IQWiG Reports – Commission No. A20-70

Nintedanib (systemic sclerosis associated interstitial lung disease) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nintedanib (interstitielle Lungenerkrankung bei systemischer Sklerose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 November 2020). Please note: This document was translated by an external translator and 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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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.

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List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	diffusing capacity of the lungs for carbon monoxide
dcSSc	diffuse cutaneous form of systemic sclerosis
EULAR	European League Against Rheumatism
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
FACIT	Functional Assessment of Chronic Illness Therapy
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAQ-DI	Health Assessment Questionnaire – Disability Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMF	mycophenolate mofetil
MTX	methotrexate
PT	preferred term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George's Respiratory Questionnaire
SHAQ	Scleroderma Health Assessment Questionnaire
SMD	standardized mean difference
SOC	System Organ Class
SSc-ILD	systemic sclerosis-associated interstitial lung disease
VAS	visual analogue scale

2 Benefit assessment

2.1 Extract of dossier 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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 12 August 2020.

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

Research question

The aim of the present report is to assess the added benefit of nintedanib in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) for treating adults with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

The ACT specified by the G-BA served as the basis for the research question presented in Table 2 of this benefit assessment.

Table 2: Research questions of the benefit assessment of nintedanib

Therapeutic indication	**ACT[a]**
Adults with SSc-ILD	BSC[b, c]

a. Presentation of the ACT specified by the G-BA.
b. BSC is defined as the therapy which ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.
c. As part of BSC, physical therapy (according to the Guideline on Remedies [*Heilmittelrichtlinie*]) may be indicated as well. The drugs azathioprine, MMF, N-acetylcysteine, rituximab, cyclophosphamide, ciclosporin, and tacrolimus are not approved for treating progressive interstitial lung disease. In principle, lung transplantation would be a treatment option for patients with progressive interstitial lung disease. In practice, however, it cannot be assumed to represent a standard option for patients in this therapeutic indication (e.g. due to comorbidities or limited availability of suitable donor organs).

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; MMF: mycophenolate mofetil; SSc-ILD: systemic sclerosis-associated interstitial lung disease

The company followed the G-BA's specification of 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 added benefit.

Results

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

Study design

The included SENSCIS study is a completed, multinational, double-blind RCT comparing nintedanib with placebo.

The SENSCIS study included adult SSc-ILD patients. SSc-ILD had to fulfil the criteria of the American College of Rheumatology (ACR) or, as applicable, the European League Against Rheumatism (EULAR), and the diagnosis had to be confirmed by high-resolution computed tomography taken within 12 months before study inclusion, showing an extent of fibrotic disease in the lung of ≥ 10%. Further inclusion criteria were a diffusing capacity of the lungs for carbon monoxide (DLCO) of 30% to 89% of predicted normal and a forced vital capacity (FVC) of ≥ 40% of predicted normal at baseline. SSc onset had to be a maximum of 5 years (or 7 years [amendment 2.0 of the study protocol]) before inclusion. The included patients tended to be in an early stage of SSc and lung fibrosis.

In total, 580 patients were randomized in a 1:1 ratio and allocated to treatment with nintedanib or placebo. In the SENSCIS study, nintedanib was administered in accordance with approval. Patients in the comparator arm received identically looking placebo capsules at the same time points.

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

Relevant subpopulation

The population not receiving concomitant mycophenolate mofetil (MMF) treatment (non-MMF population, representing about 50% of the total population) was used for the benefit assessment because MMF has not been approved for treating patients with SSc-ILD. Furthermore, it is unclear whether MMF was primarily administered to alleviate symptoms and improve quality of life and could therefore be viewed as an adequate implementation of BSC.

Implementation of the ACT (in the non-MMF population)

In principle, drugs indicated for individual patients were allowed in both study arms at the physician's discretion so long as they were not explicitly excluded by the study protocol. All told, the supportive therapies allowed in the relevant subpopulation of the SENSCIS study are deemed sufficient for implementing the ACT of BSC.

Analysis time points

For all patient-relevant outcomes of the study, the company presented analyses from 2 different time points: after 52 weeks of treatment as well as at the end of the study, at which point

treatment durations differed between patients. For the purposes of the benefit assessment regarding this chronic disease, a longer follow-up period is deemed prudent. Therefore, the assessment relied primarily on analyses at the end of study, taking into account the data for the total study duration. For patient-reported outcomes (PROs), in contrast, the earlier analysis time point at 52 weeks of treatment was preferred because the data for the total study duration were deemed less valid and more difficult to interpret. This was owed to the fact that PRO outcomes were measured only once after 52 weeks, with individual treatment periods differing among patients.

Risk of bias

The risk of bias at study level was rated as low. Likewise, the risk of bias for the results on all outcomes included in the benefit assessment is rated as low.

Results

Mortality

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

Morbidity

Functional Assessment of Chronic Illness Therapy [FACIT]-Dyspnoea

For the dyspnoea score, no statistically significant difference between treatment groups was found. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

For the related functional limitations score, there was a statistically significant difference to the disadvantage of nintedanib. The standardized mean difference (SMD) in the form of Hedges' g was employed to check the relevance of the result. The 95% confidence interval (CI) of the SMD is not fully outside of the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

Scleroderma Health Assessment Questionnaire

No statistically significant difference between treatment groups was found for the scales of Health Assessment Questionnaire – Disability Index (HAQ-DI), pain visual analogue scale (VAS), lung involvement VAS, and overall disease severity VAS. For each of these outcomes, there was therefore no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

For the gastrointestinal involvement VAS, there was a statistically significant difference to the disadvantage of nintedanib + BSC. The SMD in the form of Hedges' g was examined to assess the relevance of the result. The 95% CI of the SMD is fully outside of the irrelevance range of

−0.2 to 0.2. This is interpreted as a relevant effect. For the gastrointestinal involvement VAS, this results in an indication of lesser benefit of nintedanib + BSC in comparison with placebo + BSC.

For both the Raynaud's phenomenon VAS and the digital ulcers VAS, there was a statistically significant difference to the disadvantage of nintedanib + BSC. The SMD in the form of Hedges' g was examined to assess the relevance of the results. The 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC for either of them; an added benefit is therefore not proven.

Health status (European Quality of Life Questionnaire – 5 dimensions [EQ-5D VAS] as well as Patient Global Impression of Health VAS)

No statistically significant difference between treatment groups was found for the health status outcomes of EQ-5D VAS or for the Patient Global Impression of Health VAS. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC for either of them; an added benefit is therefore not proven.

Health-related quality of life

St. George's Respiratory Questionnaire (SGRQ)

For the SGRQ total score, no statistically significant difference between treatment groups was found. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

AEs

Serious adverse events (SAEs)

For the outcome of SAEs, no statistically significant difference between treatment groups was found. Consequently, no hint of greater or lesser harm from nintedanib + BSC can be derived in comparison with placebo + BSC; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference to the disadvantage of nintedanib + BSC was found. However, the extent of the effect is at most marginal. Consequently, no hint of greater or lesser harm from nintedanib + BSC in comparison with placebo + BSC can be derived for this outcome; greater or lesser harm is therefore not proven.

