IQWiG Reports – Commission No. A20-96

Ozanimod (multiple sclerosis) –

Addendum to Commission A20-59[1]

Addendum

Commission: A20-96
Version: 1.0
Status: 10 December 2020

[1] Translation of addendum A20-96 *Ozanimod (multiple Sklerose) – Addendum zum Auftrag A20-59* (Version 1.0; Status: 10 December 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Ozanimod (multiple sclerosis) – Addendum to Commission A20-59

Commissioning agency
Federal Joint Committee

Commission awarded on
24 November 2020

Internal Commission No.
A20-96

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Bernhard Liebenhoff
- Klaus Gossens
- Matthias Maiworm
- Volker Vervölgyi

Keywords: Ozanimod, Multiple Sclerosis – Relapsing-Remitting, Benefit Assessment, NCT02047734, NCT02294058

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
EDSS	Expanded Disability Status Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IFN	interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SOC	System Organ Class

1 Background

On 24 November 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-59 (Ozanimod – Benefit assessment according to §35a Social Code Book V) [1].

The pharmaceutical company (hereinafter referred to as the "company") presented the randomized controlled trials (RCTs) RADIANCE B and SUNBEAM for the benefit assessment of ozanimod in adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features. Both studies were included and pooled in a meta-analysis for both research questions of the benefit assessment (treatment-naive patients and pretreated patients with non-highly active RRMS [research question 1]; pretreated patients with highly active RRMS [research question 2]). Both studies compared ozanimod with interferon (IFN)-β1a.

In dossier assessment A20-59, a meaningful choice of specific adverse events (AEs) for both research questions was not possible, as the company's dossier did not provide complete presentations of the individual results for 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, and information on month 24 (RADIANCE B) or end of treatment (SUNBEAM) was missing [2,3]. Furthermore, the company's dossier did not contain information on the annualized relapse rate and the proportion of patients with (at least) one event in the subgroup analyses for the characteristic of sex for the outcome "confirmed relapses" (Expanded Disability Status Scale [EDSS]-based] for research question 2.

In its comments of 5 November 2019, the company subsequently submitted the analyses on side effects according to the criteria of the dossier template for both research questions, as well as the missing information on the subgroup analyses for research question 2 [4].

The G-BA commissioned IQWiG with the assessment of the following additional data submitted by the company under consideration of the information provided in the dossier:

- assessment of the analyses subsequently submitted on the specific AEs for research questions 1 and 2
- assessment of the data subsequently submitted on the outcome "confirmed relapses" (EDSS-based) with regard to the effect modification by the characteristic of sex (research question 2)

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

2 Assessment

The aspects commissioned by the G-BA are assessed in the following sections. The assessment is divided as follows:

- Section 2.1: assessment of the data on specific AEs subsequently submitted for research question 1 (treatment-naive patients and pretreated patients with non-highly active RRMS)
- Section 2.2: assessment of the data on specific AEs and on the subgroup analysis for the outcome "confirmed relapses" (EDSS) subsequently submitted for research question 2 (pretreated patients with highly active RRMS)
- Section 2.3 summarizes the result of the benefit assessment of ozanimod under consideration of dossier assessment A20-59 and the present addendum.

2.1 Research question 1: treatment-naive patients and pretreated patients with non-highly active RRMS

2.1.1 Assessment of the subsequently submitted data on specific AEs

The company's 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. In its comments, the company subsequently submitted analyses on side effects that meet the requirements in the dossier template.

A list of the individual events according to SOC and PT for the AEs can be found for month 12 in Appendix A.2, and for month 24 (RADIANCE B study) and end of treatment (SUNBEAM study) in Appendix A.2.2. For the outcome "serious adverse events (SAEs)", no SOC or PT met the frequency criteria for presentation. The company did not provide a separate presentation of discontinuations due to AEs by research question, study and date of analysis (a presentation of the results at month 12 pooled across the studies can be found in Module 4 A, Section 4.3.1.3.1.10).

