IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
EDSS	Expanded Disability Status Scale
FIS	Fatigue Impact Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN-β1a	interferon beta-1a
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MS	multiple sclerosis
RCT	randomized controlled trial
RMS	relapsing multiple sclerosis
RRMS	relapsing remitting multiple sclerosis
SC	subcutaneous
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug teriflunomide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 October 2013.

Research question

The aim of this report is to assess the added benefit of teriflunomide in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsing remitting multiple sclerosis (RRMS).

The G-BA specified the ACT for the therapeutic indication of relapsing multiple sclerosis (RMS) as follows: beta interferons (1a or 1b) or glatiramer acetate, in each case under consideration of the approved therapeutic indication.

Because RRMS is a subset of RMS, the G-BA's specification also applies to the approved therapeutic indication of teriflunomide.

The company chose interferon beta-1a (IFN-β1a) from the options specified by the G-BA, but limited itself to IFN-β1a 44µg subcutaneous (SC) 3 times a week (Rebif), one of the preparations from this drug group. A search targeted at the comparison with Rebif would not identify studies on the comparison with other preparations of this drug group. According to the G-BA's specification however, all dosage forms, and thus all IFN-β1a preparations, are to be considered. Overall, the company's limitation of the comparator therapy had no consequence for the present result of the assessment.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA IFN-β1a.

The assessment was based on patient-relevant outcomes.

Results

Study pool

One randomized controlled trial (RCT) on the direct comparison of teriflunomide with the ACT was included (TENERE). The study was open-label and compared teriflunomide with IFN-β1a 44 µg SC (Rebif). The treatment duration of patients varied between 48 weeks minimum and (expected) 118 weeks maximum.

To support the direct comparison, the company conducted an indirect comparison of teriflunomide versus IFN-β1a 44 µg SC (Rebif), for which it presented 3 studies. Two studies compared teriflunomide with placebo (TEMSO, TOWER), and 1 study compared IFN-β1a 44 µg SC (Rebif) with placebo (PRISMS). The company conducted an indirect comparison according to Bucher using the common comparator placebo ("indirect comparison") and summarized the resulting effect estimate with the result of the direct comparative TENERE study to an overall conclusion ("indirect comparison + TENERE"). However, this indirect comparison was unsuitable to support conclusions on the added benefit of teriflunomide resulting from the direct comparison. On the one hand, the study pool of the indirect comparison was incomplete because of the limitation to the drug preparation IFN-β1a 44 µg SC (Rebif) chosen by the company. On the other hand, there are doubts about the similarity of the content of the studies in several aspects. Moreover, the heterogeneity between the studies TEMSO and TOWER were not considered adequately in the indirect comparisons.

Because the indirect comparison was unsuitable to support conclusions on the added benefit of teriflunomide, the assessment was based solely on the direct comparative TENERE study. The risk of bias at the study level was rated as low for this study. The risk of bias of the relevant outcomes (except for all-cause mortality) was rated as high because of the lack of blinding of patient and treating staff and the generally subjective component in the recording of the outcomes.

Mortality

No patients died in the treatment arms of the TENERE study. However, due to its size and duration, the study was not designed to reveal differences in mortality. Lesser benefit/added benefit of teriflunomide is not proven for this outcome.

Morbidity

There were no statistically significant differences between the treatment groups with regards to relapse-related outcomes or with regards to outcomes on disability progression.

With respect to relapse-related outcomes, the effect estimates rather showed an unfavourable effect of teriflunomide. With respect to the outcomes on disability progression, the effect estimates were around the null effect. Due to the wide confidence intervals, more than a doubling of the risk to the disadvantage of teriflunomide cannot be excluded for both outcomes. Due to the short study duration, the study was unsuitable to prove relevant effects with regards to disability progression. A negative effect of teriflunomide versus IFN-β1a regarding the outcomes on morbidity cannot be excluded with certainty. An added benefit of teriflunomide is not proven for these morbidity outcomes.

Health-related quality of life

Symptom-specific health-related quality of life was recorded in the TENERE study, which is associated with the symptoms of fatigue. It was measured using the Fatigue Impact Scale (FIS). There was no statistically significant difference between the treatment groups in FIS

total score and in the scores of the 3 subscales (cognitive, physical and psychosocial domain). When interpreting the available results it is to be considered that a large part of the data was not explicitly observed after 48 weeks (teriflunomide: 23 [22%], Rebif: 32 [33%]). It remained unclear to what extent the assumptions on which the mixed-effects model with repeated measures (MMRM) is based actually applied.

Other instruments for recording health-related quality of life (e.g. generic instruments) were not used in the TENERE study. Overall, an added benefit of teriflunomide is not proven for health-related quality of life.

Adverse events

The proportion of patients with serious adverse events was not considerably different between the treatment groups, and the result was not statistically significant. Greater/lesser harm from teriflunomide is not proven for this outcome.

In the outcome "discontinuation due to adverse events", there was no statistically significant difference between the treatment groups. Treatment discontinuations due to pregnancy or investigations (change in laboratory values) were not rated as relevant events. A sensitivity analysis, which also considered treatment discontinuations due to investigations (change in laboratory values), also showed no statistically significant difference between the treatment groups. Greater/lesser harm from teriflunomide is not proven for the outcome "discontinuation due to adverse events".

Injection site reactions and flu-like symptoms were more common under IFN-β1a treatment than under teriflunomide. In each case, the result was statistically significant. The majority of these events were of mild or moderate intensity. Under consideration of the high risk of bias of both outcomes, there is a hint of lesser harm from teriflunomide both for injection-site reactions and for flu-like symptoms.

Alopecia and diarrhoea were more common under teriflunomide treatment than under IFN-β1a. In each case, the result was statistically significant. The majority of these events were of mild or moderate intensity. Under consideration of the high risk of bias of both outcomes, there is a hint of greater harm from teriflunomide both for alopecia and for diarrhoea.

