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Nintedanib (idiopathic pulmonary fibrosis) –

Addendum to Commission A19-36[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
BSC	best supportive care
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPF	idiopathic pulmonary fibrosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SPC	Summary of Product Characteristics

1 Background

On 26 August 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-36 (Nintedanib – Benefit assessment according to §35a Social Code Book V) [1].

The pharmaceutical company (hereinafter referred to as "the company") presented the 3 randomized controlled trials (RCTs) INPULSIS-1, INPULSIS-2 and 1199.187 for the benefit assessment of nintedanib in patients with idiopathic pulmonary fibrosis (IPF). In addition, the TOMORROW study excluded by the company was identified as relevant for the benefit assessment. These 4 RCTs were included in the dossier assessment of nintedanib [1].

The TOMORROW study was a dose-ranging study. The study compared several dosages of nintedanib (50 mg once daily, 50 mg twice daily, 100 mg twice daily, 150 mg twice daily) with placebo. The recommended dose according to the Summary of Product Characteristics (SPC) is 150 mg twice daily [2]. Correspondingly, the study arm with the dosage of 150 mg twice daily was considered in the dossier assessment.

In its written comments, the company submitted a pooled analysis of all relevant studies, which for the TOMORROW study also considered the 100 mg study arm besides the 150 mg arm.

The G-BA commissioned IQWiG with the presentation and the assessment of the study results on mortality and further available outcomes under consideration of the study arm with the dosage of 100 mg twice daily of the TOMORROW study.

In addition, a responder analysis for a change ≤ -4 points for the St. George's Respiratory Questionnaire (SGRQ) was to be assessed. The responder analyses on the SGRQ were not used in the benefit assessment because they are not sufficiently validated [1].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

Changes in comparison with Version 1.0

The present Version 1.1 of 2 October 2019 replaces Version 1.0 of the addendum of 13 September 2019. The following change is contained in Version 1.1 compared with Version 1.0:

- There was a wrong presentation of the direction of effect of the results of the individual studies in the description of the result and in the corresponding forest plots on the responder analyses on health-related quality of life. The information in Section 2.2 and the forest plots in Appendix A.2 of the present Version 1.1 have been corrected accordingly.

The result of the assessment was not affected by this change.

2 Assessment

With its comments [3], the company presented an analysis of the outcome "overall survival", which it referred to as "sensitivity analysis". Besides the results of INPULSIS-1, INPULSIS-2, 1199.187 and of the 150 mg arm of the TOMORROW study, the results of the 100 mg arm of the TOMORROW study were additionally included in this meta-analysis. Section 2.1 presents the results for all outcomes under inclusion of both nintedanib arms (100 mg and 150 mg) of the TOMORROW study. Section 2.2 shows the responder analyses of the SGRQ. The forest plots can be found in Appendix A.

2.1 Results of relevant studies including the 100 mg arm of the TOMORROW study

In its dossier [4], the company excluded the TOMORROW study as irrelevant from its assessment. Since the reasons given for this approach were inadequate, the TOMORROW study was included in dossier assessment A19-36.

The TOMORROW study was a dose-ranging study. The study compared several dosages of nintedanib (50 mg once daily, 50 mg twice daily, 100 mg twice daily, 150 mg twice daily) with placebo. The recommended dose according to the SPC is 150 mg twice daily. A dose of 100 mg twice daily is only recommended to be used in patients who do not tolerate the 150 mg dose [2]. Hence, initial treatment with 100 mg twice daily does not comply with the approval. In the benefit assessment, only the 150 mg arm of the TOMORROW study was therefore considered for the meta-analysis of all relevant studies.

In its comments, the company did not address the relevance of the TOMORROW study it had excluded before. Instead, it argued that the 100 mg is approved and relevant for the provision of health care. As described above, these arguments are inadequate because the patients in the 100 mg arm had not been pretreated with the 150 mg dosage.

In accordance with the commission, the results of the 4 studies are presented below under consideration of the 100 mg arm of the TOMORROW study. Dossier assessment A19-36 [1] provides a detailed description of the characteristics of the included studies and of the risk of bias as well as the presentation of the results.

Table 1 to Table 3 summarize the results from the benefit assessment, supplemented by the data of the 100 mg arm of the TOMORROW study, on the comparison of nintedanib + best supportive care (BSC) with placebo + BSC in patients with IPF. Where necessary, calculations conducted by the Institute supplement the data from company's dossier and comments. Outcomes not recorded in the TOMORROW study are not presented below; these can be found in dossier assessment A19-36.

The company used a fixed-effect model for the meta-analyses presented in the comments. As explained in dossier assessment A19-36 [1], it is generally not realistic to assume a fixed effect for several studies. Hence, deviating from the company, new calculations of meta-analyses were

conducted with a random-effects model according to Knapp and Hartung [5] for outcomes for which results from several studies were available.