Specific AEs were chosen according to the procedure in the dossier assessment based on the results at month 12. For this purpose, on the one hand, the outcomes were selected on the basis of the events that had occurred in the studies, based on the frequency and the differences between the treatment arms and under consideration of the patient relevance. On the other, specific AEs of particular importance for the disease or for the drugs used in the study could be chosen. Based on the described procedure, the following specific AEs were used:

- infections and infestations (SOC, AEs)
- psychiatric disorders (SOC, AEs)

- influenza like illness (PT, AEs)
- bradycardia (PT, AEs)

The risk of bias for the results of the outcomes for which usable data were available was rated as low. At most proof, e.g. of an added benefit, can therefore be determined.

The results for the specific AEs at month 12 identified for research question 1 are presented in Table 1. The company did not present any p-values for the meta-analysis of the studies RADIANCE B and SUNBEAM. Therefore, the statistical significance was determined on the basis of the 95% confidence intervals (CIs). Statistical significance is considered to be achieved if the 95% CI does not cover the zero effect.

Table 1: Results (side effects) – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive 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]
Side effects					
Infections and infestations (SOC, AEs)					
RADIANCE B	371	108 (29.1)	366	121 (33.1)	0.88 [0.71; 1.09]; 0.247
SUNBEAM	383	100 (26.1)	358	77 (21.5)	1.21 [0.94; 1.57]; 0.142
Total[b]					1.01 [0.86; 1.19]; ND
Psychiatric disorders (SOC, AEs)					
RADIANCE B	371	29 (7.8)	366	28 (7.6)	1.02 [0.62; 1.68]; 0.933
SUNBEAM	383	23 (6.0)	358	21 (5.9)	1.02 [0.58; 1.82]; 0.936
Total[b]					1.02 [0.70; 1.49]; ND
Influenza like illness (PT, AEs)					
RADIANCE B	371	21 (5.7)	366	191 (52.2)	0.11 [0.07; 0.17]; < 0.001
SUNBEAM	383	16 (4.2)	358	188 (52.5)	0.08 [0.05; 0.13]; < 0.001
Total[b]					0.09 [0.07; 0.13]; ND
Bradycardia (PT, AEs)					
RADIANCE B	371	ND[c]	366	ND[c]	ND[c]
SUNBEAM	383	ND	358	ND	ND
Total					ND

a. p-value: Cochran-Mantel-Haenszel test.
b. Meta-analysis with fixed effect (inverse variance).
c. The RADIANCE B study did not show a statistically significant difference between the treatment arms for the superordinate SOC "cardiac disorders" (12 [3.2%] patients in the ozanimod arm vs. 9 [2.5%] patients in the IFN arm).

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; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SOC: serious adverse event; vs.: versus

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "infections and infestations" (SOC, AEs) and "psychiatric disorders" (SOC, AEs). This resulted in no hint of greater or lesser harm from ozanimod in comparison with IFN-β1a, greater or lesser harm for these outcomes is therefore not proven.

The meta-analysis showed a statistically significant difference in favour of ozanimod for the outcome "influenza like illness" (PT, AEs). This resulted in proof of lesser harm from ozanimod in comparison with IFN-β1a.

The company did not provide any data for the outcome "bradycardia" (PT, AEs) because the number of events for this outcome did not meet the frequency criteria for presentation. This resulted in no hint of greater or lesser harm from ozanimod in comparison with IFN-β1a, greater or lesser harm for this outcome is therefore not proven.

2.1.2 Subgroup analyses and other effect modifications

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

2.1.3 Overall conclusion on added benefit

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit for research question 1 from dossier assessment A20-59.

The following table summarizes the results considered in the overall conclusion on the extent of added benefit for research question 1.

Table 2: 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" Non-serious/non-severe side effects ▪ Influenza like illness: proof of lesser harm – extent: "considerable"	–
IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis	

The assessment of the data subsequently submitted resulted in proof of a lesser harm of considerable extent for the outcome "influenza like illness" (PT, AEs).

Overall, the data subsequently submitted did not change the result of the overall conclusion on the added benefit on subpopulation 1 from dossier assessment A20-59 [1].

In summary, there is therefore proof of considerable added benefit of ozanimod in comparison with the appropriate comparator therapy IFN-β1a for treatment-naive patients and for pretreated patients with non-highly active RRMS (see Table 6).

