IQWiG Reports – Commission No. A19-36

Nintedanib (idiopathic pulmonary fibrosis) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Nintedanib (idiopathische Lungenfibrose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 July 2019). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CASA-Q	Cough and Sputum Assessment Questionnaire
CI	confidence interval
EQ-5D VAS	European Quality of Life-5 Dimensions visual analogue scale
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HRCT-QLF	High Resolution Computerized Tomography Quantitative Lung Fibrosis
IPF	idiopathic pulmonary fibrosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
PGIC	Patient Global Impression of Change
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George’s Respiratory Questionnaire
SOBQ	Shortness of Breath Questionnaire
SOC	System Organ Class
SPC	Summary of Product Characteristics

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 11 April 2019.

Research question

The aim of the present report was to assess the added benefit of nintedanib in comparison with the appropriate comparator therapy (ACT) in adult patients with idiopathic pulmonary fibrosis (IPF).

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 2.

Table 2: Research question of the benefit assessment of nintedanib

Therapeutic indication	**ACT**[a]
Adults with idiopathic pulmonary fibrosis (IPF)	Pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to the approval) or **best supportive care**[b, c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care 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.
c: The G-BA points out that, in principle, lung transplant is a treatment option for patients with IPF, but that, given the limited availability of suitable donor organs, this cannot be assumed to be a general treatment option. Nevertheless, patients in studies that are used for the benefit assessment could be considered also in case of a lung transplant in the course of the study in the sense of a permitted treatment switch. Such a treatment switch may correspond to the actual health care setting. Observation of these patients should be continued even after completion of the experimental or comparator intervention of the study.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IPF: idiopathic pulmonary fibrosis

The company named best supportive care (BSC) as comparator therapy 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. This concurs with the company's inclusion criteria.

Results

Study design

The studies INPULSIS-1 and INPULSIS-2 were 2-arm, controlled, double-blind phase 3 studies, randomized in a 3:2 ratio, with identical study design and a treatment duration of 52 weeks each. They compared nintedanib 150 mg twice daily with placebo.

Study 1199.187 was a randomized (1:1 ratio) phase 3b study comparing nintedanib 150 mg twice daily with placebo. It was originally designed to have a treatment duration of 52 weeks. In the framework of a global amendment, the 2-arm blinded phase was shortened to 24 weeks.

The TOMORROW study was a 5-arm, controlled, double-blind phase 2 dose-ranging study with a study duration of 52 weeks. Of the 5 arms, the study arms with placebo and with nintedanib 150 mg twice daily were included in the present benefit assessment.

All 4 studies enrolled adults aged ≥ 40 years with diagnosis of IPF according to international guidelines [3,4]. The INPULSIS 1 study enrolled a total of 515 adults (nintedanib + BSC: 309, placebo + BSC: 206), INPULSIS 2 a total of 551 adults (nintedanib + BSC: 331, placebo + BSC: 220). Study 1199.187 enrolled a total of 113 patients (nintedanib + BSC: 56, placebo + BSC: 57) and TOMORROW a total of 173 patients (nintedanib + BSC: 86, placebo + BSC: 87).

Treatment with nintedanib was in compliance with the Summary of Product Characteristics (SPC) in all 4 studies. On occurrence of adverse events (AEs), all studies mandated a dose reduction to 100 mg nintedanib twice daily or treatment interruption. Both INPULSIS studies and study 1199.187 mandated re-escalation of the dosage to 150 mg twice daily or re-initiation of treatment, preferably with the reduced (100 mg twice daily) or with the original dosage (150 mg twice daily), once AEs have resolved. TOMORROW did not mandate re-initiation of treatment or re-escalation of the dosage. This was not assumed to have a relevant influence on the results of the benefit assessment, however.

Primary outcome in the studies INPULSIS-1, INPULSIS-2 and TOMORROW was the annual rate of decline in forced vital capacity (FVC). Primary outcome in study 1199.187 was the change in High Resolution Computerized Tomography (HRCT) Quantitative Lung Fibrosis (QLF) score. Patient-relevant secondary outcomes in all 4 studies were recorded on overall survival, morbidity, health-related quality of life and AEs.

Implementation of the appropriate comparator therapy

Based on guideline recommendations and the information available in the studies on the concomitant medication, and despite the comparison versus placebo, it is assumed that the patients included in all 4 included studies – INPULSIS 1, INPULSIS 2, 1199.187 and TOMORROW – received BSC in the sense of the ACT.

Hereinafter, the comparator therapy is referred to as “placebo + BSC” and the intervention as “nintedanib + BSC”.

Risk of bias

The risk of bias across outcomes was rated as low for all 4 studies. For the studies INPULSIS-1, INPULSIS-2 and 1199.187, this concurs with the assessment of the company. The company did not include TOMORROW and therefore provided no assessment of the risk of bias across outcomes in Module 4 A.

INPULSIS-1 and INPULSIS-2

For both studies, the risk of bias was rated as low for the results of the following outcomes: overall survival, cough (Cough and Sputum Assessment Questionnaire [CASA-Q]), health status (European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]), health-related quality of life (St. George’s Respiratory Questionnaire [SGRQ]), serious AEs (SAEs), discontinuation due to AEs, and the specific AE “gastrointestinal disorders”. The risk of bias for the outcome “respiratory status” (Patient Global Impression of Change [PGIC]) was rated as high for both studies. There were differences in the risk of bias between both studies for the results of the outcomes “adjudicated acute exacerbations” and “dyspnoea” (Shortness of Breath Questionnaire ([SOBQ]), which was rated as low in INPULSIS-2 and as high in INPULSIS-1.

1199.187

For study 1199.187, the risk of bias was rated as low for the results of the following outcomes: overall survival, adjudicated acute exacerbations, endurance (6-minute walking test), SAEs, discontinuation due to AEs, and gastrointestinal disorders. The risk of bias of the results on the outcomes “dyspnoea” (SOBQ) and “health-related quality of life” (SGRQ) was rated as high.

TOMORROW

The risk of bias was rated as low for the results on the following outcomes: overall survival, acute exacerbations, supplemental oxygen use, SAEs, discontinuation due to AEs, and gastrointestinal disorders. The risk of bias of the results on the outcomes “endurance” (6-minute walking test) and “health-related quality of life” (SGRQ) was rated as high.

Mortality

Overall survival

The meta-analysis of the 4 studies INPULSIS-1, INPULSIS-2, 1199.187 and TOMORROW showed no statistically significant difference between the treatment groups for the outcome “overall survival”. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

Morbidity

Adjudicated acute exacerbations

The meta-analysis of the 4 studies INPULSIS-1, INPULSIS-2, 1199.187 and TOMORROW showed a statistically significant difference in favour of nintedanib + BSC for the outcome "time to first adjudicated acute exacerbation". This resulted in proof of an added benefit of nintedanib + BSC in comparison with BSC.

Supplemental oxygen use

There was no statistically significant difference between the treatment groups for the outcome "supplemental oxygen use" recorded in the TOMORROW study. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

Change in respiratory status (PGIC)

The meta-analysis of INPULSIS-1 and INPULSIS-2 showed a statistically significant difference in favour of nintedanib + BSC versus placebo + BSC for the outcome "change in respiratory status" (PGIC). The effect in this outcome from the category of non-serious/non-severe symptoms was no more than marginal, however. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC; an added benefit is therefore not proven.

Endurance (6-minute walking test)

No suitable statistical model with a meaningfully interpretable confidence interval (CI) is available for a meta-analysis for the outcome "endurance" (6-minute walking test) recorded in 1199.187 and TOMORROW. The results on this outcome were therefore interpreted on the basis of the results of the individual studies 1199.187 and TOMORROW by checking whether the effects pointed in the same direction.

Neither 1199.187 nor TOMORROW showed a statistically significant difference between the treatment groups for the outcome "endurance" (6-minute walking test). This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

Cough (CASA-Q)

The meta-analysis of the 2 studies INPULSIS-1 and INPULSIS-2 showed no statistically significant difference between the treatment groups for the outcome both in cough symptoms and in cough impact. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

Dyspnoea (SOBQ)

No statistical model with a meaningfully interpretable CI is available for a meta-analysis for the outcome "dyspnoea" (SOBQ). The results on this outcome were therefore interpreted on the basis of the results of the individual studies INPULSIS-1, INPULSIS-2 and 1199.187 by

checking whether the effects pointed in the same direction. None of the studies showed a statistically significant difference between the treatment groups. 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 (EQ-5D VAS)

The meta-analysis of INPULSIS-1 and INPULSIS-2 showed a statistically significant difference in favour of nintedanib + BSC for the outcome "health status" recorded with the EQ-5D VAS. However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. 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

Health-related quality of life (SGRQ)

No suitable statistical model with meaningfully interpretable effect estimation and meaningfully interpretable CI is available for a meta-analysis for the outcome "health status" measured with the SGRQ, which was recorded in all 4 studies. The results on this outcome were therefore interpreted on the basis of the results of the 4 individual studies by checking whether the effects pointed in the same direction.