Table 1: Results (mortality and morbidity, time to event) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Outcome category **Outcome** **Study**	**Nintedanib + BSC** **N[a]**	**Nintedanib + BSC** **Median time to event in weeks [95% CI]** **Patients with event n (%)**	**Placebo + BSC** **N[a]**	**Placebo + BSC** **Median time to event in weeks [95% CI]** **Patients with event n (%)**	**Nintedanib + BSC vs. placebo + BSC** **HR [95% CI][b]; p-value[c]**
Mortality					
Overall survival					
INPULSIS-1 (52 weeks)	309	ND 13 (4.2)	204	ND 13 (6.4)	0.63 [0.29; 1.36]; 0.288
INPULSIS-2 (52 weeks)	329	ND 22 (6.7)	219	ND 20 (9.1)	0.74 [0.40; 1.35]; 0.300
1199.187 (24 weeks)	56	ND 1 (1.8)	57	ND 4 (7.0)	0.15 [0.02; 1.39]; 0.194
TOMORROW[d] (52 weeks)	171[e]	ND 11 (6.4)	85[e]	ND 9 (10.6)	0.55 [0.23; 1.34]; 0.246
Total					_[f]
Morbidity					
Adjudicated acute exacerbations					
INPULSIS-1	309	ND 7 (2.3)	204	ND 8 (3.9)	0.55 [0.20; 1.54]; 0.302
INPULSIS-2	329	ND 5 (1.5)	219	ND 16 (7.3)	0.20 [0.07; 0.56]; 0.001
Study 1199.187	56	ND 1 (1.8)	57	ND 2 (3.5)	0.39 [0.03; 4.91]; 0.576
TOMORROW[d] (52 weeks)	172	ND 8 (4.7[g])	87	ND 12 (13.8)	ND
Total					_[h]
Supplemental oxygen use					
INPULSIS-1 (52 weeks)	Outcome not recorded				
INPULSIS-2 (52 weeks)	Outcome not recorded				
1199.187 (24 weeks)	Outcome not recorded				
TOMORROW[d] (52 weeks)	172	ND 5 (2.9)[g]	87	ND 3 (3.4)	ND
Total					_[h]

(continued)

Table 1: Results (mortality and morbidity, time to event) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

a: All randomized patients (studies INPULSIS-1 and INPULSIS-2) or those for whom the intake of at least one dose of the study medication was documented (studies 1199.187 and TOMORROW).
b: Effect and CI calculated using the Cox proportional hazards model, adjusted by treatment, sex, age and height; in the TOMORROW study additionally by region.
c: p-value calculated with log-rank test.
d: The patient numbers of the 2 intervention arms of nintedanib 100 mg and nintedanib 150 mg were pooled. Since no subsequent adjudication of exacerbations was conducted in the TOMORROW study, non-adjudicated acute exacerbations were used for this study.
e: Number of patients in the treated set.
f: No analysis using a suitable model with meaningfully interpretable effect estimation and CI available (see description of the results on the respective outcome).
g: Institute's calculation.
h: No meta-analysis conducted as the company did not provide any data on the effect estimation (TOMORROW); original analysis: see dossier assessment A19-36 [1].
BSC: best supportive care; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; RCT: randomized controlled trial; vs.: versus

Table 2: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Outcome category Outcome Study	Nintedanib + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Nintedanib + BSC vs. placebo + BSC MD [95% CI]; p-value
Morbidity							
Endurance (6-minute walking test, [m])[b]							
INPULSIS-1 (52 weeks)	Outcome not recorded						
INPULSIS-2 (52 weeks)	Outcome not recorded						
1199.187 (24 weeks)	55	345.46 (140.71)	4.93 (11.43)[c]	52	347.69 (146.26)	−13.01 (11.49)[c]	17.93 [−14.26; 50.12]; 0.272[c]
TOMORROW[d] (52 weeks)	135	433.16 (110.33)[e]	−33.32 (8.86)[e]	69	411.1 (15.90[f])	−35.67 (12.73)[g]	2.35 [−27.90; 32.60]; 0.878[h]
Total							–[i]
Health-related quality of life							
SGRQ total score[j]							
INPULSIS-1 (52 weeks)	289	39.55 (17.63)	4.34 (0.80)[c]	200	39.79 (18.48)	4.39 (0.96)[c]	−0.05 [−2.50; 2.40]; 0.966[c]
INPULSIS-2 (52 weeks)	320	39.46 (20.47)	2.80 (0.73)[c]	213	39.39 (18.65)	5.48 (0.89)[c]	−2.69 [−4.95; −0.43]; 0.020[c] Hedges' g: −0.21 [−0.38; −0.03][k]
1199.187 (24 weeks)	55	35.75 (17.49)	−2.44 (1.54)[c]	53	44.39 (18.49)	−2.75 (1.55)[c]	0.31 [−4.10; 4.72]; 0.889[c]
TOMORROW (52 weeks)[d]	157	41.82 (17.29)[e]	0.46 (1.19)[e]	79	41.8 (2.03[f])	5.46 (1.73)[g]	−5.00 [−9.10; −0.90]; 0.017[h] Hedges' g: −0.33 [−0.60; −0.06][k]
Total							–[i]
SGRQ domains (supplementary)							
Symptoms[j]							
INPULSIS-1 (52 weeks)	300	45.67 (22.05)	1.56 (1.10)[c]	202	45.23 (22.89)	3.89 (1.35)[c]	−2.32 [−5.74; 1.10][c]
INPULSIS-2 (52 weeks)	323	43.04 (23.50)	2.03 (1.06)[c]	214	43.84 (21.64)	3.43 (1.30)[c]	−1.40 [−4.69; 1.88][c]
1199.187 (24 weeks)	No data available						
TOMORROW[d] (52 weeks)	158	44.13 (22.88)[e]	−0.30 (1.69)[e]	79	42.8 (2.47[f])	6.45 (2.45)[g]	−6.75 [−12.56; −0.94][h]

(continued)