Gastrointestinal disorders (System Organ Class [SOC], AEs), diarrhoea (preferred term [PT], severe AEs), metabolic and nutritional disorders (SOC, AEs), and vascular disorders (SOC, AEs)

For each of the outcomes of gastrointestinal disorders (SOC, AEs), diarrhoea (PT, severe AEs), metabolic and nutritional disorders (SOC, AEs), and vascular disorders (SOC, AEs), a

statistically significant difference to the disadvantage of nintedanib + BSC was found. For each of these outcomes, this results in an indication of greater harm from nintedanib + BSC in comparison with placebo + BSC.

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

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

The overall analysis showed nothing but unfavourable effects of varying extents for nintedanib in comparison with BSC, each with the probability of indication. These effects predominantly relate to AE outcomes, particularly gastrointestinal AEs, of various degrees of severity. An unfavourable effect was also found for the gastrointestinal involvement VAS. However, given the known gastrointestinal AE profile of nintedanib, the observed unfavourable effect on this outcome might conceivably be due to AEs rather than to changes in disease-specific symptoms.

In summary, for patients with SSc-ILD, there is an indication of lesser benefit of nintedanib in comparison with the ACT of BSC.

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

Table 3: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with SSc-ILD	BSC	Indication of lesser benefit
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SSc-ILD: systemic sclerosis-associated interstitial lung disease		

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

[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].

2.2 Research question

The aim of the present report is to assess the added benefit of nintedanib in comparison with BSC as the ACT for treating adults with SSc-ILD.

The ACT specified by the G-BA served as the basis for the research question presented in Table 4 of this benefit assessment.

Table 4: Research questions of the benefit assessment of nintedanib

Therapeutic indication	**ACT[a]**
Adults with SSc-ILD	BSC[b, c]

a. Presentation of the ACT specified by the G-BA.
b. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.
c. As part of BSC, physical therapy (according to the Guideline on Remedies [*Heilmittelrichtlinie*]) may be indicated as well. The drugs azathioprine, MMF, N-acetylcysteine, rituximab, cyclophosphamide, ciclosporin, and tacrolimus are not approved for treating progressive interstitial lung disease. In principle, lung transplantation would be a treatment option for patients with progressive interstitial lung disease. In practice, however, it cannot be assumed to represent a standard option for patients in this therapeutic indication (e.g. due to comorbidities or limited availability of suitable donor organs).

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; MMF: mycophenolate mofetil; SSc-ILD: systemic sclerosis-associated interstitial lung disease

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of 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 cited by the company in the dossier:

- Study list on nintedanib (as of 9 June 2020)
- Bibliographic literature search on nintedanib (most recent search on 2 June 2020)
- Search in trial registries / study results databases on nintedanib (most recent search on 2 June 2020)
- Search on the G-BA website on nintedanib (most recent search on 2 June 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on nintedanib (most recent search on 21 August 2020)

The check did not identify any additional relevant studies.

2.3.1 Included studies

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

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

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
1199.214 (SENSCIS[d])	Yes	Yes	No	No[e]	Yes [3-6]	Yes [7-10]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: other publicly accessible documents on the SENSCIS study.
d. In the tables below, the study will be referred to using this short name.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

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

2.3.2 Study characteristics

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: nintedanib + BSC versus placebo + BSC

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
SENSCIS	RCT, double-blind, parallel-group	Adult patients (≥ 18 years of age) with ▪ SSc diagnosis in accordance with ACR / EULAR 2013[b], ▪ SSc-associated ILD[c] (with ≥ 10% pulmonary fibrosis as confirmed by HRCT scan), ▪ FVC ≥ 40% of predicted normal at randomization and ▪ DLCO: 30% to 89% of predicted normal at randomization (adjusted for haemoglobin)	Nintedanib (N = 290) Placebo (N = 290) Relevant subpopulation thereof[d]: Nintedanib (n = 151) Placebo (n = 148)	Screening: ≥ 4 days and ≤12 weeks before treatment start Treatment: minimum of 52 weeks[e] Follow-up observation: 28 days after the end of treatment[f]	194 study centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, Thailand, United Kingdom, United States 11/2015–11/2018	Primary: annual rate of decline in FVC over 52 weeks Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. SSc disease onset (defined as the occurrence of the first non-Raynaud symptom) had to be a maximum of 5 years before study start. Amendment 2.0 (1/2017) changed the criterion from SSc diagnosis within 5 years before study start to 7 years.
c. The study excluded patients with other disorders (e.g. airway obstruction, relevant pulmonary hypertension, severe [digital] ulcers, or pre-existing conditions with severe digital necrosis and hospitalization, increased risk of bleeding).
d. Patients who received no MMF treatment at baseline ("non-MMF population" see "Relevant subpopulation" section).
e. The primary efficacy evaluation was planned at 52 weeks. After week 52, patients remained blinded in the study until the last randomized participant completed the planned treatment duration of 52 weeks, up to a maximum of 100 weeks.
f. Outcomes in the categories of morbidity and health-related quality of life were surveyed until the end of treatment. Outcomes in the mortality and AE outcome categories as well as pulmonary function parameters were followed up for 28 days after the end of treatment. In patients who prematurely discontinued treatment but continued to come in for visits, AEs were to be surveyed until the individual patient left the study.

ACR: American College of Rheumatology; AE: adverse event; BSC: best supportive care; DLCO: diffusing capacity of the lungs for carbon monoxide; EULAR: European League Against Rheumatism; FVC: forced vital capacity: HRCT: high-resolution computed tomography; ILD: interstitial lung disease; MMF: mycophenolate mofetil; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; SSc: systemic sclerosis

Table 7: Characterization of the intervention – RCT, direct comparison: nintedanib + BSC versus placebo + BSC

Study	Intervention	Comparison
SENSCIS	Nintedanib 150 mg twice daily[a], orally + BSC	Placebo twice daily[a], orally + BSC
	Dose adjustments due to AEs ▪ In case of treatment-related AEs: ▫ Dose reduction to 100 mg twice daily or treatment interruption ≤ 4 weeks with resumption at a reduced dose (100 mg twice daily) allowed ▫ Reescalation to 150 mg within ≤ 4 weeks after reduction or after resumption at a reduced dose allowed ▪ In case of non-treatment-related AEs: ▫ Interruption ≤ 8 weeks permitted ▫ Resumption of therapy at full (or reduced) dose permitted ▪ Treatment discontinuation in case of substantial toxicity or if the reduced dose was not tolerated **Permitted concomitant treatment** ▪ Except for drugs explicitly prohibited, individually indicated drugs were allowed at the physician's discretion. ▪ Diarrhoea was to be treated with standard therapy (e.g. loperamide, electrolyte replacement therapy) as early as possible. ▪ It was possible to continue stable prior therapy with MMF[b, c], MTX[b, c] (each for at least 6 months) or low-dose corticosteroids (≤ 10 mg/day of prednisone or equivalent) during the study. ▪ Low-dose platelet aggregation inhibitors (e.g. acetylsalicylic acid up to 325 mg/day, clopidogrel up to 75 mg/day) ▪ Prophylactic, low-dose heparins (e.g. enoxaparin 4000 IU/day) **Non-permitted prior and concomitant treatment** ▪ Prednisone (equivalent) > 10 mg/day[c] (had to be discontinued no later than 2 weeks before randomization) ▪ Azathioprine, hydroxychloroquine, colchicine, D-penicillamine, sulfasalazine within 8 weeks before randomization as well as during the treatment phase[c] ▪ Cyclophosphamide, ciclosporin A, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, or newer anti-arthritic treatments such as tofacitinib, potassium para-aminobenzoate within 6 months before randomization as well as during the treatment phase[c] ▪ High-dose platelet aggregation inhibitors as well as anticoagulants (had to be discontinued at study start) ▪ Pirfenidone ▪ Nintedanib before study start ▪ Other experimental therapies	

a. The capsules were to be taken with a glass of water after a meal, 12 hours apart.
b. MMF and MTX are not approved in the therapeutic application to be assessed (see text on the relevant subpopulation in Section 2.3.2).
c. Dose increases or administration of the substances during the study was permitted only in case of clinically relevant deterioration (e.g. absolute FVC decline by >10% from baseline or at the investigator's discretion).

