IQWiG Reports – Commission No. A20-59

Ozanimod (multiple sclerosis) –

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

Extract

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Gd	gadolinium
9-HPT	9-Hole Peg Test
IFN	interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCLA	low-contrast letter acuity
MD	mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MHCS	mental health composite score
MSFC	Multiple Sclerosis Functional Composite
MSQoL-54	Multiple Sclerosis Quality of Life-54
PASAT-3	Paced Auditory Serial Addition Test-3
PHCS	physical health composite score
PT	Preferred Term
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SDMT	Symbol Digit Modalities Test
SF-36	Short Form 36 Health Survey
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics
T25-FW	Timed 25-Foot Walk

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 ozanimod. 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 15 July 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 ozanimod in comparison with the appropriate comparator therapy (ACT) in patients with relapsing remitting multiple sclerosis (RRMS).

Table 2: Research questions of the benefit assessment of ozanimod

Research question	Subindication	ACT[a]
1	Adult patients with RRMS who have not yet received disease-modifying therapy or adult patients with RRMS with non-highly active disease pretreated with disease-modifying therapy	**Interferon beta-1a** or interferon beta-1b or glatiramer acetate or ocrelizumab under consideration of the approval
2	Adult patients with RRMS with highly active disease despite treatment with a disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutic agents (**interferon beta-1a** or interferon beta-1b or glatiramer acetate under consideration of the approval)

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Appropriate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on disability progression, treatment with a disease-modifying therapy can be less than 6 months and has to be justified.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RRMS: relapsing remitting multiple sclerosis

In the present benefit assessment, the following terms are used for the research questions:

- Research question 1: treatment-naive patients as well as pretreated patients with non-highly active RRMS

- Research question 2: pretreated patients with highly active RRMS

The company followed the G-BA's specification of the ACTs and chose interferon beta-1a (IFN-β1a) as ACT for both research questions.

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 12 months were used for the derivation of the added benefit.

Results for research question 1: treatment-naive patients as well as pretreated patients with non-highly active RRMS

The studies RADIANCE B und SUNBEAM were included in the benefit assessment.

Study design

The studies RADIANCE B and SUNBEAM have a similar study design, which only differs in treatment duration.

The studies RADIANCE B and SUNBEAM are randomized, double-blind, actively controlled parallel-group studies comparing ozanimod with IFN-β1a in patients with RRMS. Both studies were conducted worldwide at about the same time and in the same regions.

The studies included adult patients (18 to 55 years of age) who had ≥ 1 relapse within the last 12 months prior to enrolment, or ≥ 1 relapse within the last 24 months and ≥ 1 Gadolinium(Gd)-enhancing lesion within the last 12 months prior to enrolment. The patients had to have an Expanded Disability Status Scale (EDSS) score of no more than 5.0 and a documented diagnosis of RRMS meeting the revised 2010 McDonald criteria.

A total of 2666 patients were included in both studies and randomly assigned to treatment with 1 mg ozanimod per day (N = 881), 0.5 mg ozanimod per day (N = 894) or 30 µg IFN-β1a per week (N = 891). Since the dosage of 0.5 mg is not in compliance with the approval, this treatment arm is not relevant for the present benefit assessment and is not considered further in the following.

The patients were treated in compliance with the recommendations of the respective Summaries of Product Characteristics (SPCs). The treatment duration in the RADIANCE B study was 24 months, whereas the treatment duration in the SUNBEAM study was at least 12 months and was continued until the last patient was treated for 12 months (median about 14 months).

Primary outcome of both studies was the annualized relapse rate. Secondary outcomes were outcomes on morbidity, health-related quality of life and side effects.

Both studies have been completed and the present benefit assessment is based on the meta-analytical summary of both studies, mainly at month 12, which was planned for the outcome "confirmed disease progression" and was conducted for the approval. However, consideration

of the longer observation period (24 months) would in principle be preferable for the present benefit assessment. A meta-analytical summary of the results at month 24 of the RADIANCE B study with those at month 12 of the SUNBEAM study does not appear to be appropriate due to the notable difference in observation periods, however. It was therefore checked for the benefit assessment whether there were differences in the effects of both dates of analysis in the RADIANCE B study. No important deviations between the 12-month and the 24-month analyses were shown for the outcomes for which data were available. Although corresponding data are not available for all outcomes, it is overall assumed that a meta-analytical summary of the results at month 12 is possible in the present situation without any relevant loss of information. The results of the RADIANCE B study at month 24 are presented as supplementary information.

Subpopulation relevant for research question 1

The population relevant for research question 1 comprised patients who had not yet received disease-modifying therapy for RRMS and patients with non-highly active disease who had been pretreated with a disease-modifying therapy. Thus, the relevant population comprised a subpopulation of the total population of the RADIANCE B study and of the SUNBEAM study. The company presented data of the relevant subpopulation. It formed this population by including patients who had either received no or no appropriate pretreatment, or, if they had received appropriate pretreatment, had non-high disease activity.

The company defined patients with appropriate pretreatment as patients who had been treated with a disease-modifying therapy for ≥ 6 months in the year prior to the start of the study (only the last treatment was relevant in each case). The company operationalized high disease activity as ≥ 1 qualifying relapse (i.e. a relapse during or up to a maximum of 2 months after appropriate pretreatment) in the previous year or ≥ 1 Gd lesion at baseline despite appropriate treatment with a disease-modifying therapy.

The criteria used by the company are suitable for an adequate representation of the subpopulation relevant for research question 1. In both studies, the relevant subpopulation comprised about 84% of the total population.

Risk of bias

The risk of bias across outcomes was rated as low for both studies.

The outcome “fatigue” was not recorded in the studies RADIANCE B and SUNBEAM. There were no usable analyses in Module 4 A for a choice of specific AEs; the risk of bias was therefore not assessed. The risk of bias for the results of all other outcomes was rated as low.

Based on the available data, no more than proof, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

There was no event for the outcome "all-cause mortality". This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a; an added benefit is therefore not proven.

Morbidity

Confirmed relapses (EDSS-based)

The meta-analysis of the annualized relapse rates of confirmed relapses showed a statistically significant difference in favour of ozanimod in comparison with IFN-β1a for the outcome "confirmed relapses". This resulted in proof of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "confirmed relapses".

Confirmed disability progression (EDSS-based)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "confirmed disability progression after 6 months". This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "confirmed disability progression"; an added benefit is therefore not proven.

Disability severity (recorded using the Multiple Sclerosis Functional Composite [MSFC] score)

The meta-analysis for the z-score of the MSFC showed no statistically significant difference between the treatment groups for the outcome "disability severity". This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "disability severity"; an added benefit is therefore not proven.

Visual acuity (low-contrast letter acuity [LCLA])

No statistically significant difference between the 2 treatment arms was shown for the outcome "visual acuity". This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

Fatigue

No data are available for the outcome "fatigue", as this outcome was not recorded in the studies RADIANCE B and SUNBEAM. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Disease-specific quality of life (Multiple Sclerosis Quality of Life [MSQoL]-54)

The meta-analysis showed a statistically significant advantage of ozanimod in comparison with IFN-β1a for the physical health composite score (PHCS). However, the 95% confidence interval (CI) for the standardized mean difference (SMD) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect was relevant. There was no statistically significant difference between the 2 treatment arms for the outcome "mental health

composite score (MHCS)". Overall, this resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for disease-specific quality of life; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

The meta-analysis showed no statistically significant difference for SAEs between the treatment groups. This resulted in no hint of lesser or greater harm of ozanimod in comparison with IFN-β1a; lesser or greater harm is therefore not proven.

Discontinuation due to adverse events (AEs)

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of lesser or greater harm of ozanimod in comparison with IFN-β1a; lesser or greater harm is therefore not proven.

Specific AEs

A choice of specific AEs on the basis of the frequencies and differences between the treatment arms is not meaningfully possible for the present benefit assessment, since the company in Module 4 A did not present the individual events for the outcomes of the category of side effects separately by research question, study and data cut-off according to the frequency criteria specified in the dossier template.

Results on research question 2: pretreated patients with highly active RRMS

The studies RADIANCE B and SUNBEAM were included in the benefit assessment of ozanimod in comparison with IFN-β1a in pretreated patients with highly active RRMS (research question 2). These are the same studies that were also included for the assessment of ozanimod in treatment-naive patients and pretreated patients with non-highly active RRMS (research question 1) (see above).

Study design

The design of the studies RADIANCE B and SUNBEAM is described under research question 1.

Subpopulation relevant for research question 2

The population relevant for research question 2 comprises patients with highly active RRMS despite treatment with a disease-modifying therapy. Consequently, only a subpopulation of the studies RADIANCE B and SUNBEAM is relevant for the present research question. Based on the criteria already described under research question 1 (see above), the company formed a subpopulation of patients with highly active RRMS despite appropriate disease-modifying therapy. In addition, the company excluded all patients from this subpopulation who had been treated directly before study inclusion for ≥ 6 months with the comparator therapy IFN-β1a used in the studies, as there had to be a change within the basic therapeutic agents according to

the G-BA's specification of the ACT. The proportion of the subpopulation relevant for research question 2 was about 12% of the total population in each of the 2 studies.

Risk of bias

As already described in research question 1, the risk of bias of the studies RADIANCE B and SUNBEAM at study level was rated as low for both studies.

The risk of bias at outcome level for research question 2 concurs with the risk of bias described for research question 1, with the difference that a high risk of bias was derived for the results of the outcome "visual acuity" (LCLA) in the RADIANCE B study for the present research question. Based on the available data, no more than proof, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

There was no event for the outcome "all-cause mortality". This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a; an added benefit is therefore not proven.

Morbidity

Confirmed relapses (EDSS-based)

The meta-analysis of the annualized relapse rates of confirmed relapses showed a statistically significant difference in favour of ozanimod in comparison with IFN-β1a. In addition, there was an interaction by the characteristic "sex" for the outcome "confirmed relapses" for the relevant subpopulation. For men, there was proof of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "confirmed relapses". For women, there was no hint of an added benefit of ozanimod in comparison with IFN-β1a; an added benefit for women is therefore not proven.

Confirmed disability progression (EDSS-based)

The meta-analysis on confirmed disability progression after 6 months showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "confirmed disability progression"; an added benefit is therefore not proven.

Disability severity (MSFC)

The meta-analysis showed no statistically significant difference between the treatment groups for the z-score of the MSFC. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "disability severity"; an added benefit is therefore not proven.

Visual acuity (LCLA)

No statistically significant difference between the 2 treatment arms was shown for the outcome "visual acuity" recorded using the LCLA. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

Fatigue

No data are available for the outcome "fatigue", as this outcome was not recorded in the studies RADIANCE B and SUNBEAM. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Disease-specific quality of life (MSQoL-54)

The meta-analysis showed no statistically significant difference between the treatment arms for the PHCS or for the MHCS. Overall, this resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for disease-specific quality of life; an added benefit is therefore not proven.

Side effects

SAEs

The meta-analysis showed no statistically significant difference for SAEs between the treatment groups. This resulted in no hint of lesser or greater harm of ozanimod in comparison with IFN-β1a; lesser or greater harm is therefore not proven.

Discontinuation due to AEs

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of lesser or greater harm of ozanimod in comparison with IFN-β1a; lesser or greater harm is therefore not proven.

Specific AEs

A choice of specific AEs on the basis of the frequencies and differences between the treatment arms is not meaningfully possible for the present benefit assessment, since the company in Module 4 A did not present the individual events for the outcomes of the category of side effects separately by research question, study and data cut-off according to the frequency criteria specified in the dossier template.

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

Based on the results presented, probability and extent of the added benefit of the drug ozanimod in comparison with the ACT are assessed as follows:

Research question 1: treatment-naive patients as well as pretreated patients with non-highly active RRMS

In the overall consideration, there is only one positive effect in the category of serious/severe symptoms or late complications. For the outcome "confirmed relapses", there is proof of an added benefit of ozanimod versus IFN-β1a of considerable extent.

In summary, there is therefore proof of considerable added benefit of ozanimod in comparison with the ACT IFN-β1a for treatment-naive patients and for pretreated patients with non-highly active RRMS.

Research question 2: pretreated patients with highly active RRMS

In the overall consideration, there is only one positive effect in the category of serious/severe symptoms or late complications for the subgroup of men. Due to the effect modification by sex, the added benefit is derived separately for women and men.