Table 2: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

Outcome category Outcome Study	Nintedanib + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Placebo + BSC N[a]	Values at baseline mean (SD)	Change at end of study mean (SE)	Nintedanib + BSC vs. placebo + BSC MD [95% CI]; p-value
Activity[j]							
INPULSIS-1 (52 weeks)	295	52.2 (20.62)	4.62 (0.91)[c]	200	52.1 (21.22)	5.81 (1.10)[c]	−1.19 [−3.99; 1.61][c]
INPULSIS-2 (52 weeks)	322	51.8 (23.44)	3.89 (0.86)[c]	214	52.8 (21.34)	7.20 (1.05)[c]	−3.31 [−5.97; −0.64][c]
1199.187 (24 weeks)	No data available						
TOMORROW[d] (52 weeks)	157	56.06 (19.35)[e]	1.72 (1.32)[e]	79	54.5 (2.50[f])	7.48 (1.91)[g]	−5.76 [−10.28; −1.24][h]
Impact[j]							
INPULSIS-1 (52 weeks)	291	30.1 (18.65)	4.87 (0.92)[c]	202	30.3 (19.39)	4.01 (1.11)[c]	0.86 [−1.97; 3.70][c]
INPULSIS-2 (52 weeks)	320	30.8 (21.92)	2.85 (0.85)[c]	215	29.7 (20.94)	5.93 (1.04)[c]	−3.08 [−5.71; −0.45][c]
1199.187 (24 weeks)	No data available						
TOMORROW[d] (52 weeks)	157	32.35 (18.82)[e]	0.35 (1.37)[e]	79	33.8 (2.24[f])	4.21 (1.99)[g]	−3.86 [−8.56; 0.84][h]

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b: A negative change indicates worse endurance; a positive group difference corresponds to an advantage of nintedanib.
c: MMRM analysis adjusted for treatment, visit, baseline value and study participant, as well as interaction terms for treatment and visit, baseline value and visit.
d: Data for the intervention arm are based on the pooling of the 100 mg study arm and the 150 mg study arm.
e: Institute's calculation of mean, standard deviation and standard error according to the methods described in the Cochrane handbook [6] for pooling of effect estimations from 2 study arms.
f: Standard error.
g: ANCOVA with imputation of missing values according to LOCF, adjusted for treatment, baseline value and region.
h: MD and CI: Institute's calculation; if p-value available: Institute's calculation of t-test.
i: Analysis using a suitable model with meaningfully interpretable effect estimation and CI not available.
j: A higher value indicates greater impact; a negative group difference corresponds to an advantage of nintedanib.
k: Institute's calculation based on effect estimation of mean difference and CI.

ANCOVA: analysis of covariance; BSC: best supportive care; CI: confidence interval; LOCF: last observation carried forward; m: metre; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SGRQ: St. George's Respiratory Questionnaire; vs.: versus

Table 3: Results (side effects) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Outcome category Outcome Study	Nintedanib + BSC N[a]	 Patients with event n (%)	Placebo + BSC N	 Patients with event n (%)	Nintedanib + BSC vs. placebo + BSC RR [95% CI]; p-value[b]
Side effects					
AEs (supplementary information)					
INPULSIS-1	309	298 (96.4)	204	181 (88.7)	–
INPULSIS-2	329	311 (94.5)	219	198 (90.4)	–
1199.187	56	55 (98.2)	57	52 (91.2)	–
TOMORROW[c]	171[d]	162 (94.7)[d]	85	77 (90.6)	–
SAEs					
INPULSIS-1	309	96 (31.1)	204	55 (27.0)	1.15 [0.87; 1.53]; 0.318
INPULSIS-2	329	98 (29.8)	219	72 (32.9)	0.91 [0.70; 1.17]; 0.444
1199.187	56	8 (14.3)	57	9 (15.8)	0.90 [0.38; 2.18]; 0.823
TOMORROW	171[d]	41 (24.0)[d]	85	26 (30.6)	0.78 [0.52; 1.19]; 0.308[e]
Total					0.96 [0.74; 1.25]; 0.689[f]
Discontinuation due to AEs					
INPULSIS-1	309	65 (21.0)	204	22 (10.8)	1.95 [1.24; 3.06]; 0.002
INPULSIS-2	329	58 (17.6)	219	33 (15.1)	1.17 [0.79; 1.73]; 0.430
1199.187	56	8 (14.3)	57	3 (5.3)	2.71 [0.76; 9.71]; 0.106
TOMORROW[c]	171[d]	38 (22.2)[d]	85	22 (25.9)	0.86 [0.54; 1.35]; 0.598[e]
Total					*Heterogeneity[g]: Q=7.95; p-value = 0.047; I^2 = 62.3%*
Gastrointestinal disorders (SOC)					
INPULSIS-1	309	235 (76.1)	204	71 (34.8)	2.19 [1.79; 2.66]; < 0.001[e]
INPULSIS-2	329	253 (76.9)	219	97 (44.3)	1.74 [1.48; 2.04]; < 0.001[e]
1199.187	56	48 (85.7)	57	30 (52.6)	1.63 [1.25; 2.13]; < 0.001[e]
TOMORROW[c]	171[d]	112 (65.5)[d]	85	27 (31.8)	2.06 [1.48; 2.87]; < 0.001[e]
Total					1.88 [1.51; 2.34]; 0.003[f]
Including:					
Diarrhoea (PT)					
INPULSIS-1	*309*	*190 (61.5)*	*204*	*38 (18.6)*	*3.30 [2.45; 4.46]; < 0.001*
INPULSIS-2	*329*	*208 (63.2)*	*219*	*40 (18.3)*	*3.46 [2.58; 4.64]; < 0.001*
1199.187	*56*	*40 (71.4)*	*57*	*21 (36.8)*	*1.94 [1.33; 2.83]; < 0.001*
TOMORROW[c]	*171[d]*	*79 (46.2)[d]*	*85*	*13 (15.3)*	*3.02 [1.79, 5.11]; < 0.001[e]*
Total					*2.90 [1.90; 4.44]; 0.004[f]*

