the negative effects of diseases and their treatment on the quality of life in chronic diseases. The PF-IQOLS is derived from Flanagan's Quality of Life Scale (QOLS) [14] and comprises the same 16 dimensions. The QOLS was adapted and validated for the first time for the therapeutic indication of asthma (A-IQOLS) [15]. Each dimension is rated by the patient on a 5-point Likert scale. The PF-IQOLS summary score is calculated from the mean of the individual dimension ratings.

Module 4 A did not provide sufficient information to assess the validity of the PF-IQOLS for patients with PF-ILD.

L-PF

The L-PF questionnaire was derived from the one for L-IPF, which was developed for patients with IPF and in turn is a further development of the A Tool to Assess Quality of Life in IPF (ATAQ-IPF) questionnaire [16]. The L-PF comprises 44 items and is divided into the modules of symptoms (23 items) and impacts (21 items). The symptoms module yields both physical activity and its avoidance within the last 24 hours. Scores on dyspnoea, cough, and fatigue can be calculated from the symptoms module. The impacts module, on the other hand, yields only a single score. Based on these individual scores, the total score is calculated, which ranges from 0 to 100, whereby the higher the score, the greater the impairment.

Module 4 A did not provide sufficient information to assess the validity of the L-PF for patients with PF-ILD. However, since the L-PF was developed for the therapeutic indication of PF-ILD and appears to be suitable for representing symptoms in PF-ILD, the results for the L-PF are presented as supplementary information in Appendix C of the full dossier assessment.

2.4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study	Study level	Outcomes									
		Overall survival	Acute exacerbation or death	Symptoms (K-BILD)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AEs)	Diarrhoea (PT, severe AEs[a])	Further specific AEs[b]
INBUILD	L	L	L	L	L	–[c]	L	L	L	L	L

a. Based on the operationalization of CTCAE grade ≥ 3 (Version 4 [13])
b. The following events (MedDRA coding) are considered: "hepatobiliary disorders (SOC, SAEs)", "decreased appetite (PT, AEs)".
c. The instruments L-PF and PF-IQOLS were used in the INBUILD study. The validity of both instruments could not be sufficiently assessed.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; K-BILD: King's Brief Interstitial Lung Disease Questionnaire; L: low; L-PF: Living with Pulmonary Fibrosis; MedDRA: Medical Dictionary for Regulatory Activities; PF-IQOLS: Pulmonary Fibrosis Impact on Quality of Life Scale; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias for the results of all outcomes included in the benefit assessment was rated as low. This assessment concurs with that of the company.

2.4.3 Results

Table 13, Table 14 and Table 15 summarize the results of the comparison of nintedanib + BSC with placebo + BSC in patients with chronic PF-ILD. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for the outcomes "overall survival" and "acute exacerbation or death" are presented in Appendix A and the results on common AEs, SAEs, and discontinuations due to AEs in Appendix B of the full dossier assessment.

Table 13: Results (mortality, morbidity, time to event) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study Outcome category Outcome	Nintedanib + BSC N	Nintedanib + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Nintedanib + BSC vs. placebo + BSC HR [95% CI]; p-value[a]
INBUILD					
Mortality (total study duration)[b]					
Overall survival	332	NA 36 (10.8)	331	NA 45 (13.6)	0.78 [0.50; 1.21]; 0.259
Morbidity (total study duration)[b]					
Acute exacerbation[c] or death	332	NA 46 (13.9)	331	NA 65 (19.6)	0.67 [0.46; 0.98]; 0.039
Acute exacerbation[c]	332	ND 23 (6.9)	331	ND 35 (10.6)	0.63 [0.37; 1.07]; 0.087

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified according to HRCT pattern (UIP-like HRCT pattern vs. other HRCT pattern).
b. Time at which the last randomized participant had completed the planned treatment duration of 52 weeks.
c. Acute exacerbation was defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following characteristics:
- previous or concurrent diagnosis of ILD
- acute worsening or development of dyspnoea typically less than 1 month duration
- CT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with fibrosing ILD
- deterioration not fully explained by cardiac failure or fluid overload

BSC: best supportive care; CI: confidence interval; CT: computed tomography; HR: hazard ratio; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; UIP: usual interstitial pneumonia; vs.: versus