In terms of statistical significance, the results pointed in the same direction. For Hedges' g, however, there were no effects in the same direction regarding the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect was relevant. Hence, there was no hint of an added benefit of nintedanib + BSC in comparison with BSC in the overall conclusion on the outcome "health-related quality of life" (SGRQ); an added benefit is therefore not proven.

Side effects

Serious adverse events

The meta-analysis of the 4 included studies showed no statistically significant difference between the treatment groups 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 adverse events

The meta-analysis of the 4 included studies showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". 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.

Specific adverse event "gastrointestinal disorders"

The meta-analysis of the 4 included studies showed a statistically significant difference to the disadvantage of nintedanib + BSC in comparison with placebo + BSC for the specific AE "gastrointestinal disorders" (System Organ Class [SOC]). There was a low risk of bias for the outcome. This resulted in proof of greater harm from nintedanib + BSC in comparison with BSC.

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:

The overall consideration shows one positive and one negative effect of nintedanib + BSC versus BSC, each with the probability "proof" and the extent "considerable".

The positive effect was shown in the outcome category of serious/severe symptoms/late complications, the negative effect in the outcome category of non-serious/non-severe side effects. The negative effect in the SOC "gastrointestinal disorders" did not completely outweigh the advantage in exacerbations, but resulted in a downgrading of the extent of the added benefit.

In summary, there is proof of a minor added benefit of nintedanib + BSC versus BSC for patients with IPF.

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

[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].

Table 3: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with idiopathic pulmonary fibrosis (IPF)	Pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to the approval) or **best supportive care**[b, c]	Proof of minor added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care 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.
c: The G-BA points out that, in principle, lung transplant is a treatment option for patients with IPF, but that, given the limited availability of suitable donor organs, this cannot be assumed to be a general treatment option. Nevertheless, patients in studies that are used for the benefit assessment could be considered also in case of a lung transplant in the course of the study in the sense of a permitted treatment switch. Such a treatment switch may correspond to the actual health care setting. Observation of these patients should be continued even after completion of the experimental or comparator intervention of the study.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IPF: idiopathic pulmonary fibrosis

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 was to assess the added benefit of nintedanib in comparison with the ACT in adult patients with IPF.

The G-BA's specification of the ACT resulted in one research question, which is presented in the following Table 4.

Table 4: Research question of the benefit assessment of nintedanib

Therapeutic indication	**ACT**[a]
Adults with idiopathic pulmonary fibrosis (IPF)	Pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to the approval) or **best supportive care**[b, c]

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care 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.
c: The G-BA points out that, in principle, lung transplant is a treatment option for patients with IPF, but that, given the limited availability of suitable donor organs, this cannot be assumed to be a general treatment option. Nevertheless, patients in studies that are used for the benefit assessment could be considered also in case of a lung transplant in the course of the study in the sense of a permitted treatment switch. Such a treatment switch may correspond to the actual health care setting. Observation of these patients should be continued even after completion of the experimental or comparator intervention of the study.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IPF: idiopathic pulmonary fibrosis

The company named BSC as comparator therapy 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: 8 February 2019)
- bibliographical literature search on nintedanib (last search on 17 January 2019)
- search in trial registries for studies on nintedanib (last search on 17 January 2019)

To check the completeness of the study pool:

- search in trial registries for studies on nintedanib (last search on 18 April 2019)

The TOMORROW study was identified as additional relevant study from the check.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

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

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study 1199.32 (INPULSIS 1[b])	Yes	Yes	No
Study 1199.34 (INPULSIS 2[b])	Yes	Yes	No
Study 1199.187	No	Yes	No
Study 1199.30 (TOMORROW[b])	Yes[c]	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. c: Contrary to the information provided by the company in Module 4 A, the study was part of the basis for the approval. BSC: best supportive care; RCT: randomized controlled trial; vs.: versus			

Besides the studies INPULSIS-1, INPULSIS-2 and 1199.187 included by the company, the study pool for the benefit assessment of nintedanib additionally included the TOMORROW study. This is justified below.

The TOMORROW study was a randomized placebo-controlled study on nintedanib in patients with IPF (see Section 2.3.2 for a detailed description). The ACT BSC was adequately implemented in the TOMORROW study (see Section 2.3.2). For the treatment with nintedanib, the SPC provides the option of dose reduction or treatment interruption in case of AEs until the AEs have resolved [5]. This was implemented in the TOMORROW study. Regarding the continuation of therapy after the AEs have resolved, treatment may be resumed at the full dose of 150 mg twice daily or at a reduced dose of 100 mg twice daily, according to the SPC [5]. The TOMORROW study did not mandate re-escalation of the dose to the starting dose after temporary treatment interruption or dose reduction due to AEs, which is why the company excluded the study. In this situation, however, the study selection should consider the proportion of patients affected by a treatment that potentially deviates from the SPC. In the TOMORROW study, these were 27 (about 13%) patients who received a dose reduction. Of these 27 patients, 4 patients received re-escalation to the original dose (which was contrary to the study protocol, but in compliance with the SPC). The proportion of patients for whom re-escalation of the dosage could have been an option is therefore well below 20%, so that the exclusion of the study is not justified.

It should additionally be taken into account that the population investigated in the studies INPULSIS-1, INPULSIS-2 and 1199.187 was comparable to the one investigated in TOMORROW. In these studies, a total of about 20% of the patients received a dose reduction. About 25% of these patients received a re-escalation to the starting dose. Applied to the situation in the TOMORROW study, a small proportion of patients for whom a re-escalation would have been a potential option can therefore be assumed for this study. It can therefore be assumed that the missing option of dose re-escalation had no relevant effects on the study results.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the studies 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]
INPULSIS-1	RCT, double-blind, parallel	Adult patients (≥ 40 years) diagnosed with IPF[b], DL_{CO} 30–79%[c, d], FVC ≥ 50%[c, e] and whose life expectancy due to other conditions was not < 2.5 years	Nintedanib + BSC (N = 309) placebo + BSC (N = 206)	Screening: up to 12 weeks Treatment: 52 weeks Follow-up: 28 days	98 centres in Australia, Belgium, China, Czech Republic, France, Germany, India, Ireland, Israel, Italy, Japan, United Kingdom, USA 5/2011–10/2013	Primary: annual FVC decline (mL) Secondary: overall survival, morbidity, health-related quality of life, AEs
INPULSIS-2	RCT, double-blind, parallel	Adult patients (≥ 40 years) diagnosed with IPF[b], DL_{CO} 30-79%[c, d], FVC ≥ 50%[c, e] and whose life expectancy due to other conditions was not < 2.5 years	Nintedanib + BSC (N = 331) placebo + BSC (N = 220)	Screening: up to 12 weeks Treatment: 52 weeks Follow-up: 28 days	107 centres in Canada, Chile, China, Finland, France, Germany, Greece, India, Japan, Korea, Mexico, Netherlands, Portugal, Russia, Spain, Turkey, USA 5/2011–10/2013	Primary: annual FVC decline (mL) Secondary: overall survival, morbidity, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
1199.187	RCT, double-blind, parallel	Adult patients (≥ 40 years) diagnosed with IPF[f], DL_{CO} 30–79%[d], FVC ≥ 50%[c], if oxygen use: ≤ 12 L/min, 6 MWT without cane possible	Nintedanib + BSC (N = 56) placebo + BSC (N = 57)	Screening: up to 4 weeks Treatment: blinded 24 weeks[g], then unblinded single-arm extension phase with nintedanib + BSC for up to 54 more weeks Follow-up: 28 days	26 centres in Canada, Turkey, USA 12/2013–10/2016	Primary: change in HRCT-QLF score from baseline to week 24 Secondary: overall survival, morbidity, health-related quality of life, AEs
TOMORROW	RCT, double-blind, parallel	Adult patients (≥ 40 years) diagnosed with IPF[h], DL_{CO} 30–79%[d], FVC ≥ 50%[e], if oxygen use: < 15 hours/day	Nintedanib 50 mg/once daily + BSC (N = 87)[i] nintedanib 50 mg/twice daily + BSC (N = 86)[i] nintedanib 100 mg/twice daily + BSC (N = 86)[i] nintedanib 150 mg/twice daily + BSC (N = 86) placebo + BSC (N = 87)	Screening: up to 6 weeks Treatment: 12 months, then optional continued treatment[j] with the allocated dose possible, the placebo arm is switched to nintedanib 50 mg/once daily + BSC Follow-up: 2 weeks	92 centres in 25 countries in Europe, North and South America, Asia and South Africa 9/2007–6/2010	Primary: annual FVC decline (mL) Secondary: overall survival, symptoms, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

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: IPF diagnosed within 5 years before screening according to ATS/ERS/JRS/ALAT guidelines (2011), and confirmed by chest HRCT pattern, and if available surgical lung biopsy pattern, as assessed by central reviewers. Confirmation of diagnosis by chest HRCT within 52 weeks before screening.
c: Values at screening in % of normal value.
d: Adapted to haemoglobin.
e: Patients with pre-bronchodilator FEV1/FVC < 0.7 were excluded as well as patients likely to have a lung transplant during study (being on a transplant list was not an exclusion criterion).
f: IPF diagnosed within 5 years before screening according to ATS/ERS/JRS/ALAT guidelines (2011), and reaffirmed applying these guidelines if diagnosed > 2 years and ≤ 5 years before screening. Confirmation of diagnosis by chest HRCT within 24 weeks after visit 1.
g: Amendment 1 to the study protocol shortened the originally planned blinded period from 52 to 24 weeks.
h: IPF diagnosed within the last 5 years before screening according to ATS/ERS criteria (2000), confirmed by HRCT within 12 months after randomization and lung biopsy, as assessed by central reviewers.
i: The arm is not relevant for the assessment and is no longer presented in the following tables.
j: Up to 42 months, depending on study recruitment.