AE: adverse event; BSC: best supportive care; FVC: forced vital capacity; ILD: interstitial lung disease; IU: international unit; MMF: mycophenolate mofetil; MTX: methotrexate; RCT: randomized controlled trial; SSc: systemic sclerosis

The included SENSCIS study is a completed, multinational, double-blind RCT comparing nintedanib with placebo.

The SENSCIS study included adults with SSc-ILD. The diagnosis of SSc-ILD had to meet the applicable ACR or EULAR criteria [11] and be confirmed by high-resolution computed tomography taken within 12 months before study start, showing an extent of fibrotic disease in the lung ≥ 10%. Further inclusion criteria were a DLCO of 30% to 89% of predicted normal and an FVC ≥ 40% of predicted normal at baseline. Onset of SSc (defined as onset of first non-Raynaud symptom) had to be a maximum of 5 years (or 7 years [Amendment 2.0 of the study protocol]) before study start. According to the European Medicines Agency, the included patients tended to be in an earlier stage of SSc and pulmonary fibrosis; during the scientific consultation provided to the company regarding the study design, this stage distribution was also recommended as such since the decline in lung function progresses most rapidly in the first 3 years of the disease [10].

In total, 580 patients were randomized in a 1:1 ratio and allocated to treatment with nintedanib or placebo (stratification factor: anti-topoisomerase antibody status). In both arms, 288 patients actually received the allocated treatment. The analyses (on the total population) presented by the company are based on this total of 576 patients. All patients who were treated with the study drug until the end of the study were eligible for continued nintedanib treatment within the 1-arm, open-label extension study SENSCIS-ON [12] (N = 428), which has been disregarded in this benefit assessment.

In the SENSCIS study, nintedanib was administered in accordance with its approval [13]. Patients in the comparator arm received identically looking placebo capsules at the same time points. Unless they were explicitly prohibited, drugs indicated for individual patients were allowed in both study arms at the physician's discretion.

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

Relevant subpopulation

During the SENSCIS study, all patients were permitted to continue stable prior therapy with MMF or methotrexate (MTX) (see Table 7). However, MMF and MTX are not approved for the treatment of patients with SSc-ILD [14,15]. About 50% of the total population received additional MMF treatment (see Table 26), and about 7% received MTX [7]. For the relevant subpopulation, no data on MTX treatment are available. Since add-on MTX treatment was administered to < 20% of study participants – based on both the total population and the relevant subpopulation – this lack of data is of no consequence for the benefit assessment [1]. The handling of patients who continued stable MMF treatment during the study is discussed below.

MMF is currently approved only as an immunosuppressant for the prevention of acute graft rejection [14]. MMF has also been investigated in the therapeutic indication of SSc-ILD [16,17] and is currently used off label as an immunosuppressant in the routine care of SSc-ILD [10,18-20]. However, the effectiveness of MMF in patients with SSc-ILD has not yet been

comprehensively investigated [10,21]. In the European healthcare context, MMF is taken by about 13% of patients with SSc-ILD [22], that is, by far fewer patients than was the case in the SENSCIS study.

Furthermore, it is unclear whether MMF was primarily administered to alleviate symptoms and improve quality of life and could therefore be viewed as an adequate implementation of BSC. The company did not comment on this issue. However, use of the immunosuppressant MMF in patients with the autoimmune disease SSc (or SSc-ILD) can be assumed to be motivated by a desire to modify the disease rather than to primarily alleviate symptoms as in BSC.

The benefit assessment analysed the population of patients not treated with MMF ("non-MMF population") primarily because MMF is not approved for patients with SSc-ILD (also see G-BA note in Table 4). In Module 4, the company presents the results from all patient-relevant outcomes for both the total population and the non-MMF population. The results of the total population are presented as supplementary information in Appendix C of the full dossier assessment and are essentially comparable with those of the non-MMF population.

Implementation of the ACT (in the non-MMF population)

The G-BA specified BSC as the ACT. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life. The company followed the G-BA's specification and deems the ACT as having been implemented in the placebo-controlled SENSCIS study.

In principle, the physicians involved in the study were free to use drugs indicated for individual patients in both study arms so long as these drugs were not explicitly excluded by the study protocol (see Table 7). The concomitant therapies prohibited by the study protocol (e.g. azathioprine, cyclophosphamide, high-dose platelet aggregation inhibitors) do not jeopardize the adequate implementation of BSC since they are not approved in the therapeutic indication to be assessed and would not primarily serve the symptomatic treatment of the disease as in BSC. Module 4 does not provide any specific data on the extent and frequency at which supportive measures as in BSC were used in the study or the relevant subpopulation.

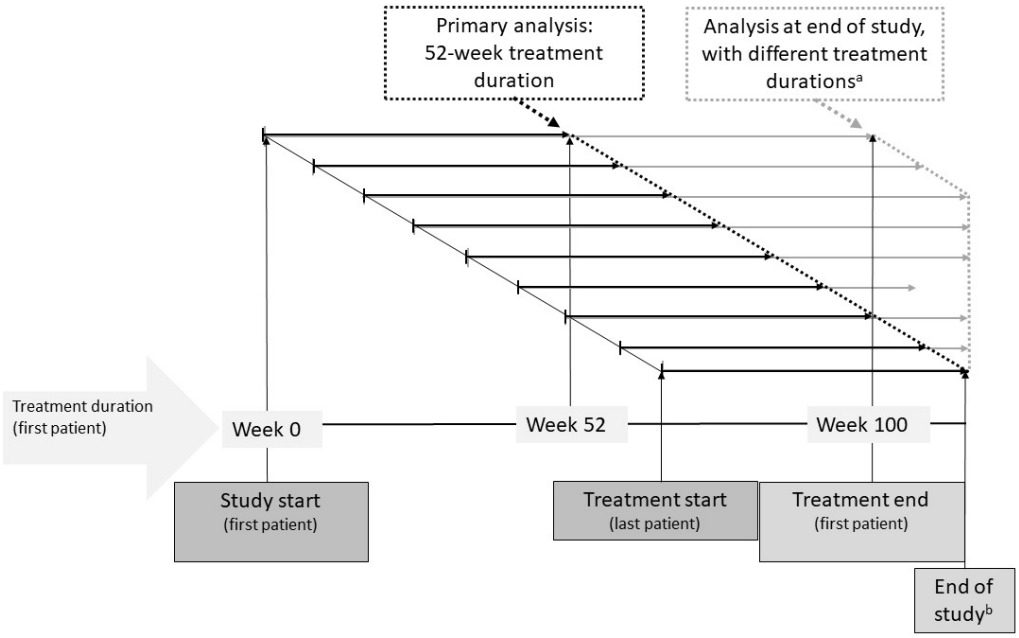
Overall, the supportive therapies allowed in the subpopulation of the SENSCIS study are deemed sufficient for the implementation of the ACT of BSC.