(continued)

Table 3: Results (side effects) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC (continued)

Outcome category Outcome Study	Nintedanib + BSC N[a]	 Patients with event n (%)	Placebo + BSC N	 Patients with event n (%)	Nintedanib + BSC vs. placebo + BSC RR [95% CI]; p-value[b]
Nausea (PT)					
INPULSIS-1	*309*	*70 (22.7)*	*204*	*12 (5.9)*	*3.85 [2.14; 6.92]; < 0.001*
INPULSIS-2	*329*	*86 (26.1)*	*219*	*16 (7.3)*	*3.58 [2.16; 5.93]; < 0.001*
Study 1199.187	*56*	*16 (28.6)*	*57*	*13 (22.8)*	*1.25 [0.67; 2.36]; 0.483*
TOMORROW[c]	*171*[d]	*37 (21.6)*[d]	*85*	*8 (9.4)*	*2.30 [1.12, 4.27]; 0.017*[e]
Total					*Heterogeneity*[g]*:* *Q=8.70;* *p-value = 0.034; I^2 = 65.5%*
Vomiting (PT)					
INPULSIS-1	*309*	*40 (12.9)*	*204*	*4 (2.0)*	*6.60 [2.40; 18.2]; < 0.001*
INPULSIS-2	*329*	*34 (10.3)*	*219*	*7 (3.2)*	*3.23 [1.46; 7.16]; 0.002*
Study 1199.187	*56*	*9 (16.1)*	*57*	*3 (5.3)*	*3.05 [0.87; 10.70]; 0.062*
TOMORROW[c]	*171*[d]	*22 (12.9)*[d]	*85*	*4 (4.7)*	*2.73 [0.97, 7.68]; 0.043*[e]
Total					*3.65 [1.97; 6.76]; 0.007*[f]
Abdominal pain upper (PT)					
INPULSIS-1	*309*	*23 (7.4)*	*204*	*9 (4.4)*	1.69 [0.80; 3.57]; 0.187[e]
INPULSIS-2	*329*	*18 (5.5)*	*219*	*6 (2.7)*	2.00 [0.81; 4.95]; 0.135[e]
Study 1199.187	*56*	*3 (5.4)*	*57*	*3 (5.3)*	*1.02 [0.21; 4.83]; > 0.999*[e]
TOMORROW[c]	*171*[d]	*12 (7.0)*[d]	*85*	*3 (3.5)*	*1.99 [0.58, 6.86]; 0.308*[e]
Total					*–*[h]

a: Patients for whom the intake of at least one dose of the study medication was documented (treated set).
b: χ^2 test.
c: The patient numbers of the 2 intervention arms of nintedanib 100 mg and nintedanib 150 mg were pooled.
d: Institute's calculation.
e: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [7]).
f: Institute's calculation from meta-analysis with random effects (Knapp-Hartung method).
g: Q test for heterogeneity.
h: No analysis using a suitable model with meaningfully interpretable effect estimation and CI available (see description of the results on the respective outcome).

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

Mortality

Overall survival

For the outcome "overall survival", the meta-analysis of the studies INPULSIS-1, INPULSIS-2, 1199.187 and TOMORROW with random-effects models showed that none of these models produced a meaningfully interpretable confidence interval (CI). Hence, in the present situation, first the conservative estimation approach according to Knapp-Hartung (95% CI: [0.36; 1.09]) and the anti-conservative estimation approach according to DerSimonian-Laird (95% CI: [0.41; 0.94]) were considered. This produced a statistically significant difference between the treatment groups only for the model according to DerSimonian-Laird, but not for the model according to Knapp-Hartung. The results on this outcome were therefore interpreted on the basis of the results of the individual studies INPULSIS-1, INPULSIS-2 and 1199.187 and TOMORROW by checking whether the effects pointed in the same direction [8].

None of the studies showed a statistically significant difference between the treatment groups. According to the corresponding methodological requirements, the results cannot be considered as pointing in the same direction [8]. Neither an advantage nor a disadvantage of nintedanib results from this.

Morbidity

Adjudicated acute exacerbations

No usable analyses for the joint consideration of the 150 mg arm and the 100 mg arm of the TOMORROW study were available for the outcome "acute exacerbations". The results of the meta-analysis of the studies INPULSIS-1, INPULSIS-2 and 1199.187 and TOMORROW (150 mg) are presented in dossier assessment A19-36 [1].

Supplemental oxygen use

No usable analyses for the joint consideration of the 150 mg arm and the 100 mg arm of the TOMORROW study were available for the outcome "supplemental oxygen use". The outcome was not recorded in the studies INPULSIS-1, INPULSIS-2 and 1199.187. The results of the 150 mg arm of the TOMORROW study are presented in dossier assessment A19-36 [1].

Endurance (6-minute walking test)

For the outcome "endurance", the meta-analysis of the studies 1199.187 and TOMORROW with random-effects models showed that none of these models produced a meaningfully interpretable CI. Hence, in the present situation, first the conservative estimation approach according to Knapp-Hartung (95% CI: [−89.13; 108.45]) and the anti-conservative estimation approach according to DerSimonian-Laird (95% CI: [−12.39; 31.70]) were considered. There was no statistically significant difference between the treatment groups for either of both approaches. Neither an advantage nor a disadvantage of nintedanib results from this.