Nausea and vomiting were more common under teriflunomide treatment than under IFN-β1a. The result was statistically significant with only marginal effect size. In the context of the early benefit assessment, greater harm from teriflunomide is not proven for this outcome.

Subgroup analyses

Subgroup analyses were only available in the company's dossier for the relevant outcome "annual relapse rate". For this outcome, there were no relevant subgroup effects or effect modifications for the characteristics investigated (sex, age, region, baseline Expanded Disability Status Scale [EDSS] score, number of relapses experienced in the past 2 years, and

pretreatment with disease-modifying multiple sclerosis [MS] drugs). Due to the lack of subgroup analyses on other relevant outcomes, no overall assessment of heterogeneous treatment effects could be conducted.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of teriflunomide compared with the ACT is assessed as follows:

On the basis of adverse events of special interest, there are positive and negative effects with the same reliability of conclusions ("hint") and outcome category (non-serious/non-severe adverse events). On both sides, the extent "considerable" is reached. The positive effects (injection site reactions, flu-like symptoms) each have the extent "considerable", whereas on the negative side, 1 effect has the extent "considerable" (alopecia), and 1 effect has the extent "minor" (diarrhoea). With regards to the morbidity outcomes "relapses" or "disability progression", a negative effect of teriflunomide versus IFN-β1a cannot be excluded with certainty.

In weighing up the positive and negative effects, there is no proof of added benefit of teriflunomide over the ACT.

Hence there are also no patient groups for whom a therapeutically important added benefit could be derived.

Table 2 summarizes the results of the assessment of the added benefit of teriflunomide versus the ACT in the approved therapeutic indication.

Table 2: Teriflunomide– extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with relapsing remitting multiple sclerosis	**Beta interferon (1a** or 1b) or glatiramer acetate	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specifications of the ACT, could choose an ACT from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

[4] 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), see [1]. 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, no added benefit, or less benefit), see [2].

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

2.2 Research question

The aim of this report is to assess the added benefit of teriflunomide in comparison with the ACT in adult patients with RRMS [3].

For the therapeutic indication of RMS, the G-BA specified the ACT as follows:

- beta interferons (1a or 1b) or glatiramer acetate under consideration of the approved therapeutic indication.

Because RRMS is a subset of RMS, the G-BA's specification also applies to the approved therapeutic indication of teriflunomide.

The company chose IFN-β1a from the options specified by the G-BA as ACT, but limited itself to IFN-β1a 44µg SC 3 times a week (Rebif [4]), one of the preparations from this drug group. A search targeted at the comparison with Rebif would not identify studies on the comparison with other preparations of this drug group (see Section 2.7.1 of the full dossier assessment). According to the G-BA's specification however, all dosage forms, and thus all IFN-β1a preparations, are to be considered. Overall, the company's limitation of the comparator therapy had no consequence for the present result of the assessment.

The present benefit assessment was conducted in comparison with the ACT IFN-β1a.

The assessment was conducted based on patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on teriflunomide (studies completed up to 29 July 2013)
- bibliographical literature search on teriflunomide (last search on 19 August 2013)
- search in trial registries for studies on teriflunomide (last search on 29 July 2013)

The Institute's own search to check the completeness of the study pool:

- bibliographical literature search on teriflunomide (last search on 31 October 2013)
- search in trial registries for studies on teriflunomide (last search on 15 October 2013)

One relevant study on the direct comparison of teriflunomide with the ACT was identified from the steps of information retrieval mentioned. The resulting study pool for direct comparative studies corresponded to that of the company.

In addition, the company presented an indirect comparison. This was unsuitable for the present research question, however (see Section 2.7.2.3.2 of the full dossier assessment).

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The studies included in the benefit assessment are presented in Table 3.

Table 3: Study pool – RCT, direct comparison: teriflunomide vs. IFN-β1a

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
TENERE	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. IFN-β1a: interferon beta-1a; RCT: randomized controlled trial; vs.: versus			

The study pool for direct comparative studies with teriflunomide and the ACT corresponded to that used by the company.

Section 2.6 contains a reference list for the studies included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 4 and Table 5 describe the TENERE study included in the benefit assessment.

Table 4: Characteristics of the studies included – RCT, direct comparison: teriflunomide vs. IFN-β1a

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TENERE	RCT, open-label[b], parallel	Patients (≥ 18 years) with relapsing subtypes of MS meeting the McDonald criteria for MS diagnosis (2005 revision [5]) and EDSS score ≤ 5.5	Teriflunomide 7 mg (N = 109) Teriflunomide 14 mg (N = 111) IFN-β1a 44 µg (Rebif) (N = 104) Relevant subpopulation with RRMS[c]: Teriflunomide 14 mg (n = 108) IFN-β1a 44 µg (Rebif) (n = 104)	Screening: 4 weeks Treatment duration (expected): between 48 weeks minimum and 118 weeks maximum[d] (fixed end for all patients after treatment for 48 weeks of the last randomized patient) Follow-up (including elimination phase): 16 weeks	53 centres in 13 countries (Belgium, Germany, France, Greece, Great Britain, Italy, Canada, Poland, Switzerland, Spain, Czech Republic, Tunisia, Hungary) 4/2009–9/2011	Primary: time to treatment failure (relapse or discontinuation of treatment) Secondary: mortality, relapse-related outcomes, disability progression, health-related quality of life (symptom-specific [FIS]), adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for this benefit assessment.
b: With regard to the drugs teriflunomide and IFN-β1a 44 µg (Rebif) to be compared; the teriflunomide arms (7 mg and 14 mg) were double-blind.
c: Only the approval-compliant dose of teriflunomide 14 mg is presented.
d: The actual maximum treatment duration (first randomized patient) was approximately 115 weeks. The median actual treatment durations with the investigated drugs teriflunomide (14 mg) vs. IFN-β1a 44 µg (Rebif) at the end of the study were 449.5 vs. 421.0 days (with a minimum of 27 vs. 19 days and a maximum of 755 vs. 800 days).