For pretreated men with highly active RRMS, there is proof of a non-quantifiable added benefit of ozanimod in comparison with IFN-β1a of at least considerable extent for the outcome "confirmed relapses". The extent is "non-quantifiable" because Module 4 A of the company provides no information on the proportion of patients with (at least one) event and on the annualized relapse rate per treatment arm. It is therefore not possible to estimate how many patients in the respective subgroup contributed to the confirmed relapses that occurred.

For women, there is neither a positive nor a negative effect in the overall consideration; an added benefit of ozanimod for pretreated women with highly active RRMS is therefore not proven.

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

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Ozanimod – probability and extent of added benefit

Subindication	ACT[a]	Probability and extent of added benefit
Adult patients with RRMS who have not yet received disease-modifying therapy or adult patients with RRMS with non-highly active disease pretreated with disease-modifying therapy[b]	**Interferon beta-1a** or interferon beta-1b or glatiramer acetate or ocrelizumab under consideration of the approval	Proof of considerable added benefit
Adult patients with RRMS with highly active disease despite treatment with a disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutic agents (**interferon beta-1a** or interferon beta-1b or glatiramer acetate under consideration of the approval)	▪ Men: proof of non-quantifiable[c] added benefit, at least "considerable" ▪ Women: 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 specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Appropriate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on disability progression, treatment with a disease-modifying therapy can be less than 6 months and has to be justified.
c. Due to missing information on the proportion of patients with (at least one) event and on the annualized relapse rate per treatment arm, the extent is non-quantifiable.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RRMS: relapsing remitting multiple sclerosis

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

2.2 Research question

The aim of the present report is to assess the added benefit of ozanimod in comparison with the ACT in patients with RRMS.

For the benefit assessment, the research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of ozanimod

Research question	Subindication	ACT[a]
1	Adult patients with RRMS who have not yet received disease-modifying therapy or adult patients with RRMS with non-highly active disease pretreated with disease-modifying therapy	**Interferon beta-1a** or interferon beta-1b or glatiramer acetate or ocrelizumab under consideration of the approval
2	Adult patients with RRMS with highly active disease despite treatment with a disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutic agents (**interferon beta-1a** or interferon beta-1b or glatiramer acetate under consideration of the approval)

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Appropriate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on disability progression, treatment with a disease-modifying therapy can be less than 6 months and has to be justified.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RRMS: relapsing remitting multiple sclerosis

In the present benefit assessment, the following terms are used for the research questions:

- Research question 1: treatment-naive patients as well as pretreated patients with non-highly active RRMS
- Research question 2: pretreated patients with highly active RRMS

The company followed the G-BA's specification of the ACTs and chose IFN-β1a as ACT for both research questions.

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 12 months were used for the derivation of the added benefit.

This largely concurs with the inclusion criteria used by the company, which included studies with a duration of 6 months or more, however. This had no consequence, however, as the company did not identify any study with a study duration of ≤ 12 months.

2.3 Research question 1: treatment-naive patients as well as pretreated patients with non-highly active RRMS

2.3.1 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 ozanimod (status: 16 April 2020)
- bibliographical literature search on ozanimod (last search on 16 April 2020)
- search in trial registries/trial results databases for studies on ozanimod (last search on 24 April 2020)
- search on the G-BA website for ozanimod (last search on 17 April 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ozanimod (last search on 20 July 2020)

The check did not identify any additional relevant studies.

2.3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment of ozanimod in comparison with IFN-β1a in treatment-naive patients as well as pretreated patients with non-highly active RRMS (research question 1).

Table 5: Study pool – RCT, direct comparison: ozanimod vs. IFN-β1a

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
RPC01-201B (RADIANCE B[c])	Yes	Yes	No	No[d]	Yes [3,4]	Yes [5]
RPC01-301 (SUNBEAM[c])	Yes	Yes	No	No[d]	Yes [6-8]	Yes [9]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. 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.

CSR: clinical study report; IFN-β: interferon beta; RCT: randomized controlled trial; vs.: versus

The study pool concurs with that of the company.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: ozanimod vs. IFN-β1a (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
RADIANCE B	RCT, double-blind, parallel	Adults (18–55 years) with RRMS[b], ≥ 1 relapse within 12 months prior to study start or ≥ 1 relapse within 24 months prior to study start and ≥ 1 Gd-enhancing lesion within 12 months, EDSS 0–5.0	Ozanimod 1 mg (N = 434) ozanimod 0.5 mg (N = 443)[c] IFN-β1a (N = 443) Relevant subpopulations thereof: ▪ Research question 1[d]: ozanimod 1 mg (n = 370) IFN-β1a (n = 367) ▪ Research question 2[e]: ozanimod 1 mg (n = 47) IFN-β1a (n = 56)	Screening: 30 days Treatment: 24 months; then optional participation in open-label extension study Observation: 28 days, at most until death, discontinuation of participation in the study or end of study	150 centres in Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Canada, Croatia, Georgia, Greece, Hungary, Italy, Moldova, Poland, Romania, Serbia, Slovakia, South Africa, Spain, Ukraine, United Kingdom, USA 12/2013–4/2017	Primary: annualized relapse rate Secondary: morbidity, health-related quality of life, AEs
SUNBEAM	RCT, double-blind, parallel	Adults (18–55 years) with RRMS[b], ≥ 1 relapse within 12 months prior to study start or ≥ 1 relapse within 24 months prior to study start and ≥ 1 Gd-enhancing lesion within 12 months, EDSS 0–5.0	Ozanimod 1 mg (N = 447) ozanimod 0.5 mg (N = 451)[c] IFN-β1a (N = 448) Relevant subpopulations thereof: ▪ Research question 1[d]: ozanimod 1 mg (n = 383) IFN-β1a (n = 360) ▪ Research question 2[e]: ozanimod 1 mg (n = 44) IFN-β1a (n = 60)	Screening: 30 days Treatment: 12 months; then optional participation in open-label extension study Observation: 28 days, at most until death, discontinuation of participation in the study or end of study	158 centres in Belarus, Bosnia-Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Germany, Latvia, Lithuania, Moldova, New Zealand, Poland, Portugal, Romania, Russia, Serbia, Spain, Sweden, Ukraine, USA 12/2014–12/2016	Primary: annualized relapse rate Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Documented diagnosis of RRMS meeting the revised 2010 McDonald criteria [10].
c. The arm is not in compliance with the approval and is not shown in the next tables.
d. Treatment-naive patients with RRMS or pretreated patients with non-highly active disease.
e. Pretreated patients with highly active RRMS.

Table 6: Characteristics of the studies included – RCT, direct comparison: ozanimod vs. IFN-β1a (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AE: adverse event; EDSS: Expanded Disability Status Scale; Gd: gadolinium; IFN-β: interferon beta; n: relevant subpopulation; N: number of randomized (included) patients; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus						

Table 7: Characteristics of the intervention – RCT, direct comparison: ozanimod vs. IFN-β1a

Study	Intervention	Comparison
RADIANCE B	Ozanimod 1 mg capsule, orally, once daily + placebo injection once weekly	Placebo capsule, orally, once daily + IFN-β1a 30 µg IM injection once weekly
SUNBEAM	Ozanimod 1 mg capsule, orally, once daily + placebo injection once weekly	Placebo capsule, orally, once daily + IFN-β1a 30 µg IM injection once weekly
	RADIANCE B, SUNBEAM: **Permitted pretreatment:** ▪ non-lymphocyte-depleting, disease-modifying MS agents (e.g. glatiramer acetate, interferon) to be discontinued from signing of informed consent ▪ documentation of positive Varicella zoster virus immunoglobulin G antibody status, or complete Varicella zoster virus vaccination ≥ 30 days prior to study start **Non-permitted pretreatment:** ▪ systemic corticosteroids, adrenocorticotrophic hormone ≤ 30 days prior to study start ▪ investigational agents ≤ 6 months prior to study start ▪ live vaccination ≤ 4 prior to randomization ▪ lymphocyte-depleting drugs (e.g. alemtuzumab, anti-CD4, cladribine, rituximab, ocrelizumab, cyclophosphamide, mitoxantrone) ▪ total body irradiation, bone marrow transplantation ▪ immunosuppressants (e.g. azathioprine, ciclosporin, methotrexate, mycophenolate) ≤ 6 months prior to randomization ▪ lymphocyte trafficking blockers (e.g. natalizumab, fingolimod, other $S1P_1$ receptor modulators) ▪ IV immunoglobulins or plasmapheresis ≤ 3 months prior to randomization ▪ disease-modifying therapies (e.g. dimethyl fumarate, teriflunomide, daclizumab, laquinimod) ≤ 3 months prior to randomization ▪ therapies that have an impact on the cytochrome P450 3A4 metabolism ≤ 4 weeks prior to randomization **Permitted concomitant treatment:** ▪ anti-inflammatory drugs or paracetamol until 24 h after study medication ▪ methylprednisolone 1 g/day over 5 consecutive days for protocol-defined relapse ▪ drugs for the treatment of spasticity, incontinence, pain and fatigue **Non-permitted concomitant treatment:** ▪ drugs with a known impact on the cardiac conduction system (e.g. beta-blockers, calcium channel blockers, class Ia or class III antiarrhythmics) ▪ QT interval prolonging drugs (e.g. citalopram, chlorpromazine, haloperidol, methadone, erythromycin)	

IFN-β: interferon beta; IM: intramuscular; IV: intravenous; MS: multiple sclerosis; RCT: randomized controlled trial; $S1P_1$: sphingosine 1-phosphate receptor subtype 1; vs.: versus

Description of the study design

The studies RADIANCE B and SUNBEAM have a similar study design, which only differs in treatment duration. For this reason, both studies are described together below wherever possible.

The studies RADIANCE B and SUNBEAM are randomized, double-blind, actively controlled parallel-group studies comparing ozanimod with IFN-β1a in patients with RRMS. Both studies were conducted worldwide at about the same time and in the same regions.

The studies included adult patients (18 to 55 years of age) who had ≥ 1 relapse within the last 12 months prior to enrolment, or ≥ 1 relapse within the last 24 months and ≥ 1 Gd-enhancing lesion within the last 12 months prior to enrolment. The patients had to have an EDSS score of no more than 5.0 and a documented diagnosis of RRMS meeting the revised 2010 McDonald criteria [10].

A total of 2666 patients were included in both studies and randomly assigned to treatment with 1 mg ozanimod per day (N = 881), 0.5 mg ozanimod per day (N = 894) or 30 µg IFN-β1a per week (N = 891). Since the dosage of 0.5 mg is not in compliance with the approval, this treatment arm is not relevant for the present benefit assessment and is not considered further in the following [11]. Randomization was stratified by baseline EDSS score (≤ 3.5 versus > 3.5) and country. Blinding was carried out using a double-dummy design.

The patients were treated in compliance with the regimen described in Table 7. This was in compliance with the specifications of the SPCs [11,12]. The treatment duration in the RADIANCE B study was 24 months, whereas patients in the SUNBEAM study were treated until the last patient was treated for 12 months (median about 14 months). Overall, the treatment durations according to the information provided by the company in Module 4 A for both research questions were comparable between the treatment groups of the respective studies. After the respective blinded treatment phase, patients from both studies could voluntarily participate in an open-label single-arm extension study. The follow-up observation phase was 28 days in both studies. The present assessment is exclusively based on data of the blinded treatment phase.

Primary outcome of both studies was the annualized relapse rate. Secondary outcomes were outcomes on morbidity, health-related quality of life and AEs.

Both studies have been completed and the present benefit assessment is based on the meta-analytical summary of both studies, mainly at month 12 (see Section 2.3.2.1). The meta-analysis was planned for the outcome “confirmed disease progression” [5] and was conducted for the approval [13].

Subpopulation relevant for research question 1

The population relevant for research question 1 comprised patients who had not yet received disease-modifying therapy for RRMS and patients with non-highly active disease who had been pretreated with a disease-modifying therapy. Thus, the relevant population comprised a subpopulation of the total population of the RADIANCE B study and of the SUNBEAM study. The company presented analyses of the relevant subpopulation. It formed this population by

including patients who had either received no or no appropriate pretreatment, or, if they had received appropriate pretreatment, had non-high disease activity.

The company defined patients with appropriate pretreatment as patients who had been treated with a disease-modifying therapy for ≥ 6 months in the year prior to the start of the study (only the last treatment was relevant in each case). The company operationalized high disease activity as ≥ 1 qualifying relapse (i.e. a relapse during or up to a maximum of 2 months after appropriate pretreatment) in the previous year or ≥ 1 Gd-enhancing lesion at baseline despite appropriate treatment with a disease-modifying therapy.

