Nintedanib (clinically significant, progressive fibrosing interstitial lung diseases, 6 to 17 years)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Nintedanib (klinisch signifikante progredient fibrosierende interstitielle Lungenerkrankungen, 6 bis 17 Jahre) – Nutzenbewertung gemäß § 35a SGB V*. 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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Medical and scientific advice

- Thomas O. F. Wagner

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

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I List of abbreviations

Abbreviation	Meaning
6MWT	6-minute walking test
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HRCT	high-resolution computed tomography
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
PedsQL	Pediatric Quality of Life Inventory
PF-ILD	progressive fibrosing interstitial lung diseases
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SOC	System Organ Class
SSc-ILD	systemic sclerosis-associated interstitial lung disease

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 17 February 2025.

Research question

The aim of this report is to assess the added benefit of nintedanib in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in children and adolescents aged 6 to 17 years with clinically significant, progressive fibrosing interstitial lung diseases (PF-ILD).

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of nintedanib

Therapeutic indication	**ACT**[a]
Children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases (PF-ILD)[b]	BSC[c, d]

a. Presented is 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 the quality of life.
d. Further comments from the G-BA
- Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung disease, but are of secondary importance in PF-ILD. Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue can help to alleviate symptoms. The type and scope of the interventions used must be documented.
- In principle, a lung transplant is a treatment option that can be considered for patients with progressive interstitial lung disease. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication. Nevertheless, patients in studies used for the benefit assessment could also be included in the event of a lung transplantation during the course of the study, in terms 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; BSC: best supportive care; G-BA: Federal Joint Committee; PF-ILD: progressive fibrosing interstitial lung disease

Concurring with the G-BA, the company determined BSC as the ACT.

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.

Study pool and study design

The study pool for the present benefit assessment consisted of the InPedILD study.

The InPedILD study is a randomized, double-blind, parallel-group study comparing nintedanib with placebo, each in addition to standard of care at the physician's discretion. The study was conducted from 2020 to 2022. Following the 24-week double-blind phase of the study, patients from both study arms were able to enter an open-label phase and were treated with nintedanib until the end of the study. Children and adolescents aged 6 to 17 years with clinically significant fibrosing interstitial lung disease (ILD) were enrolled. Fibrosing disease had to have been established within 12 months prior to Visit 1 by an investigator using high-resolution computed tomography (HRCT), and confirmed by a central review based on predefined criteria. In addition, patients had to have clinically significant disease at Visit 2, characterized by a Fan score ≥ 3 or one characteristic of clinical progression. Another inclusion criterion was a forced vital capacity (FVC) of ≥ 25% predicted, recorded at Visit 2.

The InPedILD study included a total of 39 patients who were randomly allocated in a 2:1 ratio to treatment with nintedanib (N = 26) or with placebo (N = 13). The stratification factor was the age category (6 to < 12 years versus 12 to ≤ 17 years). Treatment with nintedanib was in compliance with the summary of product characteristics (SmPC). Patients in the intervention arm received analogous placebo treatment. In addition, individually indicated drugs could be used in both study arms at the investigator's discretion unless they were explicitly prohibited. The supportive therapies allowed in the InPedILD study were considered to be a sufficient implementation of the ACT BSC.

The primary outcomes of the study were dose exposure at Week 2 and Week 26 and the safety profile at Week 24. Patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Notes on the study population of the InPedILD study

Patients with PF-ILD of various aetiologies and other underlying diseases

The InPedILD study included patients with clinically significant fibrosing ILD of various aetiologies. The company justified the grouping of different underlying diseases with a fibrosing phenotype with common pathophysiological processes, in which, depending on the underlying disease, different types of lung damage (e.g. inflammatory processes) can cause pulmonary fibrosis. An ad hoc expert group convened by the European Medicines Agency

(EMA) as part of the authorization process for nintedanib considered a grouping of fibrosing ILD of various aetiologies to be an acceptable solution, especially due to the similar pathomechanisms and the rarity of the individual underlying diseases. In summary, these assessments by the company and the EMA were based on pathophysiological considerations and were not supported by data. Overall, it remained unclear whether the results of the InPedILD study were transferable to other underlying ILD diseases that were underrepresented or not represented in the study.

Patients with progressive disease

Nintedanib is approved for the treatment of fibrosing ILD with a progressive phenotype, among other conditions. However, inclusion in the study was not limited to patients with progressive diseases. According to the inclusion criteria of the InPedILD study, patients had to have clinically significant disease. This was characterized by a Fan score ≥ 3 or one feature of clinical progression. Accordingly, inclusion in the study was possible even without documented signs of clinical progression based on a Fan score ≥ 3. The patient characteristics showed that around 10% had no clinical progression at baseline. In the authorization process, the EMA's ad-hoc expert group discussed the uncertainty regarding the diagnosis of progressive fibrosing diseases in children and adolescents, particularly regarding the lack of uniform criteria and the heterogeneity of the diseases, and emphasized the need for a multidisciplinary team for diagnosis and therapy. In addition, the information in the clinical study report (CSR) showed that there were protocol violations regarding the inclusion criteria for the presence of fibrosing ILD (approx. 5%). In principle, it was possible for a patient to not fulfil more than one of the above criteria. It was therefore unclear how many patients were affected in total.

Despite the uncertainties described above, the study population of the InPedILD study was presumed to adequately represent patients with clinically significant PF-ILD.

Patients with systemic sclerosis-associated interstitial lung disease

The InPedILD study included patients with clinically significant fibrosing ILD of various aetiologies. The patient characteristics showed that approximately 18% of the patients had a diagnosis of systemic sclerosis-associated interstitial lung disease (SSc-ILD). These were not covered by the therapeutic indication of the present benefit assessment. In Module 4 A, the company presented the results of the total population, including patients with SSc-ILD. As the patients who were not covered by the therapeutic indication of the given research question only represented a small proportion, the data from the overall population was used.

Data cuts

The InPedILD study is a completed study with a 24-week double-blind phase followed by an open-label phase. The data from the double-blind treatment phase at Week 24 were used for

this benefit assessment, as only these allowed a direct comparison of nintedanib + BSC with placebo + BSC.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for the InPedILD study.

The risk of bias for the results of the outcomes all-cause mortality, acute exacerbations or death, and of the outcomes in the category of side effects was assessed as low. For the outcome health-related quality of life, recorded using the Pediatric Quality of Life Inventory (PedsQL), the risk of bias for the results was assessed as high due to the large proportion (> 10%) of patients not considered in the analysis. Since no suitable analyses were available for the outcome endurance, recorded with the 6-minute walking test (6MWT), the risk of bias for this outcome was not assessed.

Taking into account the information provided by the company in Module 4 A of the dossier, it can be assumed that not all patients included in the InPedILD study were covered by the therapeutic indication of this research question of clinically significant PF-ILD. This assessment was based on the fact that some of the patients did not fulfil the criteria of a fibrosing disease according to the inclusion criteria, did not show any clinically documented signs of progression and, in addition, some of the patients fall under the therapeutic indication of SSc-ILD. The certainty of conclusions of the study results for the given research question was therefore limited. Based on the available information from the InPedILD study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

Results

Mortality

No deaths occurred in the course of the study. There is no hint of an added benefit of nintedanib + BSC in comparison with BSC for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Acute exacerbation or death

No statistically significant difference was shown between the treatment groups for the outcome acute exacerbation or death. There is no hint of an added benefit of nintedanib + BSC in comparison with BSC; an added benefit is therefore not proven.