Table 14: Results (morbidity, continuous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study Outcome category Outcome	Nintedanib + BSC			Placebo + BSC			Nintedanib + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at week 52 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at week 52 mean[b] (SE)	MD [95% CI]; p-value[b]
INBUILD							
Morbidity							
Symptoms (K-BILD total score[c])	332	52.5 (11.0)	0.6 (0.6)	330	52.3 (9.9)	−0.8 (0.6)	1.34 [−0.31; 2.98]; 0.112
Health status (EQ-5D VAS[c])	331	64.7 (20.0)	0.5 (1.0)	330	62.9 (19.6)	−2.2 (1.0)	2.62 [−0.03; 5.28]; 0.053
Health-related quality of life	No usable data[d]						

a. Number of patients with values at baseline. Presumably, this concurs with the number of patients considered in the analysis for the calculation of the effect estimation.
b. Mean, SE (per treatment group) and MD, CI and p-value (group comparison): MMRM analysis with fixed effects for baseline value, HRCT pattern, visit, interaction terms between treatment and visit and between baseline value and visit; random effect for patient.
d. Higher (increasing) values indicate fewer symptoms/better health status; positive effects ([nintedanib + BSC] – [placebo + BSC]) indicate an advantage for nintedanib + BSC.
d. The instruments L-PF and PF-IQOLS were used in the INBUILD study. The validity of both instruments could not be sufficiently assessed.

BSC: best supportive care; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HRCT: high-resolution computed tomography; K-BILD: King's Brief Interstitial Lung Disease Questionnaire; L-PF: Living with Pulmonary Fibrosis; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; PF-IQOLS: Pulmonary Fibrosis Impact on Quality of Life Scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Table 15: Results (side effects) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study Outcome category Outcome	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
INBUILD					
Side effects (total study duration)[b]					
AEs[c] (supplementary information)	332	326 (98.2)	331	308 (93.1)	–
SAEs[c]	332	140 (42.2)	331	151 (45.6)	0.92 [0.78; 1.10]; 0.530
Discontinuation due to AEs	332	73 (22.0)	331	48 (14.5)	1.52 [1.09; 2.11]; 0.013
Gastrointestinal disorders[d] (SOC, AEs)	332	279 (84.0)	331	164 (49.5)	1.70 [1.51; 1.91]; < 0.001
Diarrhoea (PT, severe AEs[e])	332	33 (9.9)	331	6 (1.8)	5.48 [2.33; 12.91]; < 0.001
Hepatobiliary disorders[f] (SOC, SAEs)	332	12 (3.6)	331	4 (1.2)	2.99 [0.97; 9.18]; 0.044
Decreased appetite (PT, AEs)	332	54 (16.3)	331	23 (6.9)	2.34 [1.47; 3.72]; < 0.001

a. p-value: Institute's calculation (unconditional exact test, CSZ method according to [17]). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.
b. Time at which the last randomized participant had completed the planned treatment duration of 52 weeks.
c. Without consideration of acute exacerbations.
d. PTs that occurred within the SOC in ≥ 10% patients in at least one study arm: abdominal pain, diarrhoea, nausea and vomiting (see Table 24 of the full dossier assessment).
e. Based on the operationalization of CTCAE grade ≥ 3 (Version 4 [13])
f. PTs that occurred within the SOC in ≥ 10 patients in at least one study arm: liver function abnormal (see Table 24 of the full dossier assessment).

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

In contrast to the analyses for the outcomes in the categories of mortality and side effects, the analyses for PROs refer to the analysis date of 52 weeks.

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit for this outcome is therefore not proven.

This deviates from the assessment of the company, which derived an indication of considerable added benefit for this outcome. On the one hand, this assessment was based on the outcome "FVC", which the company presented as a valid surrogate for overall survival. A corresponding surrogate validation was presented in Module 4 A, Section 4.5. Although the data for surrogate validation are in principle suitable for validating FVC as surrogate for overall survival, the methodical implementation of this validation was flawed, which led to an underestimation of the STE. Overall, the effect on the surrogate was not large enough in the present situation to derive an effect on overall survival. In this benefit assessment, FVC was therefore not considered to be a valid surrogate for overall survival. A detailed justification, as well as a detailed description of the company's approach can be found in Appendix D of the full dossier assessment. On the other hand, the company included the composite outcome "acute exacerbation or death" as a mortality-associated outcome in its assessment, for which a statistically significant advantage of nintedanib was shown (see next section on morbidity). The company presented a meta-analysis of the studies with nintedanib in the therapeutic indications of PF-ILD and IPF as supplementary information. This analysis showed a statistically significant advantage of nintedanib over placebo across several therapeutic indications.

Morbidity

Acute exacerbation or death

A statistically significant difference in favour of nintedanib + BSC was shown between the treatment arms for the composite outcome of acute exacerbation or death. This resulted in an indication of an added benefit of nintedanib + BSC in comparison with BSC.

This deviates from the assessment of the company, which overall derived an indication of considerable added benefit for the outcome category of morbidity. Besides the outcome "acute exacerbation or death", it used results of the composite outcome "non-elective hospitalization or death" and of the L-PF for this purpose.