The criteria used by the company are suitable for an adequate representation of the subpopulation relevant for research question 1. In both studies, the relevant subpopulation comprised about 84% of the total population.

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

Table 8: Characteristics of the relevant subpopulation – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS) (multipage table)

Study	RADIANCE B		SUNBEAM	
Characteristic	Ozanimod	IFN-β1a	Ozanimod	IFN-β1a
Category	N[a] = 370	N[a] = 367	N[a] = 383	N[a] = 360
Age [years], mean (SD)	36 (9)	35 (9)	34 (9)	36 (9)
Sex [F/M], %	68/32	69/31	64/36	67/33
Family origin, n (%)				
White	367 (99.2)	359 (97.8)	382 (99.7)	359 (99.7)
Black	3 (0.8)	6 (1.6)	0 (0)	0 (0)
Asian	0 (0)	1 (0.3)	1 (0.3)	0 (0)
Other	0 (0)	1 (0.3)	0 (0)	1 (0.3)
Region, n (%)				
Eastern Europe	325 (87.8)	317 (86.4)	355 (92.7)	340 (94.4)
Western Europe	28 (7.6)	36 (9.8)	13 (3.4)	8 (2.2)
North America	13 (3.5)	11 (3.0)	12 (3.1)	11 (3.1)
Southern Africa	4 (1.1)	3 (0.8)	0 (0)	0 (0)
New Zealand	0 (0)	0 (0)	3 (0.8)	1 (0.3)
EDSS at baseline, n (%)				
≤ 2.0	176 (47.6)	181 (49.3)	189 (49.3)	169 (46.9)
2.5–3.5	140 (37.8)	140 (38.1)	123 (32.1)	132 (36.7)
4.0–5.0	53 (14.3)	46 (12.5)	71 (18.5)	59 (16.4)
> 5.0	1 (0.3)	0 (0)	0 (0)	0 (0)
Gd-enhancing T1 lesions				
Mean (SD)	1.6 (3.9)	1.8 (3.4)	1.9 (3.4)	1.7 (3.2)
Median [min; max]	0.0 [0; 53]	0.0 [0; 20]	0.0 [0; 18]	0.0 [0; 20]
Number of relapses 1 year before baseline, n (%)				
0	7 (1.9)	4 (1.1)	8 (2.1)	5 (1.4)
1	262 (70.8)	253 (68.9)	278 (72.6)	262 (72.8)
2–3	101 (27.3)	106 (28.9)	97 (25.3)	92 (25.6)
≥ 4	0 (0)	4 (1.1)	0 (0)	1 (0.3)
Number of relapses in the 2 years before baseline, n (%)				
1	181 (48.9)	156 (42.5)	169 (44.1)	168 (46.7)
2–3	178 (48.1)	195 (53.1)	198 (51.7)	183 (50.8)
≥ 4	11 (3.0)	16 (4.4)	16 (4.2)	9 (2.5)
Time between first MS symptoms and randomization [years], mean (SD)	6.7 (6.3)	5.9 (6.1)	6.3 (6.1)	6.4 (5.8)
Time between first diagnosis and randomization [years], mean (SD)	3.6 (5.1)	3.1 (4.5)	3.0 (3.9)	3.2 (4.4)

Table 8: Characteristics of the relevant subpopulation – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS) (multipage table)

Study	RADIANCE B		SUNBEAM	
Characteristic	Ozanimod	IFN-β1a	Ozanimod	IFN-β1a
Category	N[a] = 370	N[a] = 367	N[a] = 383	N[a] = 360
Pretreatment with any MS therapy, n (%)				
Yes	339 (91.6)	333 (90.7)	358 (93.5)	339 (94.2)
No	31 (8.4)[b]	34 (9.3)[b]	25 (6.5)[b]	21 (5.8)[b]
Pretreatment with disease-modifying therapy, n (%)				
Yes	60 (16.2)	52 (14.2)	64 (16.7)	63 (17.5)
No	310 (83.8)[b]	315 (85.8)[b]	319 (83.3)[b]	297 (82.5)[b]
Treatment discontinuation, n (%)	ND	ND	ND	ND
Study discontinuation, n (%)	ND	ND	ND	ND

a. Number of analysed patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.

EDSS: Expanded Disability Status Scale; F: female; Gd: gadolinium; IFN-β: interferon beta; M: male; max: maximum; min: minimum; MS: multiple sclerosis; n: number of patients in the category; N: number of included patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; vs.: versus

Based on the available data, there were no noteworthy differences between treatment groups for the subpopulations. The patient characteristics were balanced also between the studies. The mean age of the patients in the relevant subpopulation was 35 years, about 2 thirds of them were female and over 99% were of white family origin. It is notable that over 90% of the patients were from Eastern Europe.

About 85% of the patients had a baseline EDSS score of < 4 and bout 98% had ≥ 1 relapse in the year before the start of the study. The mean disease duration before the start of the study was about 6 years. The proportion of patients with ≥ 1 prior therapy (disease-modifying or non-disease-modifying) was about 93%. The proportion of patients with prior disease-modifying therapy was only about 16%, however.

The company did not provide any information on treatment and study discontinuations in the studies for the relevant subpopulation. For the total population, the proportion of study discontinuations was 10% (RADIANCE B) and 7% (SUNBEAM) of the patients in the ozanimod arm, and 15% (RADIANCE B) and 8% (SUNBEAM) in the IFN-β1a arm.

Risk of bias across outcomes (study level)

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

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: ozanimod 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
			Patients	Treating staff			
RADIANCE B	Yes	Yes	Yes	Yes	Yes	Yes	Low
SUNBEAM	Yes	Yes	Yes	Yes	Yes	Yes	Low
IFN-β1a: interferon beta-1a; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

Transferability of the study results to the German health care context

From the company's point of view, the results of the studies RADIANCE B and SUNBEAM can be transferred to the German health care context due to the study design, the key characteristics of the investigated patient population and the approval-compliant use of both ozanimod and the comparator IFN-β1a. The company referred to a similar sex distribution, a similar EDSS score and a similar age of the patients at diagnosis in comparison with the RRMS population recorded in the German NeuroTransData registry [14].

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- morbidity
  - relapses (EDSS-based)
  - confirmed disability progression (EDSS-based, confirmed over a period of 6 months)
  - disability severity (recorded using the MSFC score)
  - visual acuity (confirmed using the LCLA test)

- fatigue
- Health-related quality of life
  - disease-specific quality of life measured using the MSQoL-54 questionnaire
- Side effects
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

Apart from the outcomes "relapses" and "confirmed disability progression" as well as the outcomes on the specific AEs presented by the company, results for the RADIANCE B study are available at month 12 and month 24, whereas results for the SUNBEAM study are available at month 12 or at the end of treatment (median about 14 months) depending on the outcome. Consideration of the longer observation period (24 months) would in principle be preferable for the present benefit assessment. A meta-analytical summary of the results at month 24 of the RADIANCE B study with those at month 12 of the SUNBEAM study does not appear to be appropriate due to the notable difference in observation periods, however. It was therefore checked for the benefit assessment whether there were differences in the effects of both dates of analysis in the RADIANCE B study. No important deviations between the 12-month and the 24-month analyses were shown for the outcomes for which data were available. Although corresponding data are not available for all outcomes, it is overall assumed that a meta-analytical summary of the results at month 12 or at the end of treatment is possible in the present situation without any relevant loss of information. The company did not provide such a check in its dossier. The results of the RADIANCE B study at month 24 are presented as supplementary information in Appendix A of the full dossier assessment.

The choice of patient-relevant outcomes deviates from the choice of the company, which used further outcomes in the category of side effects in the dossier (Module 4 A) and presented outcomes on imaging features (lesion load and cerebral atrophy) as supplementary information.

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

Table 10: Matrix of outcomes – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS)

Study	Outcomes									
	All-cause mortality	Relapses	Confirmed disability progression[a] (EDSS)	Disability severity (MSFC)[b, c]	Visual acuity (LCLA)[c]	Fatigue	Health-related quality of life (MSQoL-54)[c]	SAEs[c]	Discontinuation due to AEs[c]	Further specific AEs
RADIANCE B	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	No[e]
SUNBEAM	Yes	Yes	Yes	Yes	Yes	No[d]	Yes	Yes	Yes	No[e]

a. Defined as EDSS increase ≥ 1 point; confirmation after 6 months.
b. The validated version of the instrument comprises the T25-FW (walking ability), the 9-HPT (coordination) and the PASAT-3 (cognition). In the SUNBEAM study, the SDMT was recorded instead of the PASAT-3.
c. The time point of 12 months is analysed; results for 24 months are only available for the RADIANCE B study and are presented as supplementary information in Appendix A of the full dossier assessment.
d. Outcome not recorded.
e. No usable analyses are available for the choice of specific AEs; the company did not present analyses on SOCs and PTs in accordance with the required threshold values for all AE categories (see Section 2.3.2.1).

9-HPT: 9-Hole Peg Test; AE: adverse event; EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; LCLA: low-contrast letter acuity; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; PASAT-3: Paced Auditory Serial Addition Test-3; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test; SOC: System Organ Class; T25-FW: Timed 25-Foot Walk; vs.: versus

Only data over the entire course of the study are available for the outcome "relapses" and "confirmed disability progression". The company did not provide information on the extent to which the results for these outcomes of the RADIANCE B study differed between year 1 and year 2. It is therefore not possible to determine to what extent a potential effect in year 1 continues in year 2.

For each study, the company presented the mean difference (MD), determined by means of analysis of covariance (ANCOVA), for the continuous outcomes "severity of disability progression", "visual acuity" and "health-related quality of life". To assess the clinical relevance, it additionally presented an SMD, which it referred to as "Hedges' g". The company used exclusively the SMDs for the meta-analytical summary of the studies RADIANCE B and SUNBEAM. To enable interpretation at the scale level, the MDs must also be considered at the meta-analysis level. For this reason, the meta-analyses for the outcomes mentioned were recalculated in the present benefit assessment using a fixed-effect model (inverse variance method) based on the MDs. In the case of a statistically significant MD, the SMD of the company was used to assess clinical relevance.

The outcome “fatigue” was not recorded in the studies RADIANCE B and SUNBEAM.

Module 4 A of the dossier provided only an incomplete presentation of the individual events for the outcomes of the category of side effects according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC)/Preferred Term (PT) classification in line with the frequency criteria separately by research question, study and data cut-off specified in the dossier template. These data at month 12 are available completely for research question 1, but not for research question 2, as the company used deviating frequency criteria here. The required threshold values for these outcomes are events that occurred in at least 10% of the patients in one study arm for non-serious AEs or in at least 5% of the patients in one study arm for SAEs. The company used the threshold values on the basis of the meta-analysis of both studies. For AEs, it used a threshold value of 10 patients, corresponding to about 17 to 20% of the patients in both studies. For SAEs, it chose a threshold value of 5 (ozanimod arm) and 6 (IFN-β1a arm) patients for both studies, corresponding to about 10% of the patients in both studies.

In addition, data on individual events on the outcomes of the category of side effects are missing for the RADIANCE B study at month 24 and for the SUNBEAM study at the end of treatment.

Due to the incomplete overall situation, a choice of specific AEs on the basis of the frequencies that occurred in the course of the study and possibly different operationalizations is therefore not meaningfully possible and is omitted.

2.3.2.2 Risk of bias

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

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS)

Study		Outcomes									
	Study level	All-cause mortality	Relapses	Confirmed disability progression[a] (EDSS)	Disability severity (MSFC)[b, c]	Visual acuity (LCLA)[c]	Fatigue	Health-related quality of life (MSQoL-54)[c]	SAEs[c]	Discontinuation due to AEs[c]	Further specific AEs
RADIANCE B	L	L	L	L	L	L	–[d]	L	L	L	–[e]
SUNBEAM	L	L	L	L	L	L	–[d]	L	L	L	–[e]

a. Defined as EDSS increase ≥ 1 point; confirmation after 6 months.
b. The validated version of the MSFC comprises the T25-FW (walking ability), the 9-HPT (coordination) and the PASAT-3 (cognition). In the SUNBEAM study, the SDMT was recorded instead of the PASAT-3.
c. The time point of 12 months is analysed; results for 24 months are only available for the RADIANCE B study and are presented as supplementary information in Appendix A of the full dossier assessment.
d. Outcome not recorded.
e. No usable analyses are available for the choice of specific AEs; the company did not present analyses on SOCs and PTs in accordance with the required threshold values for all AE categories (see Section 2.3.2.1).