EDSS: Expanded Disability Status Scale; FIS: Fatigue Impact Scale; IFN-β1a: interferon beta-1a; MS: multiple sclerosis; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: teriflunomide vs. IFN-β1a

Study	Intervention	Comparison
TENERE	Teriflunomide 14 mg orally once daily ▪ Elimination phase (wash-out): patients who discontinued treatment or who discontinued the study and did not participate in the optional extension study underwent an accelerated elimination procedure (cholestyramine 8 g every 8 hours [24 g/day] or 50 g activated charcoal powder every 6 hours [200g/day], each for 11 days). ▪ Treatment of acute relapses with 1 g intravenous methylprednisolone sodium succinate daily for 3–5 days	IFN-β1a 44 µg SC (Rebif) 3 times a week ▪ 2 week up-titration phase with 8.8 µg, followed by 2 weeks with 22 µg, and administration of 44 µg from week 5. ▪ In case of poor tolerability, the dose could be reduced to 22 µg[a] ▪ Administration of a non-steroidal anti-inflammatory drug was recommended before injection ▪ Treatment of acute relapses with 1 g intravenous methylprednisolone sodium succinate daily for 3–5 days
a: Dose reduction was performed in 12 patients during the study. IFN-β1a: interferon beta-1a; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus		

The TENERE study was a multicentre, randomized, controlled approval study on the comparison of teriflunomide (in 2 dosages) with IFN-β1a 44 µg (Rebif). With respect to the relevant comparison, this was an open-label study.

Patients with RMS were enrolled in the study. The MS was diagnosed using the revised McDonald criteria (2005) [5]. Only patients with an EDSS score of ≤ 5.5 were included. Hence only a part of the patient population for whom teriflunomide is approved was investigated. Patients with greater disease severity who already need a walking aid according to the EDSS were excluded from the study.

The patients were randomized to the 3 treatment arms (teriflunomide 7 mg, teriflunomide 14 mg and IFN-β1a 44 µg [Rebif]) in a ratio of 1:1:1. The randomization was stratified according to region and baseline EDSS score (≤ 3.5/> 3.5). The proportion of the subpopulation with RRMS, which was relevant for the benefit assessment, was 97.3% in the treatment arm with the approval-compliant dosage of teriflunomide (14 mg) and 100% in the treatment arm with IFN-β1a 44 µg (Rebif). Because the proportion of the subpopulation that was not compliant with the approval was only very small in the study arm with teriflunomide (14 mg), the overall results of the study were used. The treatment arm with teriflunomide 7 mg will not be further considered here.

Patients in the intervention arm (teriflunomide) received 1 tablet of teriflunomide 14 mg daily. Patients in the comparator arm received IFN-β1a 44 µg 3 times a week (Rebif) as SC injection. IFN-β1a 44 µg (Rebif) was administered according to the Summary of Product Characteristics (SPC) [4], with a 2-week up-titration phase with 8.8 µg IFN-β1a, followed by 2 weeks with 22 µg IFN-β1a, and with administration of the maintenance dose of 44 µg IFN-β1a from week 5, each 3 times a week. Furthermore, as recommended in the approval,

dose reduction to the lower dose of 22 µg, was allowed in case of poor tolerability. Administration of a non-steroidal anti-inflammatory drug was recommended before injection.

The treatment duration of patients varied between 48 weeks minimum and (expected) 118 weeks maximum (the actual maximum treatment duration for the first randomized patient was approximately 115 weeks). All patients in the study were treated until the last randomized patient had completed the 48 weeks of treatment. The median actual treatment durations with the investigated drugs teriflunomide vs. IFN-β1a 44 µg (Rebif) at the end of the study were 449.5 vs. 421.0 days. Hence the median treatment duration was shorter than recommended by the regulatory authorities, which stipulate a minimum observation duration of 2 years [6,7]. This aspect has to be considered when interpreting the results or assessing the informative value of the evidence, particularly with regards to events that usually occur long-term, such as mortality, disability progression and malignancies. The marginal difference between the treatment durations of the 2 treatment groups (28.5 days) was assessed as negligible with regards to the interpretability of the study results in the present assessment.

After the treatment phase, there was a 16-week follow-up phase. In the treatment arm with teriflunomide, this included an 11-day elimination phase (wash-out) for patients who discontinued treatment with teriflunomide or who discontinued the study and did not participate in the optional extension phase afterwards. To avoid bias with regards to the elimination phase conducted, the observation period during the treatment (i.e. before the elimination phase) was considered and the corresponding results are presented in the benefit assessment see Section 2.7.2.4.3 of the full dossier assessment).

Table 6 shows the characteristics of the patients in the study included.