AE. adverse event; ALAT: Latin American Thoracic Association; ATS: American Thoracic Society; BSC: best supportive care; DL_{CO}: Diffusing Capacity of the Lung for Carbon Monoxide; ERS: European Respiratory Society; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HRCT: high-resolution computed tomography; HRCT QLF: High Resolution Computerized Tomography Quantitative Lung Fibrosis; IPF: idiopathic pulmonary fibrosis; JRS: Japanese Respiratory Society; 6 MWT: 6-minute walking test; N: number of randomized patients, RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
INPULSIS-1	Nintedanib 150 mg orally twice daily[a]	Placebo orally twice daily[a]
INPULSIS-2 Study 1199.187	**Dose adjustments due to AEs** ▪ On occurrence of treatment-associated AEs dose reduction to 100 mg twice daily or treatment interruption ≤ 4 weeks allowed. Re-escalation to 150 mg within ≤ 4 weeks after reduction or re-initiation at a reduced dose possible. ▪ On occurrence of AEs not associated with treatment and acute exacerbations, interruption ≤ 8 weeks possible. Re-initiation of treatment within ≤ 8 weeks at a full dose possible. **Concomitant treatment** ▪ in case of acute exacerbations: any indicated medication at the physician's choice, except pirfenidone (e.g. high-dose prednisone, azathioprine, cyclophosphamide, ciclosporin A or NAC) ▪ prophylactic low-dose heparin or heparin "flush" ▪ prophylactic platelet aggregation inhibitors ▪ if on a stable dose for ≥ 8 weeks before visit 1: prednisone ≤ 15 mg daily or ≤ 30 mg every 2 days or equivalent corticosteroid **Non-permitted concomitant treatment[b]** ▪ pirfenidone or other investigational treatments for IPF (from 8 weeks before visit 1) ▪ fibrinolysis treatment (from 4 weeks before visit 1)[c] ▪ full-dose therapeutic anticoagulation (from 4 weeks before visit 1)[c] ▪ high-dose platelet aggregation inhibitor therapy (from 4 weeks before visit 1)[c] ▪ azathioprine, cyclophosphamide, ciclosporin A (from 8 weeks before visit 1; in case of deterioration of the IPF allowed after 24 weeks of treatment) ▪ NAC, prednisone > 15 mg daily (or > 30 mg/2 days) or equivalent oral corticosteroid (from 2 weeks before screening; in case of deterioration of the IPF allowed after 24 weeks of treatment) ▪ bronchodilators before spirometry[d]	

(continued)

Table 7: Characteristics of the interventions – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

Study	Intervention	Comparison
TOMORROW	Nintedanib 150 mg orally twice daily[a] + BSC	Placebo orally twice daily[a] + BSC
	Dose adjustments due to AEs ▪ on occurrence of AEs one treatment interruption up to 2 weeks possible, then dose reduction to 100 mg twice daily ▪ on occurrence of AEs not associated with treatment re-initiation of treatment under 150 mg twice daily possible **Concomitant treatment** ▪ in case of acute exacerbations: any indicated medication at the physician's choice (e.g. high-dose prednisone, azathioprine, cyclophosphamide or NAC) ▪ prophylactic low-dose heparin ▪ prophylactic low-dose or short-term platelet aggregation inhibitors, e.g. ASA ▪ in case of deterioration of the IPF allowed after 24 weeks: prednisone with azathioprine ± NAC or cyclophosphamide, at the physician's discretion or, if already under prednisone treatment, supplementary azathioprine ± NAC ▪ if on a stable dose for ≥ 8 weeks before visit 1: prednisone ≤ 15 mg daily or ≤ 30 mg every 2 days or equivalent corticosteroid **Non-permitted concomitant treatment[b]** ▪ pirfenidone, imatinib, etanercept or other investigational treatments ▪ drugs that increase the risk of bleeding, including: ▫ full-dose anticoagulants ▫ high-dose platelet aggregation inhibitors ▪ azathioprine, NAC, cyclophosphamide (from 8 weeks before visit 2; in case of deterioration of the IPF allowed after 24 weeks of treatment) ▪ low-dose prednisone not on a stable dose and high-dose prednisone (in case of deterioration of the IPF allowed after 24 weeks of treatment)	

a: If possible after meals at 12-hour intervals.
b: Non-permitted concomitant treatments from screening over the total treatment periods of the studies.
c: If treatment with these drugs became necessary during the INPULSIS studies, a 4-week wash-out phase of the study medication was to be conducted before their use.
d: Before the spirometry, long-acting bronchodilators were not allowed for 24 hours, and short-acting bronchodilators for 8 hours (wash-out phase).
AE: adverse event; ASA: acetylsalicylic acid; BSC: best supportive care; IPF: idiopathic pulmonary fibrosis; NAC: N-acetylcysteine; RCT: randomized controlled trial; vs.: versus

Since the included studies had a similar design, they are described below in summarized form.

The studies INPULSIS-1 and INPULSIS-2 were 2-arm, controlled, double-blind phase 3 studies, randomized in a 3:2 ratio, with identical study design and a treatment duration of 52 weeks each. They compared nintedanib 150 mg twice daily with placebo.

Study 1199.187 was a randomized (1:1 ratio) phase 3b study, which was originally designed with a 2-arm double-blind treatment (nintedanib 150 mg twice daily versus placebo) and a

treatment duration of 52 weeks. In the framework of a global amendment, the 2-arm blinded phase was shortened to 24 weeks, and all patients were switched to the nintedanib study arm for up to 54 weeks. For part of the population, the blinded phase was longer than 24 weeks (depending on the time point of study inclusion in relation to the time point of the global amendment). The total blinded 2-arm phase is relevant for the present benefit assessment.

The TOMORROW study was a 5-arm, controlled, double-blind phase 2 dose-ranging study with a study duration of 52 weeks. Randomization to the study arms was staggered: The study arms of the intervention nintedanib were released successively with increasing dosage (50 mg once daily, 50 mg twice daily, 100 mg twice daily, 150 mg twice daily). With the release of each new study arm, newly included patients were randomized in different proportions to all study arms released at that time. Thus, a total randomization of 1:1:1:1:1 to the individual study arms was achieved by the end of the study. The study arms with placebo and with nintedanib 150 mg twice daily were included in the present benefit assessment.

All 4 studies enrolled adults aged ≥ 40 years with diagnosis of IPF according to international guidelines [3,4]. The INPULSIS 1 study enrolled a total of 515 adults (nintedanib + BSC: 309, placebo + BSC: 206), INPULSIS 2 a total of 551 adults (nintedanib + BSC: 331, placebo + BSC: 220). Study 1199.187 enrolled a total of 113 patients (nintedanib + BSC: 56, placebo + BSC: 57) and TOMORROW a total of 173 patients (nintedanib + BSC: 86, placebo + BSC: 87).

Treatment with nintedanib in the studies INPULSIS-1, INPULSIS-2 and 1199.187 was in compliance with the SPC [5]. Treatment with nintedanib in the TOMORROW study was also in compliance with the SPC (see Section 2.3.1). On occurrence of AEs, all studies mandated a dose reduction to 100 mg nintedanib twice daily or treatment interruption. Both INPULSIS studies and study 1199.187 mandated re-escalation of the dosage to 150 mg twice daily or re-initiation of treatment, preferably with the reduced (100 mg twice daily) or with the original dosage (150 mg twice daily), once AEs have resolved. TOMORROW did not mandate re-initiation of treatment or re-escalation of the dosage (see Section 2.3.1).

Primary outcome in the studies INPULSIS-1, INPULSIS-2 and TOMORROW was the annual rate of decline in FVC. Primary outcome in study 1199.187 was the change in HRCT QLF score. Patient-relevant secondary outcomes in all 4 studies were recorded on overall survival, morbidity, health-related quality of life and AEs.

Implementation of the appropriate comparator therapy BSC

It can be inferred from guidelines that only few supportive and/or symptomatic treatments, such as oxygen therapy or pulmonary rehabilitation, which may be used in the framework of BSC, are available outside drug treatment with nintedanib or pirfenidone in the present therapeutic indication. [6-8].