Analysis time points provided by the company

SENSCIS is a completed study. For all patient-relevant outcomes of the study, the company presented analyses from 2 different time points:

- Analysis time point: 52 weeks
- Analysis time point: total study period (= study end)

Figure 1 graphically presents the study design and the resulting 2 analysis time points provided by the company.



a. For individual patients, beyond 52 weeks until the end of study, up to a maximum of 100 weeks
b. The end of study was defined as the point in time at which the last randomized patient completed (the minimum of) 52 weeks of treatment as required by the protocol.

Figure 1: Study design as well as analysis time points of the SENSCIS study (modified from [23])

The primary efficacy evaluation was planned to be conducted after all patients had been treated for 52 weeks and was based, for all patients, on the data between baseline and Week 52.

After the 52-week time point was reached, patients remained blinded in the study and continued to receive treatment until the last randomized participant had completed the planned treatment duration of 52 weeks, up to a maximum of 100 weeks. Since the study ended at the time the last randomized patient had finished 52 weeks of treatment, not all study participants had the opportunity to be treated for 100 weeks within this study. Depending on when individual patients joined the study, the study design causes both the treatment and the follow-up periods to be of different lengths (see Figure 1).

For the purposes of the benefit assessment regarding this chronic disease, a longer follow-up period is deemed prudent. Therefore, the assessment relied primarily on analyses at the end of study, taking into account the data for the total study duration.

For patient-reported outcomes (PROs), however, the earlier time point after 52 weeks of treatment was used for the following reasons: Unlike outcomes from the mortality and AE categories, which were continuously surveyed, PROs were measured only at 2 or 3 time points, specifically at Week 24 and Week 52 (or at treatment end in case of premature study

discontinuation) and only once after Week 52, i.e. at the time of treatment discontinuation or the planned end of study [4]. The third and last PRO measurement time point depended on the individual recruitment time and was therefore not conducted at the same planned time point for all patients, but rather differed greatly between them. After Week 52, the number of participating patients steadily decreased, and only a minority of patients were followed up for 100 weeks. The Kaplan-Meier curves on overall survival reflect this as well (see Figure 2). This limits the validity of the analyses over the entire study period and makes the results more difficult to interpret. In line with the company's approach, the analysis time point after 52 weeks of treatment was therefore used for the PRO outcomes.

Table 8 shows the patient characteristics of the included study.

[4] Time at which the last randomized participant completed the planned minimum treatment duration of 52 weeks.

Table 8: Characterization of the non-MMF population[a] – RCT, direct comparison: nintedanib + BSC versus placebo + BSC

Study **Characteristic** **Category**	**Nintedanib + BSC** **N = 149**	**Placebo + BSC** **N = 148**
SENSCIS		
Age [years], mean (SD)	57 (11)	55 (13)
Sex [f/m], %	80/20	75/25
Region, n (%)		
Europe	76 (51)	68 (45.9)
Canada and USA	12 (8.1)	16 (10.8)
Asia	52 (34.9)	59 (39.9)
Rest of the world	9 (6.0)	5 (3.4)
Time since ILD diagnosis [years], mean (SD)	2.4 (1.8)	2.3 (1.9)
Time since first non-Raynaud symptom [years], mean (SD)	3.4 (1.7)	3.4 (1.9)
SSc subtype, n (%)		
Diffuse cutaneous	74 (50)	72 (49)
Limited cutaneous	75 (50)	76 (51)
Extent of pulmonary fibrosis (%)[b] mean (SD)	35.8 (21.2)	34.7 (20.6)
ATA status, [positive/negative], %	60/40	60/40
MMF treatment [yes/no], %	0/100	0/100
MTX therapy [yes/no], %	ND	ND
FVC		
mL, mean (SD)	2423 (748)	2503 (819)
% of predicted normal, mean (SD)	74 (18)	74 (17)
DLCO, % of predicted normal	55 (16)	54 (15)
mRSS[c], mean (SD)	10.3 (8.9)	10.5 (9.2)
Treatment discontinuation, n (%)		
52 weeks	16 (10.7)	8 (5.4)
Total study duration	29 (19.5)	23 (15.5)
Study discontinuation, n (%)		
52 weeks	32 (21.5)	21 (14.2)
Total study duration	44 (29.5)	29 (19.6)

a. Patients who received no MMF treatment at study start.
b. Measured using an HRCT scan within 12 months before baseline.
c. Skin thickness score for patients with SSc. The total score ranges from 0 to 51 points, with a high total score corresponding to greater skin thickness [24].

ATA: anti-topoisomerase antibody; BSC: best supportive care; DLCO: diffusing capacity of the lungs for carbon monoxide; f: female; FVC: forced vital capacity: HRCT: high-resolution computed tomography; ILD: interstitial lung disease; m: male; MMF: mycophenolate mofetil; mRSS. modified Rodnan skin score; MTX: methotrexate; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SSc: systemic sclerosis; SD: standard deviation

For the non-MFF population, the two treatment arms were comparable in terms of demographic and disease-specific patient characteristics. The mean patient age was 56 years, and the majority of patients were female (80% and 75%, respectively). In both treatment arms, about 50% had diffuse cutaneous SSc and about 50% limited cutaneous SSc. The extent of lung fibrosis was about 35% in each arm, and FVC was approx. 75% of predicted normal in each treatment arm. Mean FVC was 2503 mL in the comparator arm and slightly lower, at 2423 mL, in the nintedanib arm.

More patients in the nintedanib arm than in the placebo arm discontinued treatment or the study at both analysis time points.

Table 9 presents the mean and median treatment durations and the mean and median follow-up periods for patients, each for the two analysis time points presented by the company (52 weeks and total study duration, see Analysis time points section).

Table 9: Information on the course of the study – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC, non-MMF population[a]

Study **Duration of the study phase** **Outcome category**	**Nintedanib + BSC** **N = 149**	**Placebo + BSC** **N = 148**
SENSCIS		
Treatment duration [months]		
52 weeks		
Median [min; max]	12.2 [0.5; 12.2]	12.2 [0.4; 12.2]
Mean (SD)	10.3 (3.6)	11.1 (2.7)
Total study duration (= study end)[b]		
Median [min; max]	12.2[c] [0.5; 23.2]	15.6 [0.4; 23.5]
Mean (SD)	13.9 (6.7)	15.6 (6.1)
Follow-up period[d] [months]		
52 weeks		
Median [min; max]	12.2 [1.0; 12.4]	12.2 [2.8; 12.4]
Mean (SD)	11.4 (2.5)	11.9 (1.5)
Total study duration (= study end)[b]		
Median [min; max]	16.4 [1.0; 24.2]	16.8 [2.8; 24.6]
Mean (SD)	16.3 (5.9)	17.7 (5.2)

a. Patients who received no MMF treatment at study start.
b. Time at which the last randomized participant completed the planned minimum treatment period of 52 weeks, up to a maximum of 100 weeks.
c. The data on median treatment duration are from Module 4 (Tables 4-13). However, the information on the intervention arm is assumed to be erroneous since the median treatment duration at study end is reported as identical to the median treatment duration at the 52-week analysis time point. This is not plausible, particularly since the mean treatment duration as well as the follow-up duration increased when compared to the Week 52 and the majority of patients were treated until the study end.
d. The data on the follow-up duration are not available on the outcome level.