Table 6: Characteristics of the study populations – RCT, direct comparison: teriflunomide vs. IFN-β1a (TENERE study)

Characteristics **Category**	**Teriflunomide** **N = 111**	**IFN-β1a** **N = 104**
Age (years)		
Mean (SD)	36.8 (10.3)	37.0 (10.6)
< 38 years (n [%])	62 (55.9)	60 (57.7)
≥ 38 years (n [%])	49 (44.1)	44 (42.3)
Sex (n [%])		
Female	78 (70.3)	71 (68.3)
Male	33 (29.7)	33 (31.7)
Time since first diagnosis of MS (years)		
Mean (SD)	3.68 (6.2)	3.82 (5.7)
Median (min–max)	0.75 (0.1–36.5)	1.00 (0.1-30.3)
Number of relapses in previous 2 years		
Mean (SD)	1.7 (0.9)	1.7 (1.1)
0 (n [%])	7 (6.3)	11 (10.6)
1 (n [%])	41 (36.9)	39 (37.5)
2 (n [%])	41 (36.9)	30 (28.8)
3 (n [%])	20 (18.0)	18 (17.3)
≥ 4 (n [%])	2 (1.8)	6 (5.8)
MS subtype (n [%])		
RRMS	108 (97.3)	104 (100)
SPMS	1 (0.9)	0 (0)
PRMS	2 (1.8)	0 (0)
Pretreatment with MS drugs in previous 2 years (n [%])		
Yes	13 (11.7)	25 (24.0)
No	98 (88.3)	79 (76.0)
Baseline EDSS score		
Mean (SD)	2.33 (1.35)	2.04 (1.19)
≤ 3.5 (n [%])	95 (85.6)	94 (90.4)
> 3.5 (n [%])	16 (14.4)	10 (9.6)
Treatment discontinuations (n [%])	22 (19.8)	30 (28.8)

EDSS: Expanded Disability Status Scale; IFN-β1a: interferon beta-1a; MS: multiple sclerosis; N: number of randomized patients; n: number of patients in the category; PRMS: progressive relapsing multiple sclerosis; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis; vs.: versus

The mean age of the patients in the treatment groups was 37 years; they had MS for approximately 4 years on average, and the majority were female (about 70%). Most patients

were treatment-naive (88% of the patients in the teriflunomide arm and 76% in the IFN-β1a arm of the study). The patients enrolled in the study presented with rather mild symptoms (with regards to the baseline EDSS score or the number of relapses within the previous 2 years), which was to be expected considering the inclusion criteria.

Table 7 shows the risk of bias at study level.

Table 7: Risk of bias at study level – RCT, direct comparison: teriflunomide vs. IFN-β1a

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
TENERE	Yes	Yes	No	No	Yes	Yes	Low
IFN-β1a: interferon beta-1a; RCT: randomized controlled trial; vs.: versus							

The risk of bias at the study level was rated as low for the TENERE study. This concurs with the company's assessment (see Section 2.7.2.4.2 of the full dossier assessment).

Further information about the study design, study populations and risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

2.4.1 Relevant outcomes

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- mortality
  - deaths
- morbidity
  - relapse-related outcomes
    - patients with confirmed relapse
    - time to confirmed relapse
    - annual relapse rate
  - disability progression
    - patients with disability progression (sustained for at least 12 weeks)

- time to disability progression (sustained for at least 12 weeks)

- health-related quality of life
  - FIS for recording the symptom-specific health-related quality of life (fatigue)
- adverse events
  - overall rate of serious adverse events
  - discontinuations due to adverse events
  - injection site reactions
  - flu-like symptoms
  - alopecia
  - diarrhoea
  - nausea and vomiting

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in Module 4 of the dossier. These included the following outcomes: patients without relapse, mean change of EDSS score, time to treatment failure, patient's satisfaction, overall rate of adverse events, liver dysfunction, hypersensitivity/skin reactions, neutropenia, infections and infestations, hypertension, peripheral neuropathy (including paraesthesia) and headache (see Section 2.7.2.4.3 of the full dossier assessment).

2.4.2 Data availability and risk of bias

Table 8 shows for which outcomes data were available in the study included. Table 9 shows the risk of bias for these outcomes.

Table 8: Matrix of outcomes – RCT, direct comparison: teriflunomide vs. IFN-β1a

Study	Outcomes											
	All-cause mortality	Relapse-related outcomes	Disability progression	Health-related quality of life (generic/disease-specific)	Health-related quality of life (symptom-specific [fatigue])	Serious adverse events	Discontinuation due to adverse events	Injection site reactions	Flu-like symptoms	Alopecia	Diarrhoea	Nausea and vomiting
TENERE	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
IFN-β1a: interferon beta-1a; RCT: randomized controlled trial; vs.: versus												

Table 9: Risk of bias at study and outcome level – RCT, direct comparison: teriflunomide vs. IFN-β1a

Study	Study level	Outcomes											
		All-cause mortality	Relapse-related outcomes	Disability progression	Health-related quality of life (generic/disease-specific)	Health-related quality of life (symptom-specific [fatigue])	Serious adverse events	Discontinuation due to adverse events	Injection site reactions	Flu-like symptoms	Alopecia	Diarrhoea	Nausea and vomiting
TENERE	L	L	H	H	–[a]	H	H	H	H	H	H	H	H

a: Outcome not recorded.
H: high; IFN-β1a: interferon beta-1a; L: low; RCT: randomized controlled trial; vs.: versus

The risk of bias of the relevant outcomes – except for all-cause mortality – was rated as high because of the lack of blinding of patient and treating staff and the subjective component generally present in the recording of the outcomes. This deviates from the company's assessment, which assumed a low risk of bias for relapse-related outcomes, adverse events, serious adverse events, discontinuation due to adverse events, injection site reactions, flu-like symptoms and alopecia (see Section 2.7.2.4.2 for comprehensive comments on the risk of bias at outcome level).

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.4.3 Results

Table 10, Table 11 and Table 12 summarize the results on the comparison of teriflunomide and IFN-β1a. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations.[5]

Due to the high risk of bias of nearly all the outcomes of the TENERE study, in principle, only the derivation of "hints" is possible with regards to the probability of the added benefit. A derivation of an "indication" is only possible for mortality.

[5] The odds ratio offers a good approximation of the relative risk in low numbers of events. Hence in event rates of ≤ 1% (in at least one cell), the Peto odds ratio instead of the relative risk was calculated as effect measure and used for the assessment.