Symptoms (K-BILD total score)

There was no statistically significant difference between the treatment arms for the outcome "symptoms", represented by the K-BILD total score. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

This deviates from the assessment of the company, which assigned the K-BILD total score together with the PF-IQOLS summary score, the L-PF impacts score and the EQ-5D VAS to health-related quality of life, and overall derived an indication of a minor added benefit of nintedanib + BSC in comparison with BSC for this outcome category.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment arms for the outcome "health status" recorded using the EQ-5D VAS. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

This deviates from the assessment of the company, which assigned the EQ-5D VAS together with the PF-IQOLS summary score, the L-PF impacts score and the K-BILD total score to health-related quality of life, and overall derived an indication of a minor added benefit of nintedanib + BSC in comparison with BSC for this outcome category.

Health-related quality of life

No usable results were available for the outcome category "health-related quality of life" (see Section 2.4.1). This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC; an added benefit is therefore not proven.

This deviates from the assessment of the company, which assigned the K-BILD total score, the PF-IQOLS summary score, the L-PF impacts score and the EQ-5D VAS to health-related quality of life, and overall derived an indication of a minor added benefit of nintedanib + BSC in comparison with BSC for this outcome category.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of nintedanib + BSC was shown for the outcome "discontinuation due to AEs". The extent of the effect was no more than marginal, however. This resulted in no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC for this outcome; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived lesser benefit of nintedanib + BSC in comparison with BSC for this outcome.

Specific AEs

Gastrointestinal disorders, diarrhoea, hepatobiliary disorders

A statistically significant difference to the disadvantage of nintedanib + BSC was shown for the following outcomes: gastrointestinal disorders (SOC, AEs), diarrhoea (PT, severe AEs), and hepatobiliary disorders (SOC, SAEs). This resulted in an indication of greater harm from nintedanib + BSC in comparison with BSC for each of these outcomes.

Decreased appetite

A statistically significant difference to the disadvantage of nintedanib + BSC was shown for the outcome "decreased appetite (PT, AEs)". However, there was an effect modification by the characteristic "age". This resulted in an indication of greater harm from nintedanib + BSC in

comparison with BSC for patients < 65 years of age. For patients ≥ 65 years of age, there was no hint of greater or lesser harm of nintedanib + BSC in comparison with BSC; greater or lesser harm for this patient group is therefore not proven (see Section 2.4.4).

The assessment regarding the specific AEs deviates from the assessment of the company, which, based on the overall rates and further specific AEs, described disadvantages for nintedanib + BSC in comparison with BSC, particularly due to gastrointestinal side effects, but did not quantify these disadvantages. For the other chosen specific AEs, the company presented results, but did not use them to derive greater or lesser harm from nintedanib + BSC in comparison with BSC.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (male/female)

Subgroup analyses were available for all outcomes included.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 summarizes the subgroup results on the comparison of nintedanib + BSC versus placebo + BSC in adult patients with PF-ILD.

Table 16: Subgroups (side effects) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study Outcome Characteristic Subgroup	Nintedanib + BSC N	Nintedanib + BSC Patients with event n (%)	Placebo + BSC N	Placebo + BSC Patients with event n (%)	Nintedanib + BSC vs. placebo + BSC RR [95% CI]	 p-value[a]
INBUILD						
Side effects (total study duration)						
Decreased appetite (PT, AEs)						
Age						
< 65 years	139	22 (15.8)	121	2 (1.7)	9.58 [2.30; 39.89]	< 0.001
≥ 65 years	193	32 (16.6)	210	21 (10.0)	1.66 [0.99; 2.77]	0.053
					Interaction:	0.023[b]

a. Institute's calculation (unconditional exact test, CSZ method according to [17]).
b. Institute's calculation, Q test.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Side effects

Decreased appetite

For the outcome "decreased appetite (PT, AEs)", there was a statistically significant interaction for the characteristic of age.

A statistically significant difference to the disadvantage of nintedanib + BSC was shown for the age group < 65 years. This resulted in an indication of greater harm from nintedanib + BSC in comparison with BSC for patients < 65 years of age.

There was no statistically significant difference between the treatment groups in the age group ≥ 65 years. This resulted in no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC. Greater or lesser harm for this outcomes is therefore not proven for patients ≥ 65 years.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for outcomes on symptoms and side effects

The dossier does not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Acute exacerbation or death

Exacerbations are a potentially life-threatening event for patients with chronic PF-ILD and are also associated with a noticeable worsening of symptoms and prognosis. This outcome was therefore assigned to the outcome category "serious/severe symptoms/late complications".

Discontinuation due to AEs

There was no information about the severity grade attributable to the AEs that resulted in treatment discontinuation. Therefore, the outcome "discontinuation due to AEs" was assigned to the outcome category of non-serious/non-severe side effects.

Gastrointestinal disorders and decreased appetite

The vast majority of the events that occurred in the specific AEs "gastrointestinal disorders (SOC)" and "decreased appetite (PT)" were non-serious. The outcomes were therefore assigned to the category non-serious/non-severe side effects.