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

At the 52-week analysis time point, the median treatment duration was 12.2 months in both treatment arms, which corresponds to the median follow-up duration of patients included in the study.

While the company's reported data show the median treatment duration at study end to substantially differ between the two treatment arms (12.2 versus 15.6 months), the data on the intervention arm are presumably erroneous. This is believed, in part, because the follow-up duration after treatment is comparable in both study arms at study end.

The data on the follow-up duration are not available on the outcome level. However, since all outcomes were to be surveyed for the entire study duration, the follow-up duration for individual outcomes can be assumed to equal the follow-up duration on the study level and therefore to be largely comparable between study arms. As a consequence, AEs were analysed using the results based on relative risk (RR) because similar median follow-up periods can be assumed on the basis of the study design. Despite interpatient differences in follow-up durations, the RR is deemed interpretable since the interpatient differences in follow-up durations are not due to informative reasons (e.g. different progression rates) and the follow-up periods can be assumed to be similarly distributed between treatment groups.

Risk of bias across outcomes (study level)

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

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

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
SENSCIS	Yes	Yes	Yes	Yes	Yes	Yes	Low
BSC: best supportive care; RCT: randomized controlled trial							

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

Transferability of the study results to the German healthcare context

The company reports that the study was in part conducted in German study centres and that the average age of all patients in the included study as well as the high percentage of women reflect the realities in terms of the provided care. Also with regard to other criteria (time since disease onset, degree of pulmonary fibrosis, ancestry), the company believes the study results to be transferable to the German healthcare context. Conceding that the percentage of patients with

the diffuse cutaneous form of SSc (dcSSC) is lower in the healthcare system than in the study, the company argues that this can be explained by the higher probability of dcSSC patients developing SSc-ILD. The comparatively high percentage of SENSCIS participants receiving MMF treatment is reportedly due to regional differences in prescribing practices. Overall, the company views the study population as adequately reflecting the population to be investigated and the study results as being transferable to the German healthcare context.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - FACIT-Dyspnoea, consisting of the dyspnoea score and related functional limitations score
  - Scleroderma Health Assessment Questionnaire (SHAQ), consisting of HAQ-DI and 6 VAS measuring scleroderma-specific symptoms of disease
  - Health status as measured by the EQ-5D VAS
  - Health status as measured by the Patient Global Impression of Health VAS
- Health-related quality of life
  - Health-related quality of life (SGRQ)
- AEs
  - SAEs
  - Discontinuation due to AEs
  - Gastrointestinal disorders (SOC, AEs)
  - Diarrhoea (PT, severe AEs; based on the operationalization from Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - further specific AEs, if any

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

Outcome category of AEs

Diarrhoea (PT, severe AEs): According to the study protocol, severe diarrhoea was surveyed in addition to diarrhoea (as a PT, AEs). It was operationalized according to CTCAE (Version 4 [25]) and included all types of diarrhoea of CTCAE grade ≥ 3. In the study protocol, grade 3 was defined as an increase of ≥ 7 stools per day over baseline or faecal incontinence, while grade 4 was defined as diarrhoea with life-threatening consequences, and grade 5 as diarrhoea resulting in death. However, this definition departs from the CTCAE version cited by the company, in which grade 3 diarrhoea additionally includes other potential operationalizations (e.g. hospitalization indicated). Despite the differences to CTCAE grading (version 4), the operationalization presented by the company and defined a priori was deemed an adequate approximation for representing severe diarrhoea.

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

Table 11: Matrix of outcomes – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC, non-MMF population

Study	Outcomes										
	Overall survival	FACIT-Dyspnoea[a]	SHAQ[b]	Health status (EQ-5D VAS)	Health status (Patient Global Impression of Health VAS)	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AEs)	Diarrhoea (PT, severe AEs[c])	Further specific AEs[d]
SENSCIS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[e]

a. Consisting of the dyspnoea score and the related functional limitations score.
b. Consisting of the HAQ-DI and 6 sclerodermy-specific VAS.
c. Based on the operationalization of CTCAE grade ≥ 3 (Version 4 [25]).
d. The following events were assessed (MedDRA coding): "metabolic and nutritional disorders (SOC, AEs)" and "vascular disorders (SOC, AEs)".
e. The company presented analyses for any severe PTs and SOCs which occurred in at least 10 patients of a study arm. According to the dossier template, however, all SAEs which occurred in at least 5% of patients of a study arm must be presented in this data situation. Given the study size, all events which occurred in at least 8 patients would therefore need to be presented. Since the resulting deviation is only minor, however, it does not affect the assessment.

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACIT-Dyspnoea: Functional Assessment of Chronic Illness Therapy-Dyspnoea; HAQ-DI: Health Assessment Questionnaire-Disability Index; MedDRA: Medical Dictionary for Regulatory Activities; MMF: mycophenolate mofetil; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SGRQ: St. George's Respiratory Questionnaire; SHAQ: Scleroderma Health Assessment Questionnaire; SOC: system organ class; VAS: visual analogue scale

2.4.2 Risk of bias

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

Table 12: Risk of bias at study and outcome levels – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC, non-MMF population

Study		Outcomes										
	Study level	Overall survival	FACIT-Dyspnoea[a]	SHAQ[b]	Health status (EQ-5D VAS)	Health status (Patient Global Impression of Health VAS)	Health-related quality of life (SGRQ)	SAEs	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AEs)	Diarrhoea (PT, severe AEs[c])	Further specific AEs[d]
SENSCIS	L	L	L	L	L	L	L	L	L	L	L	L

a. Consisting of the dyspnoea score and the related functional limitations score.
b. Consisting of the HAQ-DI and 6 sclerodermy-specific VAS.
c. Based on the operationalization of CTCAE grade ≥ 3 (Version 4 [25], see Section 2.4.1).
d. The following events were assessed (MedDRA coding): "metabolic and nutritional disorders (SOC, AEs)" and "vascular disorders (SOC, AEs)".

AE: adverse event; BSC: best supportive care; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACIT-Dyspnoea: Functional Assessment of Chronic Illness Therapy-Dyspnoea; H: high; HAQ-DI: Health Assessment Questionnaire-Disability Index; L: low; MedDRA: Medical Dictionary for Regulatory Activities; MMF: mycophenolate mofetil; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SHAQ: Scleroderma Health Assessment Questionnaire; SOC: system organ class; VAS: visual analogue scale

The risk of bias for the results on all outcomes included in the benefit assessment is rated as low. This concurs with the company's assessment.

2.4.3 Results

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

The Kaplan-Meier curve for the outcome of overall survival is presented in Appendix A of the full dossier assessment, and the results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix B of the full dossier assessment.

Table 13: Results (mortality) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC, non-MMF population[a]

Study Outcome category Outcome	Nintedanib + BSC N	Nintedanib + BSC Median time to event in months [95% CI] Patients with event n (%)	Placebo + BSC N	Placebo + BSC Median time to event in months [95% CI] Patients with event n (%)	Nintedanib + BSC vs. placebo + BSC HR [95% CI]; p-value[c]
SENSCIS					
Mortality (total study duration)[d]					
Overall survival	149	NR 6 (4.0)	148	NR 7 (4.7)	0.93 [0.31; 2.77]; 0.895

a. Patients who received no MMF treatment at baseline.
b. Calculated using Cox regression with treatment as a covariate, stratified by ATA status.
c. Calculated using the Wald test.
d. Time at which the last randomized participant completed the planned minimum treatment duration of 52 weeks, up to a maximum of 100 weeks.