Health-related quality of life

Health-related quality of life (SGRQ)

For the outcome "health-related quality of life", recorded with the SGRQ, the meta-analysis of the studies INPULSIS-1, INPULSIS-2, 1199.187 and TOMORROW with random-effects models showed that none of these models produced a meaningfully interpretable CI. In the present situation, the conservative estimation approach according to Knapp-Hartung (95% CI: [−5.41; 1.83]) and the anti-conservative estimation approach according to DerSimonian-Laird (95% CI: [−3.93; 0.37]) were considered. There was no statistically significant difference between the treatment groups for either of both approaches. Neither an advantage nor a disadvantage of nintedanib results from this.

Side effects

Serious adverse events

The meta-analysis of the 4 included studies showed no statistically significant difference between the treatment groups for the outcome "serious adverse events (SAEs)". In summary, neither an advantage nor a disadvantage of nintedanib results from this.

Discontinuation due to adverse events

Since there was heterogeneity between the 4 studies for the outcome "discontinuation due to adverse events (AEs)", the results were not pooled in a meta-analysis. The results on this outcome were therefore interpreted on the basis of the results of the 4 individual studies by checking whether the effects pointed in the same direction.

The INPULSIS-1 study showed a statistically significant effect to the disadvantage of nintedanib. None of the studies INPULSIS-2, 1199.187 and TOMORROW showed a statistically significant difference between the treatment arms. Hence, the effects did not point in the same direction. In summary, neither an advantage nor a disadvantage of nintedanib results from this.

Specific adverse event "gastrointestinal disorders"

The meta-analysis of the 4 included studies showed a statistically significant difference to the disadvantage of nintedanib + BSC in comparison with placebo + BSC for the specific AE "gastrointestinal disorders" (System Organ Class [SOC]). This effect was largely due to events in the Preferred Terms (PTs) diarrhoea, nausea and vomiting. In summary, there was a disadvantage of nintedanib.

Subgroups and other effect modifiers

No results are available on subgroup analyses based on the individual studies, so that no meaningful interpretation of the results on subgroups is possible (see dossier assessment A19-36 [1]).

2.2 Results for the responder analyses on health-related quality of life, recorded with the SGRQ instrument

The company presented responder analyses of the SGRQ in its dossier. The company defined patients with an improvement in health-related quality of life (i.e. decrease) by ≤ −4 points as SGRQ responders. As explained in dossier assessment A19-36, the response criterion of ≤ −4 is not sufficiently validated in the IPF population [1].

Table 4 shows the results of the responder analysis of the SGRQ. The meta-analysis of the 4 studies was conducted both only with the approval-compliant 150 mg arm of the TOMORROW study and under inclusion of the 100 mg arm.

Table 4: Results (morbidity, dichotomous) – RCT, direct comparison: nintedanib + BSC vs. placebo + BSC

Outcome category Outcome Study	Nintedanib + BSC N[a]	 Patients with event n (%)	Placebo + BSC N[a]	 Patients with event n (%)	Nintedanib + BSC vs. placebo + BSC RR [95% CI]; p-value[b]
Health-related quality of life					
SGRQ responders[c] (TOMORROW including data of the 150 mg arm)					
INPULSIS-1 (52 weeks)	309	63 (20.39)	204	49 (24.02)	0.85 [0.61; 1.18]; 0.351
INPULSIS-2 (52 weeks)	329	83 (25.23)	219	37 (16.89)	1.49 [1.05; 2.11]; 0.022
1199.187 (24 weeks)	56	14 (25.00)	57	22 (38.60)	0.65 [0.37; 1.13]; 0.132
TOMORROW (52 weeks)	86	25 (29.1)	87	14 (16.1)	1.81 [1.01; 3.23]; 0.048
Total					*Heterogeneity[e]: Q=11.62; p-value = 0.009; I² = 74.20%*
SGRQ responders[c] (TOMORROW including data of the arms: 100 mg and 150 mg)					
INPULSIS-1 (52 weeks)	309	63 (20.39)	204	49 (24.02)	0.85 [0.61; 1.18]; 0.351
INPULSIS-2 (52 weeks)	329	83 (25.23)	219	37 (16.89)	1.49 [1.05; 2.11]; 0.022
1199.187 (24 weeks)	56	14 (25.00)	57	22 (38.60)	0.65 [0.37; 1.13]; 0.132
TOMORROW[d] (52 weeks)	172[d]	53 (30.8)[d]	87	14 (16.1)	1.91 [1.13; 3.25]; 0.011
Total					*Heterogeneity[e]: Q=13.08; p-value = 0.004; I² = 77.1%*

a: All randomized patients (studies INPULSIS-1 and INPULSIS-2) or those for whom the intake of at least one dose of the study medication was documented (studies 1199.187 and TOMORROW).
b: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [7]).
c: Responder defined as absolute change in SGRQ total score by ≤ −4 points from baseline to week 52 or week 24 (study 1199.187) (corresponding to an improvement).
d: The patient numbers of the 2 intervention arms of nintedanib 100 mg and nintedanib 150 mg were pooled.
e: Q test for heterogeneity.
BSC: best supportive care; CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least) one event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George's Respiratory Questionnaire; vs.: versus

Important heterogeneity between the 4 studies was shown in each case for the responder analyses on the SGRQ (excluding or including the 100 mg arm of the TOMORROW study); hence, no meta-analysis of the results was conducted. The results on this outcome were

therefore interpreted on the basis of the results of the 4 individual studies by checking whether the effects pointed in the same direction [8].

Two studies (INPULSIS-2 and TOMORROW) showed a statistically significant difference in favour of nintedanib, but the effect estimation of the other studies pointed in the direction of a disadvantage of nintedanib. Hence, the effects of the studies did not point in the same direction. In summary, neither an advantage nor a disadvantage of nintedanib results from this.

2.3 Summary

The additional assessment of the 100 mg arm of the TOMORROW study as well as the responder analyses of the SGRQ have not changed the conclusion on the added benefit of nintedanib from dossier assessment A19-36.