Endurance (6MWT)

No suitable data are available for the outcome of endurance recorded with the 6MWT. There is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

Health-related quality of life (PedsQL)

No statistically significant difference between treatment groups was found for the outcome of health-related quality of life, recorded using the PedsQL. There is no hint of an added benefit of nintedanib + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes of serious adverse events (SAEs) or discontinuation due to adverse events (AEs). In each case, there is no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Specific AEs

Hepatobiliary disorders (SAEs), gastrointestinal disorders (AEs), diarrhoea (AEs)

No statistically significant difference between treatment groups was found for any of the outcomes hepatobiliary disorders (SAEs), gastrointestinal disorders (AEs) or diarrhoea (AEs). In each case, there is no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Evidence transfer

For the assessment of the added benefit of nintedanib in children and adolescents, in addition to the InPedILD study, the company used the INBUILD study with adults already known from dossier assessment A20-71 as part of an evidence transfer. The INBUILD study is a placebo-controlled, randomized parallel-group study on nintedanib. The study included adult patients with chronic PF-ILD, defined by features of diffuse fibrosing lung disease of > 10% extent on HRCT, among others. 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. Further inclusion criteria were a diffusing capacity of the lungs for carbon monoxide of 30 to 80% predicted and an FVC of ≥ 45% predicted. In principle, the physicians participating in the study could use individually indicated drugs in addition to the study medication in both study arms at their own discretion, unless they were explicitly excluded according to the study protocol. Overall, the supportive therapies allowed in the INBUILD study were considered to be a sufficient implementation of the ACT BSC.

Approach of the company

For the assessment of added benefit, the company used the overall population of the INBUILD study with adults in order to transfer its results to the target population of children and adolescents in the present therapeutic indication. It justified the need for an evidence transfer

by stating that the InPedILD study presented in its Module 4 A was designed as a pharmacokinetics and safety study within the paediatric investigation plan, due to the low prevalence in children and adolescents. Efficacy outcomes were only recorded as supportive information in the InPedILD study. According to the company, the marketing authorization of the paediatric therapeutic indication of nintedanib was based on the presented InPedILD study and was also justified by the transferability of efficacy and safety from the adult patient population to the paediatric patient population.

The company was of the opinion that the requirements for an evidence transfer were met. Referencing the EMA, it cited various criteria. It stated that the mechanism of action of nintedanib is comparable in adults, children and adolescents, and the pathogenesis and clinical picture are sufficiently similar. It added that the ACT determined by the G-BA for adults, children and adolescents was identical, and an added benefit of nintedanib was determined in adults in the therapeutic indication of other chronic PF-ILDs. The company additionally mentioned consistent effects in favour of nintedanib in the outcomes FVC and oxygen saturation, as well as comparable results regarding the safety of nintedanib in paediatric and adult patients.

Assessment of the company's data and approach

The derivation of the added benefit for adults in the therapeutic indication of chronic PF-ILD was mainly based on the outcome acute exacerbations or death. In the INBUILD study, acute exacerbations were defined as acute, clinically significant, respiratory deteriorations characterized by evidence of new widespread alveolar abnormality with further defining characteristics. In contrast, there were indications of greater harm from nintedanib for various outcomes in the side effects category.

In view of the data situation in the given very small sample and the problem that the operationalization in the relevant outcome acute exacerbations may not be comparable between InPedILD and INBUILD, a transfer of evidence is not possible in this situation.

Regardless of this, the company did not conduct an up-to-date information retrieval on the adult population in Module 4 A of the dossier and did not properly prepare a sufficiently suitable adjacent age stratum as a preferred approximation of the target population. It should be noted that addressing these aspects would not change the conclusion regarding the suitability of the evidence transfer in the given research question.

In summary, based on the available data, it is not possible to transfer the results of adults from the INBUILD study to children and adolescents.

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 InPedILD study showed neither effects in favour nor effects to the disadvantage of nintedanib in comparison with BSC.

In summary, there is no hint of an added benefit of nintedanib in comparison with the ACT BSC for patients aged 6 to 17 years with clinically significant PF-ILD.

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**
Children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases (PF-ILD)[b]	BSC[c, d]	Added benefit not proven

a. Presented is 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 the quality of life.
d. Further comments from the G-BA
- Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung disease, but are of secondary importance in PF-ILD. Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue can help to alleviate symptoms. The type and scope of the interventions used must be documented.
- In principle, a lung transplant is a treatment option that can be considered for patients with progressive interstitial lung disease. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication. Nevertheless, patients in studies used for the benefit assessment could also be included in the event of a lung transplantation during the course of the study, in terms 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; BSC: best supportive care; G-BA: Federal Joint Committee; PF-ILD: progressive fibrosing interstitial lung disease

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

I 2 Research question

The aim of this report is to assess the added benefit of nintedanib in comparison with BSC as the ACT in children and adolescents aged 6 to 17 years with clinically significant, PF-ILD.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of nintedanib

Therapeutic indication	**ACT**[a]
Children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases (PF-ILD)[b]	BSC[c, d]

a. Presented is 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 the quality of life.
d. Further comments from the G-BA
- Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung disease, but are of secondary importance in PF-ILD. Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue can help to alleviate symptoms. The type and scope of the interventions used must be documented.
- In principle, a lung transplant is a treatment option that can be considered for patients with progressive interstitial lung disease. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication. Nevertheless, patients in studies used for the benefit assessment could also be included in the event of a lung transplantation during the course of the study, in terms 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; BSC: best supportive care; G-BA: Federal Joint Committee; PF-ILD: progressive fibrosing interstitial lung disease

Concurring with the G-BA, the company determined BSC as the ACT.

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.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on nintedanib (status: 2 December 2024)
- Bibliographical literature search on nintedanib (last search on 2 December 2024)
- Search of trial registries/trial results databases for studies on nintedanib (last search on 2 December 2024)
- Search on the G-BA website for nintedanib (last search on 2 December 2024)

To check the completeness of the study pool:

- Search in trial registries for studies on nintedanib (last search on 11 March 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

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

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

Study	Study category			Available sources		
	Study for the marketing authorization 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 and other sources[c] (yes/no [citation])
Study 1199-0337 (InPedILD[d])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7-9]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

ACT: appropriate comparator therapy; BSC: best supportive care; CSR: clinical study report ; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 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 (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
InPedILD	RCT, double-blind, parallel	Children and adolescents (6 to 17 years) with clinically significant fibrosing ILD defined by ▪ Clinical significance[b] ▪ Features of fibrosing disease[c] ▪ FVC ≥ 25% predicted[d]	Nintedanib + BSC (N = 26) Placebo + BSC (N = 13)	Screening: up to 12 weeks Treatment: at least 24 weeks[e] Observation: 28 days[f]	43 centres in Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Great Britain, Greece, Hungary, Italy, Mexico, Norway, Poland, Portugal, Russia, Spain, Ukraine, United States 2/2020–5/2022 Data cut-offs: 16 March 2022 (primary analysis)[g] 15 June 2022 (final analysis)[h]	Primary: AUCτ,ss at Week 2 and 26, AEs at Week 24 Secondary: mortality, morbidity, health-related quality of life, AEs