There was no information regarding the implementation of non-drug interventions, such as pulmonary rehabilitation, for any of the 4 studies. It therefore remains unclear to what extent these interventions were used. However, it could be inferred from the results on the concomitant medication used that supportive interventions such as oxygen therapy, bronchodilators or antitussive drugs were used both in the intervention and in the comparator arm of all 4 studies. Lung transplants were also performed during the studies. Furthermore, the 3 studies had only few restrictions regarding concomitant medication, such as azathioprine or N-acetylcysteine. The restricted drugs are also not recommended in guidelines [6,7]. In addition, the investigators could use any drug of their choice, with the exception of pirfenidone, for the treatment of acute exacerbations. It is therefore assumed that the patients in all 4 included studies received BSC in the sense of the ACT. This concurs with the company's approach.

Hereinafter, the comparator therapy is referred to as "placebo + BSC" and the intervention as "nintedanib + BSC".

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

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

Study Characteristics Category	INPULSIS-1		INPULSIS-2		Study 1199.187		TOMORROW	
	Nintedanib + BSC	Placebo + BSC	Nintedanib + BSC	Placebo + BSC	Nintedanib + BSC	Placebo + BSC	Nintedanib + BSC	Placebo + BSC
	N = 309	N = 204	N = 329	N = 219	N = 56	N = 57	N = 85	N = 85
Age [years], mean (SD)	67 (8)	67 (8)	66 (8)	67 (8)	69 (8)	66 (9)	65 (8)	65 (9)
Sex [F/M], %	19/81	20/80	22/78	22/78	20/80	35/65	24/76	26/74
Ethnicity, n (%)								
White	198 (64.1)	135 (66.2)	162 (49.2)	113 (51.6)	54 (96.4)	54 (94.7)	61 (71.8)	65 (76.5)
Asian	66 (21.4)	41 (20.1)	128 (38.9)	86 (39.3)	2 (3.6)	3 (5.3)	24 (28.2)	20 (23.5)
Black	0 (0)	0 (0)	2 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown[a]	45 (14.6)	28 (13.7)	37 (11.2)	19 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)
Time since IPF diagnosis [years], mean (SD)	1.7 (1.4)	1.6 (1.4)	1.6 (1.3)	1.6 (1.3)	1.5 (1.4)	1.5 (1.4)	1.0 (1.2)	1.4 (1.5)
Smoking status, n (%)								
Never-smoker	71 (23.0)	51 (25.0)	103 (31.1)	71 (32.4)	14 (25.0)	17 (29.8)	25 (29.4)	28 (32.9)
Ex-smoker	217 (70.2)	144 (70.6)	218 (66.3)	139 (63.5)	41 (73.2)	40 (70.2)	58 (68.2)	51 (60.0)
Smoker	21 (6.8)	9 (4.4)	8 (2.4)	9 (4.1)	1 (1.8)	0 (0)	2 (2.4)	6 (7.1)
Centrilobular emphysema, n (%)								
No	191 (61.8)	126 (61.8)	193 (58.7)	131 (59.8)	ND	ND	62 (72.9)[b]	66 (77.6)[b]
Yes	118 (38.2)	78 (38.2)	136 (41.3)	88 (40.2)	ND	ND	23 (27.1)	19 (22.4)
FEV1 [% predicted], mean (SD)	79.5 (17.0)	80.5 (17.3)	80 (18.1)	78.1 (19.0)	78.0 (17.4)	78.1 (19.4)	79.1 (18.5)	81.7 (17.6)
FEV1:FVC [%], mean (SD)	81.5 (5.4)	80.8 (6.1)	81.8 (6.3)	82.4 (5.7)	ND	ND	81.0 (7.3)	81.8 (5.6)
SpO_2 [%], mean (SD)	95.9 (2.0)	95.9 (1.9)	95.8 (2.6)	95.7 (2.1)	95.1 (2.4)	95.1 (2.5)	95.6 (1.7)	95.3 (2.2)
DL_{CO} [mmol/min/kPa], mean (SD)	4.0 (1.2)	4.0 (1.1)	3.8 (1.2)	3.8 (1.3)	4.4 (1.2)	4.3 (1.4)	3.7 (1.0)	3.8 (1.1)

(continued)

Table 8: Characteristics of the study populations – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

Study	INPULSIS-1		INPULSIS-2		Study 1199.187		TOMORROW	
Characteristics Category	Nintedanib + BSC	Placebo + BSC	Nintedanib + BSC	Placebo + BSC	Nintedanib + BSC	Placebo + BSC	Nintedanib + BSC	Placebo + BSC
	N = 309	N = 204	N = 329	N = 219	N = 56	N = 57	N = 85	N = 85
DL_{CO} [% predicted], mean (SD)	ND	ND	ND	ND	53.6 (13.6)	52.5 (14.7)	47.5 (11.0)	48.4 (12.9)
Prior therapy								
Bronchodilator	61 (19.7)	34 (16.7)	68 (20.7)	38 (17.4)	13 (23.2)	16 (28.1)	ND	ND
Systemic corticosteroids	68 (22.0)	43 (21.1)	68 (20.7)	46 (21.0)	3 (5.4)	8 (14.0)	10 (11.8)	8 (9.4)
Oxygen	28 (9.1)	16 (7.8)	29 (8.8)	19 (8.7)	4 (7.1)	7 (12.3)	ND	ND
Treatment discontinuation, n (%)	78 (25.2)	36 (17.6)	78 (23.7)	44 (20.1)	13 (23.2)	14 (24.6)	32 (37.6)	24 (28.2)
Study discontinuation, n (%)	49 (15.9)	30 (14.7)	57 (17.3)	40 (18.3)	4 (7.1)	6 (10.5)	ND	ND

a: The characteristic “ethnicity” was not recorded in France due to corresponding legal regulations.
b: Institute’s calculation.

BSC: best supportive care; DL_{co}: Diffusing Capacity of the Lung for Carbon Monoxide; F: female; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; M: male; n: number of patients in the category; N: number of randomized and treated patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SpO_2: oxygen saturation; vs.: versus

The patient characteristics were largely comparable both between the studies and between the treatment arms of the individual studies. In all 4 studies, the average age of the included patients was about 65 to 69 years, most patients were men (between 76% and 81% in the nintedanib + BSC arms and between 65% and 80% in the comparator arms) and ex-smokers (about 66% to 73% under nintedanib + BSC versus about 60% to 71% under placebo + BSC). A large part of the population was white, with a notably higher proportion in study 1199.187 (about 96%) than in the studies INPULSIS-1, INPULSIS-2 and TOMORROW (about 50% to 77%). About 7% to 9% (nintedanib + BSC) and about 8% to 12% (placebo + BSC) of the patients included had already received oxygen treatment in their prior therapy. In all 4 studies, the mean time since diagnosis was between 1 and just under 2 years.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: 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			
INPULSIS-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
INPULSIS-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
1199.187	Yes	Yes	Yes	Yes	Yes	Yes	Low
TOMORROW	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for all 4 studies. For the studies INPULSIS-1, INPULSIS-2 and 1199.187, this concurs with the assessment of the company. The company did not include TOMORROW and therefore provided no assessment of the risk of bias across outcomes in Module 4 A.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival

- Morbidity
  - adjudicated acute exacerbations
  - supplemental oxygen use
  - change in respiratory status (PGIC)
  - endurance (6-minute walking test)
  - cough (CASA-Q)
  - dyspnoea (SOBQ)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life (SGRQ)
- Side effects
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: nintedanib + BSC versus placebo + BSC

Study	Outcomes											
	Overall survival	Adjudicated acute exacerbations	Supplemental oxygen use	Change in respiratory status (PGIC)	Endurance (6-minute walking test)	Cough (CASA-Q[a])	Dyspnoea (SOBQ)	Health status (EQ-5D VAS)	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs	Specific AEs[b]
INPULSIS-1	Yes	Yes	No[c]	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
INPULSIS-2	Yes	Yes	No[c]	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1199.187	Yes	Yes	No[c]	No[c]	Yes	No[c]	Yes	No[c]	Yes	Yes	Yes	Yes
TOMORROW	Yes	Yes	Yes	No[c]	Yes	No[c]	No[c]	No[c]	Yes	Yes	Yes	Yes

a: Recorded using the domains cough symptoms and cough impact from the CASA-Q questionnaire.
b: The following events (MedDRA coding) are considered: gastrointestinal disorders (AE, SOC).
c: Outcome not recorded.