2.2 Research question 2: pretreated patients with highly active RRMS

It became clear from the comments and the oral hearing on the benefit assessment of ozanimod that, in the present research question, a change within the basic therapy is not equivalent to an escalation therapy [5]. Furthermore, it became clear that a change within the basic therapy is only an option under certain individual conditions. However, there is no conclusive definition

of the individual criteria on which the decision-making process as to whether escalation therapy or a change within the basic therapy is an option can be based, and these criteria are the subject of current scientific debate. The present addendum takes this situation into account by deriving the added benefit separately according to whether escalation therapy or a change within the basic therapy is an option for the patients. The results from the 2 studies RADIANCE B and SUNBEAM presented by the company for research question 2 therefore only allow conclusions to be drawn about those patients for whom a change within the basic therapy is an option.

2.2.1 Assessment of the subsequently submitted data on specific AEs

The processing of the subsequently submitted data for the choice of specific AEs corresponds to that for research question 1 (see Section 2.1.1). Based on the described procedure, the same specific AEs were identified as for research question 1 (see Section 2.1.1). A low risk of bias was also derived for the results of these outcomes, for which usable results were available. At most proof, e.g. of an added benefit, can therefore be determined.

A list of the individual events according to SOC and PT for the AEs that met the frequency criteria can be found for month 12 in Appendix A.3.1, and for month 24 (RADIANCE B study) and end of treatment (SUNBEAM study) in Appendix A.3.2. For the outcome “SAEs”, no SOC or PT met the frequency criteria for presentation. The company did not provide a separate presentation of discontinuations due to AEs by research question, study and date of analysis (a presentation of the results at month 12 pooled across the studies can be found in Module 4 A, Section 4.3.1.3.1.10).

The results for the specific AEs at month 12 identified for research question 2 are presented in Table 3. Due to missing p-values, 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.

Table 3: Results (side effects) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option), 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-βa RR [95% CI]; p-value[a]
Side effects					
Infections and infestations (SOC, AEs)					
RADIANCE B	47	14 (29.8)	56	13 (23.2)	1.28 [0.67; 2.45]; 0.452
SUNBEAM	44	14 (31.8)	60	20 (33.3)	0.95 [0.54; 1.67]; 0.871
Total[b]					1.09 [0.71; 1.66]; ND
Psychiatric disorders (SOC, AEs)					
RADIANCE B	47	5 (10.6)	56	3 (5.4)	1.99 [0.50; 7.88]; 0.321
SUNBEAM	44	2 (4.5)	60	7 (11.7)	0.39 [0.08; 1.79]; 0.204
Total[b]					0.89 [0.35; 2.30]; ND
Influenza like illness (PT, AEs)					
RADIANCE B	47	3 (6.4)	56	15 (26.8)	0.24 [0.07; 0.77]; 0.007
SUNBEAM	44	0 (0.0)	60	27 (45.0)	0.02 [0.00; 0.39]; < 0.001
Total[b]					0.10 [0.04; 0.30]; ND
Bradycardia (PT, AEs)					–
RADIANCE B	47	ND	56	ND	ND
SUNBEAM	44	ND	60	ND	ND
Total					ND

a. p-value: Cochran-Mantel-Haenszel test.
b. 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; PT: Preferred Term; RR: relative risk; RRMS: relapsing remitting multiple sclerosis; SOC: serious adverse event; vs.: versus

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "infections and infestations" (SOC, AEs) and "psychiatric disorders" (SOC, AEs). This resulted in no hint of greater or lesser harm from ozanimod in comparison with IFN-β1a, greater or lesser harm for these outcomes is therefore not proven.

The meta-analysis showed a statistically significant difference in favour of ozanimod for the outcome "influenza like illness" (PT, AEs). This resulted in proof of lesser harm from ozanimod in comparison with IFN-β1a.

The company did not provide any data for the outcome "bradycardia" (PT, AEs) because the number of events for this outcome did not meet the frequency criteria for presentation. This

resulted in no hint of greater or lesser harm from ozanimod in comparison with IFN-β1a, greater or lesser harm for this outcome is therefore not proven.