9-HPT: 9-Hole Peg Test; AE: adverse event; EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; L: low; LCLA: low-contrast letter acuity; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; PASAT-3: Paced Auditory Serial Addition Test-3; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test; SOC: System Organ Class; T25-FW: Timed 25-Foot Walk; vs.: versus

The outcome "fatigue" was not recorded in the studies RADIANCE B and SUNBEAM.

There were no usable analyses in Module 4 A for a choice of specific AEs (see Section 2.3.2.1); the risk of bias was therefore not assessed.

The risk of bias for the results of all other outcomes was rated as low. This concurs with the company's assessment.

2.3.2.3 Results

Table 12, Table 13, Table 14 and Table 15 summarize the results of the comparison of ozanimod with IFN-β1a in treatment-naive patients as well as pretreated patients with non-highly active RRMS. The individual events on the outcomes of the category of side effects (AEs, SAEs and discontinuation due to AEs) as well as on the outcomes on specific AEs from the studies RADIANCE B and SUNBEAM are not listed (see Section 2.3.2.1).

Results of the RADIANCE B study at month 24 are presented in Appendix A of the full dossier assessment. Kaplan-Meier curves for the outcome "confirmed disability progression" can be found in Appendix B of the full dossier assessment.

Table 12: Results (mortality, side effects) – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS), time point 12 months

Outcome category Outcome Study	Ozanimod		IFN-β1a		Ozanimod vs. IFN-β1a
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Mortality					
All-cause mortality					
RADIANCE B	371	0 (0)	366	0 (0)	–
SUNBEAM	383	0 (0)	358	0 (0)	–
Side effects					
AEs (supplementary information)					
RADIANCE B	371	228 (61.5)	366	280 (76.5)	–
SUNBEAM	383	215 (56.1)	358	263 (73.5)	–
SAEs					
RADIANCE B	371	15 (4.0)	366	12 (3.3)	1.23 [0.59; 2.60]; 0.581
SUNBEAM	383	10 (2.6)	358	8 (2.2)	1.17 [0.47; 2.93]; 0.740
Total					1.21 [0.68; 2.15]; ND[b]
Discontinuation due to AEs					
RADIANCE B	371	8 (2.2)	366	11 (3.0)	0.72 [0.29; 1.76]; 0.467
SUNBEAM	383	10 (2.6)	358	12 (3.4)	0.78 [0.34; 1.78]; 0.553
Total					0.75 [0.41; 1.38]; ND[b]

a. RR and CI: according to the company "stratified logistic regression" without any information provided by the company on the factors used; p-value: Cochran-Mantel-Haenszel test.
b. Meta-analysis with fixed effect (inverse variance).

AE: adverse event; IFN-β: interferon beta; n: number of patients with (at least one) event; CI: confidence interval; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; vs.: versus

Table 13: Results (morbidity, confirmed relapses) – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS)

Outcome category Outcome	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
Study	N	n_E	Annualized relapse rate [95% CI][a]	N	n_E	Annualized relapse rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]
Morbidity							
Confirmed relapses (EDSS-based)							
Annualized relapse rate (total)							
RADIANCE B	370	127	0.17 [0.13; 0.23]	367	188	0.25 [0.19; 0.33]	0.68 [0.51; 0.92]; 0.011
SUNBEAM	383	83	0.16 [0.11; 0.24]	360	139	0.29 [0.20; 0.42]	0.55 [0.41; 0.75]; < 0.001
Total							0.62 [0.50; 0.76]; ND[b]
Thereof serious[c] (supplementary information)							
RADIANCE B	*370*	*57*	*ND*	*367*	*95*	*ND*	*ND*
SUNBEAM	*383*	*42*	*ND*	*360*	*68*	*ND*	*ND*
Total							*ND*

a. Adjusted annualized relapse rate and CI (per treatment arm) as well as rate ratio with CI and p-value (group comparison): negative binomial model, adjusted according to region, age and number of Gd-enhancing lesions at baseline; logarithm of observation period as offset variable.
b. Meta-analysis with fixed effect (inverse variance).
c. Relapses requiring hospitalization.

CI: confidence interval; EDSS: Expanded Disability Status Scale; Gd: gadolinium; IFN-β: interferon beta; n_E: number of events; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Table 14: Results (morbidity, time to event) – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS)

Outcome category Outcome Study	Ozanimod N	Ozanimod Median time to event in months [95% CI] Patients with event n (%)	IFN-β1a N	IFN-β1a Median time to event in months [95% CI] Patients with event n (%)	Ozanimod vs. IFN-β1a HR [95% CI]; p-value[a]
Morbidity					
Confirmed disability progression (EDSS-based)[b]					
RADIANCE B	370	NA 30 (8.1)	367	NA 23 (6.3)	1.31 [0.76; 2.27]; 0.326
SUNBEAM	383	NA 8 (2.1)	360	NA 6 (1.7)	1.04 [0.33; 3.26]; 0.946
Total					1.26 [0.77; 2.06]; ND[c]
Fatigue					
RADIANCE B	Outcome not recorded				
SUNBEAM	Outcome not recorded				

a. HR, CI and p-value from Cox proportional hazards model stratified by region, age and EDSS at baseline.
b. Defined as EDSS increase ≥ 1 point from baseline; confirmation after 6 months (or at premature study discontinuation).
c. Meta-analysis with fixed effect (inverse variance).

CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IFN-β: interferon beta; N: number of analysed patients; n: number of patients with event; NA: not achieved; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS) (multipage table)

Outcome category Outcome Study	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
Morbidity							
Disability severity							
MSFC z-score[c]							
RADIANCE B	370	0.03 (0.68)	−0.10 (0.03)	367	0.05 (0.67)	−0.09 (0.03)	−0.01 [−0.06; 0.04]; 0.739
SUNBEAM[d]	383	0.09 (0.67)	−0.02 (0.03)	360	0.01 (0.69)	−0.06 (0.03)	0.04 [−0.01; 0.09]; 0.158
Total[e]							0.02 [−0.02; 0.05][e]; 0.406[e]
Walking ability (T25-FW [seconds][f])							
RADIANCE B	350	5.8 (2.2)	0.7 (0.2)	342	5.7 (2.7)	0.6 (0.2)	0.05 [−0.21; 0.30]
SUNBEAM	365	5.9 (2.2)	0.4 (0.2)	342	6.1 (2.9)	0.4 (0.2)	−0.00 [−0.27; 0.27]
Total							0.03 [−0.16; 0.21][e]
Coordination (9-HPT [seconds][f])							
RADIANCE B	351	22.4 (6.7)	0.6 (0.3)	344	21.8 (5.5)	0.6 (0.3)	0.05 [−0.42; 0.52]
SUNBEAM	365	22.6 (6.4)	−0.6 (0.3)	342	23.3 (6.6)	−0.4 (0.3)	−0.15 [−0.66; 0.37]
Total							−0.04 [−0.39; 0.31][e]
Cognition (PASAT-3 [correct answers][c])							
RADIANCE B	351	48.0 (11.4)	0.1 (0.5)	344	48.2 (10.4)	0.2 (0.5)	−0.10 [−0.99; 0.80]
SUNBEAM	Instrument not used						
Cognition (SDMT [correct answers][c])							
RADIANCE B	Instrument not used						
SUNBEAM	364	48.1 (13.8)	0.6 (0.7)	342	47.9 (13.3)	−1.0 (0.7)	1.61 [0.51; 2.72]
Visual acuity (LCLA contrast 100% [letters correctly identified][c])							
RADIANCE B	348	53.6 (8.6)	−0.5 (0.5)	339	53.4 (8.2)	−0.3 (0.5)	−0.19 [−1.06; 0.67]; 0.660
SUNBEAM	364	52.9 (8.2)	−0.3 (0.4)	341	51.8 (10.2)	−0.4 (0.5)	0.10 [−0.61; 0.80]; 0.791
Total							−0.02 [−0.56; 0.53][e]; 0.955[e]

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS) (multipage table)

Outcome category Outcome Study	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
Health-related quality of life							
MSQoL-54[c]							
PHCS sum score[g]							
RADIANCE B	370	69.2 (18.0)	−0.6 (0.9)	367	72.0 (16.4)	−2.4 (0.9)	1.82 [0.21; 3.43]; 0.027
SUNBEAM	380	68.6 (18.5)	−0.1 (1.1)	357	70.1 (18.6)	−1.6 (1.1)	1.59 [−0.10; 3.28]; 0.066
Total							1.71 [0.54; 2.88][e]; 0.004[e] SMD: 0.15 [0.05; 0.25]
MHCS sum score[h]							
RADIANCE B	370	73.0 (17.7)	−1.8 (1.1)	367	73.4 (17.6)	−2.4 (1.1)	0.64 [−1.37; 2.65]; 0.535
SUNBEAM	382	71.2 (19.1)	−1.1 (1.3)	360	71.7 (18.6)	−1.6 (1.4)	0.47 [−1.65; 2.59]; 0.662
Total							0.56 [−0.90; 2.02][e]; 0.452[e]
Physical functioning							
RADIANCE B	370	73.5 (24.3)	−1.7 (1.2)	367	77.7 (22.8)	−3.6 (1.2)	1.90 [−0.22; 4.01]
SUNBEAM	382	74.4 (24.3)	−1.3 (1.4)	360	74.6 (25.8)	−2.3 (1.4)	0.96 [−1.19; 3.11]
Total							1.44 [−0.07; 2.95][e]
Physical role functioning							
RADIANCE B	370	63.6 (41.7)	−5.9 (2.4)	367	68.0 (39.4)	−8.1 (2.4)	2.17 [−2.21; 6.55]
SUNBEAM	382	59.0 (41.5)	1.6 (2.9)	360	61.9 (41.8)	−0.4 (3.0)	2.03 [−2.61; 6.66]
Total							2.10 [−1.08; 5.29][e]
Emotional role functioning							
RADIANCE B	370	79.1 (35.4)	−7.6 (2.6)	367	77.9 (36.1)	−8.5 (2.6)	0.96 [−3.76; 5.68]
SUNBEAM	382	73.2 (37.8)	−3.4 (3.0)	360	72.5 (38.1)	−3.5 (3.1)	0.08 [−4.80; 4.96]
Total							0.53 [−2.86; 3.93][e]
Pain							
RADIANCE B	370	79.3 (21.6)	−3.6 (1.3)	367	80.0 (20.7)	−4.6 (1.3)	0.95 [−1.42; 3.32]
SUNBEAM	382	77.7 (23.1)	−1.6 (1.5)	360	81.4 (21.6)	−3.2 (1.5)	1.63 [−0.70; 3.96]
Total							1.30 [−0.37; 2.96][e]

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS) (multipage table)

Outcome category Outcome	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
Study	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
Mental wellbeing							
RADIANCE B	370	70.5 (17.1)	−1.3 (1.1)	367	70.3 (16.1)	−1.5 (1.1)	0.22 [−1.77; 2.21]
SUNBEAM	382	69.3 (18.1)	−0.5 (1.3)	360	69.0 (18.6)	−1.3 (1.3)	0.78 [−1.32; 2.88]
Total							0.48 [−0.96; 1.93][e]
Vitality							
RADIANCE B	370	59.1 (19.7)	−0.5 (1.1)	367	59.6 (19.2)	−2.1 (1.1)	1.59 [−0.43; 3.60]
SUNBEAM	382	58.1 (19.6)	−3.1 (1.4)	360	59.9 (20.0)	−3.6 (1.4)	0.52 [−1.69; 2.73]
Total							1.10 [−0.38; 2.59][e]
Health perception							
RADIANCE B	370	56.3 (19.0)	−0.8 (1.2)	367	58.1 (18.4)	−2.2 (1.2)	1.38 [−0.77; 3.53]
SUNBEAM	382	56.0 (19.4)	−0.9 (1.3)	360	57.2 (20.4)	−2.0 (1.4)	1.08 [−1.04; 3.21]
Total							1.23 [−0.28; 2.74][e]
Social functioning							
RADIANCE B	370	80.2 (19.6)	−3.7 (1.1)	367	82.4 (18.1)	−4.7 (1.1)	1.01 [−1.05; 3.06]
SUNBEAM	382	79.4 (19.4)	−1.2 (1.4)	360	80.4 (19.3)	−3.2 (1.4)	1.99 [−0.20; 4.19]
Total							1.47 [−0.03; 2.97][e]
Cognitive functioning							
RADIANCE B	370	76.1 (21.8)	−0.0 (1.1)	367	79.0 (20.3)	−0.1 (1.1)	0.09 [−1.99; 2.16]
SUNBEAM	382	76.8 (22.9)	−1.7 (1.3)	360	79.0 (20.2)	−1.5 (1.4)	−0.26 [−2.47; 1.96]
Total							−0.07 [−1.59; 1.44][e]
Health distress							
RADIANCE B	370	67.9 (22.7)	1.9 (1.2)	367	70.7 (21.3)	0.3 (1.2)	1.63 [−0.62; 3.88]
SUNBEAM	382	68.4 (21.7)	1.6 (1.5)	360	69.5 (23.6)	0.6 (1.6)	1.02 [−1.41; 3.46]
Total							1.35 [−0.30; 3.00][e]
Quality of life							
RADIANCE B	370	70.4 (14.9)	−1.3 (1.0)	367	69.9 (16.0)	−2.0 (1.0)	0.70 [−1.07; 2.47]
SUNBEAM	382	68.9 (17.3)	−0.0 (1.2)	360	70.5 (17.1)	−0.8 (1.2)	0.80 [−1.08; 2.68]
Total							0.75 [−0.54; 2.04][e]
Sexual functioning							
RADIANCE B	370	82.7 (24.2)	−1.6 (1.3)	367	85.2 (22.5)	−2.3 (1.3)	0.73 [−1.68; 3.13]
SUNBEAM	380	84.4 (23.0)	−1.0 (1.5)	357	84.2 (21.5)	−2.1 (1.6)	1.13 [−1.30; 3.55]
Total							0.93 [−0.78; 2.64][e]