Table 10: Results (mortality and morbidity) – RCT, direct comparison: teriflunomide vs. IFN-β1a (TENERE study)

Category Outcome	Teriflunomide		IFN-β1a		Teriflunomide vs. IFN β-1a	
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]**	**p-value**
Mortality						
Deaths	110	0 (0)	101	0 (0)	-	-
Morbidity						
Relapse-related outcomes (based on EDSS)						
Patients with confirmed relapse	111	26 (23.4)	104	16 (15.4)	1.52 [0.87; 2.67]	0.143
	N	**KM estimate[a] [95% CI]**	**N**	**KM estimate[a] [95% CI]**	**HR [95% CI]**	**p-value**
Time to confirmed relapse	111	0.29 [0.19; 0.40]	104	0.19 [0.10; 0.27]	1.46 [0.78; 2.73]	0.229
	N	**Annual relapse rate[b] [95% CI]**	**N**	**Annual relapse rate[b] [95% CI]**	**IDR [95% CI]**	**p-value**
Annual relapse rate[c]	111	0.26 [0.15; 0.44]	104	0.22 [0.11; 0.42]	1.20 [0.62; 2.30]	0.590[d]
Disability progression[e] (based on EDSS)						
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]**	**p-value**
Patients with disability progression	111	10 (9.0)	104	9 (8.7)	1.04 [0.44; 2.46]	0.927
	N	**KM estimate[a] [95% CI]**	**N**	**KM estimate[a] [95% CI]**	**HR [95% CI]**	**p-value**
Time to disability progression	111	0.12 [0.05; 0.20]	104	0.10 [0.04; 0.16]	0.98 [0.40; 2.42]	0.969

a: Probability of an event at week 96 (time-to-event analysis [defined as time from the day of randomization to the day of the first occurrence of the event]).
b: Adjusted annual relapse rate from a Poisson model with the total number of confirmed relapses between randomization and last dosage as dependent variable, adjusted according to baseline EDSS score and region, log-transformed treatment duration as offset variable.
c: Number of confirmed relapses (during the treatment phase) divided by the number of patient years.
d: Chi-square test from the estimate of the rate ratio.
e: Disability progression sustained for at least 12 weeks.

CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IDR: incidence density ratio (rate ratio); IFN-β1a: interferon beta-1a; ITT: intention to treat; KM: Kaplan-Meier; N: number of analysed patients in relation to the ITT population, except mortality (safety population); RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

No patients died in the 2 relevant treatment arms of the TENERE study. However, due to its size and duration, the study was not designed to reveal differences in mortality. An added benefit of teriflunomide is not proven for this outcome.

Morbidity

There were no statistically significant differences between the treatment groups with regards to relapse-related outcomes or with regards to outcomes on disability progression.

With respect to relapse-related outcomes, the effect estimates rather showed an unfavourable effect of teriflunomide. With respect to the outcomes on disability progression, the effect estimates were around the null effect. Due to the wide confidence intervals, more than a doubling of the risk to the disadvantage of teriflunomide cannot be excluded for both outcomes (Table 10). Due to the short study duration, the study was unsuitable to prove relevant effects with regards to disability progression. The Kaplan-Meier curves of the time to confirmed relapse and of the time to disability progression (sustained for at least 12 weeks) are presented for illustration in Figure 1 and Figure 2. As for other long-term events, observation periods of at least 2 years are required for adequate interpretability, particularly for disability progression [6].

Overall, a negative effect of teriflunomide versus IFN-β1a cannot be excluded with certainty with regards to the outcomes on morbidity. An added benefit of teriflunomide is not proven for these morbidity outcomes.

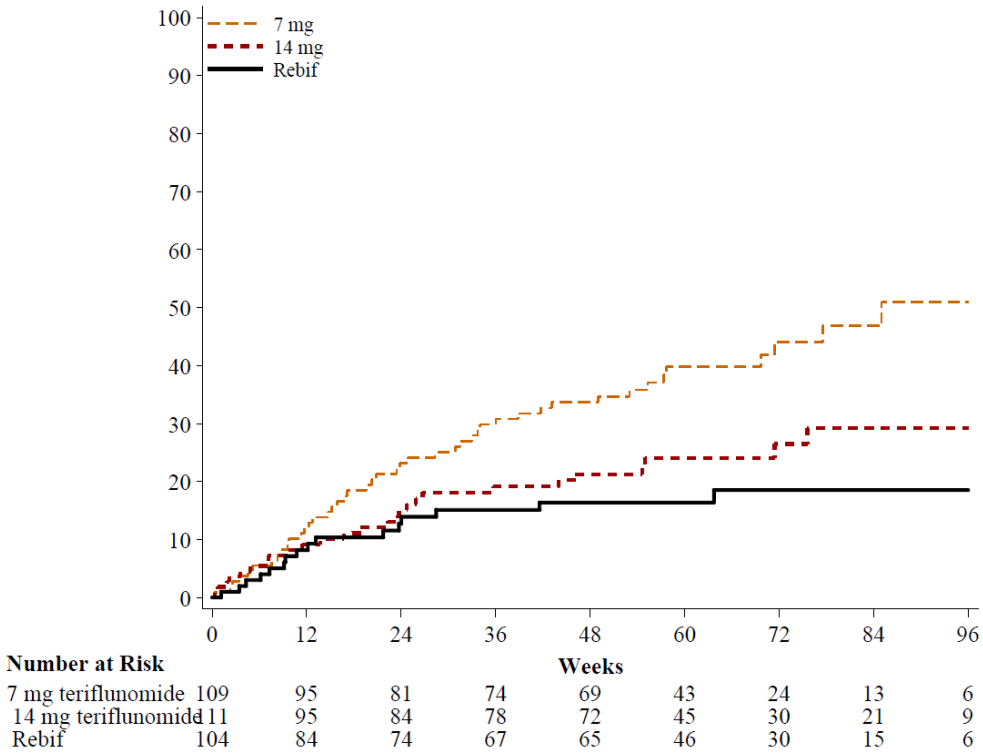

Figure 1: Kaplan-Meier curves of the time to confirmed relapse (intention to treat [ITT] population)