2.2.2 Subgroup analyses and other effect modifications

Outcomes on specific AEs

In accordance with the methods described in the dossier assessment, no relevant effect modification by age or sex was identified for the outcomes on specific AEs for which usable analyses were available and which were assessed in the present addendum.

Confirmed relapses (EDSS-based)

An effect modification by the characteristic of sex was determined for the outcome "confirmed relapses" (EDSS-based). For the subgroup analyses, the company only presented the effect estimations per subgroup and study and the result of the meta-analysis in its dossier. Information on the relapse rate or number of events in the individual treatment arms of the respective subgroups was not available. The company subsequently submitted this information in its comments. The data of the subgroups on the outcome "confirmed relapses" of the subpopulation relevant for research question 2 are presented in Table 4.

Table 4: Subgroups (morbidity, confirmed relapses) – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option)

Outcome Characteristic	Ozanimod			IFN-β1a			Ozanimod vs. IFN-β1a
Study Subgroup	N	n_E[a]	Annualized relapse rate [95% CI][b]	N	n_E[a]	Annualized relapse rate [95% CI][b]	Rate ratio [95% CI]; p-value[b]
Morbidity							
Confirmed relapses (EDSS-based)							
Annualized relapse rate (total)							
Sex							
RADIANCE B							
Men	13	1	–[c]	16	16	–[c]	0.09 [0.01; 0.68]; 0.020
Women	34	13	0.22 [0.12; 0.39]	40	22	0.35 [0.21; 0.57]	0.62 [0.31; 1.24]; 0.180
SUNBEAM							
Men	17	2	–[c]	19	13	–[c]	0.19 [0.04; 0.83]; 0.028
Women	27	8	0.19 [0.06; 0.60]	41	20	0.33 [0.12; 0.93]	0.56 [0.24; 1.30]; 0.179
Total						Interaction:	p-value = 0.034
Men							0.14 [0.04; 0.48][d]; ND
Women							0.60 [0.35; 1.02][d]; ND

a. According to the company, number of patients with (at least) one event. Since in the relevant subpopulation for research question 2, 14 relapses occurred in the ozanimod arm and 38 relapses in the control arm of the RADIANCE B study, and 10 relapses occurred in the ozanimod arm and 33 relapses in the control arm of the SUNBEAM study, it is assumed that each patient with event had exactly one relapse during the studies.
b. Annualized relapse rate and CI (per treatment arm) as well as rate ratio with CI (group comparison): negative binomial model.
c. No presentation of the annualized relapse rate, as the information provided by the company is not plausible in comparison with the events that occurred. Information provided by the company for men in the RADIANCE B study (ozanimod vs. IFN-β1a, annualized relapse rate [95% CI]): 0.00 [0.00; 3.17 x 10^{210}] vs. 0.00 [0.00; 3.52 x 10^{211}], and for men in the SUNBEAM study: 0.00 [0.00; 6.611 x 10^{46}] vs. 0.01 [0.00; 3.571x 10^{47}].
d. 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

Regarding confirmed relapses (EDSS-based), the meta-analysis showed a statistically significant advantage of ozanimod in comparison with the appropriate comparator therapy for men. This resulted in proof of an added benefit of ozanimod in comparison with IFN-β1a.

For women, the meta-analysis showed no statistically significant difference between the treatment arms for the outcome "confirmed relapses" (EDSS-based). This resulted in no hint of an added benefit of ozanimod in comparison with IFN-β1a for women; an added benefit is therefore not proven.

2.2.3 Overall conclusion on added benefit

Table 5 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 5: Positive and negative effects from the assessment of ozanimod in comparison with IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option)

Positive effects	**Negative effects**
Morbidity: serious/severe symptoms/late complications ▪ Confirmed relapses (EDSS-based) ▫ Sex (men): proof of added benefit – extent: "major" Non-serious/non-severe side effects ▪ Influenza like illness: proof of lesser harm – extent: "considerable"	–
No data are available for pretreated patients with highly active RRMS for whom escalation therapy is an option.	
EDSS: Expanded Disability Status Scale; IFN-β: interferon beta; RRMS: relapsing remitting multiple sclerosis	

Due to the effect modification by the characteristic of sex for the outcome "confirmed relapses" (EDSS-based), the added benefit was derived separately for women and men.