Table 17: Extent of added benefit at outcome level: nintedanib + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nintedanib + BSC vs. placebo + BSC** **Median time to event in months or proportion of events (%) or mean change at week 52** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. NA HR: 0.78 [0.50; 1.21]; p = 0.259	Lesser benefit/added benefit not proven
Morbidity		
Acute exacerbation or death	NA vs. NA HR: 0.67 [0.46; 0.98]; p = 0.039 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Symptoms (K-BILD total score)	0.6 vs. −0.8 MD: 1.34 [−0.31; 2.98]; p = 0.112	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	0.5 vs. −2.2 MD: 2.62 [−0.03; 5.28]; p = 0.053	Lesser benefit/added benefit not proven
Health-related quality of life	No usable data[c]	
Side effects		
SAEs	42.2% vs. 45.6% RR: 0.92 [0.78; 1.10]; p = 0.530	Greater/lesser harm not proven
Discontinuation due to AEs	22% vs. 14.5% RR: 1.52 [1.09; 2.11]; RR: 0.66 [0.47; 0.92][d]; p = 0.013 probability: "indication"	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ greater/lesser harm not proven[e]
Gastrointestinal disorders (SOC, AEs)	84% vs. 49.5% RR: 1.70 [1.51; 1.91]; RR: 0.59 [0.52; 0.66][d]; p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Diarrhoea (PT, severe AEs)	9.9% vs. 1.8% RR: 5.48 [2.33; 12.91]; RR: 0.18 [0.08; 0.43][d]; p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"

Table 17: Extent of added benefit at outcome level: nintedanib + BSC vs. BSC (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nintedanib + BSC vs. placebo + BSC** **Median time to event in months or proportion of events (%) or mean change at week 52** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Hepatobiliary disorders (SOC, SAEs)	3.6% vs. 1.2% RR: 2.99 [0.97; 9.18]; RR: 0.33 [0.11; 1.03][d]; p = 0.044 probability: "indication"	Outcome category: serious/severe side effects greater harm, extent: "minor"[f]
Decreased appetite (PT, AEs) Age		
< 65 years	15.8% vs. 1.7% RR: 9.58 [2.30; 39.89]; RR: 0.10 [0.03; 0.43][d]; p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
≥ 65 years	16.6% vs. 10.0% RR: 1.66 [0.99; 2.77]; p = 0.053	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. The instruments L-PF and PF-IQOLS were used in the INBUILD study. The validity of both instruments could not be sufficiently assessed.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; the basis for the assessment of the extent is the p-value.

AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; K-BILD: King's Brief Interstitial Lung Disease Questionnaire; L-PF: Living with Pulmonary Fibrosis; MD: mean difference; NA: not achieved; PF-IQOLS: Pulmonary Fibrosis Impact on Quality of Life Scale; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of nintedanib in comparison with BSC

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Acute exacerbation or death: indication of added benefit – extent: "minor"	—
—	Non-serious/non-severe side effects ▪ Gastrointestinal disorders (SOC, AEs): indication of greater harm – extent: "considerable" ▪ Decreased appetite (PT, AEs) ▫ Age < 65 years indication of greater harm – extent "considerable"
—	Serious/severe side effects ▪ Diarrhoea (PT, severe AEs): indication of greater harm – extent: "major" ▪ Hepatobiliary disorders (SOC, SAEs): indication of greater harm – extent: "minor"
AE: adverse event; BSC: best supportive care; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class	

Overall, there is a positive effect in the outcome category of morbidity for the outcome "acute exacerbation or death" for nintedanib in comparison with BSC, which is accompanied by negative effects regarding side effects of different severity grades. The negative effects are mainly related to outcomes of gastrointestinal side effects. One of the negative effects is limited to patients < 65 years of age.

The composite outcome "acute exacerbation or death" considers both exacerbations and mortality. An exacerbation is an acutely life-threatening event and is associated with high lethality. The severe/serious side effects do not fully call into question the positive effect of nintedanib regarding the outcome "acute exacerbation or death".

In summary, there is an indication of a minor added benefit of nintedanib in comparison with the ACT BSC for patients with chronic PF-ILD.

The result of the assessment of the added benefit of nintedanib in comparison with the ACT is summarized in Table 19.

Table 19: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with other chronic progressive fibrosing interstitial lung diseases (PF-ILD)	BSC	Indication of minor added benefit[b]

a. Presentation of the respective ACT specified by the G-BA.
b. It is unclear whether the results of the INBUILD study are transferable to other underlying ILD diseases that are underrepresented or not represented in the study.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; ILD: interstitial lung disease; PF-ILD: progressive fibrosing interstitial lung disease

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit under consideration of further outcomes.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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