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Clinically significant ILD at Visit 2; one of the following criteria had to be met: Fan score ≥ 3, or a ≥ 5% to < 10 decline in FVC predicted accompanied by worsening symptoms, or a ≥ 10% decline in FVC predicted, or increased fibrosis on HRCT, or other measures of clinical worsening attributed to progressive lung disease (e.g. increased oxygen requirement, decreased diffusion capacity).
c. Within the last 12 months prior to Visit 1. Diagnosed by the investigator using HRCT and confirmed by central review based on predefined imaging criteria and in combination with a previous lung biopsy or a second HRCT (see running text below).
d. At Visit 2; estimated normal values were calculated according to GLI.
e. Following the 24-week double-blind phase, patients from both study arms were able to enter an open-label phase and were treated with nintedanib until the end of the study. The duration of treatment in the open-label phase depended on the respective date of entry into the study. Only the 24-week double-blind study phase is relevant for this benefit assessment.
f. Outcomes in the categories of morbidity and health-related quality of life were recorded until Week 52. Outcomes in the categories of mortality, AEs and acute ILD exacerbations were observed up to 28 days after the end of treatment if the patients did not switch to the open, single-arm extension study InPedILD-ON [10].
g. The primary analysis was performed after at least 30 of the randomized patients had completed PK sampling at Week 26.
h. The final analysis was performed after all randomized patients had completed the 4-week follow-up phase at the end of treatment or had entered the open-label extension study InPedILD-ON [10]. The treatment ended for all patients after sufficient data from the PK analyses were available for the primary data cut.

AE: adverse event; $AUC_{\tau,ss}$: area under the plasma concentration-time curve at steady state; BSC: best supportive care; FVC: forced vital capacity; GLI: Global Lung Initiative; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; N: number of randomized patients; PK: pharmacokinetics; RCT: randomized controlled trial

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

Study	Intervention	Comparison
InPedILD	Nintedanib 150 mg, 100 mg, 75 mg or 50 mg twice daily[a, b], orally + BSC	Placebo, twice daily[a, c], orally + BSC
	Dose adjustment: ▪ Interruption of treatment in case of body weight decrease to < 13.5 kg Resumption of treatment at a body weight of ≥ 13.5 kg ▪ In case of treatment-related AEs: ▫ Dose reduction to the next lower dose[d] or treatment interruption ≤ 4 weeks with re-initiation at a reduced dose allowed ▫ Re-escalation to full dose after reduction or after re-initiation at a reduced dose[d] was possible at any time ▪ In case of AEs not related to treatment, and acute exacerbations: ▫ Interruption ≤ 8 weeks with re-initiation of treatment at full dose possible ▪ Treatment discontinuation in case of major toxicity or if the reduced dose[d] was not tolerated	
	Allowed concomitant treatment ▪ Individually indicated drugs could be used at the discretion of the physician unless they were explicitly prohibited ▪ Diarrhoea should be managed as early as possible with standard treatment (e.g. loperamide) ▪ In case of acute ILD exacerbations or clinical deterioration: any treatment option considered appropriate by the investigator **Prohibited prior and concomitant treatment** ▪ Nintedanib before study start ▪ Other investigational products ≤ 1 month or 5 half-lives before Visit 2 (whichever was shorter, but at least ≥ 1 week) ▪ Fibrinolysis, full-dose anticoagulants, high-dose platelet aggregation inhibitors (e.g. acetylsalicylic acid > 325 mg/day, clopidogrel > 75 mg/day or equivalent doses of other platelet aggregation inhibitors) ▪ Potent P-glycoprotein and cytochrome P450 3A4 inhibitors and inducers ≤ 7 days before PK sampling	

a. If possible after meals at 12-hour intervals.
b. The dosage of nintedanib was based on the patient's body weight and was individually adjusted at each visit: 50 mg: 13.5 kg to < 23.0 kg; 75 mg: 23.0 kg to < 33.5 kg; 100 mg: 33.5 kg to < 57.5 kg; 150 mg: ≥ 57.5 kg.
c. After the 24-week double-blind treatment phase relevant for the benefit assessment, the patients continued treatment with nintedanib according to the dosing regimen of the intervention in the open-label phase.
d. At a dose of 50 mg, 75 mg or 100 mg twice daily, a 25 mg dose reduction to 25 mg, 50 mg or 75 mg was possible. At a dose of 150 mg twice daily, the dose was reduced to 100 mg twice daily.

AE: adverse event; BSC: best supportive care; ILD: interstitial lung disease; PK: pharmacokinetics; RCT: randomized controlled trial

The InPedILD study is a randomized, double-blind, parallel-group study comparing nintedanib with placebo, each in addition to standard of care at the physician's discretion. The study was conducted from 2020 to 2022. Following the 24-week double-blind phase of the study, patients from both study arms were able to enter an open-label phase and were treated with nintedanib until the end of the study. Children and adolescents aged 6 to 17 years with clinically significant fibrosing ILD were enrolled. Fibrosing disease had to have been established within 12 months prior to Visit 1 by an investigator using HRCT, and confirmed by a central review based on predefined criteria. Patients had to fulfil at least one of the following criteria: reticular abnormality, traction bronchiectasis, architectural distortion or honeycombing. Cystic abnormalities or ground-glass opacity were acceptable co-existing features. The number of criteria that had to be met for inclusion depended on whether the patients already had a diagnosis of fibrosing disease from a previous lung biopsy or HRCT. In the absence of lung biopsy results, at least 2 of the criteria were required on at least 2 HRCT scans. If there was a previous diagnosis of fibrosing ILD from a lung biopsy, the presence of at least one of the above criteria on HRCT was sufficient to confirm the fibrosing disease. Any of the following criteria had to be met for the confirmation of fibrosis by lung biopsy: fibrosing nonspecific interstitial pneumonia, usual interstitial pneumonia, evidence of interstitial fibrosis on a significant component of the lung biopsy, evidence of lobular remodelling on a significant component of the lung biopsy, or honeycomb lung. In addition, patients had to have clinically significant disease at Visit 2, characterized by a Fan score ≥ 3 or one characteristic of clinical progression. The criteria for clinical progression over time were defined as a ≥ 10% decline in FVC predicted, a ≥ 5% to < 10% decline in FVC predicted accompanied by worsening symptoms, increased fibrosis on HRCT, or other measures of clinical worsening attributed to progressive disease (e.g. increased oxygen requirement, decreased diffusion capacity). Another inclusion criterion was an FVC of ≥ 25% predicted, recorded at Visit 2.

The InPedILD study included a total of 39 patients who were randomly allocated in a 2:1 ratio to treatment with nintedanib (N = 26) or with placebo (N = 13). The stratification factor was the age category (6 to < 12 years versus 12 to ≤ 17 years). All patients who were treated with the study medication until the end of the study could switch to the single-arm, open-label extension study InPedILD-ON [10].

Treatment with nintedanib was in compliance with the SmPC [11]. Patients in the intervention arm received analogous placebo treatment. In addition, individually indicated drugs could be used in both study arms at the investigator's discretion unless they were explicitly prohibited (see Table 7).