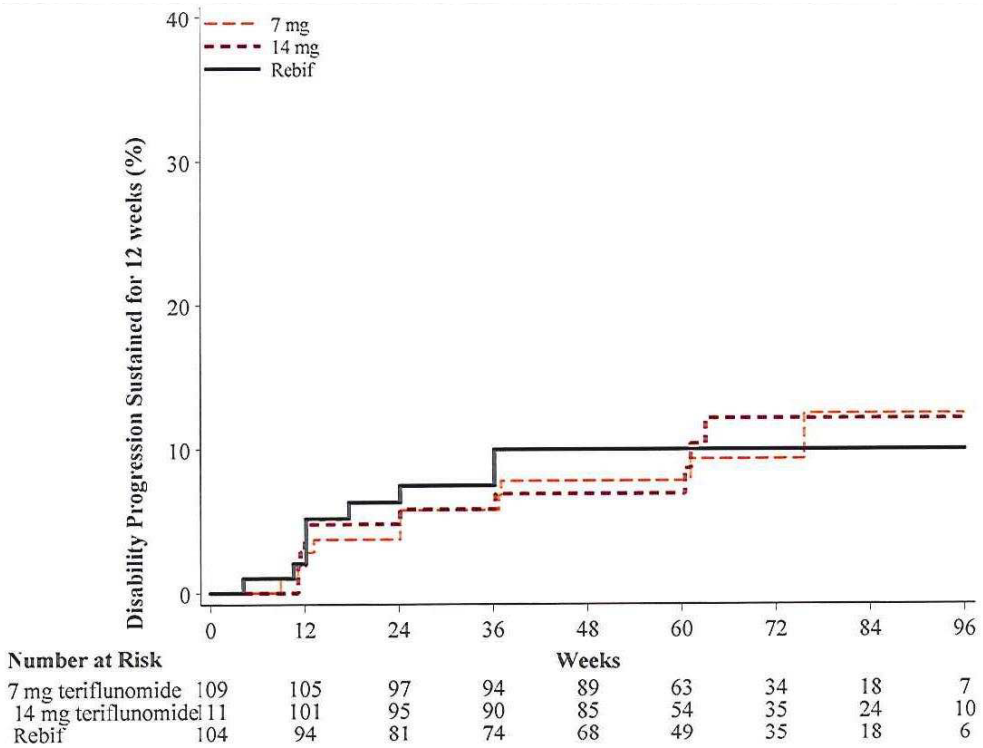

Figure 2: Kaplan-Meier curves of the time to disability progression (sustained for at least 12 weeks) (ITT population)

Health-related quality of life

The results on health-related quality of life are shown in Table 11.

Table 11: Results (health-related quality of life) – RCT, direct comparison: teriflunomide vs. IFN-β1a (TENERE study)

Outcome category Outcome	Teriflunomide			IFN-β1a			Teriflunomide vs. IFN β-1a
	N	Values at start of study mean (SD)	Change at end of study mean[a] (SD)	N	Values at start of study mean (SD)	Change at end of study mean[a] (SD)	MD[b] [95% CI]; p-value
Health-related quality of life (generic/disease-specific)							
No data available							
Health-related quality of life (symptom-specific [fatigue])							
FIS[c] total score	106	42.5 (37.8)	4.10 (3.03)	97	34.2 (32.7)	9.10 (3.21)	-5.00 [-12.31; 2.31] p = 0.179
Cognitive domain	106	10.2 (10.2)	0.87 (0.84)	97	7.8 (8.5)	2.34 (0.89)	-1.47 [-3.51; 0.58] p = 0.160
Physical domain	106	12.6 (10.2)	1.19 (0.87)	97	11.1 (9.7)	1.51 (0.92)	-0.32 [-2.37; 1.73] p = 0.762
Psychosocial domain	106	19.7 (19.5)	2.70 (1.53)	97	15.4 (16.0)	5.52 (1.62)	-2.81 [-6.51; 0.89] p = 0.136

a: Adjusted estimate from an MMRM at the time point of recording week 48.
b: MMRM, adjusted according to baseline EDSS score, region, visit, treatment x visit interaction, baseline score and treatment x visit interaction.
c: High FIS scores mean high negative influence of fatigue on quality of life (high FIS scores = low symptom-specific health-related quality of life).
CI: confidence interval; FIS: Fatigue Impact Scale; IFN-β1a: interferon beta-1a; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients in relation to the number at the start of the study (number of actually available data sets after 48 weeks in the MMRM: 83 [teriflunomide] and 65 [IFN-β1a]); RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Symptom-specific health-related quality of life was recorded in the TENERE study, which is associated with the symptoms of fatigue. It was measured using FIS. There was no statistically significant difference between the treatment groups in FIS total score and in the scores of the 3 subscales (cognitive, physical and psychosocial domain). When interpreting the available results it is to be considered that a large part of the data was not explicitly observed after 48 weeks (teriflunomide: 23 [22%], Rebif: 32 [33%]). It remained unclear to what extent the assumptions on which the MMRM is based actually applied. Moreover, there was a noticeable difference of the baseline values between the treatment groups. Patients with teriflunomide had consistently higher scores in the 3 subscales (each with an average of 0.2 standard deviations).

Other instruments for recording health-related quality of life (e.g. generic instruments) were not used in the TENERE study.

Overall, an added benefit of teriflunomide is not proven for health-related quality of life.

Adverse events

The results on adverse events are shown in Table 12.