Table 15: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS) (multipage table)

Outcome category Outcome Study	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
Satisfaction with sexual functioning (supplementary information)[i]							
RADIANCE B	*370*	*70.7 (28.9)*	*−0.5 (1.8)*	*367*	*72.2 (27.7)*	*−2.0 (1.8)*	*1.52 [−1.73; 4.76]*
SUNBEAM	*380*	*71.4 (28.8)*	*−1.0 (2.0)*	*358*	*73.3 (27.4)*	*−3.6 (2.1)*	*2.66 [−0.58; 5.91]*
Total							*2.09 [−0.20; 4.38][e]*
Change in health (supplementary information)[i]							
RADIANCE B	*370*	*43.6 (23.5)*	*10.9 (1.8)*	*367*	*46.8 (23.4)*	*8.9 (1.8)*	*1.97 [−1.29; 5.22]*
SUNBEAM	*382*	*42.3 (22.8)*	*15.1 (2.0)*	*360*	*44.1 (24.6)*	*9.7 (2.1)*	*5.35 [2.08; 8.63]*
Total							*3.65 [1.34; 5.96][e]*

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b. Mean and SE (change per treatment group) as well as MD, CI and p-value (group comparison): from ANCOVA with treatment arm and baseline value as covariates as well as "possibly stratification factors" with no information provided by the company on the factors used.
c. A positive change from baseline to end of study indicates improvement; a positive effect estimation indicates an advantage of ozanimod.
d. Results of the SDMT instead of the PASAT-3 were considered for the calculation of the z-score.
e. Institute's calculation from meta-analysis with fixed effect (inverse variance).
f. A negative change from baseline to end of study indicates improvement; a negative effect estimation indicates an advantage of ozanimod.
g. This sum score summarizes the following subscales: physical functioning, physical role functioning, pain, vitality, health perception, social functioning, health distress, sexual functioning.
h. This sum score summarizes the following subscales: emotional role functioning, mental wellbeing, cognitive functioning, health distress, quality of life.
i. The item is not taken into account in any of the sum scores.

9-HPT: 9-Hole Peg Test; ANCOVA: analysis of covariance; CI: confidence interval; IFN-β: interferon beta; LCLA: low-contrast letter acuity; MD: mean difference; MHCS: mental health composite score; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; N: number of analysed patients; ND: no data; PASAT: Paced Auditory Serial Addition Test-3; PHCS: physical health composite score; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SDMT: Symbol Digit Modalities Test; SE: standard error; SMD: standardized mean difference (according to the company according to Hedges' g); T25-FW: Timed 25-Foot Walk; vs.: versus

Based on the available data, no more than proof, e.g. of an added benefit, can be determined for all outcomes.

In Module 4 A, the company did not present any p-values for the meta-analysis of the studies RADIANCE B and SUNBEAM. For those outcomes for which the overall effect estimation was not derived from calculations conducted by the Institute, the statistical significance was determined on the basis of the 95% CIs. Statistical significance is considered to be achieved if the 95% CI does not cover the zero effect.

Mortality

All-cause mortality

There was no event for the outcome "all-cause mortality". This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Confirmed relapses (EDSS-based)

The meta-analysis of the annualized relapse rates of confirmed relapses showed a statistically significant difference in favour of ozanimod in comparison with IFN-β1a. This resulted in proof of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "confirmed relapses".

This concurs with the company's assessment.

The operationalization "confirmed relapses by severity grade" presented as supplementary information showed fewer serious relapses (relapses leading to hospitalization) in the ozanimod arm than in the IFN-β1a arm in the studies RADIANCE B and SUNBEAM.

Confirmed disability progression (EDSS-based)

The meta-analysis on confirmed disability progression after 6 months showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "confirmed disability progression"; an added benefit is therefore not proven.

This concurs with the company's assessment.

Disability severity (MSFC)

Operationalization

According to the manual [15], the MSFC z-score is calculated from the results of the Timed 25-Foot Walk (T25-FW) test for recording walking ability, of the 9-Hole Peg Test (9-HPT) for recording coordination and of the Paced Auditory Serial Addition Test-3 (PASAT-3) for recording cognition. In the SUNBEAM study, the Symbol Digit Modalities Test (SDMT), an alternative, valid and recommended instrument, was used instead of the PASAT-3 for recording the severity grade of cognitive restrictions. According to Drake et al. 2010 [16], there is a high correlation between the use of the MSFC z-score with SDMT and the MSFC-z score with PASAT-3. Both variants of the MSFC z-score were therefore used in the present assessment and summarized in a meta-analysis.

Result

The meta-analysis showed no statistically significant difference between the treatment groups for the z-score of the MSFC. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "disability severity"; an added benefit is therefore not proven.

This concurs with the approach of the company insofar as the company also derived no added benefit, but, besides the MSFC z-score, also considered the individual results of the T25-FW, the 9-HPT, the PASAT-3 and the SDMT for the change from baseline.

Visual acuity (LCLA)

No statistically significant difference between the 2 treatment arms was shown for the outcome "visual acuity" recorded using the LCLA. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which allocated this outcome to disability progression.

In addition, the company presented sensitivity analyses with alternative contrast levels (1.25% and 2.5%), which support the results of the main analysis (contrast level 100%).

Fatigue

No data are available for the outcome "fatigue", as this outcome was not recorded in the studies RADIANCE B and SUNBEAM. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Disease-specific quality of life (MSQoL-54)

Operationalization

MSQoL-54 is a questionnaire developed on the basis of Short Form 36 Health Survey (SF-36) version 1. This questionnaire contains an additional 15 questions regarding the areas of sexual functioning, health distress, global quality of life and cognitive functioning, as well as 3 further questions regarding the scales of vitality, physical pain and social functioning, which already exist in the SF-36. There are 2 sum scores (PHCS, MHCS), which include the weighted scores of the scales. The items "satisfaction with sexual functioning" and "change in health" are not included in the PHCS and MHCS sum scores and are presented as supplementary information.

The results on the SF-36 additionally presented by the company were not used for the present assessment, since the recording of the SF-36 was not planned and the information is already included in MSQoL-54.

The PHCS and the MHCS were considered for the MSQoL-54. The mean difference from baseline to month 12 from the covariance analysis was considered for each sum score.

Result

The meta-analysis showed a statistically significant advantage of ozanimod in comparison with IFN-β1a for the PHCS. However, the 95% CI (SMD) was not fully outside the irrelevance range [−0.2; 0.2]. It can therefore not be inferred that the effect was relevant. No statistically significant difference between the 2 treatment arms was shown for the MHCS.

Overall, this resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for disease-specific quality of life; an added benefit is therefore not proven.

This deviates from the company's assessment insofar as the company derived proof of an added benefit of ozanimod in comparison with IFN-β1a based on the results of the MSQoL-54 and the SF-36 for health-related quality of life.

Side effects

SAEs

The meta-analysis showed no statistically significant difference for SAEs between the treatment groups. This resulted in no hint of lesser or greater harm of ozanimod in comparison with IFN-β1a; lesser or greater harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of lesser or greater harm of ozanimod in comparison with IFN-β1a; lesser or greater harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

A choice of specific AEs on the basis of the frequencies and differences between the treatment arms is not meaningfully possible for the present benefit assessment, since the company in Module 4 A did not present the individual events for the outcomes of the category of side effects separately by research question, study and data cut-off according to the frequency criteria specified in the dossier template (see Section 2.3.2.1).

2.3.2.4 Subgroups and other effect modifiers

Age (≤ 40, > 40 years) and sex (female, male) were considered as potential effect modifiers for the present benefit assessment.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

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

In accordance with the methods described, no relevant effect modification by age or sex was identified for the outcomes for which usable analyses were available.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 16).

Determination of the outcome category for the outcome "confirmed relapses"

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

In the studies RADIANCE B and SUNBEAM, confirmed relapses were recorded using the EDSS and the respective functional systems. The supplementary presentation of the relapse rates by severity grade in Table 13 shows that about half of the relapses were serious. A serious relapse according to information provided by the company requires hospitalization. Therefore, this outcome was assigned to the outcome category of serious/severe symptoms/late complications.

This concurs with the company's assessment.

Table 16: Extent of added benefit at outcome level: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS) (multipage table)

Outcome category **Outcome**	**Ozanimod vs. IFN-β1a** **Median time to event (months) or proportion of events (%) or mean change at month 12 or annualized relapse rate** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Confirmed relapses	Rate: 0.16–0.17 vs. 0.25–0.29[c] rate ratio: 0.62 [0.50; 0.76]; p = ND probability: "proof"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Confirmed disability progression	Median: NA vs. NA HR: 1.26 [0.77; 2.06]; p = ND	Lesser benefit/added benefit not proven
Disability severity MSFC z-score	Change: −0.10 to −0.02 vs. −0.09 to −0.06[c] MD: 0.02 [−0.02; 0.05]; p = 0.406	Lesser benefit/added benefit not proven
Visual acuity LCLA	Change: −0.5 to −0.3 vs. −0.4 to −0.3[c] MD: -0.02 [-0.56; 0.53]; p = 0.955	Lesser benefit/added benefit not proven
Fatigue	Outcome not recorded	Lesser benefit/added benefit not proven
Health-related quality of life		
MSQoL-54		
PHCS	Change: −0.6 to −0.1 vs. −2.4 to −1.6[c] MD: 1.71 [0.54; 2.88]; p = 0.004 SMD: 0.15 [0.05; 0.25][d]	Lesser benefit/added benefit not proven
MHCS	Change: −1.8 to −1.1 vs. −2.4 to −1.6[c] MD: 0.56 [-0.90; 2.02]; p = 0.452	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS) (multipage table)

Outcome category **Outcome**	**Ozanimod vs. IFN-β1a** **Median time to event (months) or proportion of events (%) or mean change at month 12 or annualized relapse rate** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	2.6–4.0% vs. 2.2–3.3%[c] RR: 1.21 [0.68; 2.15]; p = ND	Greater/lesser harm not proven
Discontinuation due to AEs	2.2–2.6% vs. 3.0–3.4%[c] RR: 0.75 [0.41; 1.38]; p = ND	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Minimum and maximum proportions of events or change at month 12 or annualized rate per treatment arm in the studies included.
d. If the CI for the SMD 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 inferred.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; HR: hazard ratio; IFN-β: interferon beta; LCLA: low-contrast letter acuity; MD: mean difference; MHCS: mental health composite score; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; NA: not achieved; ND: no data; PHCS: physical health composite score; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SMD: standardized mean difference; vs.: versus

2.3.3.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of ozanimod in comparison with IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS)

Positive effects	**Negative effects**
Morbidity: serious/severe symptoms/late complications ▪ Confirmed relapses proof of added benefit – extent: “considerable”	–
There are no usable results on specific AEs.	
AE: adverse event; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis	

In the overall consideration, there is only one positive effect in the category of serious/severe symptoms or late complications. For the outcome "confirmed relapses", there is proof of an added benefit of ozanimod versus IFN-β1a of considerable extent.