AE: adverse event; BSC: best supportive care; CASA-Q: Cough and Sputum Assessment Questionnaire; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOBQ: Shortness of Breath Questionnaire; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: 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	Adjudicated acute exacerbations	Supplemental oxygen use	Change in respiratory status (PGIC)	Endurance (6-minute walking test)	Cough (CASA-Q[a])	Dyspnoea (SOBQ)	Health status (EQ-5D VAS)	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs	Specific AEs[b]
INPULSIS-1	L	L	H[c]	–[d]	H[e]	–[d]	L	H[f]	L	L	L	L	L
INPULSIS-2	L	L	L	–[d]	H[e]	–[d]	L	L	L	L	L	L	L
1199.187	L	L	L	–[d]	–[d]	L	–[d]	H[f]	–[d]	H[f]	L	L	L
TOMORROW	L	L	L	L	–[d]	H[f, g]	–[d]	–[d]	–[d]	H[f, g]	L	L	L

a: Recorded using the domains cough symptoms and cough impact from the CASA-Q questionnaire.
b: The following events (MedDRA coding) are considered: gastrointestinal disorders (AE, SOC), including decisively diarrhoea (AE, PT).
c: Questionable whether sufficient blinding was maintained in the adjudication process (see Section 2.7.4.2 of the full dossier assessment).
d: Outcome not recorded.
e: High proportion of values imputed using non-responders (about 20%) with unclear reason for the lack of values at week 52.
f: High proportion of patients not included in the analysis (> 10%) or large difference between the treatment groups (> 5 percentage points).
g: Unclear proportion of LOCF-imputed values.

AE: adverse event; BSC: best supportive care; CASA-Q: Cough and Sputum Assessment Questionnaire; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; LOCF: last observation carried forward; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOBQ: Shortness of Breath Questionnaire; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

INPULSIS-1 and INPULSIS-2

For both studies, the risk of bias was rated as low for the results of the following outcomes: overall survival, cough (CASA-Q), health status (EQ-5D VAS), health-related quality of life (SGRQ), SAEs, discontinuation due to AEs, and the specific AE "gastrointestinal disorders". The risk of bias for the outcome "respiratory status" (PGIC) was rated as high for the results of both studies. The reason for this in both studies is a high proportion of about 20% of values imputed using non-responders, with the reason why the values at week 52 are missing being unclear. There were differences in the risk of bias between both studies for the outcome "adjudicated acute exacerbations" and "dyspnoea" (SOBQ). Whereas the risk of bias for the

results of these outcomes was rated as low in INPULSIS-2, it was rated as high in INPULSIS-1. For the results of the outcome "adjudicated acute exacerbations", this is due to the fact that it is questionable for the INPULSIS-1 study whether sufficient blinding of group allocation was maintained in the adjudication process (see Section 2.7.4.2 of the full dossier assessment). Although the INPULSIS-2 study was conducted following the same protocol, there were no indications of this in this study, so that the risk of bias for the results on the outcome "adjudicated acute exacerbations" was rated as low. For the outcome "dyspnoea" (SOBQ), the high risk of bias of the results in the INPULSIS-1 study was due to the fact that > 10% of the patients were not included in the analysis.

The assessment of the risk of bias deviates from that of the company, which assumed a low risk of bias for the results on the outcome "change in respiratory status" (PGIC) in both studies and for the results on the outcomes "adjudicated acute exacerbations" and "dyspnoea" (SOBQ) also in INPULSIS-1.

1199.187

For study 1199.187, the risk of bias was rated as low for the results of the following outcomes: overall survival, acute exacerbations, endurance (6-minute walking test), SAEs, discontinuation due to AEs, and gastrointestinal disorders. The risk of bias of the results on the outcomes "dyspnoea" (SOBQ) and "health-related quality of life" (SGRQ) was rated as high due to a difference between the treatment groups of > 5 percentage points of patients included in the analysis.

This deviates from the assessment of the company, which assumed a low risk of bias for the results on the outcomes "dyspnoea" (SOBQ) and "health-related quality of life" (SGRQ).

TOMORROW

The risk of bias was rated as low for the results on the following outcomes: overall survival, acute exacerbations, supplemental oxygen use, SAEs, discontinuation due to AEs, and gastrointestinal disorders. The risk of bias for the results on the outcomes "endurance" (6-minute walking test) and "health-related quality of life" (SGRQ) was rated as high due to a proportion of > 10% of patients not included in the assessment and due to the unclear proportion of values imputed using last observation carried forward (LOCF).

The company did not include the TOMORROW study in its benefit assessment and hence did not address the risk of bias of the results on the outcomes.

2.4.3 Results

Table 12 to Table 15 summarize the results on the comparison of nintedanib + BSC with placebo + BSC in patients with IPF. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. If available, Kaplan-Meier curves on the outcomes included are presented in Appendix B of the full dossier assessment. Results on common AEs are presented in Appendix C of the full dossier assessment.

Unless stated otherwise, results were recorded at week 52 in the studies INPULSIS-1, INPULSIS-2 and TOMORROW, and at week 24 in study 1199.187.

Table 12: Results (mortality and morbidity, time to event) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Outcome category **Outcome** **Study**	**Nintedanib + BSC** **N[a]**	**Nintedanib + BSC** **Median time to event in weeks [95% CI]** **Patients with event n (%)**	**Placebo + BSC** **N[a]**	**Placebo + BSC** **Median time to event in weeks [95% CI]** **Patients with event n (%)**	**Nintedanib + BSC vs. placebo + BSC** **HR [95% CI][b]; p-value[c]**
Mortality					
Overall survival					
INPULSIS-1	309	ND; 13 (4.2)	204	ND; 13 (6.4)	0.63 [0.29; 1.36]; 0.288
INPULSIS-2	329	ND; 22 (6.7)	219	ND; 20 (9.1)	0.74 [0.40; 1.35]; 0.300
1199.187	56	ND; 1 (1.8)	57	ND; 4 (7.0)	0.15 [0.02; 1.39]; 0.194
TOMORROW	86	ND; 7 (8.1)	87	ND; 9 (10.3)	0.73 [0.27; 1.98]; 0.538
Total					0.66 [0.37; 1.17]; 0.103[d]
Morbidity					
Adjudicated acute exacerbations					
INPULSIS-1	309	ND; 7 (2.3)	204	ND; 8 (3.9)	0.55 [0.20; 1.54]; 0.302
INPULSIS-2	329	ND; 5 (1.5)	219	ND; 16 (7.3)	0.20 [0.07; 0.56]; 0.001
Study 1199.187	56	ND 1 (1.8)	57	ND 2 (3.5)	0.39 [0.03; 4.91]; 0.576
TOMORROW[d]	86	ND 2 (2.3)	87	ND 12 (13.8)	0.16 [0.04; 0.71]; 0.016
Total					0.29 [0.11; 0.77]; 0.028[e]
Supplemental oxygen use					
INPULSIS-1				Outcome not recorded	
INPULSIS-2				Outcome not recorded	
1199.187				Outcome not recorded	
TOMORROW	86	ND 2 (2.3)	87	ND 3 (3.4)	0.66 [0.11; 4.00]; 0.652

(continued)

Table 12: Results (mortality and morbidity, time to event) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

a: All randomized patients (studies INPULSIS-1 and INPULSIS-2) or those for whom the intake of at least one dose of the study medication was documented (studies 1199.187 and TOMORROW).
b: Effect and CI calculated using the Cox proportional hazards model, adjusted by treatment, sex, age and height; in the TOMORROW study additionally by region.
c: p-value calculated with log-rank test.
d: Since no subsequent adjudication of exacerbations was conducted in the TOMORROW study, non-adjudicated acute exacerbations were used for this study.
e: Institute's calculation from meta-analysis with random effects (Knapp-Hartung method).
BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 13: Results (morbidity, dichotomous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Outcome category **Outcome** **Study**	**Nintedanib + BSC**		**Placebo + BSC**		**Nintedanib + BSC vs. placebo + BSC**
	N[a]	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Change in respiratory status (PGIC)[b]					
INPULSIS-1	309	188 (60.84)	204	112 (54.90)	1.11 [0.95; 1.29][c]
INPULSIS-2	329	203 (61.70)	219	118 (53.88)	1.15 [0.99; 1.33][c]
1199.187	Outcome not recorded				
TOMORROW	Outcome not recorded				
Total					1.13 [1.01; 1.25]; 0.028[d]