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Nintedanib (idiopathische Lungenfibrose): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-36 [online]. 11.07.2019 [Accessed: 17.07.2019]. (IQWiG-Berichte; Volume 790). URL: https://www.iqwig.de/download/A19-36_Nintedanib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

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Appendix A – Forest plots

A.1 – Forest plots of the results under inclusion of the 100 mg arm of the TOMORROW study

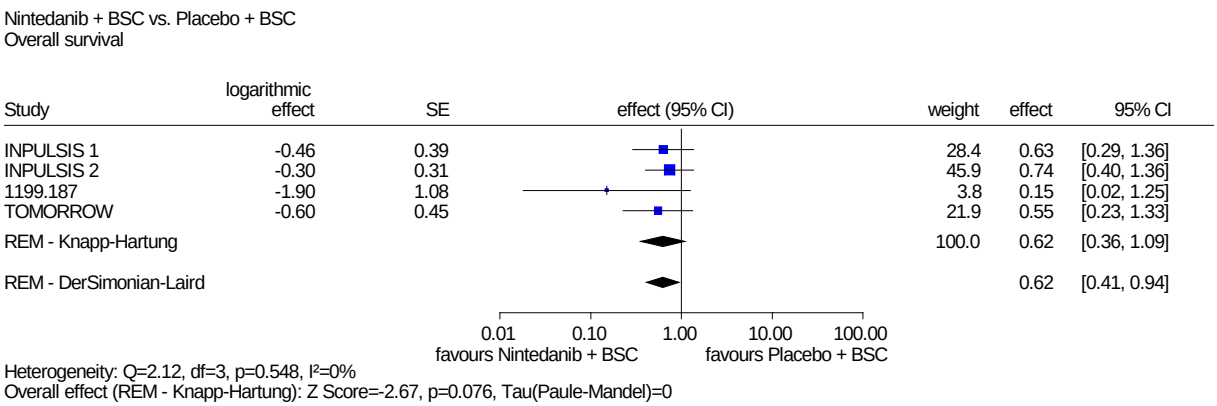


Figure 1: Meta-analysis, overall survival, nintedanib + BSC vs. placebo + BSC; effect estimate: HR

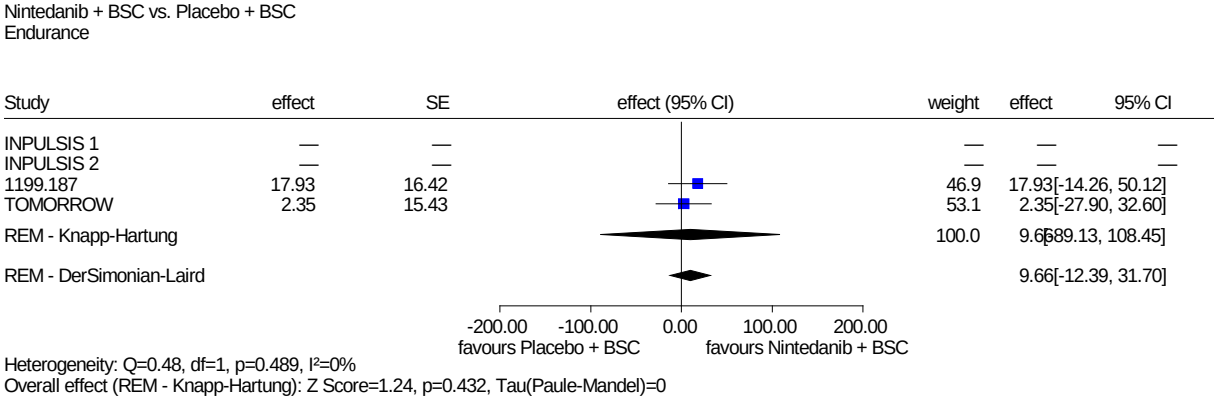


Figure 2: Meta-analysis, endurance (6-minute walking test), nintedanib + BSC vs. placebo + BSC; effect estimate: mean difference

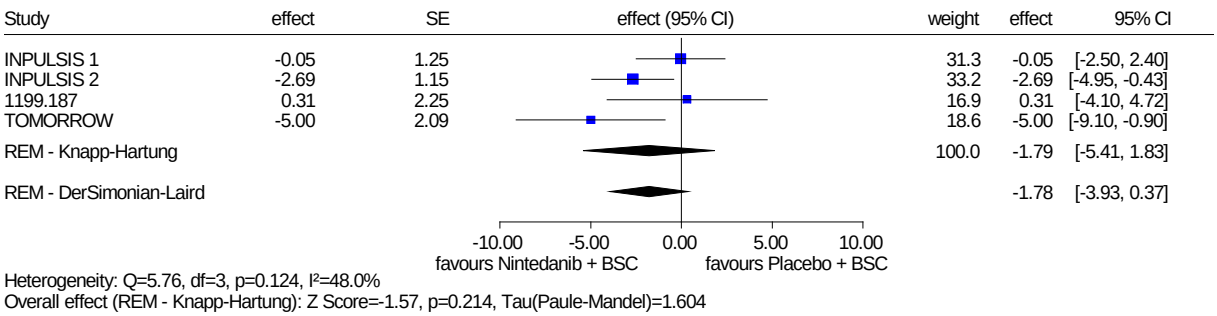


Figure 3: Meta-analysis, SGRQ, nintedanib + BSC vs. placebo + BSC; effect estimate: mean difference