The primary outcomes of the study were dose exposure at Week 2 and Week 26 and the safety profile at Week 24. Patient-relevant secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Implementation of the appropriate comparator therapy best supportive care

The G-BA defined BSC as the 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. Concurring with the G-BA, the company defined BSC as the ACT and considered it to be implemented in the placebo-controlled InPedILD study.

There are no high-quality guidelines for the treatment of ILD in children and adolescents: For Germany, there is currently only an S1 guideline on diagnostics in adults [12] and an S2k guideline on pharmacotherapy in adults [13]. The main guideline for the diagnosis and management of ILD in neonates and infants from the American Thoracic Society [14] dates from 2013.

Only systemic corticosteroids (methylprednisolone, prednisolone and prednisone [15-17]) are currently approved for the treatment of children with ILD. Other immunosuppressants such as hydroxychloroquine or antibiotics such as azythromycin are additionally used off-label depending on the severity of the disease and other patient-specific factors [18]. Supplemental oxygen is recommended as a non-drug therapy. In rare cases with severe progression, lung transplantation may be required [14].

In principle, patient-specific, clinically necessary standard of care in addition to intervention or comparator medication was allowed in both study arms, according to the study protocol. Adjustment of the existing standard therapy was allowed throughout the study. In addition, 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). In Module 4 A, the company did not present any concrete information on the extent and frequency of supportive measures in terms of BSC that were used in the study, and referred to the CSR.

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

Data cuts

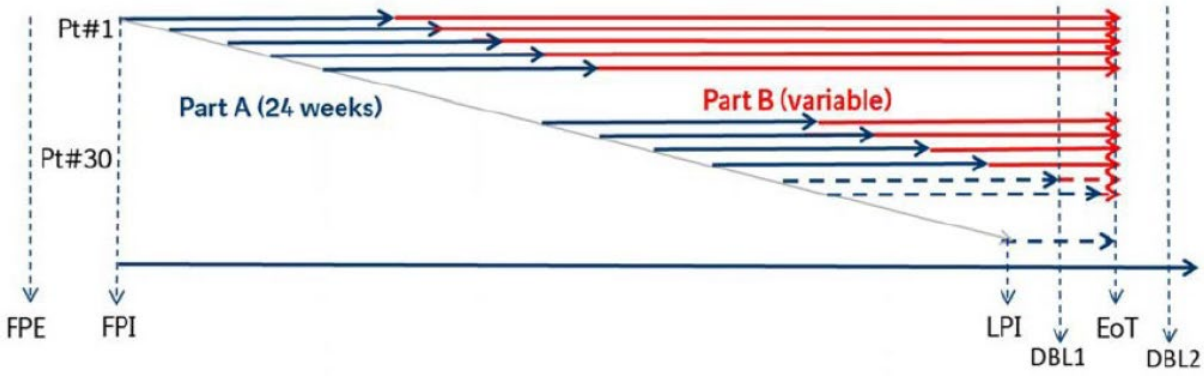
The InPedILD study is a completed study with a 24-week double-blind phase followed by an open-label phase. Analyses were planned at 2 points in time:

- First data cut-off: primary analysis after at least 30 randomized patients had completed pharmacokinetic sampling at Week 26.

- Second data cut-off: final analysis after all randomized patients had completed the 4-week follow-up phase at the end of treatment or had entered the open-label extension study InPedILD-ON.

The end of treatment and the subsequent 4-week follow-up phase, as defined for the second data cut-off, was determined for all patients by the availability of sufficient data from the pharmacokinetic analyses performed as part of the first data cut-off. The time of the end of treatment was independent of the completion of the double-blind phase and could take place during the double-blind or open-label study phase, depending on the time of study entry. In principle, it is therefore possible that patients had not yet completed the 24-week randomized phase when they ended treatment. In the InPedILD study, this applied to 2 patients in the intervention arm and 2 patients in the comparator arm.

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



DBL: database lock; EoT: end of treatment; FPE: first patient enrolled; FPI: first patient in (first patient randomized); LPI: last patient in, Pt: patient

Figure 1: Study design of the InPedILD study including primary analysis (DBL1) and final data cut-off (DBL2) [19]

In Module 4 A, the company presented analyses of the final data cut for the double-blind phase of the InPedILD study, i.e. up to Week 24. After reaching Week 24, the patients were able to remain in the study and enter the open-label phase. In this phase, the patients in both study arms were treated with nintedanib until the end of the study. The data from the double-blind treatment phase at Week 24 were used for this benefit assessment.

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**Nintedanib + BSC** **N[a] = 26**	**Placebo + BSC** **N[a] = 13**
InPedILD		
Age [years], mean (SD)	12.5 (3.6)	12.9 (2.8)
Sex [F/M], %	62/39	62/39
Body weight [kg], mean (SD)	40.9 (16.0)	44.7 (21.5)
Body weight, n (%)		
< 13.5 kg	0 (0)	0 (0)
≥ 13.5 kg to < 23.0 kg	5 (19)	3 (23)
≥ 23.0 kg to < 33.5 kg	2 (8)	3 (23)
≥ 33.5 kg to < 57.5 kg	18 (69)	3 (23)
≥ 57.5 kg	1 (4)	4 (31)
Region, n (%)		
Europe	15 (58)	4 (31)
Canada and United States	6 (23)	7 (54)
Other[b]	5 (19)	2 (15)
Time since ILD diagnosis [years], median (min; max)	4.1 [0.2; 17.0]	5.4 [1.2; 17.2]
ILD diagnosis, n (%)		
Surfactant protein deficiency	7 (27)	5 (39)
Chronic hypersensitivity pneumonitis	2 (8)	0 (0)
Toxic/radiation/drug-induced pneumonitis	3 (12)	1 (8)
Post-HSCT fibrosis	1 (4)	0 (0)
Juvenile rheumatoid arthritis	1 (4)	0 (0)
Juvenile idiopathic arthritis	0 (0)	1 (8)
Systemic sclerosis	4 (15)	3 (23)
Dermatomyositis	1 (4)	0 (0)
Other[c]	7 (27)	3 (23)
Fan score[d] ≥ 3, n (%)		
Yes	17 (65)	6 (46)
No	9 (35)	7 (54)
Presence of ≥ 1 criterion of clinical progression[e], n (%)		
Yes	22 (85)	12 (92)
No	3 (12)	1 (8)
Missing	1 (4)	0 (0)
FVC [mL], mean (SD)	1632.8 (913.5)	1931.6 (991.4)
FVC [in% predicted[f]]), mean (SD)	57.7 (21.8)	62.9 (22.6)
Pulse SpO_2 [%], mean (SD)	96.5 (3.0)	96.5 (4.1)
DLCO, corrected for Hb [in% predicted][g], mean (SD)	52.9 (26.7)	63.1 (10.7)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (multipage table)

Study **Characteristic** **Category**	**Nintedanib + BSC** **N[a] = 26**	**Placebo + BSC** **N[a] = 13**
Treatment discontinuation at Week 24, n (%)[h]	3 (12)	0 (0)
Study discontinuation at Week 24, n (%)	0 (0)	0 (0)