Men

In the outcome category of serious/severe symptoms, there was proof of an added benefit of major extent for the outcome "confirmed relapses" (EDSS-based). Furthermore, there was proof of an added benefit of considerable extent in the category of non-serious/non-severe side effects regarding the specific AEs "influenza like illness" (PT, AEs). Overall, this resulted in proof of a major added benefit for men.

Women

In women, there was neither a positive nor a negative effect for the outcome "confirmed relapses" (EDSS-based). However, there was proof of an added benefit of considerable extent in the category of non-serious/non-severe side effects regarding the specific AEs "influenza like illness" (PT, AEs). This resulted in proof of a considerable added benefit for women.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure as well as the findings from the comments and the hearing changed the conclusion on the added benefit of ozanimod from dossier assessment A20-59 for research question 2: For men, there is proof of a major added benefit of ozanimod in comparison with IFN-β1a. For women, there is proof of a considerable added benefit of ozanimod in comparison with IFN-β1a. For the research question 1, there is no change in comparison with dossier assessment A20-59.

The following Table 6 shows the result of the benefit assessment of ozanimod under consideration of dossier assessment A20-59 and the present addendum.

Table 6: Ozanimod – probability and extent of added benefit

<table>
<tr><th>Therapeutic indication</th><th>ACT[a]</th><th>Probability and extent of added benefit[b]</th></tr>
<tr><td>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[c]</td><td>Interferon beta-1a or interferon beta-1b or glatiramer acetate or ocrelizumab under consideration of the approval</td><td>Proof of considerable added benefit</td></tr>
<tr><td rowspan="2">Adult patients with RRMS with highly active disease despite treatment with a disease-modifying therapy[c]</td><td rowspan="2">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)</td><td>Patients for whom escalation therapy is an option:
added benefit not proven</td></tr>
<tr><td>▪ Patients for whom a change within the basic therapy is an option:
▪ Men: proof of major added benefit
▪ Women: proof of considerable added benefit</td></tr>
<tr><td colspan="3">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. Changes in comparison with dossier assessment A20-59 are printed in bold.
c. 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.</td></tr>
<tr><td colspan="3">ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RRMS: relapsing remitting multiple sclerosis</td></tr>
</table>

The G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ozanimod (multiple Sklerose): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 21.10.2020]. URL: https://www.iqwig.de/download/A20-59_Ozanimod_Nutzenbewertung-35a-SGB-V_V1_0.pdf.

2. Celgene. Ozanimod (Zeposia): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2020 [Accessed: 02.12.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/566/.

3. Gemeinsamer Bundesausschuss. Anlage II.6: Modul 4 – Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen; Dokumentvorlage, Version vom 21.02.2019 [online]. 2019 [Accessed: 08.12.2020]. URL: https://www.g-ba.de/downloads/17-98-4825/2019-02-21_Anl2_6_Modul4.pdf.

4. Celgene. Stellungnahme zum IQWiG-Bericht Nr. 980: Ozanimod (multiple Sklerose); Nutzenbewertungen gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/566/#beschluesse in the document "Zusammenfassende Dokumentation"].

5. Gemeinsamer Bundesausschuss. Zusammenfassende Dokumentation zum Nutzenbewertungsverfahren zum Wirkstoff Ozanimod (Schubförmig remittierende Multiple Sklerose). [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/566/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A – Results on side effects

The following tables present events for the MedDRA SOCs and PTs for the overall rates of AEs and SAEs on the basis of the following criteria:

- overall rate of AEs (irrespective of the severity grade): events that occurred in at least 10% of the patients in one study arm
- overall rates of SAEs: events that occurred in at least 5% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

For the outcome "discontinuation due to AEs", a complete presentation of all events (SOCs/PTs) that resulted in discontinuation was to be shown. However, the company did not provide a separate presentation of the discontinuations due to AEs by research question, study and date of analysis. Hence, there is no presentation of the outcome "discontinuation due to AEs" (a presentation of the results at month 12 pooled across the studies can be found in Module 4 A, Section 4.3.1.3.1.10).