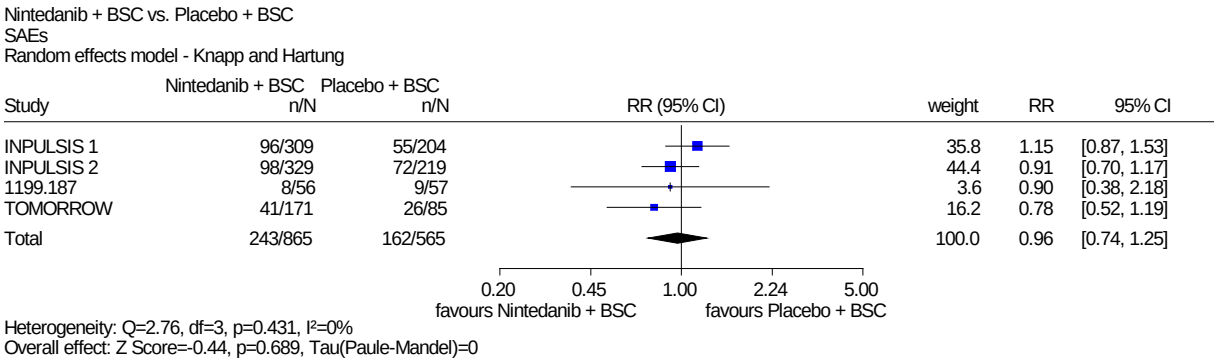


Figure 4: Meta-analysis, SAEs, nintedanib + BSC vs. placebo + BSC; effect estimate: RR

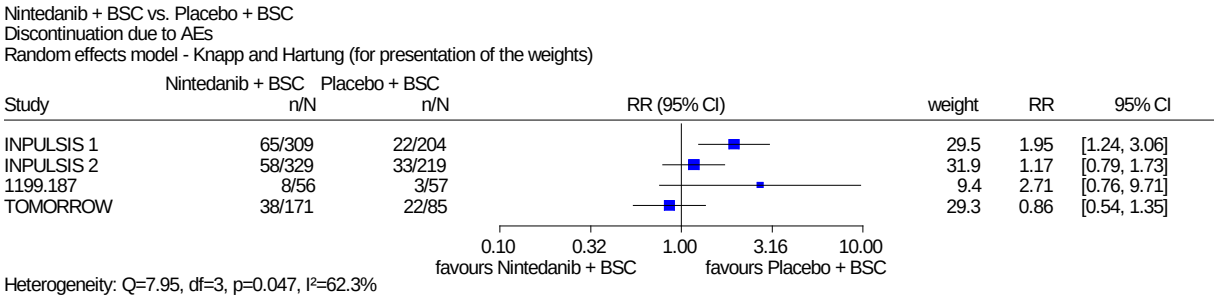


Figure 5: Meta-analysis, discontinuation due to AEs, nintedanib + BSC vs. placebo + BSC; effect estimate: RR

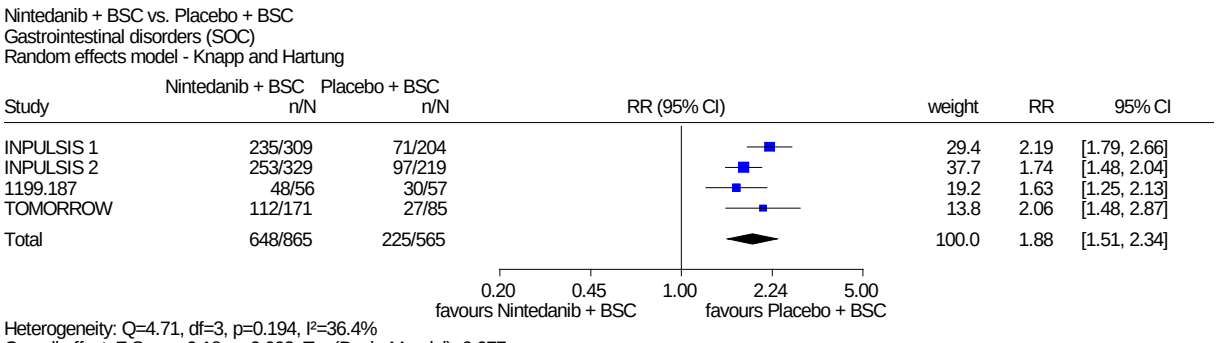


Figure 6: Meta-analysis, gastrointestinal disorders (SOC), nintedanib + BSC vs. placebo + BSC; effect estimate: RR

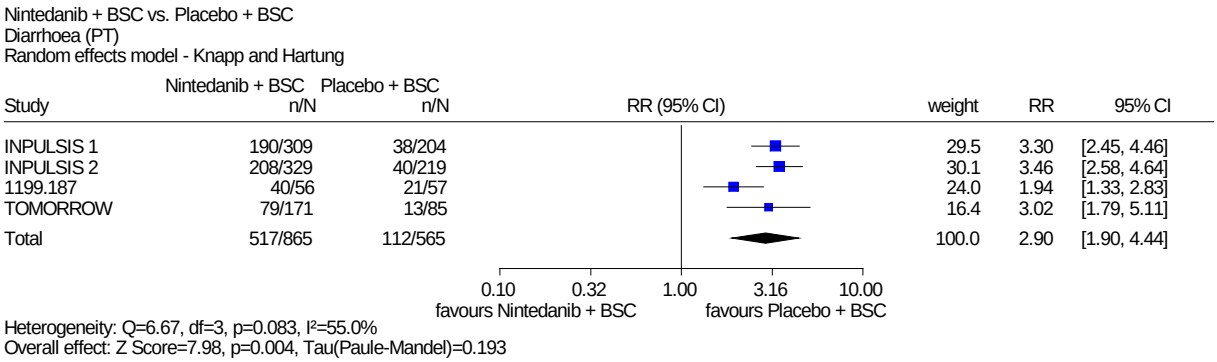


Figure 7: Meta-analysis, diarrhoea (PT), nintedanib + BSC vs. placebo + BSC; effect estimate: RR