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 Argentina, Brazil and Mexico.
c. According to the EPAR, patients with the following diseases [7] were included here: Copa Syndrome, Copa Gene Mutation, Undifferentiated Connective Tissue Disease, Post-Infectious Bronchiolitis Obliterans, Unspecified ILD, Idiopathic, Sting-associated Vasculopathy in the intervention arm, and Desquammative Interstitial Pneumonitis, Influenza H1N1, Unclear (Chronic Diffuse Pulmonary Lung Disease) in the comparator arm.
d. Classification of severity according to [20]: 1) asymptomatic; 2) symptomatic, normal room air oxygen saturation under all conditions; 3) symptomatic, normal resting room air saturation, but abnormal saturation (< 90%) with sleep or exercise; 4) symptomatic, abnormal resting room air saturation (< 90%); 5) symptomatic with pulmonary hypertension.
e. Documented evidence of clinical progression over time: a ≥ 5% to < 10 decline in FVC predicted accompanied by worsening symptoms, or a ≥ 10% decline in FVC predicted, or increased fibrosis on HRCT, or other measures of clinical worsening attributed to progressive lung disease (e.g. increased oxygen requirement, decreased diffusion capacity).
f. According to the company, predicted values were calculated at each visit according to a methodology developed and validated by the Global Lung Function Initiative.
g. Data based on 18 patients vs. 9 patients.
h. Common reasons for treatment discontinuation in the intervention vs. the control arm were the following (percentages refer to randomized patients): AEs (7.7% vs. 0). Furthermore, 81% vs. 85% of the patients completed treatment as planned.

AE: adverse event; BSC: best supportive care; DLCO: diffusing capacity of the lungs for carbon monoxide; EPAR: European Public Assessment Report; F: female; FVC: forced vital capacity; Hb: haemoglobin; HRCT: high-resolution computed tomography; HSCT: haematopoietic stem cell transplantation; ILD: interstitial lung disease; M: male; Max: maximum; Min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; SpO_2: oxygen saturation

The demographic and clinical characteristics were largely balanced between the 2 treatment arms.

The mean age of the patients was 13 years; most of them were female (62%) and of European or North American family origin. Patients received their first diagnosis of ILD a median of 4 to 5 years before the start of the study. The most common diagnosis among the patients with PF-ILD included in the study was surfactant protein deficiency (approx. 31%).

Notes on the study population of the InPedILD study

Patients with PF-ILD of various aetiologies and other underlying diseases

The InPedILD study included patients with clinically significant fibrosing ILD of various aetiologies. The company justified the grouping of different underlying diseases with a fibrosing phenotype with common pathophysiological processes, in which, depending on the underlying disease, different types of lung damage (e.g. inflammatory processes) can cause pulmonary fibrosis. It added that, given the fact that some of the underlying diseases are extremely rare and some cannot be clearly classified, it was not possible or meaningful to evaluate the patient relevance and validity of the outcomes separately for each underlying disease. From the company's point of view, the similarities in pathophysiology, clinical picture and clinical course of the disease provided the rationale to jointly assess the patient relevance of the outcomes for all children and adolescents in the therapeutic indication of fibrosing ILD, regardless of the underlying disease. The company did not draw any further conclusions on the extent to which the results of the InPedILD study can be transferred to patients with PF-ILD with other underlying diseases not represented in the study.

As part of the authorization process for nintedanib, an ad hoc expert group was convened by EMA to discuss whether patients with fibrosing ILD of different aetiology could be considered together. This expert group found the grouping of fibrosing ILD of various aetiologies to be an acceptable solution, especially due to the similar pathomechanisms and the rarity of the individual underlying diseases [7]. The experts described the limitations regarding the transferability of the results to fibrosing ILD of other underlying diseases and the need to investigate this aspect further.

In summary, these assessments by the company and the EMA were based on pathophysiological considerations and were not supported by data. The characteristic "underlying ILD diagnosis" (surfactant protein deficiency; chronic hypersensitivity pneumonitis; toxic/radiation/drug-induced pneumonitis; post-haematopoietic stem cell transplantation fibrosis; sarcoidosis; autoimmune ILD; other ILD) was to be investigated in the study as part of subgroup analyses. According to the company, these were ultimately not conducted because the proportion of patients per subgroup was too small. The InPedILD study was not designed to demonstrate such effect modifications, however. Overall, it remained unclear whether the results of the InPedILD study were transferable to other underlying ILD diseases that were underrepresented or not represented in the study. The described uncertainty was taken into account in the certainty of conclusions (see Section I 4.2).

Patients with progressive disease

Nintedanib is approved for the treatment of fibrosing ILD with a progressive phenotype, among other conditions. However, inclusion in the study was not limited to patients with progressive diseases. According to the inclusion criteria of the InPedILD study, patients had to

have clinically significant disease. This was characterized by a Fan score ≥ 3 or one feature of clinical progression (see above). The Fan score [20] is a non-evaluated scale that classifies severity based on parameters such as oxygen saturation and symptoms. Accordingly, if a patient had a Fan score ≥ 3 at baseline, inclusion was possible even without documented signs of clinical progression.

The patient characteristics showed that around 10% had no clinical progression at baseline (see Table 8). In the authorization process, the EMA's ad-hoc expert group discussed the uncertainty regarding the diagnosis of progressive fibrosing diseases in children and adolescents, particularly regarding the lack of uniform criteria and the heterogeneity of the diseases, and emphasized the need for a multidisciplinary team for diagnosis and therapy. In addition, the information in the CSR showed that there were protocol violations regarding the inclusion criteria for the presence of fibrosing ILD (approx. 5%). In principle, it was possible for a patient to not fulfil more than one of the above criteria. It was therefore unclear how many patients were affected in total.

Despite the uncertainties described above, the study population of the InPedILD study was presumed to adequately represent patients with clinically significant PF-ILD.

Patients with systemic sclerosis-associated interstitial lung disease

The InPedILD study included patients with clinically significant fibrosing ILD of various aetiologies. The patient characteristics showed that approximately 18% of the patients had a diagnosis of SSc-ILD (see Table 8). These were not covered by the therapeutic indication of the present benefit assessment (see Table 4). In Module 4 A, the company presented the results of the total population, including patients with SSc-ILD. As the patients who were not covered by the therapeutic indication of the given research question only represented a small proportion, the data from the overall population was used.

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	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
InPedILD	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the InPedILD study.

Transferability of the study results to the German health care context

The company stated that the therapeutic indication of fibrosing ILD in children and adolescents aged 6 to 17 years grouped patients with different underlying diseases whose common feature was the occurrence of ILD with a fibrosing phenotype. It further described that, due to the high number and rarity of the possible underlying diseases, there was little evidence on the frequency of the individual underlying diseases in Germany and that, in addition, the lack of a standardized classification system made it difficult to compare the underlying diseases of the study population with literature data. Against the background of the rare nature of the disease, it was therefore hardly possible to conduct a meaningful comparison of the distribution of the different underlying diseases in everyday health care in Germany on the one hand and the study population of the InPedILD study on the other, according to the company. It added that due to the large number of different types of ILD that could develop a fibrosing phenotype, it could be assumed that not all underlying diseases of fibrosing ILD occurring in Germany were fully represented in the study population. Furthermore, the company stated that different average ages of disease onset and gender ratios had to be assumed for the underlying diseases. However, it argued that approx. 50% of the patients were treated at European study centres. From the company's point of view, the plausibility of transferring the evidence from the given study population to the German health care context resulted from the common pathophysiological processes underlying the development and persistence of the fibrosing phenotype. Despite the described limitations in the feasibility of comparing the study population with the target population in Germany, the company assumed that the study results were transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context. For the transferability of the study results, see also the text section "Notes on the study population of the InPedILD study".