ATA: anti-topoisomerase antibody; BSC: best supportive care; CI: confidence interval; HR: hazard ratio; MMF: mycophenolate mofetil; n: number of patients with an event; N: number of analysed patients; NR: not reached; RCT: randomized controlled trial

Table 14: Results (morbidity, health-related quality of life) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC, non-MMF population[a] (multi-page table)

Study Outcome category Outcome (Sub)Scale	Nintedanib + BSC			Placebo + BSC			Nintedanib + BSC vs. placebo + BSC
	N[b]	Values at baseline mean (SD)	Change by Week 52 Mean (SE)[c]	N[b]	Values at baseline mean (SD)	Change by Week 52 Mean (SE)[c]	MD [95% CI][d]; p-value
SENSCIS							
Morbidity (52 weeks)							
FACIT-Dyspnoea[e]							
Dyspnoea score	147	45.6 (9.6)	0.89 (0.58)	146	44.5 (9.8)	0.61 (0.58)	0.28 [−1.34; 1.90]; 0.733
Related functional limitations score	148	45.2 (9.2)	1.66 (0.56)	147	44.9 (9.8)	−0.06 (0.56)	1.73 [0.17; 3.28]; 0.030 Hedges' g: 0.27 [0.03; 0.51]
SHAQ[f]							
HAQ-DI	146	0.51 (0.63)	0.08 (0.04)	145	0.56 (0.65)	0.03 (0.04)	0.05 [−0.05; 0.15]; 0.324
Pain VAS	135	2.60 (2.67)	0.11 (0.20)	141	2.59 (2.42)	−0.12 (0.20)	0.23 [−0.32; 0.79]; 0.406
Gastrointestinal involvement VAS	134	1.79 (2.59)	1.70 (0.22)	140	1.31 (2.03)	−0.25 (0.21)	1.95 [1.35; 2.55]; < 0.001 Hedges' g: 0.82 [0.57; 1.08]
Lung involvement VAS	134	2.60 (2.65)	0.33 (0.19)	140	2.58 (2.71)	0.08 (0.19)	0.25 [−0.29; 0.79]; 0.357
Raynaud's phenomenon VAS	133	2.69 (3.01)	0.43 (0.21)	140	2.99 (3.05)	−0.45 (0.21)	0.88 [0.29; 1.47]; 0.004 Hedges' g: 0.38 [0.12; 0.63]
Digital ulcers VAS	133	1.28 (2.42)	0.58 (0.20)	140	1.52 (2.58)	−0.05 (0.20)	0.62 [0.06; 1.18]; 0.030 Hedges' g: 0.28 [0.03; 0.53]
Overall disease severity VAS	134	3.52 (2.74)	0.06 (0.20)	140	3.60 (2.74)	−0.22 (0.20)	0.27 [−0.29; 0.83]; 0.337
Health status (EQ-5D VAS)[g]	149	68.51 (20.32)	−1.87 (1.45)	148	68.01 (18.89)	0.37 (1.45)	−2.24 [−6.28; 1.80]; 0.276
Health status (Patient Global Impression of Health VAS)[g]	148	6.14 (2.05)	−0.30 (0.18)	147	6.28 (1.97)	0.09 (0.18)	−0.40 [−0.90; 0.10]; 0.120
Health-related quality of life (52 weeks)							
SGRQ total score[h]	145	37.95 (19.71)	1.44 (1.21)	145	37.75 (21.89)	−0.35 (1.20)	1.79 [−1.57; 5.16]; 0.294

Table 14: Results (morbidity, health-related quality of life) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC, non-MMF population[a] (multi-page table)

Study Outcome category	Nintedanib + BSC			Placebo + BSC			Nintedanib + BSC vs. placebo + BSC
Outcome (Sub)Scale	N[b]	Values at baseline mean (SD)	Change by Week 52 Mean (SE)[c]	N[b]	Values at baseline mean (SD)	Change by Week 52 Mean (SE)[c]	MD [95% CI][d]; p-value

a. Patients who received no MMF treatment at baseline.
b. Number of patients included in the analysis for calculating the effect estimator; the figures at baseline (and any other times) may be based on different patient numbers.
c. Change from baseline over the analysis period from MMRM.
d. Calculated from MMRM with fixed effects for ATA status, visit, treatment x visit, and baseline value x visit.
e. Higher (increasing) values represent more pronounced symptoms; positive effects (intervention minus control) indicate a disadvantage for the intervention. The range of possible values for the dyspnoea score is 27.7 through 75.9. The range of possible values for the related functional limitations score is 29.7 through 76.7.
f. Higher (increasing) values represent more pronounced symptoms; positive effects (intervention minus control) indicate a disadvantage for the intervention. The HAQ-DI score can lie between 0 and 3. For the VAS scales, the possible results range from 0 to 10.
g. Higher values indicate better health status; positive effects (intervention minus control) indicate an advantage for the intervention. Possible results for EQ-5D VAS range from 0 to 100, and for the Patient Global Impression of Health VAS, from 0 to 10.
h. Higher (increasing) values represent poorer quality of life; positive effects (intervention minus control) indicate a disadvantage for the intervention. The SGRQ total score can range from 0 to 100 and is composed of 3 domains (Symptoms, Activity, and Impact).

ATA: anti-topoisomerase antibody; BSC: best supportive care; CI: confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACIT-Dyspnoea: Functional Assessment of Chronic Illness Therapy-Dyspnoea; HAQ-DI: Health Assessment Questionnaire-Disability Index; MD: mean difference; MMRM: mixed effect model repeated measurement; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire; SHAQ: Scleroderma Health Assessment Questionnaire; VAS: visual analogue scale

Table 15: Results (AEs) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC, non-MMF population[a]

Study Outcome category Outcome	Nintedanib + BSC		Placebo + BSC		Nintedanib + BSC vs. placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][b]; p-value[c]
SENSCIS					
AEs[d] (total study duration[e])					
AEs (supplementary information)	149	147 (98.7)	148	144 (97.3)	–
SAEs	149	43 (28.9)	148	51 (34.5)	0.84 [0.60; 1.17]; 0.306
Discontinuation due to AEs	149	33 (22.1)	148	18 (12.2)	1.82 [1.07; 3.09]; 0.024
Gastrointestinal disorders[f] (SOC, AEs)	149	133 (89.3)	148	85 (57.4)	1.55 [1.34; 1.80]; < 0.001
Diarrhoea (PT, severe AEs[g])	149	18 (12.1)	148	4 (2.7)	4.47 [1.55; 12.89]; 0.002
Metabolic and nutritional disorders[h] (SOC, AEs)	149	25 (16.8)	148	7 (4.7)	3.55 [1.58; 7.95]; < 0.001
Vascular disorders (SOC, AEs)	149	25 (16.8)	148	11 (7.4)	2.26 [1.15; 4.42]; 0.015

a. Patients who received no MMF treatment at baseline.
b. Calculated using the Cochran-Mantel-Haenszel method.
c. IQWiG calculation (unconditional exact test, CSZ method according to [26]).
d. Events based on the progression of the underlying disease were also recorded as AEs.
e. Time point at which the last randomized participant completed the planned minimum treatment duration of 52 weeks, up to a maximum of 100 weeks.
f. PTs which occurred within the SOC in ≥ 10 patients in at least 1 study arm: abdominal pain, upper abdominal pain, diarrhoea, nausea and vomiting (see Table 23).
g. Based on the operationalization of CTCAE grade ≥ 3 (version 4 [25]).
h. PTs which occurred within the SOC in ≥ 10 patients in at least 1 study arm: reduced appetite (see Table 23)

AE: adverse event; BSC: best supportive care; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least 1) event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: system organ class

The available data allow deriving at most indications, e.g. of an added benefit, for all outcomes.