a: All randomized patients (studies INPULSIS-1 and INPULSIS-2).
b: Responder defined as "very much improved", "much improved", "minimally improved" or "no change". Missing values were rated as non-responders.
c: Institute's calculation of relative risk, CI (asymptotic).
d: Institute's calculation using meta-analysis with fixed effect.
BSC: best supportive care; CI: confidence interval; N: number of analysed patients; n: number of patients with (at least one) event; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Outcome category Outcome Study	Nintedanib + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Nintedanib + BSC vs. placebo + BSC MD [95% CI]; p-value
Morbidity							
Endurance (6-minute walking test, [m])[b]							
INPULSIS-1	Outcome not recorded						
INPULSIS-2	Outcome not recorded						
1199.187	55	345.46 (140.71)	4.93 (11.43)[c]	52	347.69 (146.26)	−13.01 (11.49)[c]	17.93 [−14.26; 50.12]; 0.272[c]
TOMORROW	63	437.0 (13.69)[d]	−29.35 (12.96)[e]	69	411.1 (15.90)[d]	−35.67 (12.73)[e]	6.32 [−27.08; 39.72]; 0.710[e]
Total							–[f]
Cough (CASA-Q)[g]							
Cough symptoms							
INPULSIS-1	302[h]	58.63 (23.59)	−0.76 (1.14)[c]	202[h]	56.29 (22.86)	−0.52 (1.40)[c]	−0.24 [−3.78; 3.30]; 0.894[c]
INPULSIS-2	323[h]	61.60 (23.89)	−0.33 (1.09)[c]	215[h]	62.52 (21.42)	−2.38 (1.33)[c]	2.05 [−1.31; 5.41]; 0.233[c]
1199.187	Outcome not recorded						
TOMORROW	Outcome not recorded						
Total							0.95 [−1.49; 3.38]; 0.445[i]
Cough impact							
INPULSIS-1	302[h]	74.22 (22.84)	−2.36 (1.01)[c]	202[h]	74.18 (22.34)	−4.00 (1.24)[c]	1.64 [−1.49; 4.77]; 0.304[c]
INPULSIS-2	322[h]	75.55 (24.12)	−2.58 (0.99)[c]	215[h]	77.04 (21.88)	−4.39 (1.21)[c]	1.81 [−1.26; 4.88]; 0.248[c]
1199.187	Outcome not recorded						
TOMORROW	Outcome not recorded						
Total							1.73 [−0.46; 3.92]; 0.121[i]

(continued)

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

Outcome category Outcome Study	Nintedanib + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Nintedanib + BSC vs. placebo + BSC MD [95% CI]; p-value
Dyspnoea (SOBQ)[j]							
INPULSIS-1	267	32.58 (22.98)	6.73 (1.11)[c]	178	32.24 (23.35)	7.61 (1.38)[c]	−0.88 [−4.35; 2.60]; 0.620[c]
INPULSIS-2	302	33.10 (25.70)	6.69 (1.07)[c]	204	33.53 (24.08)	9.07 (1.30)[c]	−2.38 [−5.68; 0.93]; 0.159[c]
1199.187	53	25.39 (19.89)	3.42 (2.07)[c]	50	42.25 (24.55)	−2.48 (2.10)[c]	5.90 [−0.15; 11.95]; 0.056[c]
TOMORROW	Outcome not recorded						
Total							–[f]
Health status							
EQ-5D VAS[k]							
INPULSIS-1	293[h]	66.71 (17.42)	−2.95 (0.94)[c]	197[h]	68.02 (16.34)	−6.04 (1.17)[c]	3.09 [0.14; 6.03]; 0.040[c]
INPULSIS-2	312[h]	69.77 (18.85)	−2.50 (0.91)[c]	211[h]	67.75 (16.47)	−6.90 (1.11)[c]	4.39 [1.59; 7.20]; 0.002[c]
1199.187	Outcome not recorded						
TOMORROW	Outcome not recorded						
Total							3.81 [1.78; 5.85]; < 0.001[i] Hedges' g: 0.25 [0.12; 0.39][l]
Health-related quality of life							
SGRQ total score[m]							
INPULSIS-1	289	39.55 (17.63)	4.34 (0.80)[c]	200	39.79 (18.48)	4.39 (0.96)[c]	−0.05 [−2.50; 2.40]; 0.966[c]
INPULSIS-2	320	39.46 (20.47)	2.80 (0.73)[c]	213	39.39 (18.65)	5.48 (0.89)[c]	−2.69 [−4.95; −0.43]; 0.020[c] Hedges' g: −0.21 [−0.38; −0.03][l]
1199.187	55	35.75 (17.49)	−2.44 (1.54)[c]	53	44.39 (18.49)	−2.75 (1.55)[c]	0.31 [−4.10; 4.72]; 0.889[c]
TOMORROW	75	40.2 (2.09)[d]	−0.66 (1.71)[e]	79	41.8 (2.03)[d]	5.46 (1.73)[e]	−6.12 [−10.57; −1.67]; 0.007[e] Hedges' g: −0.43 [−0.75; −0.11][l]
Total							–[f]

(continued)

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

Outcome category Outcome Study	Nintedanib + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Nintedanib + BSC vs. placebo + BSC MD [95% CI]; p-value
SGRQ domains (supplementary)							
Symptoms[m]							
INPULSIS-1	300	45.67 (22.05)	1.56 (1.10)[c]	202	45.23 (22.89)	3.89 (1.35)[c]	−2.32 [−5.74; 1.10][c]
INPULSIS-2	323	43.04 (23.50)	2.03 (1.06)[c]	214	43.84 (21.64)	3.43 (1.30)[c]	−1.40 [−4.69; 1.88][c]
1199.187	No data available						
TOMORROW	76	43.2 (2.96)[d]	−3.14 (2.40)[e]	79	42.8 (2.47)[d]	6.45 (2.45)[e]	−9.60 [−15.86; −3.34][e]
Activity[m]							
INPULSIS-1	295	52.2 (20.62)	4.62 (0.91)[c]	200	52.1 (21.22)	5.81 (1.10)[c]	−1.19 [−3.99; 1.61][c]
INPULSIS-2	322	51.8 (23.44)	3.89 (0.86)[c]	214	52.8 (21.34)	7.20 (1.05)[c]	−3.31 [−5.97; −0.64][c]
1199.187	No data available						
TOMORROW	75	53.5 (2.37)[d]	0.32 (1.89)[e]	79	54.5 (2.50)[d]	7.48 (1.91)[e]	−7.16 [−12.06; −2.26][e]
Impact[m]							
INPULSIS-1	291	30.1 (18.65)	4.87 (0.92)[c]	202	30.3 (19.39)	4.01 (1.11)[c]	0.86 [−1.97; 3.70][c]
INPULSIS-2	320	30.8 (21.92)	2.85 (0.85)[c]	215	29.7 (20.94)	5.93 (1.04)[c]	−3.08 [−5.71; −0.45][c]
1199.187	No data available						
TOMORROW	75	31.1 (2.21)[d]	−0.14 (1.97)[e]	79	33.8 (2.24)[d]	4.21 (1.99)[e]	−4.35 [−9.46; 0.76][e]

(continued)

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b: A negative change indicates worse endurance; a positive group difference corresponds to an advantage of nintedanib + BSC.
c: MMRM analysis adjusted for treatment, visit, baseline value and study participant, as well as interaction terms for treatment and visit, baseline value and visit.
d: Standard error.
e: ANCOVA with imputation of missing values according to LOCF, adjusted for treatment, baseline value and region.
f: No analysis using a suitable model with meaningfully interpretable effect estimation and confidence interval available (see description of the results on the respective outcome).
g: A higher value indicates fewer cough symptoms or less impact of cough; a negative group difference corresponds to a disadvantage of nintedanib + BSC.
h: Module 4 A of the dossier provides a higher number of patients included in the analysis than Module 5. The information from Module 5 is presented here.
i: Meta-analysis by the company based on individual patient data.
j: A low total score indicates less impact of shortness of breath; a negative group difference corresponds to an advantage of nintedanib + BSC.
k: A higher value indicates better health status; a positive group difference corresponds to an advantage of nintedanib + BSC.
l: Institute's calculation based on effect estimation of the mean difference and the CI of the MMRM or the ANCOVA or the meta-analysis with fixed effect.
m: A higher value indicates greater impact; a negative group difference corresponds to an advantage of nintedanib + BSC.

ANCOVA: analysis of covariance; BSC: best supportive care; CASA-Q: Cough and Sputum Assessment Questionnaire; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LOCF: last observation carried forward; m:metre; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SGRQ: St. George's Respiratory Questionnaire; SOBQ: Shortness of Breath Questionnaire; VAS: visual analogue scale; vs.: versus