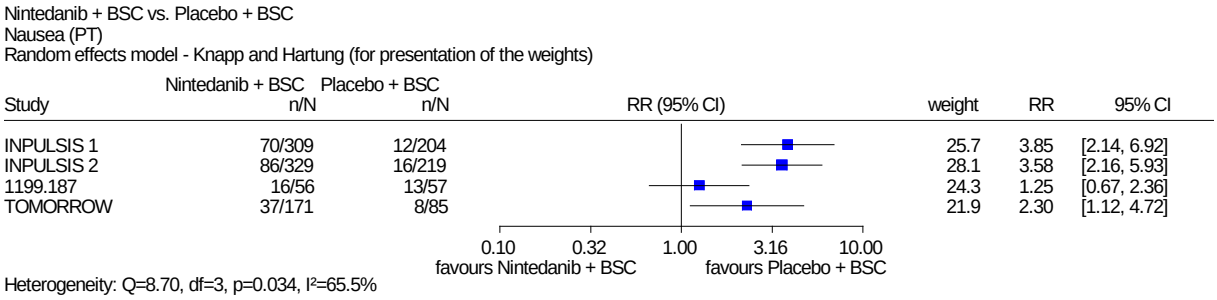


Figure 8: Meta-analysis, nausea (PT), nintedanib + BSC vs. placebo + BSC; effect estimate: RR

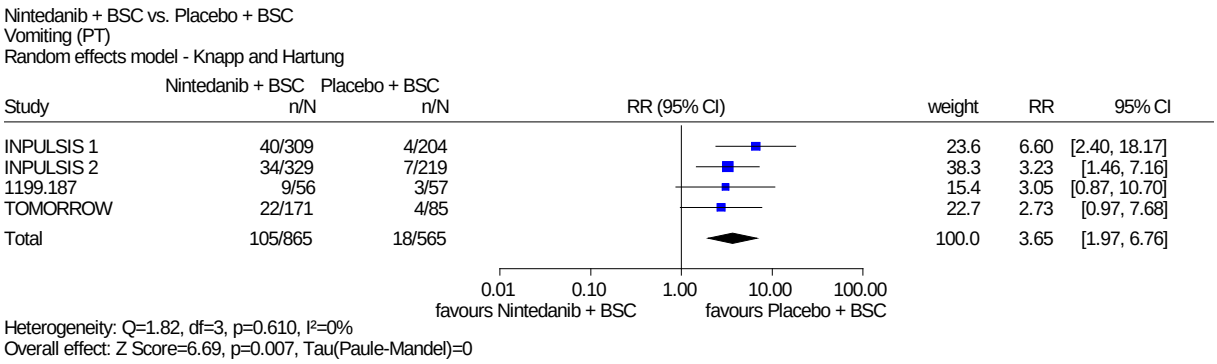
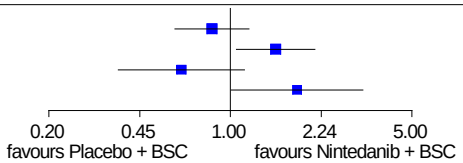


Figure 9: Meta-analysis, vomiting (PT), nintedanib + BSC vs. placebo + BSC; effect estimate: RR

A.2 – Forest plots of the responder analyses of the SGRQ

Nintedanib + BSC vs. Placebo + BSC
SGRQ responders
Random effects model - Knapp and Hartung (for presentation of the weights)

Study	Nintedanib + BSC n/N	Placebo + BSC n/N	RR (95% CI)	weight	RR	95% CI
INPULSIS 1	63/309	49/204		28.4	0.85	[0.61, 1.18]
INPULSIS 2	83/329	37/219		27.9	1.49	[1.05, 2.11]
1199.187	14/56	22/57		22.1	0.65	[0.37, 1.13]
TOMORROW	25/86	14/87		21.5	1.81	[1.01, 3.23]

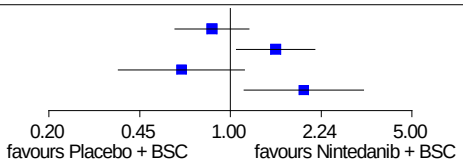


Heterogeneity: Q=11.62, df=3, p=0.009, I²=74.2%

Figure 10: Meta-analysis, SGRQ responder analyses, nintedanib + BSC vs. placebo + BSC; effect estimate: RR (including the 150 mg arm of the TOMORROW study)

Nintedanib + BSC vs. Placebo + BSC
SGRQ responders
Random effects model - Knapp and Hartung (for presentation of the weights)

Study	Nintedanib + BSC n/N	Placebo + BSC n/N	RR (95% CI)	weight	RR	95% CI
INPULSIS 1	63/309	49/204		27.7	0.85	[0.61, 1.18]
INPULSIS 2	83/329	37/219		27.3	1.49	[1.05, 2.11]
1199.187	14/56	22/57		22.1	0.65	[0.37, 1.13]
TOMORROW	53/172	14/87		22.9	1.91	[1.13, 3.25]



Heterogeneity: Q=13.08, df=3, p=0.004, I²=77.1%

Figure 11: Meta-analysis, SGRQ responder analyses, nintedanib + BSC vs. placebo + BSC; effect estimate: RR (including the 100 mg arm and the 150 mg arm of the TOMORROW study)