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - All-cause mortality
- Morbidity
  - Acute exacerbation or death
  - Endurance based on the 6MWT
- Health-related quality of life
  - PedsQL
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Hepatobiliary disorders (System Organ Class [SOC], SAE)
  - Gastrointestinal disorders (SOC, AE)
  - Diarrhoea (Preferred Term [PT], AE)
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviates from those of the company, which used further outcomes in the dossier (Module 4 A).

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

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

Study	Outcomes									
	All-cause mortality[a]	Acute exacerbation or death	Endurance (6 MWT)	Health-related quality of life (PedsQL)	SAEs	Discontinuation due to AEs	Hepatobiliary disorders (SOC, SAEs)	Gastrointestinal disorders (SOC, AEs)	Diarrhoea (PT, AEs)	Other specific AEs
InPedILD	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	No[c]

a. The results for all-cause mortality are based on the data on fatal AEs or the recordings of vital status in the eCRF.
b. No suitable data available; see running text below for reasons.
c. No further specific AEs were identified based on the AEs occurring in the relevant study.

6MWT: 6-minute walking test; AE: adverse event; BSC: best supportive care; eCRF: electronic case report form; PedsQL: Pediatric Quality of Life Inventory; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Notes on the outcomes

Acute exacerbation or death

In Module 4 A, the company presented analyses on the composite outcome of acute exacerbations or death. 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.

In the InPedILD study, an acute exacerbation was defined as significant worsening of the respiratory condition that necessitated a change in regular management. To be classified as such, 2 or more of the following criteria, which were assessed as part of the AEs, had to be met:

- Increase in respiratory rate ≥ 20%
- Increase in or development of dyspnoea
- Newly developing or increased abnormalities on chest imaging
- Increase of oxygen demand to attain the individual baseline saturation (at rest or during exercise)

- Need for an additional level of ventilatory support (in addition to oxygen)
- Decrease in spirometry in children and adolescents able to perform the tests (≥ 10% from baseline for vital capacity)
- Reduced exercise tolerance

The criteria used to define an acute exacerbation in children and adolescents with PF-ILD were based on expert consensus [21]. It remained unclear whether all events included, e.g. increase in respiratory rate, newly developing or increased abnormalities on chest imaging or decrease in spirometry, as laboratory parameters, were directly noticeable for the patients and thus directly patient relevant. In the InPedILD study, one event had occurred in the intervention arm by Week 24 (see Section I 4.3). The CSR showed that based on the PTs severe respiratory distress, severe increase in carbon dioxide and moderate increase in oxygen consumption, the definition criteria for an acute exacerbation (increase of oxygen demand to attain the individual baseline saturation and need for an additional level of ventilatory support) were met in one patient and led to hospitalization. This event could therefore be categorized as patient relevant. The operationalization of acute exacerbations was considered sufficiently patient relevant in the given data situation.

The outcome of acute exacerbation or death was used in this benefit assessment despite the described uncertainties regarding the operationalization and direct patient relevance of the applied criteria.

Endurance (recorded with the 6MWT)

For the outcome of endurance recorded with the 6MWT, the company presented continuous analyses of the changes from baseline to Week 24 for the dossier. In the study, the 6MWT was conducted at baseline (Week 0) and at Weeks 24 and 52. According to the company, the results for Week 24 were presented in Module 4 A. It added that the mixed-effects model with repeated measures (MMRM) used also included data up to Week 52, i.e. beyond the randomized treatment phase of 24 weeks. It further explained that the model used was an MMRM with fixed effects for treatment at each visit, age group and baseline value at each visit, and a random effect for the patient based on all patients with at least one additional value to the baseline value up to Week 52.

The analyses presented by the company were unsuitable for the benefit assessment, as the model used for the calculation was not clear. It was unclear whether the company considered the interactions between variables with the formulations “treatment at each visit” and “baseline value at each visit”, and whether the variables baseline value at Week 0 and treatment were included separately in the model. In addition, values from patients at Week 52 were also included in the model. As the patients switched to the open-label study phase after

Week 24, and the patients in the comparator arm were also treated with nintedanib in this phase, a clear assignment of effects after Week 24 was not possible.

Overall, the analyses presented by the company for the outcome endurance, recorded by means of the 6MWT, were therefore not suitable for the benefit assessment.

Health-related quality of life (recorded using the PedsQL)

To record health-related quality of life in the InPedILD study, the company presented the generic instrument PedsQL for recording the quality of life in children and adolescents. The questionnaire consists of 23 questions and measures health-related quality of life using the 4 dimensions of physical functioning, emotional functioning, social functioning and school functioning [22]. Different questionnaires were completed depending on the patients' age: PedsQL Young Child Report (< 8 years), PedsQL Child Report (8 bis < 13 years) und der PedsQL Report for Teens (≥ 13 years). The questionnaires were completed at screening, at Week 24 and Week 52. The company presented analyses of the patient-reported versions and analyses of the parent-reported versions for all patients. A direct evaluation of the patients' health-related quality of life using the patient-reported versions of the instruments is favoured over the parent-reported evaluation and was used to assess the added benefit.

For the outcome health-related quality of life, the company's dossier presented, among other things, responder analyses on improvement or worsening by ≥ 15 points (scale range 0 to 100), which were not prespecified in advance. The response criteria of 15 points, which were used in the analyses presented by the company, met the requirements for response criteria for reflecting with sufficient certainty a change that is perceivable for patients, as described in the *General Methods* of the Institute [1]. Due to the expected progressive course of the disease in this therapeutic indication, deterioration was considered a suitable operationalization in the present benefit assessment.

In summary, the responder analyses for the worsening by ≥ 15 points at Week 24 in the patient-reported versions were used in the benefit assessment for the outcome health-related quality of life, recorded using the PedsQL.

FVC

In Module 4 A, the company presented results for the outcome FVC for the morbidity category, describing that it considered it possible to derive conclusions on mortality from this outcome. It referred to the dossier on nintedanib in the therapeutic indication of other chronic PF-ILD [23] in adults. Concurrent with the reasons presented in the benefit assessments on nintedanib [24], the data presented by the company for surrogate validation were suitable in principle, but the implementation of the methodology for calculating the surrogate threshold effect was flawed, which led to an underestimation of the surrogate threshold effect. Overall, the effect on the surrogate was therefore not large enough in the given situation to derive an

effect on overall survival. In addition, the surrogate validation referred to by the company was a surrogate validation of FVC for mortality, but the company assigned the outcome to morbidity in this dossier. The company did not provide any further information on whether effects on the outcomes in the morbidity category could also be derived from the FVC. Furthermore, the company did not present any data that could be used to derive an effect for children and adolescents.

In summary, FVC is a prognostic parameter of lung function diagnostics and thus a surrogate outcome. The surrogate validation presented by the company was not suitable to derive an effect on the outcomes in the morbidity category. The FVC was therefore not used for this benefit assessment.