Table 12: Results (adverse events) – RCT, direct comparison: teriflunomide vs. IFN-β1a (TENERE study)

Outcome category Outcome	Teriflunomide		IFN-β1a		Teriflunomide vs. IFN β-1a
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Adverse events					
AEs	110	102 (92.7)	101	97 (96.0)	-
SAEs	110	4 (3.6)	101	6 (5.9)	0.61 [0.18; 2.11]; 0.525[a]
Discontinuation due to AEs[b]	110	7 (6.4)	101	9 (8.9)	0.71 [0.28; 1.85]; 0.529[a]
Discontinuation due to AEs[c] (including laboratory values)	110	12 (10.9)	101	20 (19.8)	0.55 [0.28; 1.07]; 0.081[a]
Adverse events of special interest[d]					
Injection site reactions[e]	110	0	101	22 (21.8)	0.10 [0.04; 0.24][f]; < 0.001
Flu-like symptoms[g]	110	3 (2.7)	101	54 (53.5)	0.05 [0.02; 0.16]; < 0.001[a]
Alopecia[h]	110	22 (20.0)	101	1 (1.0)	7.01 [2.95; 16.65][f]; < 0.001[a]
Diarrhoea[i]	110	23 (20.9)	101	8 (7.9)	2.64 [1.24; 5.63]; 0.008[a]
Nausea and vomiting[j]	110	15 (13.6)	101	5 (5.0)	2.75 [1.04; 7.31]; 0.033[a]

a: Institute's calculation.
b: Analysis in which no events were included that led to treatment discontinuation due to pregnancy (SOC "pregnancy, puerperium and perinatal conditions") or due to investigations (SOC "investigations").
c: Analysis in which no events were included that led to treatment discontinuation due to pregnancy (SOC "pregnancy, puerperium and perinatal conditions").
d: The majority of events were of mild/moderate intensity.
e: Recorded using the MedDRA HLT "injection site reactions".
f: Peto OR.
g: Recorded using the MedDRA PT "influenza-like illness"
h: Recorded using the MedDRA HLT "alopecias".
i: Recorded using the MedDRA HLT "diarrhoea (excluding infective)".
j: Recorded using the MedDRA HLT "nausea and vomiting symptoms".

AE: adverse event; CI: confidence interval; HLT: High Level Term; IFN-β1a: interferon beta-1a; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients in relation to safety population; n: number of patients with event during treatment period; OR: odds ratio; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The analysis of the adverse events refers to the observation during treatment period. This deviates from the company's approach, which considered the observation during treatment period plus follow-up period (including wash-out [accelerated elimination] phase) in Module 4 of the dossier (see Section 2.7.2.4.3 of the full dossier assessment).

The proportion of patients with serious adverse events was not considerably different between the treatment groups, and the result was not statistically significant. Greater/lesser harm from teriflunomide is not proven for this outcome.

In the outcome "discontinuation due to adverse events", there was no statistically significant difference between the treatment groups. Treatment discontinuations due to pregnancy or investigations (change in laboratory values) were not rated as relevant events (see Section 2.7.2.4.3 of the full dossier assessment). This deviates substantially from the analysis presented in Module 4 of the dossier, in which these events were recorded. The result in the dossier showed a statistically significant difference in favour of teriflunomide. A sensitivity analysis, which also considered treatment discontinuations due to investigations (change in laboratory values) (but not due to pregnancy), also showed no statistically significant difference between the treatment groups. This supports the present result. Greater/lesser harm from teriflunomide is not proven for the outcome "discontinuation due to adverse events".

Injection site reactions and flu-like symptoms were more common under IFN-β1a treatment than under teriflunomide. In each case, the result was statistically significant. The majority of these events were of mild or moderate intensity. There is a hint of lesser harm from teriflunomide for each of the 2 outcomes "injection-site reactions" and "flu-like symptoms".

Alopecia and diarrhoea were more common under teriflunomide treatment than under IFN β1a. In each case, the result was statistically significant. The majority of these events were of mild or moderate intensity. There is a hint of greater harm from teriflunomide for each of the 2 outcomes "alopecia" and "diarrhoea".

Nausea and vomiting were more common under teriflunomide treatment than under IFN-β1a. The result was statistically significant with only marginal effect size (see Section 2.5.1, Table 13). In the context of the early benefit assessment, greater harm from teriflunomide is not proven for this outcome.

2.4.4 Subgroup analyses

Subgroup analyses were only available in the company's dossier for the relevant outcome "annual relapse rate". Potential heterogeneous treatment effects were investigated for the following characteristics: sex, age, region, baseline EDSS score, number of relapses within the previous 2 years and pretreatment with disease-modifying MS drugs. The results of the interaction tests supplied no indications or proof of subgroup effects or effect modifications for this outcome.

Due to the lack of subgroup analyses on other relevant outcomes (particularly on adverse events), no overall assessment of potentially heterogeneous treatment effects could be conducted.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in IQWiG's general methods paper [1].

The approach for deriving an overall conclusion on 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 data presented in Section 0 showed 2 hints of lesser harm and 2 hints of greater harm from teriflunomide in comparison with IFN-β1a.

The extent of the respective added benefit (or lesser/greater harm) at outcome level was estimated from these results (see Table 13).