In summary, there is therefore proof of considerable added benefit of ozanimod in comparison with the ACT IFN-β1a for treatment-naive patients and for pretreated patients with non-highly active RRMS.

The assessment described above concurs with that of the company.

2.4 Research question 2: pretreated patients with highly active RRMS

2.4.1 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 ozanimod (status: 16 April 2020)
- bibliographical literature search on ozanimod (last search on 16 April 2020)
- search in trial registries/trial results databases for studies on ozanimod (last search on 24 April 2020)
- search on the G-BA website for ozanimod (last search on 17 April 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ozanimod (last search on 20 July 2020)

The check did not identify any additional relevant studies.

2.4.1.1 Studies included

The studies RADIANCE B and SUNBEAM were included in the benefit assessment of ozanimod in comparison with IFN-β1a in pretreated patients with highly active RRMS (research question 2). These are the same studies that were also included for the assessment of ozanimod in treatment-naive patients and pretreated patients with non-highly active RRMS (research question 1) (see Table 5).

2.4.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment. The design of the studies is described in Section 2.3.1.2.

Subpopulation relevant for research question 2

The population relevant for research question 2 comprises patients with highly active RRMS despite treatment with a disease-modifying therapy. Consequently, only a subpopulation of the

studies RADIANCE B and SUNBEAM is relevant for the present research question. Based on the criteria described in Section 2.3.1.2, the company formed a subpopulation of patients with highly active RRMS despite appropriate disease-modifying therapy. In addition, the company excluded all patients from this subpopulation who had been treated directly before study inclusion for ≥ 6 months with the comparator therapy IFN-β1a used in the studies, as there had to be a change within the basic therapeutic agents according to the G-BA's specification of the ACT. The proportion of the subpopulation relevant for research question 2 was about 12% of the total population in each of the 2 studies.

About 10% of the patients in the control arm had received IFN-β1a as prior therapy. Consequently, these patients had been switched from IFN-β1a to another drug before the start of the study, or the duration or time point of the treatment did not meet the criteria of an appropriate pretreatment. The company did not provide more detailed information on the treatment duration, the reasons for the treatment switch or why another IFN-β1a therapy was indicated for these patients at the start of the study. Due to the small proportion of patients with IFN-β1a pretreatment, this had no relevant consequence for the present benefit assessment, however. Despite the missing information, the presented subpopulation was used as sufficient approximation to the subpopulation relevant for research question 2 for the present assessment.

Table 18 shows the characteristics of the patients of the relevant subpopulation in the studies included.

Table 18: Characteristics of the relevant subpopulation – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Study	RADIANCE B		SUNBEAM	
Characteristic Category	Ozanimod	IFN-β1a	Ozanimod	IFN-β1a
	N[a] = 47	N[a] = 56	N[a] = 44	N[a] = 60
Age [years], mean (SD)	36 (8)	35 (9)	37 (8)	39 (8)
Sex [F/M], %	72/28	71/29	61/39	68/32
Family origin, n (%)				
White	45 (95.7)	56 (100)	44 (100)	60 (100)
Black	2 (4.3)	0 (0)	0 (0)	0 (0)
Region, n (%)				
Eastern Europe	37 (78.7)	47 (83.9)	41 (93.2)	57 (95.0)
Western Europe	5 (10.6)	2 (3.6)	3 (6.8)	2 (3.3)
North America	3 (6.4)	4 (7.1)	0 (0)	0 (0)
Southern Africa	2 (4.3)	3 (5.4)	0 (0)	0 (0)
New Zealand	0 (0)	0 (0)	0 (0)	1 (1.7)
EDSS at baseline, n (%)				
≤ 2.0	16 (34.0)	23 (41.1)	17 (38.6)	22 (36.7)
2.5–3.5	21 (44.7)	21 (37.5)	15 (34.1)	24 (40.0)
4.0–5.0	10 (21.3)	12 (21.4)	12 (27.3)	14 (23.3)
5	0 (0)	0 (0)	0 (0)	0 (0)
Gd-enhancing T1 lesions				
Mean (SD)	2.0 (3.5)	2.5 (4.7)	2.1 (4.3)	2.0 (3.3)
Median [min; max]	1.0 [0; 18]	1.0 [0; 22]	0.0 [0; 19]	1.0 [0; 18]
Number of relapses 1 year before baseline, n (%)				
0	1 (2.1)	2 (3.6)	2 (4.5)	2 (3.3)
1	42 (89.4)	39 (69.6)	33 (75.0)	47 (78.3)
2–3	4 (8.5)	15 (26.8)	9 (20.5)	11 (18.3)
Number of relapses in the 2 years before baseline, n (%)				
1	29 (61.7)	25 (44.6)	22 (50.0)	33 (55.0)
2–3	17 (36.2)	24 (42.9)	18 (40.9)	24 (40.0)
≥ 4	1 (2.1)	7 (12.5)	4 (9.1)	3 (5.0)
Time between first MS symptoms and randomization [years], mean (SD)	8.3 (5.3)	7.1 (4.4)	10.8 (6.4)	9.4 (6.5)
Time between first diagnosis and randomization [years], mean (SD)	5.7 (4.4)	5.5 (3.9)	7.5 (4.6)	6.1 (3.8)
Pretreatment with any MS therapy, n (%)				
Yes	47 (100)	56 (100)	44 (100)	60 (100)
No	0 (0)	0 (0)	0 (0)	0 (0)

Table 18: Characteristics of the relevant subpopulation – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Study	RADIANCE B		SUNBEAM	
Characteristic Category	Ozanimod	IFN-β1a	Ozanimod	IFN-β1a
	N[a] = 47	N[a] = 56	N[a] = 44	N[a] = 60
Pretreatment with disease-modifying therapy, n (%)				
Yes	47 (100)	56 (100)	44 (100)	60 (100)
No	0 (0)	0 (0)	0 (0)	0 (0)
Treatment discontinuation, n (%)	ND	ND	ND	ND
Study discontinuation, n (%)	ND	ND	ND	ND

a. Number of included patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

EDSS: Expanded Disability Status Scale; F: female; Gd: gadolinium; IFN-β: interferon beta; M: male; max: maximum; min: minimum; MS: multiple sclerosis; n: number of patients in the category; N: number of included patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; vs.: versus

Based on the available data, there were largely no noteworthy differences between treatment groups for the subpopulation. The patient characteristics were balanced also between the studies. The mean age of the patients in the relevant subpopulation was 37 years, about 2 thirds of them were female and over 99% were of white family origin. It is notable also here that a large proportion (88%) of the patients were from Eastern Europe.

About 67% of the patients had a baseline EDSS score of < 4 and bout 97% had ≥ 1 relapse in the year before the start of the study. The mean disease duration before the start of the study was about 9 years. All patients of the subpopulation had received ≥ 1 course of treatment with a disease-modifying therapy before the start of the study.

The company did not provide any information on treatment and study discontinuations in both studies for the relevant subpopulation.

Risk of bias across outcomes (study level)

As already described in Section 2.3.2.2, the risk of bias of the studies RADIANCE B and SUNBEAM at study level was rated as low for both studies. This concurs with the company's assessment (see Table 9).

Transferability of the study results to the German health care context

The company's information regarding the transferability of the study results to the German health care context is described in Section 2.3.2.2.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The patient-relevant outcomes listed in Section 2.3.2.1 on research question 1 were to be considered in the assessment of research question 2.

The meta-analytical summary of the studies RADIANCE B and SUNBEAM were used for the assessment of research question 2 (see Section 2.3.2.1 for reasons). The results of the RADIANCE B study at month 24 are presented as supplementary information in Appendix A of the full dossier assessment.

Due to incomplete information on the presentation of the individual events on the outcomes of the category of side effects, there are no usable data for the outcomes on specific AEs (see Section 2.3.2.1).

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.3.2.1).

Table 10 in Section 2.3.2.1 shows for which outcomes data were available in the included studies.

2.4.2.2 Risk of bias

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

Table 19: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS)

Study	Study level	Outcomes									
		All-cause mortality	Relapses	Confirmed disability progression[a] (EDSS)	Disability severity (MSFC)[b, c]	Visual acuity (LCLA)[c]	Fatigue	Health-related quality of life (MSQoL-54)[c]	SAEs[c]	Discontinuation due to AEs[c]	Further specific AEs
RADIANCE B	L	L	L	L	L	H[d]	–[e]	L	L	L	–[f]
SUNBEAM	L	L	L	L	L	L	–[e]	L	L	L	–[f]

a. Defined as EDSS increase ≥ 1 point; confirmation after 6 months.
b. The validated version of the MSFC comprises the T25-FW (walking ability), the 9-HPT (coordination) and the PASAT-3 (cognition). In the SUNBEAM study, the SDMT was recorded instead of the PASAT-3.
c. The time point of 12 months is analysed; results for 24 months are only available for the RADIANCE B study and are presented as supplementary information in Appendix A of the full dossier assessment.
d. Large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
e. Outcome not recorded.
f. No usable analyses are available for the choice of specific AEs; the company did not present analyses on SOCs and PTs in accordance with the required threshold values for all AE categories (see Section 2.3.2.1).

9-HPT: 9-Hole Peg Test; AE: adverse event; EDSS: Expanded Disability Status Scale; H: high; IFN-β: interferon beta; L: low; LCLA: low-contrast letter acuity; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; PASAT-3: Paced Auditory Serial Addition Test-3; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test; SOC: System Organ Class; T25-FW: Timed 25-Foot Walk; vs.: versus

The risk of bias at outcome level for research question 2 concurs with the risk of bias described in Section 2.3.2.2 for research question 1, with the difference that a high risk of bias was derived for the results of the outcome "visual acuity" (LCLA) in the RADIANCE B study for the present research question. This is due to the fact that there was a large difference in the proportion of patients not considered in the analysis (> 5 percentage points) between the treatment groups.

2.4.2.3 Results

Table 20, Table 21, Table 22 and Table 23 summarize the results of the comparison of ozanimod with IFN-β1a in treatment-naive patients as well as pretreated patients with non-highly active RRMS. The individual events on the outcomes of the category of side effects (AEs, SAEs and discontinuation due to AEs) as well as on the outcomes on specific AEs from the studies RADIANCE B and SUNBEAM are not listed (see Section 2.3.2.1).

Results of the RADIANCE B study at month 24 are presented in Appendix A of the full dossier assessment. Kaplan-Meier curves for the outcome "confirmed disability progression" can be found in Appendix B of the full dossier assessment.

Table 20: Results (mortality, side effects) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS), time point 12 months

Outcome category Outcome Study	Ozanimod N	Ozanimod Patients with event n (%)	IFN-β1a N	IFN-β1a Patients with event n (%)	Ozanimod vs. IFN-β1a RR [95% CI]; p-value[a]
Mortality					
All-cause mortality					
RADIANCE B	47	0 (0)	56	0 (0)	–
SUNBEAM	44	0 (0)	60	0 (0)	–
Side effects					
AEs (supplementary information)					
RADIANCE B	47	29 (61.7)	56	42 (75.0)	–
SUNBEAM	44	24 (54.5)	60	46 (76.7)	–
SAEs					
RADIANCE B	47	0 (0)	56	2 (3.6)	0.24 [0.01; 4.83][b]; 0.193
SUNBEAM	44	3 (6.8)	60	1 (1.7)	4.09 [0.44; 38.03]; 0.179
Total					1.28 [0.30; 5.37]; ND[c]
Discontinuation due to AEs					
RADIANCE B	47	0 (0)	56	4 (7.1)	0.13 [0.01; 2.39][b]; 0.063
SUNBEAM	44	3 (6.8)	60	2 (3.3)	2.05 [0.36; 11.73]; 0.414
Total					0.69 [0.20; 2.42]; ND[c]

a. RR and CI: according to the company "stratified logistic regression" without any information provided by the company on the factors used; p-value: Cochran-Mantel-Haenszel test.
b. Model without stratification factors.
c. Meta-analysis with fixed effect (inverse variance).