Side effects

Recording of disease-related events

The company presented analyses with and without disease-related events for the outcomes AEs and SAEs. It stated that it considered acute exacerbations recorded by the investigator to be disease-related events. In the analyses without disease-related events, it remained unclear from the available information which PTs were not considered as disease-related events. In addition, it remained unclear whether other events could be considered to be disease related. However, as the overall rate of SAEs did not include events that were clearly attributable to the underlying disease, the overall rate of SAEs without disease-related events was used for this benefit assessment.

SAEs

In addition to the recording of SAEs according to the common definition, the company's study protocol described the recording of AEs that are classified as "always serious". It referred to a list of AEs, which by their nature, can always be considered to be serious even though they do not meet the defined criteria of SAEs. It is unclear which events were included in this recording. In the given data situation, this uncertainty was of no consequence for the benefit assessment, however.

I 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		Outcomes								
	Study level	All-cause mortality[a]	Acute exacerbation or death	Endurance (6MWT)	Health-related quality of life (PedsQL)	SAEs	Discontinuation due to AEs	Hepatobiliary disorders (SOC, SAEs)	Gastrointestinal disorders (SOC, AEs)	Diarrhoea (PT, AEs)
InPedILD	L	L	L	–[b]	H[c]	L	L	L	L	L

a. The results for all-cause mortality are based on the data on fatal AEs or the recordings of vital status in the eCRF.
b. No suitable data available; for justification see Section I 4.1 of this dossier assessment.
c. Large proportion of patients (> 10%) not considered in the analysis.

6MWT: 6-minute walking test; AE: adverse event; BSC: best supportive care; eCRF: electronic case report form; H: high; L: low; PedsQL: Pediatric Quality of Life Inventory; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

The risk of bias for the results of the outcomes all-cause mortality, acute exacerbations or death, and of the outcomes in the category of side effects was assessed as low. For the outcome health-related quality of life, recorded using the PedsQL, the risk of bias for the results was assessed as high due to the large proportion (> 10%) of patients not considered in the analysis.

Since no suitable analyses were available for the outcome endurance, recorded with the 6MWT (see Section I 4.1), the risk of bias for this outcome was not assessed.

Summary assessment of the certainty of conclusions

Taking into account the information provided by the company in Module 4 A of the dossier, it can be assumed that not all patients included in the InPedILD study were covered by the therapeutic indication of this research question of clinically significant PF-ILD. This assessment was based on the fact that some of the patients did not fulfil the criteria of a fibrosing disease according to the inclusion criteria, did not show any clinically documented signs of progression and, in addition, some of the patients fall under the therapeutic indication of SSc-ILD (for a detailed explanation, see Section I 3.2). The certainty of conclusions of the study results for the given research question was therefore limited. Based on the available information from

the InPedILD study, at most hints, e.g. of an added benefit, could be derived for all outcomes presented.

I 4.3 Results

Table 12 and Table 13 summarize the results of the comparison of nintedanib + BSC with placebo + BSC in patients aged 6 to 17 years with clinically significant PF-ILD. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the time-to-event analyses are presented in I Appendix B of the full dossier assessment, and the tables on common AEs, SAEs, and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

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

Study **Outcome category** **Outcome** **Time point**	**Nintedanib + BSC**			**Placebo + BSC**			**Nintedanib + BSC vs. placebo + BSC**
	N	**Median time to event in weeks [95% CI]** **Patients with event n (%)**		**N**	**Median time to event in weeks [95% CI]** **Patients with event n (%)**		**HR [95% CI]; p-value**
InPedILD							
Mortality							
All-cause mortality[a] (at Week 24)	26	NA 0 (0)		13	NA 0 (0)		–
Morbidity (at Week 24)							
Acute exacerbation[b] or death	26	NA 1 (3.9)		13	NA 0 (0)		ND[c]
	N	**Values at baseline mean (SD)**	**Change at Week 24 mean (SE)**	**N**	**Values at baseline mean (SD)**	**Change at Week 24 mean (SE)**	**MD [95% CI]; p-value**
Endurance (6MWT)	No suitable data[d]						

a. The results for all-cause mortality are based on the data on fatal AEs or the recordings of vital status in the eCRF.

b. Acute exacerbations were defined as significant worsening of the respiratory condition that necessitates a change in regular management, based on 2 or more of the following criteria: increase in respiratory rate ≥ 20%, increase in or development of dyspnoea, newly developing or increased abnormalities on chest imaging, increase of oxygen demand to attain the individual baseline saturation (at rest or during exercise), need for an additional level of ventilatory support (in addition to oxygen), decrease in spirometry in children and adolescents able to perform the tests (≥ 10% from baseline for vital capacity), reduced exercise tolerance.

c. Due to the small number of events, the company did not conduct any calculations on the HR (including 95% CI) and p-value.

d. See Section I 4.1 for reasons.

6MWT: 6-minute walking test; BSC: best supportive care; CI: confidence interval; eCRF: electronic case report form; HR: hazard ratio; MD: mean difference; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

Table 13: Results (health-related quality of life, side effects) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Study Outcome category Outcome Time point	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]
InPedILD					
Health-related quality of life					
PedsQL – deterioration by ≥ 15 points at Week 24[b]	21	0 (0)	11	1 (9.1)	NC[c]
Side effects (at Week 24)					
AEs (supplementary information)	26	22 (84.6)	13	11 (84.6)	–
SAEs	26	1 (3.8)	13	1 (7.7)	0.5 [0.03; 7.37]; 0.734
Discontinuation due to AEs	26	2 (7.7)	13	0 (0)	2.59 [0.13; 50.38]; 0.397
Hepatobiliary disorders (SOC, SAEs)	26	0 (0)	13	0 (0)	NC
Gastrointestinal disorders (SOC, AEs)	26	22 (84.6)	13	11 (84.6)	1.00 [0.75; 1.33]; > 0.999
Diarrhoea (PT, AEs)	26	10 (38.5)	13	2 (15.4)	2.50 [0.64; 9.78]; 0.163

a. Unless stated otherwise: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [25]); in case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
b. A score decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
c. Log-link Poisson model with robust estimation of variance with the covariables baseline (continuous), age group (6 to < 12 years, 12 to < 18 years) and treatment group.

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; NC: not calculable; PedsQL: Pediatric Quality of Life Inventory; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 4.2).

Mortality

No deaths occurred in the course of the study. There is no hint of an added benefit of nintedanib + BSC in comparison with BSC for the outcome all-cause mortality; an added benefit is therefore not proven.

Morbidity

Acute exacerbation or death

No statistically significant difference was shown between the treatment groups for the outcome acute exacerbation or death. There is no hint of an added benefit of nintedanib + BSC in comparison with BSC; an added benefit is therefore not proven.

Endurance (6MWT)

No suitable data were available for the outcome endurance, recorded using the 6MWT (for reasons, see Section I 4.1). There is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

Health-related quality of life (PedsQL)

No statistically significant difference between treatment groups was found for the outcome of health-related quality of life, recorded using the PedsQL. There is no hint of an added benefit of nintedanib + BSC in comparison with BSC; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes of SAEs or discontinuation due to AEs. In each case, there is no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

Specific AEs

Hepatobiliary disorders (SAEs), gastrointestinal disorders (AEs), diarrhoea (AEs)

No statistically significant difference between treatment groups was found for any of the outcomes hepatobiliary disorders (SAEs), gastrointestinal disorders (AEs) or diarrhoea (AEs). In each case, there is no hint of greater or lesser harm from nintedanib + BSC in comparison with BSC; greater or lesser harm is therefore not proven.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (6 to < 12 years versus ≥ 12 to < 17 years)
- Sex (female versus male)

All mentioned subgroup characteristics and cut-off values had been prespecified for the primary outcomes of dose exposure and safety profile.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least 1 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.