Unlike the analyses for the outcomes in the mortality and AE categories, the analyses for the PRO outcomes are based on the analysis time point of 52 weeks (see section Analysis time points). The results for the PRO outcomes at study end, taking into account total study duration, showed largely comparable results (see Module 4 of the dossier, Sections 4.3.1.3.2 and 4.3.1.3.3).

In addition to the results for the relevant subpopulation (non-MMF population, see subsection on the relevant subpopulation in Section 2.3.2), the company used the results for the overall

population for deriving added benefit. At this point, the comparison with the data provided by the company is performed exclusively for the relevant subpopulation.

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

In addition to the outcome of overall survival, in the outcome category of mortality, the company used the results for FVC as a surrogate for mortality and, based on these results, derived an indication of non-quantifiable added benefit of nintedanib in comparison with the ACT. The company's view that FVC represents a valid surrogate outcome for mortality was not shared (see Appendix D of the full dossier assessment), and the results for the outcome of FVC were therefore not taken into account in the assessment of added benefit.

Morbidity

FACIT-Dyspnoea

Dyspnoea score

For the dyspnoea score, no statistically significant difference between treatment groups was found. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

Related functional limitations score

For the related functional limitations score, there was a statistically significant difference to the disadvantage of nintedanib. The SMD in the form of Hedges' g was employed to check the relevance of the result. The 95% CI of the SMD is not fully outside of the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

Scleroderma Health Assessment Questionnaire

HAQ-DI, pain VAS, lung involvement VAS, and overall disease severity VAS

No statistically significant difference between treatment groups was found for the scales of HAQ-DI, pain VAS, lung involvement VAS, and overall disease severity VAS. For each of

these outcomes, there was therefore no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

Regarding the description of results, this concurs with the company's view. However, the company did not use the scales of HAQ-DI, pain VAS, and overall disease severity VAS to derive added benefit since they plot the morbidity of the underlying condition (SSc) – and not SSc-ILD-specific morbidity.

Gastrointestinal involvement VAS

For the gastrointestinal involvement VAS, there was a statistically significant difference to the disadvantage of nintedanib + BSC. The SMD in the form of Hedges' g was examined to assess the relevance of the result. The 95% CI of the SMD is fully outside of the irrelevance range of −0.2 to 0.2. This is interpreted as a relevant effect. For the gastrointestinal involvement VAS, this results in an indication of lesser benefit of nintedanib + BSC in comparison with placebo + BSC.

Regarding the description of results, this concurs with the company's view. However, the company did not use this scale to derive added benefit since it reflects not SSc-ILD-specific morbidity, but the morbidity of the underlying disorder (SSc). In addition, the company considers the result to be reflective of the gastrointestinal AE profile of nintedanib.

Raynaud's phenomenon VAS and digital ulcers VAS

For both the Raynaud's phenomenon VAS and the digital ulcers VAS, there was a statistically significant difference to the disadvantage of nintedanib + BSC. The SMD in the form of Hedges' g was examined to assess the relevance of the results. The 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC for either of them; an added benefit is therefore not proven.

Regarding the description of results, this concurs with the company's view. However, the company did not use these scales to derive added benefit since they do not reflect SSc-ILD-specific morbidity, but the morbidity associated with the underlying disorder (SSc).

Health status

EQ-5D VAS

For the outcome of EQ-5D VAS used to survey health status, no statistically significant difference between treatment groups was found. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

Patient Global Impression of Health VAS

No statistically significant difference between treatment groups was found for the outcome of Patient Global Impression of Health VAS with respect to surveying the health status. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

St. George's Respiratory Questionnaire

For the SGRQ total score, no statistically significant difference between treatment groups was found. Consequently, there is no hint of an added benefit of nintedanib + BSC in comparison with placebo + BSC; an added benefit is therefore not proven.

This concurs with the company's assessment.

AEs

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. Consequently, no hint of greater or lesser harm from nintedanib + BSC can be derived in comparison with placebo + BSC; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, a statistically significant difference to the disadvantage of nintedanib + BSC was found. However, the extent of the effect is at most marginal. Consequently, no hint of greater or lesser harm from nintedanib + BSC in comparison with placebo + BSC can be derived for this outcome; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Vascular disorders (SOC, AEs)

For the outcome of vascular disorders (SOC, AEs), a statistically significant difference to the disadvantage of nintedanib + BSC was found. For this outcome, this results in an indication of greater harm from nintedanib + BSC in comparison with placebo + BSC. In the grand scheme of things, however, it is unclear whether the effect is actually due to the outcome category of AEs or might actually reflect symptoms of the disease; after all, the SENSCIS study protocol required that even events which were caused by a progression of the underlying disorder of SSc (e.g. vasculopathies) be recorded as AEs.

Regarding the description of results, this concurs with the company's view. The company's dossier did not address the possibility of benefit aspects being reflected by this outcome.

Gastrointestinal disorders (SOC, AEs), diarrhoea (PT, severe AEs) as well as metabolic and nutritional disorders (SOC, AEs)

For each of the outcomes of gastrointestinal disorders (SOC, AEs), diarrhoea (PT, severe AEs), and metabolic and nutritional disorders (SOC, AEs), a statistically significant difference to the disadvantage of nintedanib + BSC was found. For each of these outcomes, this results in an indication of greater harm from nintedanib + BSC in comparison with placebo + BSC.

For the specific AEs selected in the dossier assessment, this concurs with the company's view. However, the company used further specific AEs alongside the selected AEs.

2.4.4 Subgroups and other effect modifiers

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

- Age (< 65 / ≥ 65 years)
- Sex (male/female)

Subgroup analyses are available for all included outcomes.

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

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

Using the above-described methods, the available subgroup analyses do not reveal any relevant effect modifications.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes are taken into account. 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.

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated on the basis of the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for outcomes on symptoms and adverse events

Not for all outcomes considered in the present benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. A rationale for the classification of these outcomes is provided below.

Gastrointestinal involvement VAS

As a component of SHAQ, the gastrointestinal involvement VAS measures the impairment of daily activities due to intestinal problems over the course of the past 7 days. Possible scores ranged from 0 (no impairment) to 10 (very strong impairment). The patients included in the study tended to experience only minor impairment of daily activities due to intestinal problems at baseline (approx. 1.5; see Table 14). Module 4 does not provide any further information which would allow drawing conclusions about the severity of the outcome. The outcome "gastrointestinal involvement VAS" is therefore allocated to the outcome category of non-serious/non-severe symptoms / late complications.

Discontinuation due to AEs

No information is available on the severity of the AEs which led to treatment discontinuation. Therefore, the outcome of discontinuation due to AEs is allocated to the outcome category of non-serious/non-severe AEs.