AE: adverse event; CI: confidence interval; IFN-β: interferon beta; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; vs.: versus

Table 21: Results (morbidity, confirmed relapses) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS)

Outcome category Outcome Study	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
	N	n_E	Annualized relapse rate [95% CI][a]	N	n_E	Annualized relapse rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]
Morbidity							
Confirmed relapses (EDSS-based)							
Annualized relapse rate (total)							
RADIANCE B	47	14	0.15 [0.08; 0.27]	56	38	0.37 [0.23; 0.60]	0.39 [0.21; 0.75]; 0.005
SUNBEAM	44	10	0.13 [0.04; 0.40]	60	33	0.36 [0.13; 1.00]	0.36 [0.17; 0.74]; 0.005
Total							0.38 [0.23; 0.61]; ND[b]
Thereof serious[c] (supplementary information)							
RADIANCE B	*47*	*6*	*ND*	*56*	*26*	*ND*	*ND*
SUNBEAM	*44*	*6*	*ND*	*60*	*14*	*ND*	*ND*
Total							*ND*

a. Adjusted annualized relapse rate and CI (per treatment arm) as well as rate ratio with CI and p-value (group comparison): negative binomial model, adjusted according to region, age and number of Gd-enhancing lesions at baseline; logarithm of observation period as offset variable.
b. Meta-analysis with fixed effect (inverse variance).
c. Relapses requiring hospitalization.

CI: confidence interval; EDSS: Expanded Disability Status Scale; Gd: gadolinium; IFN-β: interferon beta; n_E: number of events; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Table 22: Results (morbidity, time to event) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS)

Outcome category Outcome Study	Ozanimod N	Ozanimod Median time to event in months [95% CI] Patients with event n (%)	IFN-β1a N	IFN-β1a Median time to event in months [95% CI] Patients with event n (%)	Ozanimod vs. IFN-β1a HR [95% CI]; p-value[a]
Morbidity					
Confirmed disability progression (EDSS-based)[b]					
RADIANCE B	47	NA 9 (19.2)	56	NA 1 (1.8)	9.89 [1.18; 83.19]; 0.035
SUNBEAM	44	NA 1 (2.3)	60	NA 1 (1.7)a	1.22 [0.08; 19.54]; 0.887
Total					4.55 [0.84; 24.63]; ND[c]
Fatigue					
RADIANCE B			Outcome not recorded		
SUNBEAM			Outcome not recorded		

a. HR, CI and p-value from Cox proportional hazards model stratified by region, age and EDSS at baseline.
b. Defined as EDSS increase ≥ 1 point from baseline; confirmation after 6 months (or at premature study discontinuation).
c. Meta-analysis with fixed effect (inverse variance).

CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; IFN-β: interferon beta; N: number of analysed patients; n: number of patients with event; NA: not achieved; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Table 23: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Outcome category Outcome Study	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
Morbidity							
Disability severity							
MSFC z-score[c]							
RADIANCE B	47	−0.20 (0.84)	−0.01 (0.10)	56	−0.31 (0.87)	−0.10 (0.09)	0.08 [−0.13; 0.29]; 0.447
SUNBEAM[d]	44	−0.16 (0.66)	0.08 (0.08)	60	−0.21 (0.90)	0.07 (0.08)	0.01 [−0.12; 0.14]; 0.912
Total							0.03 [−0.08; 0.14][e]; 0.602[e]
Walking ability (T25-FW [seconds][f])							
RADIANCE B	46	6.7 (2.5)	0.6 (0.7)	48	7.3 (3.3)	1.5 (0.7)	−0.88 [−2.45; 0.68]
SUNBEAM	43	6.7 (2.9)	−0.4 (0.5)	58	7.0 (4.1)	−0.3 (0.5)	−0.12 [−0.91; 0.66]
Total							−0.27 [−0.97; 0.43][e]
Coordination (9-HPT [seconds][f])							
RADIANCE B	46	23.3 (7.5)	0.9 (1.6)	48	24.7 (9.5)	1.7 (1.7)	−0.86 [−4.49; 2.78]
SUNBEAM	43	23.9 (6.0)	0.7 (0.8)	58	25.6 (14.8)	0.0 (0.8)	0.69 [−0.60; 1.98]
Total							0.52 [−0.70; 1.73][e]
Cognition (PASAT-3 [correct answers][c])							
RADIANCE B	46	42.9 (14.0)	3.4 (1.4)	48	40.8 (12.9)	4.2 (1.5)	−0.75 [−4.01; 2.51]
SUNBEAM				Instrument not used			
Cognition (SDMT [correct answers][c])							
RADIANCE B				Instrument not used			
SUNBEAM	43	45.4 (14.6)	1.8 (1.6)	58	43.4 (14.2)	1.1 (1.6)	0.74 [−1.94; 3.42]
Visual acuity (LCLA contrast 100% [letters correctly identified][c])							
RADIANCE B	45	51.8 (7.1)	0.9 (1.0)	48	51.7 (7.9)	0.6 (1.0)	0.28 [−1.98; 2.54]; 0.804
SUNBEAM	43	51.6 (8.3)	0.4 (1.5)	58	51.4 (8.5)	−1.5 (1.5)	1.98 [−0.42; 4.39]; 0.105
Total							1.08 [−0.57; 2.72][e]; 0.200[e]

Table 23: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Outcome category Outcome Study	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
Health-related quality of life							
MSQoL-54[c]							
PHCS sum score[g]							
RADIANCE B	47	67.4 (20.1)	−1.0 (1.8)	56	66.8 (18.7)	−2.7 (1.7)	1.75 [−2.06; 5.56]; 0.364
SUNBEAM	43	66.6 (17.8)	1.6 (2.9)	60	65.7 (19.7)	0.7 (2.9)	0.95 [−3.78; 5.68]; 0.691
Total							1.44 [−1.53; 4.40][e]; 0.343[e]
MHCS sum score[h]							
RADIANCE B	47	73.5 (18.9)	−0.5 (2.2)	56	69.1 (17.1)	−5.9 (2.2)	5.34 [0.36; 10.32]; 0.036
SUNBEAM	44	71.0 (17.7)	−1.4 (3.0)	60	69.2 (21.0)	−0.5 (3.0)	−0.91 [−5.80; 3.98]; 0.713
Total							2.16 [−1.33; 5.65][e]; 0.225[e]
Physical functioning							
RADIANCE B	47	72.4 (26.4)	−5.5 (2.6)	56	69.0 (26.2)	−1.9 (2.5)	−3.57 [−9.08; 1.95]
SUNBEAM	44	65.9 (25.8)	0.4 (4.1)	60	69.5 (25.6)	−1.3 (3.9)	1.68 [−4.75; 8.12]
Total							−1.35 [−5.53; 2.84][e]
Physical role functioning							
RADIANCE B	47	61.2 (42.3)	−4.2 (5.6)	56	56.6 (43.7)	−11.9 (5.3)	7.64 [−4.64; 19.92]
SUNBEAM	44	58.7 (37.9)	8.6 (8.7)	60	56.3 (41.8)	4.2 (8.6)	4.47 [−9.57; 18.52]
Total							6.27 [−2.98; 15.51][e]
Emotional role functioning							
RADIANCE B	47	79.4 (36.5)	−0.3 (5.9)	56	71.9 (37.4)	−19.2 (5.7)	18.90 [5.77; 32.04]
SUNBEAM	44	69.4 (37.6)	2.18 (7.7)	60	71.1 (38.6)	9.0 (7.6)	−6.82 [−19.31; 5.68]
Total							5.40 [−3.65; 14.45][e]

Table 23: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Outcome category Outcome	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
Study	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
Pain							
RADIANCE B	47	78.2 (25.2)	−2.2 (2.5)	56	78.2 (21.1)	−2.2 (2.4)	−0.07 [−5.56; 5.42]
SUNBEAM	44	78.0 (24.8)	1.0 (4.8)	60	77.8 (23.2)	0.2 (4.7)	0.83 [−6.90; 8.57]
Total							0.23 [−4.25; 4.71][e]
Mental wellbeing							
RADIANCE B	47	72.3 (17.1)	0.3 (2.3)	56	68.2 (17.8)	−4.9 (2.2)	5.15 [0.10; 10.20]
SUNBEAM	44	69.3 (18.3)	−0.6 (3.1)	60	66.6 (21.7)	−3.1 (3.1)	2.52 [−2.53; 7.57]
Total							3.84 [0.26; 7.41][e]
Vitality							
RADIANCE B	47	55.9 (21.8)	1.6 (2.5)	56	56.6 (22.2)	−3.8 (2.4)	5.42 [−0.05; 10.89]
SUNBEAM	44	58.7 (17.5)	0.4 (3.4)	60	56.7 (22.1)	−0.6 (3.3)	1.04 [−4.38; 6.46]
Total							3.21 [−0.64; 7.06][e]
Health perception							
RADIANCE B	47	55.0 (20.9)	−3.2 (2.5)	56	55.6 (18.5)	−1.3 (2.4)	−1.97 [−7.44; 3.51]
SUNBEAM	44	53.6 (18.7)	3.7 (3.2)	60	51.9 (22.0)	2.1 (3.1)	1.63 [−3.49; 6.75]
Total							−0.05 [−3.79; 3.69][e]
Social functioning							
RADIANCE B	47	79.4 (21.3)	−2.7 (2.4)	56	78.4 (18.9)	−4.8 (2.3)	2.09 [−3.14; 7.32]
SUNBEAM	44	76.0 (18.8)	0.1 (3.8)	60	78.5 (19.1)	−0.4 (3.7)	0.50 [−5.66; 6.65]
Total							1.42 [−2.56; 5.41][e]
Cognitive functioning							
RADIANCE B	47	74.8 (25.2)	−1.3 (2.5)	56	73.1 (22.9)	0.3 (2.4)	−1.55 [−6.98; 3.88]
SUNBEAM	44	78.9 (18.0)	−3.5 (3.3)	60	72.8 (24.4)	−0.4 (3.2)	−3.10 [−8.44; 2.23]
Total							−2.34 [−6.14; 1.47][e]

Table 23: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Outcome category Outcome Study	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
Health distress							
RADIANCE B	47	70.2 (23.7)	−2.1 (2.7)	56	66.8 (21.3)	−3.1 (2.6)	1.00 [−5.04; 7.04]
SUNBEAM	44	72.5 (20.9)	−5.3 (4.3)	60	70.9 (23.0)	−7.1 (4.2)	1.80 [−5.15; 8.75]
Total							1.34 [−3.21; 5.90][e]
Quality of life							
RADIANCE B	47	69.0 (15.9)	−0.6 (1.8)	56	65.3 (17.6)	−0.4 (1.7)	−0.25 [−4.24; 3.75]
SUNBEAM	44	68.3 (17.2)	−1.8 (2.9)	60	66.5 (19.5)	−2.3 (2.9)	0.50 [−4.23; 5.23]
Total							0.06 [−2.99; 3.11][e]
Sexual functioning							
RADIANCE B	47	76.7 (29.2)	2.7 (2.5)	56	83.3 (23.2)	−2.2 (2.3)	4.87 [−0.59; 10.34]
SUNBEAM	43	82.0 (26.9)	−1.0 (4.9)	60	71.4 (26.2)	−4.4 (4.8)	3.33 [−4.73; 11.40]
Total							4.39 [−0.14; 8.91][e]
Satisfaction with sexual functioning (supplementary information)[i]							
RADIANCE B	*47*	*67.3 (35.7)*	*1.7 (3.2)*	*56*	*71.0 (27.0)*	*−3.1 (3.0)*	*4.75 [−2.17; 11.68]*
SUNBEAM	*44*	*71.4 (29.2)*	*4.3 (6.2)*	*60*	*65.4 (31.3)*	*−0.9 (6.1)*	*5.16 [−4.91; 15.23]*
Total							*4.88 [−0.82; 10.59][e]*
Change in health (supplementary information)[i]							
RADIANCE B	*47*	*46.8 (19.2)*	*6.3 (3.3)*	*56*	*47.7 (23.0)*	*1.7 (3.1)*	*4.62 [−2.66; 11.89]*
SUNBEAM	*44*	*47.7 (21.4)*	*16.4 (5.4)*	*60*	*47.1 (24.0)*	*10.6 (5.2)*	*5.86 [−2.78; 14.49]*
Total							*5.13 [−0.43; 10.70][e]*

Table 23: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Outcome category Outcome Study	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change at month 12 mean[b] (SE)	MD [95% CI]; p-value[b]
a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers. b. Mean and SE (change per treatment group) as well as MD, CI and p-value (group comparison): from ANCOVA with treatment arm and baseline value as covariates as well as "possibly stratification factors" with no information provided by the company on the factors used. c. A positive change from baseline to end of study indicates improvement; a positive effect estimation indicates an advantage of ozanimod. d. Results of the SDMT instead of the PASAT-3 were considered for the calculation of the z-score. e. Institute's calculation from meta-analysis with fixed effect (inverse variance). f. A negative change from baseline to end of study indicates improvement; a negative effect estimation indicates an advantage of ozanimod. g. This sum score summarizes the following subscales: physical functioning, physical role functioning, pain, vitality, health perception, social functioning, health distress, sexual functioning. h. This sum score summarizes the following subscales: emotional role functioning, mental wellbeing, cognitive functioning, health distress, quality of life. i. The item is not taken into account in any of the sum scores. 9-HPT: 9-Hole Peg Test; ANCOVA: analysis of covariance; CI: confidence interval; IFN-β: interferon beta; LCLA: low-contrast letter acuity; MD: mean difference; MHCS: mental health composite score; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; N: number of analysed patients; ND: no data; PASAT-3: Paced Auditory Serial Addition Test-3; PHCS: physical health composite score; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SDMT: Symbol Digit Modalities Test; SE: standard error; T25-FW: Timed 25-Foot Walk; vs.: versus							

Based on the available data, no more than proof, e.g. of an added benefit, can be determined for all outcomes.