Table 13: Extent of added benefit at outcome level: teriflunomide vs. IFN-β1a

Outcome category **Outcome**	**Teriflunomide vs. IFN β-1a** **Proportion of events/KM estimates/relapse rate/mean effect estimates [95% CI]** **p-value** **probability[a]**	**Derivation of extent[b]**
Mortality		
Deaths	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Patients with confirmed relapse	23.4% vs. 15.4% RR 1.52 [0.87; 2.67] p = 0.143	Added benefit not proven
Time to confirmed relapse	0.29[c] vs. 0.19[c] HR 1.46 [0.78; 2.73] p = 0.229	Added benefit not proven
Annual relapse rate	0.26[d] vs. 0.22[d] IDR 1.20 [0.62; 2.30] p = 0.590	Added benefit not proven
Patients with disability progression	9.0% vs. 8.7% RR 1.04 [0.44; 2.46] p = 0.927	Added benefit not proven
Time to disability progression	0.12[c] vs. 0.10[c] HR 0.98 [0.40; 2.42] p = 0.969	Added benefit not proven
Health-related quality of life		
Symptom-specific (FIS) Total score (FIS)	4.10[e] vs. 9.10[e] MD −5.00 [−12.31; 2.31] p = 0.179	Added benefit not proven
Cognitive domain (FIS)	0.87[e] vs. 2.34[e] MD -1.47 [-3.51; 0.58] p = 0.160	Added benefit not proven
Physical domain (FIS)	1.19[e] vs. 1.51[e] MD -0.32 [-2.37; 1.73] p = 0.762	Added benefit not proven
Psychosocial domain (FIS)	2.70[e] vs. 5.52[e] MD -2.81 [-6.51; 0.89] p = 0.136	Added benefit not proven

(continued)

Table 13: Extent of added benefit at outcome level: teriflunomide vs. IFN-β1a (continued)

Outcome category **Outcome**	**Teriflunomide vs. IFN β-1a** **Proportion of events/KM estimates/relapse rate/mean effect estimates [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Adverse events		
Overall rate SAEs	3.6% vs. 5.9% RR 0.61 [0.18; 2.11] p = 0.525	Lesser/greater harm not proven
Discontinuation due to AEs	6.4% vs. 8.9% RR 0.71 [0.28; 1.85] p = 0.529[f]	Lesser/greater harm not proven
Injection site reactions	0% vs. 21.8% Peto OR 0.10 [0.04; 0.24] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.8$ greater harm, extent: "considerable"
Flu-like symptoms	2.7% vs. 53.5% RR 0.05 [0.02; 0.16] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.8$ greater harm, extent: "considerable"
Alopecia	20.0% vs. 1.0% Peto OR 7.01 [2.95; 16.65] Peto OR[g] 0.14 [0.06; 0.34] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.8$ greater harm, extent: "considerable"
Diarrhoea	20.9% vs. 7.9% RR 2.64 [1.24; 5.63] RR[g] 0.38 [0.18; 0.81] p = 0.008 probability: "hint"	Outcome category: non-serious/non-severe AEs $0.8 \leq CI_u < 0.9$ greater harm, extent: "minor"
Nausea and vomiting	13.6% vs. 5.0% RR 2.75 [1.04; 7.31] RR[g] 0.36 [0.14; 0.96] p = 0.033 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u \geq 0.90$ Lesser/greater harm not proven

(continued)

Table 13: Extent of added benefit at outcome level: teriflunomide vs. IFN-β1a

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: KM estimate of the probability of an event at week 96.
d: Number of confirmed relapses during the treatment phase divided by the number of patient years.
e: Mean change after week 48 in comparison with baseline (high FIS scores = low symptom-specific health-related quality of life).
f: Discontinuations due to AEs that do not include any events due to pregnancy or due to investigations (laboratory values). The effect remains not statistically significant, even when laboratory values are included in the analysis (RR 0.55 [0.28; 1.07]; p = 0.081).
g: Proportion of event IFN-β1a vs. teriflunomide (different direction of effect for the derivation of the extent of added benefit).
AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; FIS: Fatigue Impact Scale; HR: hazard ratio; IDR: incidence density ratio (rate ratio); IFN-β1a: interferon beta-1a; KM: Kaplan-Meier; MD: mean difference; OR: odds ratio; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of teriflunomide compared with IFN-β1a

Positive effects	**Negative effects**
Hint of lesser harm – extent: “considerable” (non-serious/non-severe adverse events: injection site reactions)	Hint of greater harm – extent: “considerable” (non-serious/non-severe adverse events: alopecia)
Hint of lesser harm – extent: “considerable” (non-serious/non-severe adverse events: flu-like symptoms)	Hint of greater harm – extent: “minor” (non-serious/non-severe adverse events: diarrhoea)
With regards to the morbidity outcomes “relapses”/“disability progression”, a negative effect of teriflunomide versus IFN-β1a cannot be excluded with certainty.	

On the basis of adverse events of special interest, there are positive and negative effects with the same certainty of results (“hint”) and outcome category (non-serious/non-severe adverse events). On both (positive and negative) sides, the extent “considerable” is reached. The positive effects (injection site reactions, flu-like symptoms) each have the extent “considerable”, whereas on the negative side, 1 effect has the extent “considerable” (alopecia), and 1 effect has the extent “minor” (diarrhoea). With regards to the morbidity outcomes “relapses” or “disability progression”, a negative effect of teriflunomide versus IFN-β1a cannot be excluded with certainty.

In weighing up the positive and negative effects, there is no proof of added benefit of teriflunomide over the ACT IFN-β1a.

This assessment deviates considerably from that of the company, which claimed proof of a considerable added benefit.

Table 15 summarizes the results of the assessment of extent and probability of the added benefit of teriflunomide versus the ACT in the approved therapeutic indication.

Table 15: Teriflunomide– extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Adult patients with relapsing remitting multiple sclerosis	**Beta interferon (1a** or 1b) or glatiramer acetate	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specifications of the ACT, could choose an ACT from several options, the respective choice of the company is printed in **bold**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

TENERE

Sanofi Aventis. A multi-center, randomized, parallel-group, rater-blinded study comparing the effectiveness and safety of teriflunomide and interferon beta-1a in patients with relapsing multiple sclerosis: study EFC10891; clinical study report [unpublished]. 2011.

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Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler 21 November 2013 [Epub ahead of print].

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a13_38_teriflunomid_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.3761.html.