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

Outcome category Outcome Study	Nintedanib + BSC N[a]	 Patients with event n (%)	Placebo + BSC N	 Patients with event n (%)	Nintedanib + BSC vs. placebo + BSC RR [95% CI]; p-value[b]
Side effects					
AEs (supplementary information)					
INPULSIS-1	309	298 (96.4)	204	181 (88.7)	–
INPULSIS-2	329	311 (94.5)	219	198 (90.4)	–
1199.187	56	55 (98.2)	57	52 (91.2)	–
TOMORROW	85	80 (94.1)	85	77 (90.6)	–
SAEs					
INPULSIS-1	309	96 (31.1)	204	55 (27.0)	1.15 [0.87; 1.53]; 0.318
INPULSIS-2	329	98 (29.8)	219	72 (32.9)	0.91 [0.70; 1.17]; 0.444
1199.187	56	8 (14.3)	57	9 (15.8)	0.90 [0.38; 2.18]; 0.823
TOMORROW	85	23 (27.1)	85	26 (30.6)	0.88 [0.55; 1.42]; 0.682[c]
Total					0.99 [0.79; 1.23]; 0.866[d]
Discontinuation due to AEs.					
INPULSIS-1	309	65 (21.0)	204	22 (10.8)	1.95 [1.24; 3.06]; 0.002
INPULSIS-2	329	58 (17.6)	219	33 (15.1)	1.17 [0.79; 1.73]; 0.430
1199.187	56	8 (14.3)	57	3 (5.3)	2.71 [0.76; 9.71]; 0.106
TOMORROW	85	26 (30.6)	85	22 (25.9)	1.18 [0.73; 1.91]; 0.532[c]
Total					1.44 [0.86; 2.40]; 0.109[d]
Gastrointestinal disorders (SOC)					
INPULSIS-1	309	235 (76.1)	204	71 (34.8)	2.19 [1.79; 2.66]; < 0.001[c]
INPULSIS-2	329	253 (76.9)	219	97 (44.3)	1.74 [1.48; 2.04]; < 0.001[c]
1199.187	56	48 (85.7)	57	30 (52.6)	1.63 [1.25; 2.13]; < 0.001[c]
TOMORROW	85	63 (74.1)	85	27 (31.8)	2.33 [1.67; 3.26]; < 0.001[c]
Total					1.92 [1.48; 2.49]; 0.004[d]

(continued)

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

Outcome category Outcome Study	Nintedanib + BSC N[a]	 Patients with event n (%)	Placebo + BSC N	 Patients with event n (%)	Nintedanib + BSC vs. placebo + BSC RR [95% CI]; p-value[b]
Including:					
Diarrhoea (PT)					
INPULSIS-1	*309*	*190 (61.5)*	*204*	*38 (18.6)*	*3.30 [2.45; 4.46]; < 0.001*
INPULSIS-2	*329*	*208 (63.2)*	*219*	*40 (18.3)*	*3.46 [2.58; 4.64]; < 0.001*
1199.187	*56*	*40 (71.4)*	*57*	*21 (36.8)*	*1.94 [1.33; 2.83]; < 0.001*
TOMORROW	*85*	*47 (55.3)*	*85*	*13 (15.3)*	*3.62 [2.12; 6.18]; < 0.001*[c]
Total					*2.99 [1.90; 4.70]; 0.005*[d]
Nausea (PT)					
INPULSIS-1	*309*	*70 (22.7)*	*204*	*12 (5.9)*	*3.85 [2.14; 6.92]; < 0.001*
INPULSIS-2	*329*	*86 (26.1)*	*219*	*16 (7.3)*	*3.58 [2.16; 5.93]; < 0.001*
Study 1199.187	*56*	*16 (28.6)*	*57*	*13 (22.8)*	*1.25 [0.67; 2.36]; 0.483*
TOMORROW	*85*	*20 (23.5)*	*85*	*8 (9.4)*	*2.50 [1.17; 5.36]; 0.014*[c]
Total					*Heterogeneity*[e]*:* Q = 8.57; p-value = 0.036; I^2: 65.0%
Vomiting (PT)					
INPULSIS-1	*309*	*40 (12.9)*	*204*	*4 (2.0)*	*6.60 [2.40; 18.2]; < 0.001*
INPULSIS-2	*329*	*34 (10.3)*	*219*	*7 (3.2)*	*3.23 [1.46; 7.16]; 0.002*
Study 1199.187	*56*	*9 (16.1)*	*57*	*3 (5.3)*	*3.05 [0.87; 10.70]; 0.062*
TOMORROW	*85*	*11 (12.9)*	*85*	*4 (4.7)*	*2.75 [0.91; 8.30]; 0.065*[c]
Total					*3.69 [1.99; 6.83]; 0.007*[d]
Abdominal pain upper (PT)					
INPULSIS-1	*309*	*23 (7.4)*	*204*	*9 (4.4)*	*1.69 [0.80; 3.57];* 0.187[c]
INPULSIS-2	*329*	*18 (5.5)*	*219*	*6 (2.7)*	*2.00 [0.81; 4.95];* 0.135[c]
Study 1199.187	*56*	*3 (5.4)*	*57*	*3 (5.3)*	*1.02 [0.21; 4.83][c]; ND*
TOMORROW	*85*	*10 (11.8)*	*85*	*3 (3.5)*	*3.33 [0.95; 11.69]; 0.046*[c]
Total					*1.88 [1.06; 3.32]; 0.039*[d]

a: Patients for whom the intake of at least one dose of the study medication was documented (treated set).
b: χ^2 test.
c: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [9]).
d: Institute's calculation from meta-analysis with random effects (Knapp-Hartung method).
e: Q test for heterogeneity.

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; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Based on the available data, at most proof, e.g. of an added benefit, can be derived for the following outcomes: overall survival, acute exacerbations, endurance (6-minute walking test), cough (CASA-Q), dyspnoea (SOBQ), health status (EQ-5D VAS), health-related quality of life (SGRQ), SAEs, discontinuation due to AEs, and gastrointestinal disorders. Since the outcome "supplemental oxygen use" was only recorded in one study (TOMORROW), at most an indication can be derived on the basis of the results of this outcome. Due to the high risk of bias, at most an indication can be determined for the outcome "change in respiratory status" (PGIC).

Mortality

Overall survival

In the present benefit assessment, the results of time to death, irrespective of the cause, were used for the outcome "overall survival".

The meta-analysis of the 4 studies INPULSIS-1, INPULSIS-2, 1199.187 and TOMORROW showed no statistically significant difference between the treatment groups for the outcome "overall survival". 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 derived proof of an added benefit of nintedanib for mortality across outcomes.

Morbidity

Adjudicated acute exacerbations

The meta-analysis of the 4 studies INPULSIS-1, INPULSIS-2, 1199.187 and TOMORROW showed a statistically significant difference in favour of nintedanib + BSC for the outcome "time to first adjudicated acute exacerbation". This resulted in proof of an added benefit of nintedanib + BSC in comparison with BSC.

This concurs with the company's assessment.

Supplemental oxygen use

There was no statistically significant difference between the treatment groups for the outcome "supplemental oxygen use" recorded in the TOMORROW study. This resulted in no hint of an added benefit of nintedanib + BSC in comparison with BSC. An added benefit is therefore not proven.

The company did not include the TOMORROW study, and hence the outcome "supplemental oxygen use", in its assessment of the added benefit.

Change in respiratory status (PGIC)

The change in respiratory status was recorded in INPULSIS-1 and INPULSIS-2 with the PGIC using responder analyses.

The meta-analysis of INPULSIS-1 and INPULSIS-2 showed a statistically significant difference in favour of nintedanib + BSC versus placebo + BSC for the outcome "change in respiratory status" (PGIC). The effect in this outcome from the category of non-serious/non-severe symptoms was no more than marginal, however (see Section 2.5.1). 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 allocated the outcome "change in respiratory status" (PGIC) to health-related quality of life, for which it derived an indication of added benefit of nintedanib across outcomes.

Endurance (6-minute walking test)

No suitable statistical model with a meaningfully interpretable CI is available for a meta-analysis for the outcome "endurance" (6-minute walking test) recorded in 1199.187 and TOMORROW. The results on this outcome were therefore interpreted on the basis of the results of the individual studies 1199.187 and TOMORROW by checking whether the effects pointed in the same direction [1].

Neither 1199.187 nor TOMORROW showed a statistically significant difference between the treatment groups for the outcome "endurance" (6-minute walking test). 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 approach of the company, which provided a descriptive presentation of this outcome based on study 1199.187 and therefore did not use it for the assessment of the added benefit of nintedanib.

Cough (CASA-Q)

The outcome "cough" was analysed in the studies INPULSIS-1 and INPULSIS-2 as change at end of study in both CASA-Q domains on cough symptoms and cough impact.

The meta-analysis of the 2 studies INPULSIS-1 and INPULSIS-2 showed no statistically significant difference between the treatment groups for the outcome both in cough symptoms and in cough impact. 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 allocated the outcome "cough" (CASA-Q) to health-related quality of life, for which it derived an indication of added benefit of nintedanib across outcomes.

Dyspnoea (SOBQ)

The outcome "dyspnoea" was recorded in both INPULSIS studies and in study 1199.187 using the SOBQ total score as change at end of study.

No statistical model with a meaningfully interpretable CI is available for a meta-analysis for the outcome "dyspnoea" (SOBQ). The results on this outcome were therefore interpreted on the basis of the results of the individual studies INPULSIS-1, INPULSIS-2 and 1199.187 by checking whether the effects pointed in the same direction [1]. None of the studies showed a statistically significant difference between the treatment groups. 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 allocated the outcome "dyspnoea" (SOBQ) to health-related quality of life, for which it derived an indication of added benefit of nintedanib across outcomes.

Health status (EQ-5D VAS)

The meta-analysis of INPULSIS-1 and INPULSIS-2 showed a statistically significant difference in favour of nintedanib + BSC for the outcome "health status" recorded with the EQ-5D VAS. However, the 95% CI of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. 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 allocated the outcome "health status" (EQ-5D VAS) to health-related quality of life, for which it derived an indication of added benefit of nintedanib across outcomes.