In Module 4 A, the company did not present any p-values for the meta-analysis of the studies RADIANCE B and SUNBEAM. For the present outcomes for which the overall effect estimation was not derived from calculations conducted by the Institute, the statistical significance was determined on the basis of the 95% CIs. Statistical significance is considered to be achieved if the 95% CI does not cover the zero effect.

Mortality

All-cause mortality

There was no event for the outcome "all-cause mortality". This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Confirmed relapses (EDSS-based)

The meta-analysis of the annualized relapse rates of confirmed relapses showed a statistically significant difference in favour of ozanimod in comparison with IFN-β1a. In addition, there was an interaction by the characteristic "sex" for the outcome "confirmed relapses" for the relevant subpopulation (see Section 2.4.2.4). For men, there was proof of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "confirmed relapses". For women, there was no hint of an added benefit of ozanimod in comparison with IFN-β1a; an added benefit for women is therefore not proven.

This deviates from the company's assessment. The company did not use subgroup data for the derivation of an added benefit and derived proof of an added benefit of ozanimod for the outcome "confirmed relapses" for the entire relevant subpopulation.

The operationalization "relapses by severity grade" presented as supplementary information showed fewer serious relapses (relapses leading to hospitalization) in the ozanimod arm than in the IFN-β1a arm in the studies RADIANCE B and SUNBEAM.

Confirmed disability progression (EDSS-based)

The meta-analysis on confirmed disability progression after 6 months showed no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Disability severity (MSFC)

Operationalization

The operationalization of the outcome "disability severity" concurs with the one described in Section 2.3.2.3 for research question 1.

Result

The meta-analysis showed no statistically significant difference between the treatment groups for the z-score of the MSFC. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for the outcome "disability severity"; an added benefit is therefore not proven.

This concurs with the approach of the company insofar as the company also derived no added benefit, but, besides the MSFC z-score, also considered the individual results of the T25-FW, the 9-HPT, the PASAT-3 and the SDMT for the change from baseline.

Visual acuity (LCLA)

No statistically significant difference between the 2 treatment arms was shown for the outcome "visual acuity" recorded using the LCLA. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company, which allocated this outcome to disability progression.

In addition, the company presented further sensitivity analyses with alternative contrast levels (1.25% and 2.5%) that support the results of the main analysis (contrast level 100%).

Fatigue

No data are available for the outcome "fatigue", as this outcome was not recorded in the studies RADIANCE B and SUNBEAM. This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Disease-specific quality of life (MSQoL-54)

Operationalization

The operationalization of the outcome "disease-specific quality of life" concurs with the one described in Section 2.3.2.3 for research question 1.

Result

The meta-analysis showed no statistically significant difference between the treatment arms for the PHCS or for the MHCS. Overall, this resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for disease-specific quality of life; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

SAEs

The meta-analysis showed no statistically significant difference for SAEs between the treatment groups. This resulted in no hint of lesser or greater harm of ozanimod in comparison with IFN-β1a; lesser or greater harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of lesser or greater harm of ozanimod in comparison with IFN-β1a; lesser or greater harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

A choice of specific AEs on the basis of the frequencies and differences between the treatment arms is not possible for the present benefit assessment, since the company in Module 4 A did not present the individual events for the outcomes of the category of side effects separately by research question, study and data cut-off according to the frequency criteria specified in the dossier template (see Section 2.3.2.1).

2.4.2.4 Subgroups and other effect modifiers

Age (≤ 40, > 40 years) and sex (female, male) were considered as potential effect modifiers for the present benefit assessment.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

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

Table 24 shows the subgroup results of ozanimod in comparison with IFN-β1a.

Table 24: Subgroups (morbidity, confirmed relapses) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS)

Outcome Characteristic	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
Study Subgroup	N	n_E	Annualized relapse rate [95% CI][a]	N	n_E	Annualized relapse rate [95% CI][a]	Rate ratio [95% CI]; p-value[a]
Morbidity							
Confirmed relapses (EDSS-based)							
Annualized relapse rate (total)							
Sex							
RADIANCE B							
Men	13	ND	ND	16	ND	ND	0.09 [0.01; 0.68]; ND
Women	34	ND	ND	40	ND	ND	0.62 [0.31; 1.24]; ND
SUNBEAM							
Men	17	ND	ND	19	ND	ND	0.19 [0.04; 0.83]; ND
Women	27	ND	ND	41	ND	ND	0.56 [0.24; 1.30]; ND
Total						Interaction:	p-value = 0.034
Men							0.14 [0.04; 0.48][b]; ND
Women							0.60 [0.35; 1.02][b]; ND

a. Annualized relapse rate and CI (per treatment arm) as well as rate ratio with CI (group comparison): negative binomial model.
b. Meta-analysis with fixed effect (inverse variance).

CI: confidence interval; EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; n_E: number of events; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; vs.: versus

Confirmed relapses (EDSS-based)

For the outcome "confirmed relapses", an interaction by the characteristic "sex" was shown for the relevant subpopulation. For men, the meta-analysis showed a statistically significant difference between the treatment groups in favour of ozanimod. This resulted in proof of an added benefit of ozanimod in comparison with IFN-β1a for men.

For women, the meta-analysis showed no statistically significant difference between the treatment groups; an added benefit for women is therefore not proven.

For the subgroup analyses, the company only presented the effect estimations per subgroup and study and the result of the meta-analysis in Module 4 A. There is no information on the individual treatment arms. For the outcome "confirmed relapses", data on the number of events,

the proportion of patients with (at least one) event and the annualized relapse rate are missing, in particular for the treatment arms (see Table 24). With the available data, it is therefore not possible to estimate how many patients in the respective subgroup had relapses. The assessment of the added benefit for this outcome was therefore conducted exclusively based on the effect estimations. The uncertainty caused by the missing data was considered in the evaluation of the extent (see Table 25).

The assessment deviates from that of the company. The company presented the results of the subgroup analyses of the studies, but did not use them for the derivation of an added benefit.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 25).

Determination of the outcome category for the outcome “confirmed relapses”

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

In the studies RADIANCE B and SUNBEAM, confirmed relapses were recorded using the EDSS and the respective functional systems. The supplementary presentation of the relapse rates by severity grade in Table 21 shows that more than half of the relapses were serious. A serious relapse according to information provided by the company requires hospitalization. Therefore, this outcome was assigned to the outcome category of serious/severe symptoms/late complications.

This concurs with the company’s assessment.

Table 25: Extent of added benefit at outcome level: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ozanimod vs. IFN-β1a** **Median time to event (months) or proportion of events (%) or mean change at month 12 or annualized relapse rate** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
Confirmed relapses Sex		
Men	Rate: ND rate ratio: 0.14 [0.04; 0.48]; p = ND probability: "proof"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk: ND added benefit, extent: "non-quantifiable", at least "considerable"[c]
Women	Rate: ND rate ratio: 0.60 [0.35; 1.02]; p = ND	Lesser benefit/added benefit not proven
Confirmed disability progression	Median: NA vs. NA HR: 4.55 [0.84; 24.63]; p = ND	Lesser benefit/added benefit not proven
Disability severity MSFC z-score	Change: −0.01–0.08 vs. −0.10–0.07[d] MD: 0.03 [−0.08; 0.14]; p = 0.602	Lesser benefit/added benefit not proven
Visual acuity LCLA	Change: 0.4–0.9 vs. −1.5–0.6[d] MD: 1.08 [−0.57; 2.72]; p = 0.200	Lesser benefit/added benefit not proven
Fatigue	Outcome not recorded	Lesser benefit/added benefit not proven
Health-related quality of life		
MSQoL-54		
PHCS	Change: −1.0–1.6 vs. −2.7–0.7 MD: 1.44 [−1.53; 4.40]; p = 0.343	Lesser benefit/added benefit not proven
MHCS	Change: −1.4 to −0.5 vs. −5.9 to −0.5[d] MD: 2.16 [−1.33; 5.65]; p = 0.225	Lesser benefit/added benefit not proven

Table 25: Extent of added benefit at outcome level: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ozanimod vs. IFN-β1a** **Median time to event (months) or proportion of events (%) or mean change at month 12 or annualized relapse rate** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	0–6.8% vs. 1.7–3.6%[d] RR: 1.28 [0.30; 5.37]; p = ND	Greater/lesser harm not proven
Discontinuation due to AEs	0–6.8% vs. 3.3–7.1%[d] RR: 0.69 [0.20; 2.42]; p = ND	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Due to missing information on the proportion of patients with (at least one) event and on the annualized relapse rate per treatment arm, the extent is non-quantifiable.
d. Minimum and maximum proportions of events or change at month 12 or annualized rate per treatment arm in the studies included.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; HR: hazard ratio; IFN-β: interferon beta; LCLA: low-contrast letter acuity; MD: mean difference; MHCS: mental health composite score; MSFC: Multiple Sclerosis Functional Composite; MSQoL-54: Multiple Sclerosis Quality of Life-54; NA: not achieved; ND: no data; PHCS: physical health composite score; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SMD: standardized mean difference; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 26 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 26: Positive and negative effects from the assessment of ozanimod in comparison with IFN-β1a (pretreated patients with highly active RRMS)

Positive effects	**Negative effects**
Morbidity: serious/severe symptoms/late complications ▪ Confirmed relapses ▫ Sex (men) proof of added benefit – extent: "non-quantifiable", at least "considerable"	–
There are no usable results on specific AEs.	
AE: adverse event; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis	

In the overall consideration, there is only one positive effect in the category of serious/severe symptoms or late complications for the subgroup of men. Due to the effect modification by sex, the added benefit is derived separately for women and men.

For pretreated men with highly active RRMS, there is proof of a non-quantifiable added benefit of ozanimod in comparison with IFN-β1a of at least considerable extent for the outcome "confirmed relapses". The extent is "non-quantifiable" because Module 4 A of the company provides no information on the proportion of patients with (at least one) event and on the annualized relapse rate per treatment arm (see Section 2.3.2.4).

For women, there are neither positive nor negative effects in the overall consideration; an added benefit of ozanimod for pretreated women with highly active RRMS is therefore not proven.

The assessment described above deviates from that of the company. The company did not use subgroup data for the derivation of an added benefit and derived proof of considerable added benefit of ozanimod on the basis of the outcome "confirmed relapses" for the entire relevant subpopulation.

2.5 Probability and extent of added benefit – summary

Table 27 summarizes the result of the assessment of the added benefit of ozanimod in comparison with the ACT.

Table 27: Ozanimod – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with RRMS who have not yet received disease-modifying therapy or adult patients with RRMS with non-highly active disease pretreated with disease-modifying therapy[b]	**Interferon beta-1a** or interferon beta-1b or glatiramer acetate or ocrelizumab under consideration of the approval	Proof of considerable added benefit
Adult patients with RRMS with highly active disease despite treatment with a disease-modifying therapy[b]	Alemtuzumab or fingolimod or natalizumab or, if indicated, change within the basic therapeutic agents (**interferon beta-1a** or interferon beta-1b or glatiramer acetate under consideration of the approval)	▪ Men: proof of non-quantifiable[c] added benefit, at least "considerable" ▪ Women: 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 specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. Appropriate (pre)treatment usually comprises at least 6 months. Depending on frequency and severity of the relapses as well as on disability progression, treatment with a disease-modifying therapy can be less than 6 months and has to be justified.
c. Due to missing information on the proportion of patients with (at least one) event and on the annualized relapse rate per treatment arm, the extent is non-quantifiable.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RRMS: relapsing remitting multiple sclerosis

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

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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