Using the methods described above, the available subgroup analyses did not reveal any effect modifications.

I 4.5 Evidence transfer

For the assessment of the added benefit of nintedanib in children and adolescents, in addition to the InPedILD study, the company used the INBUILD study with adults already known from dossier assessment A20-71 [24] as part of an evidence transfer. The INBUILD study is a placebo-controlled, randomized parallel-group study on nintedanib. The study included adult patients with chronic PF-ILD, defined by features of diffuse fibrosing lung disease of > 10% extent on HRCT, among others. 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. Further inclusion criteria were a diffusing capacity of the lungs for carbon monoxide of 30 to 80% predicted and an FVC of ≥ 45% predicted. Patients diagnosed with idiopathic pulmonary fibrosis were not included in the studies. In principle, the physicians participating in the study could use individually indicated drugs in addition to the study medication in both study arms at their own discretion, unless they were explicitly excluded according to the study protocol. Overall, the supportive therapies allowed in the INBUILD study were considered to be a sufficient implementation of the ACT BSC. A detailed description of the study and intervention characteristics can be found in dossier assessment A20-71 [24].

Approach of the company

For the assessment of added benefit, the company used the overall population of the INBUILD study with adults in order to transfer its results to the target population of children and adolescents in the present therapeutic indication. It justified the need for an evidence transfer by stating that the InPedILD study presented in its Module 4 A was designed as a pharmacokinetics and safety study within the paediatric investigation plan, due to the low prevalence in children and adolescents. Efficacy outcomes were only recorded as supportive information in the InPedILD study. According to the company, the marketing authorization of the paediatric therapeutic indication of nintedanib was based on the presented InPedILD study and was also justified by the transferability of efficacy and safety from the adult patient population to the paediatric patient population.

The company was of the opinion that the requirements for an evidence transfer were met. Referencing the EMA, it cited various criteria [26]. It stated that the mechanism of action of nintedanib is comparable in adults, children and adolescents, and the pathogenesis and clinical picture are sufficiently similar. It added that the ACT determined by the G-BA for adults, children and adolescents was identical, and an added benefit of nintedanib was determined in adults in the therapeutic indication of other chronic PF-ILDs. The company additionally mentioned consistent effects in favour of nintedanib in the outcomes FVC and oxygen saturation, as well as comparable results regarding the safety of nintedanib in paediatric and adult patients.

Assessment of the company's data and approach

The derivation of the added benefit for adults in the therapeutic indication of chronic PF-ILD was mainly based on the outcome acute exacerbations or death. In the INBUILD study, acute exacerbations were defined as acute, clinically significant, respiratory deteriorations 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 with a duration of less than 1 month
- Computed tomography 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

In contrast, there were indications of greater harm from nintedanib for various outcomes in the side effects category.

In view of the data situation in the given very small sample and the problem that the operationalization in the relevant outcome acute exacerbations may not be comparable between InPedILD and INBUILD, a transfer of evidence is not possible in this situation.

Regardless of this, the company did not conduct an up-to-date information retrieval on the adult population in Module 4 A of the dossier and did not properly prepare a sufficiently suitable adjacent age stratum as a preferred approximation of the target population. It should be noted that addressing these aspects would not change the conclusion regarding the suitability of the evidence transfer in the given research question.

In summary, based on the available data, it is not possible to transfer the results of adults from the INBUILD study to children and adolescents.

I 5 Probability and extent of added benefit

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 14).

Table 14: Extent of added benefit at outcome level: nintedanib vs. BSC

Outcome category **Outcome**	**Nintedanib + BSC vs. placebo + BSC** **Median time to event (weeks) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	Median: NA vs. NA HR: –	Lesser benefit/added benefit not proven
Morbidity		
Acute exacerbation or death	Median: NA vs. NA HR: –	Lesser benefit/added benefit not proven
Endurance (6MWT)	No suitable data	Lesser benefit/added benefit not proven
Health-related quality of life		
PedsQL – deterioration by ≥ 15 points at Week 24	0% vs. 9.1% RR: –	Lesser benefit/added benefit not proven
Side effects		
SAEs	3.8% vs. 7.7% RR: 0.5 [0.03; 7.37] p = 0.734	Greater/lesser harm not proven
Discontinuation due to AEs	7.7% vs. 0% RR: 2.59 [0.13; 50.38] p = 0.397	Greater/lesser harm not proven
Hepatobiliary disorders (SAEs)	0% vs. 0% RR: –	Greater/lesser harm not proven
Gastrointestinal disorders (AEs)	84.6% vs. 84.6% RR: 1.00 [0.75; 1.33] p > 0.999	Greater/lesser harm not proven
Diarrhoea (AEs)	38.5% vs. 15.4% RR: 2.50 [0.64; 9.78] p = 0.163	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).

6MWT: 6-minute walking test; AE: adverse event; BSC: best supportive care; CI: confidence interval; CI_u: upper limit of the confidence interval; HR: hazard ratio; NA: not achieved; PedsQL: Pediatric Quality of Life Questionnaire; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of nintedanib in comparison with BSC

Positive effects	**Negative effects**
–	–
There are no suitable data available for the outcome endurance (6MWT) from the morbidity category.	
6MWT: 6-minute walking test; BSC: best supportive care	

The InPedILD study showed neither effects in favour nor effects to the disadvantage of nintedanib in comparison with BSC.

In summary, there is no hint of an added benefit of nintedanib in comparison with the ACT BSC for patients aged 6 to 17 years with clinically significant PF-ILD.

The result of the assessment of the added benefit of nintedanib in comparison with the ACT is summarized in Table 16.

Table 16: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children and adolescents from 6 to 17 years old with clinically significant, progressive fibrosing interstitial lung diseases (PF-ILD)[b]	BSC[c, d]	Added benefit not proven

a. Presented is 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 the quality of life.
d. Further comments from the G-BA
- Methylprednisolone, prednisolone and prednisone are approved for the treatment of interstitial lung disease, but are of secondary importance in PF-ILD. Non-drug interventions as outlined in the German Remedies Directive or the Remedies Catalogue can help to alleviate symptoms. The type and scope of the interventions used must be documented.
- In principle, a lung transplant is a treatment option that can be considered for patients with progressive interstitial lung disease. In view of the fact that the possibility of a lung transplantation is largely determined by patient-specific criteria, including comorbidities, and that the limited availability of suitable donor organs must also be taken into account, lung transplantation cannot be assumed to be a standard treatment option for patients in the given therapeutic indication. Nevertheless, patients in studies used for the benefit assessment could also be included in the event of a lung transplantation during the course of the study, in terms 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; BSC: best supportive care; G-BA: Federal Joint Committee; PF-ILD: progressive fibrosing interstitial lung disease

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit on the basis of a transfer of evidence.

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

I 6 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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