Health-related quality of life

Health-related quality of life (SGRQ)

The outcome "health-related quality of life", measured with the SGRQ total score, contains the domains of symptoms, activity and impact. The analyses on the change in total score in comparison with baseline were included in the present benefit assessment.

No suitable statistical model with meaningfully interpretable effect estimation and meaningfully interpretable CI is available for a meta-analysis for the outcome "health status" measured with the SGRQ, which was recorded in all 4 studies. The results on this outcome were therefore interpreted on the basis of the results of the 4 individual studies by checking whether the effects pointed in the same direction [1].

In terms of statistical significance, the results pointed in the same direction. For Hedges' g, however, there were no effects in the same direction regarding the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. Hence, there was no hint of an added benefit of nintedanib + BSC in comparison with BSC in the overall conclusion on the outcome "health-related quality of life" (SGRQ); an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of added benefit of nintedanib for health-related quality of life across outcomes.

Side effects

Serious adverse events

The meta-analysis of the 4 included studies showed no statistically significant difference between the treatment groups 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 adverse events

The meta-analysis of the 4 included studies showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". 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 deviates from the assessment of the company, which saw a disadvantage of nintedanib on the basis of the results from the meta-analysis of the studies INPULSIS-1, INPULSIS-2 and 1199.187 without making a statement on probability.

Specific adverse event "gastrointestinal disorders"

The meta-analysis of the 4 included studies showed a statistically significant difference to the disadvantage of nintedanib + BSC in comparison with placebo + BSC for the specific AE "gastrointestinal disorders" (SOC). There was a low risk of bias for the outcome. This resulted in proof of greater harm from nintedanib + BSC in comparison with BSC.

This effect was based on events in the PTs diarrhoea, nausea, vomiting and abdominal pain upper, which showed consistent effects to the disadvantage of nintedanib + BSC across the studies.

This is in line with the assessment of the company, which saw a disadvantage of nintedanib for the outcome without making a statement on probability.

2.4.4 Subgroups and other effect modifiers

No results are available on subgroup analyses based on the individual studies, so that the results on subgroups cannot be interpreted meaningfully. Thus, the available subgroup results are not taken into account in the benefit assessment. The pooled evaluations of subgroup analyses presented by the company are addressed in Section 2.7.4.3.4 of the full dossier assessment.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, 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 16).

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

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Adjudicated acute exacerbations

For patients with IPF, exacerbations are associated with noticeable worsening of their symptoms and, additionally, worsening of their prognosis. They are therefore allocated to the outcome category of serious/severe symptoms/late complications.

Change in respiratory status (PGIC)

The PGIC questionnaire measures a change in symptoms, but makes no statement on their severity. In addition, despite the severity of the disease IPF, the health status of the patients included in the studies was rather good, which is confirmed by the quality of life and functional scales. There is no further information available to draw conclusions about the severity of the outcome. The outcome “change in respiratory status” (PGIC) was therefore allocated to the outcome category of non-serious/non-severe symptoms.

Gastrointestinal disorders

The events that occurred in the specific AE “gastrointestinal disorders” were largely non-serious. The outcome was therefore allocated to the category “non-serious/non-severe side effects”.

Table 16: Extent of added benefit at outcome level: nintedanib + BSC vs. placebo + BSC

Outcome category **Outcome**	**Nintedanib + BSC vs. placebo + BSC** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	1.8% to 8.1% vs. 6.4% to 10.3%[c] HR: 0.66 [0.37; 1.17]; p = 0.103	Lesser benefit/added benefit not proven
Morbidity		
Adjudicated acute exacerbations	1.8% to 2.3% vs. 3.5% to 13.8%[c] HR: 0.29 [0.11; 0.77]; p = 0.028 probability: "proof"	Outcome category: serious/severe symptoms $0.75 \leq CI_u < 0.90$ added benefit, extent "considerable"
Endurance (6-minute walking test)	−29.4 to 4.9 vs. −35.7 to −13.0[c] no significant effects in the studies	Lesser benefit/added benefit not proven
Supplemental oxygen use	2.3% vs. 3.4% HR: 0.66 [0.11; 4.00]; p = 0.652	Lesser benefit/added benefit not proven
Cough (CASA-Q)		
Cough symptoms	−0.76 to −0.33 vs. −2.38 to −0.52[c] MD: 0.95 [−1.49; 3.38]; p = 0.445	Lesser benefit/added benefit not proven
Cough impact	−2.58 to −2.36 vs. −4.39 to −4.00[c] MD: 1.73 [−0.46; 3.92]; p = 0.121	Lesser benefit/added benefit not proven
Dyspnoea (SOBQ)	3.42 to 6.73% vs. −2.48 to 9.07[c] no significant effects in the studies	Lesser benefit/added benefit not proven
Change in respiratory status (PGIC)	60.8% to 61.7% vs. 53.9% to 54.9%[c] RR: 1.13 [1.01; 1.25]; p = 0.028 RR: 0.88 [0.80; 0.99][d]	Outcome category: non-serious/non-severe symptoms $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[e]
Health status (EQ-5D VAS)	−2.50 to −2.95% vs. −6.90 to −6.04[c] MD: 3.81 [1.78; 5.85]; p < 0.001 Hedges' g: 0.25 [0.12; 0.39][f]	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: nintedanib + BSC vs. placebo + BSC (continued)

Outcome category **Outcome**	**Nintedanib + BSC vs. placebo + BSC** **Proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
SGRQ	−2.44 to 4.34 vs. −2.75 to 5.48[c] no significant or relevant effects in the studies[g]	Lesser benefit/added benefit not proven
Side effects		
SAEs	14.3% to 31.1% vs. 15.8% to 32.9%[c] RR: 0.99 [0.79; 1.23]; p = 0.866	Greater/lesser harm not proven
Discontinuation due to AEs	14.3% to 30.6% vs. 5.3% to 25.9%[c] RR: 1.44 [0.86; 2.40]; p = 0.109	Greater/lesser harm not proven
Gastrointestinal disorders (SOC, including the PTs on diarrhoea, nausea, vomiting and abdominal pain upper)	74.1% to 85.7% vs. 31.8% to 52.6%[c] RR: 1.92 [1.48; 2.49]; p = 0.004 RR: 0.52 [0.40; 0.68][d] probability: "proof"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_u).
c: Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies.
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: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
g: See Section 2.4.3 for details.

BSC: best supportive care; CASA-Q: Cough and Sputum Assessment Questionnaire; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; HR: hazard ratio; MD: mean difference; PGIC: Patient Global Impression of Change; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SOBQ: Shortness of Breath Questionnaire; SOC: System Organ Class; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of nintedanib + BSC compared with BSC

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ adjudicated acute exacerbations: proof of considerable added benefit	Non-serious/non-severe side effects ▪ gastrointestinal disorders (including diarrhoea, nausea, vomiting and abdominal pain upper): proof of greater harm – extent: "considerable"
BSC: best supportive care	

The overall consideration shows one positive and one negative effect of nintedanib + BSC versus BSC, each with the probability "proof" and the extent "considerable".

The positive effect was shown in the outcome category of serious/severe symptoms/late complications, the negative effect in the outcome category of non-serious/non-severe side effects. The negative effect in the SOC of gastrointestinal disorders did not completely outweigh the advantage in exacerbations, but resulted in a downgrading of the extent of the added benefit.

In summary, there is proof of a minor added benefit of nintedanib + BSC versus BSC for patients with IPF.

The result of the assessment of the added benefit of nintedanib in comparison with the ACT is summarized in Table 18.

Table 18: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with idiopathic pulmonary fibrosis (IPF)	Pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to the approval) or **best supportive care[b, c]**	Proof of minor added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: Best supportive care 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.
c: The G-BA points out that, in principle, lung transplant is a treatment option for patients with IPF, but that, given the limited availability of suitable donor organs, this cannot be assumed to be a general treatment option. Nevertheless, patients in studies that are used for the benefit assessment could be considered also in case of a lung transplant in the course of the study in the sense of a permitted treatment switch. Such a treatment switch may correspond to the actual health care setting. Observation of these patients should be continued even after completion of the experimental or comparator intervention of the study.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IPF: idiopathic pulmonary fibrosis

The assessment described above deviates from that of the company, which claimed an indication of considerable added benefit for nintedanib versus BSC for patients with IPF.

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

2.6 List of included studies

INPULSIS 1

Boehringer Ingelheim. A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual forced vital capacity decline, in patients with idiopathic pulmonary fibrosis (IPF) [online]. In: Clinical Trials Registry India. 26.03.2019 [Accessed: 29.04.2019]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3063.

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INPULSIS 2

Boehringer Ingelheim. A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual forced vital capacity decline, in patients with idiopathic pulmonary fibrosis (IPF) [online]. In: Clinical Trials Registry India. 26.03.2019 [Accessed: 29.04.2019]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3913.

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TOMORROW

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