Table 16: Extent of added benefit at outcome level: Nintedanib + BSC vs. placebo + BSC, non-MMF population (multi-page table)

Outcome category **Outcome** **Subscale**	**Nintedanib + BSC vs. placebo + BSC** **Median time to event (months) or event rate (%) or mean change from baseline to Week 52** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Median: NR vs. NR 4.0% vs. 4.7% HR: 0.93 [0.31; 2.77]; p = 0.895	Lesser/added benefit not proven
Morbidity		
FACIT-Dyspnoea		
Dyspnoea score	0.89 vs. 0.61 MD: 0.28 [−1.34; 1.90]; p = 0.733	Lesser/added benefit not proven
Related functional limitations score	1.66 vs. −0.06 MD: 1.73 [0.17; 3.28]; p = 0.030 Hedges' g: 0.27 [0.03; 0.51][c]	Lesser/added benefit not proven
SHAQ		
HAQ-DI	0.08 vs. 0.03 MD: 0.05 [−0.05; 0.15]; p = 0.324	Lesser/added benefit not proven
Pain VAS	0.11 vs. −0.12 MD: 0.23 [−0.32; 0.79]; p = 0.406	Lesser/added benefit not proven
Gastrointestinal involvement VAS	1.70 vs. −0.25 MD: 1.95 [1.35; 2.55]; p < 0.001 Hedges' g: 0.82 [0.57; 1.08] Probability: indication	Outcome category: non-serious/non-severe symptoms / late complications Lesser benefit; extent: non-quantifiable
Lung involvement VAS	0.33 vs. 0.08 MD: 0.25 [−0.29; 0.79]; p = 0.357	Lesser/added benefit not proven
Raynaud's phenomenon VAS	0.43 vs. −0.45 MD: 0.88 [0.29; 1.47]; p = 0.004 Hedges' g: 0.38 [0.12; 0.63][c]	Lesser/added benefit not proven
Digital ulcers VAS	0.58 vs. −0.05 MD: 0.62 [0.06; 1.18]; p = 0.030 Hedges' g: 0.28 [0.03; 0.53][c]	Lesser/added benefit not proven

Table 16: Extent of added benefit at outcome level: Nintedanib + BSC vs. placebo + BSC, non-MMF population (multi-page table)

Outcome category **Outcome** **Subscale**	**Nintedanib + BSC vs. placebo + BSC** **Median time to event (months) or event rate (%) or mean change from baseline to Week 52** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Overall disease severity VAS	0.06 vs. −0.22 MD: 0.27 [−0.29; 0.83]; p = 0.337	Lesser/added benefit not proven
Health status (EQ-5D VAS)	−1.87 vs. 0.37 MD: −2.24 [−6.28; 1.80]; p = 0.276	Lesser/added benefit not proven
Health status (Patient Global Impression of Health VAS)	−0.30 vs. 0.09 MD: −0.40 [−0.90; 0.10]; p = 0.120	Lesser/added benefit not proven
Health-related quality of life		
SGRQ	1.44 vs. −0.35 MD: 1.79 [−1.57; 5.16]; p = 0.294	Lesser/added benefit not proven
AEs		
SAEs	28.9% vs. 34.5% RR: 0.84 [0.60; 1.17]; p = 0.306	Greater/lesser harm not proven
Discontinuation due to AEs	22.1% vs. 12.2% RR: 1.82 [1.07; 3.09]; RR[d]: 0.55 [0.32; 0.93]; p = 0.024	Outcome category: non-serious/non-severe AEs $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[e]
Gastrointestinal disorders (AEs)	89.3% vs. 57.4% RR: 1.55 [1.34; 1.80]; RR[d]: 0.65 [0.56; 0.75]; p < 0.001 Probability: indication	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable
Diarrhoea (severe AEs)	12.1% vs. 2.7% RR: 4.47 [1.55; 12.89]; RR[d]: 0.22 [0.08; 0.65]; p = 0.002 Probability: indication	Outcome category: serious/severe AEs $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: considerable
Metabolic and nutritional disorders (AEs)	16.8% vs. 4.7% RR: 3.55 [1.58; 7.95]; RR[d]: 0.28 [0.13; 0.63]; p < 0.001 Probability: indication	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable

Table 16: Extent of added benefit at outcome level: Nintedanib + BSC vs. placebo + BSC, non-MMF population (multi-page table)

Outcome category **Outcome** **Subscale**	**Nintedanib + BSC vs. placebo + BSC** **Median time to event (months) or event rate (%) or mean change from baseline to Week 52** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Vascular disorders (AEs)[f]	16.8% vs. 7.4% RR: 2.26 [1.15; 4.42]; RR[d]: 0.44 [0.23; 0.87]; p = 0.015 Probability: indication	Outcome category: non-serious/non-severe AEs $0.80 \leq CI_u < 0.90$ Greater harm; extent: minor

a. Probability is stated if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper confidence limit (CI_u).
c. 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.
d. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit.
e. The extent of the effect is no more than marginal for this non-serious/non-severe outcome.
f. It is unclear, however, whether the effect is in fact attributable to the outcome category of AEs or whether it might rather reflect the symptoms of the disease.

BSC: best supportive care; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; FACIT-Dyspnoea: Functional Assessment of Chronic Illness Therapy-Dyspnoea; CI: confidence interval; CI_u: upper limit of CI; MD: mean difference; NR: not reached; RR: relative risk; SGRQ: St. George's Respiratory Questionnaire; SHAQ: Scleroderma Health Assessment Questionnaire; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

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

Table 17: Favourable and unfavourable effects from the assessment of nintedanib in comparison with BSC (non-MMF population)

Favourable effects	**Unfavourable effects**
–	Non-serious/severe symptoms / late complications ▪ Gastrointestinal involvement VAS: indication of lesser benefit – extent: non-quantifiable
–	Non-serious/non-severe AEs ▪ Gastrointestinal disorders (AEs): indication of greater harm – extent: considerable ▪ Metabolic and nutritional disorders (AEs): indication of greater harm – extent: considerable ▪ Vascular diseases (AEs)[a]: indication of greater harm – extent: minor
–	Serious/severe AEs ▪ Diarrhoea (severe AEs): indication of greater harm – extent: considerable

a. It is unclear whether the effect is in fact attributable to the outcome category of AEs or whether it rather reflects the symptoms of the disease.

AE: adverse events; BSC: best supportive care; MMF: mycophenolate mofetil; VAS: visual analogue scale

The overall analysis showed nothing but unfavourable effects of different extents for nintedanib in comparison with BSC, each with the probability of indication. These effects predominantly relate to AE outcomes, particularly gastrointestinal AEs, of various severities. An unfavourable effect was also found for the gastrointestinal involvement VAS. However, given the known gastrointestinal AE profile of nintedanib, the observed unfavourable effect on this outcome might conceivably be due to AEs rather than to changes in disease-specific symptoms.

In summary, for patients with SSC-ILD, there is an indication of lesser benefit of nintedanib in comparison with the ACT of BSC.

Table 18 presents a summary of the results of the benefit assessment of nintedanib in comparison with the ACT.

Table 18: Nintedanib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with SSc-ILD	BSC	Indication of lesser benefit
a. Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SSc-ILD: systemic sclerosis-associated interstitial lung disease		

The assessment described above differs from that of the company, which derived an indication of non-quantifiable added benefit in consideration of further outcomes (particularly FVC).

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

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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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