A.1 – Research question 1: treatment-naive patients and pretreated patients with non-highly active RRMS

A.2 – Results for the 12-month data cut-off

A.2.1 – Results from the RADIANCE B study

Table 7: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–12 months, study RADIANCE B) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ozanimod** **N = 371**	**IFN-β1a** **N = 366**
RADIANCE B		
Overall AE rate	228 (61.5)	280 (76.5)
SOC		
General disorders and administration site conditions	48 (12.9)	220 (60.1)
Eye disorders	16 (4.3)	18 (4.9)
Respiratory, thoracic and mediastinal disorders	21 (5.7)	27 (7.4)
Reproductive system and breast disorders	15 (4.0)	11 (3.0)
Skin and subcutaneous tissue disorders	17 (4.6)	18 (4.9)
Blood and lymphatic system disorders	2 (0.5)	10 (2.7)
Gastrointestinal disorders	35 (9.4)	37 (10.1)
Nervous system disorders	55 (14.8)	64 (17.5)
Vascular disorders	33 (8.9)	28 (7.6)
Cardiac disorders	12 (3.2)	9 (2.5)
Infections and infestations	108 (29.1)	121 (33.1)
Psychiatric disorders	29 (7.8)	28 (7.6)
Musculoskeletal and connective tissue disorders	32 (8.6)	34 (9.3)
Investigations	50 (13.5)	29 (7.9)
Injury, poisoning and procedural complications	17 (4.6)	18 (4.9)

Table 7: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–12 months, study RADIANCE B) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ozanimod** **N = 371**	**IFN-β1a** **N = 366**
PT		
Alanine aminotransferase increased	18 (4.8)	12 (3.3)
Respiratory tract infection	4 (1.1)	12 (3.3)
Pyrexia	6 (1.6)	24 (6.6)
Gamma-glutamyltransferase increased	14 (3.8)	6 (1.6)
Influenza like illness	21 (5.7)	191 (52.2)
Urinary tract infection	11 (3.0)	11 (3.0)
Hypertension	12 (3.2)	9 (2.5)
Upper respiratory tract infection	16 (4.3)	17 (4.6)
Headache	27 (7.3)	38 (10.4)
Nasopharyngitis	45 (12.1)	35 (9.6)
Orthostatic hypotension	17 (4.6)	14 (3.8)
Abdominal pain upper	12 (3.2)	4 (1.1)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 18.1.

AE: adverse event; IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; vs.: versus

Table 8: Common SAEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–12 months, study RADIANCE B)

Study	**Patients with event n (%)**	
	Ozanimod **N = 371**	**IFN-β1a** **N = 366**
RADIANCE B		
Overall SAE rate[b]	15 (4.0)	12 (3.3)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

A.2.1.1 – Results from the SUNBEAM study

Table 9: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–12 months, study SUNBEAM) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ozanimod N = 383**	**IFN-β1a N = 358**
SUNBEAM		
Overall AE rate	215 (56.1)	263 (73.5)
SOC		
General disorders and administration site conditions	38 (9.9)	214 (59.8)
Eye disorders	11 (2.9)	17 (4.8)
Respiratory, thoracic and mediastinal disorders	12 (3.1)	8 (2.2)
Reproductive system and breast disorders	11 (2.9)	10 (2.8)
Skin and subcutaneous tissue disorders	10 (2.6)	13 (3.6)
Blood and lymphatic system disorders	11 (2.9)	12 (3.4)
Gastrointestinal disorders	27 (7.0)	17 (4.8)
Nervous system disorders	47 (12.3)	34 (9.5)
Vascular disorders	16 (4.2)	7 (2.0)
Infections and infestations	100 (26.1)	77 (21.5)
Psychiatric disorders	23 (6.0)	21 (5.9)
Musculoskeletal and connective tissue disorders	39 (10.2)	29 (8.1)
Metabolism and nutrition disorders	18 (4.7)	13 (3.6)
Injury, poisoning and procedural complications	10 (2.6)	12 (3.4)
Investigations	46 (12.0)	26 (7.3)

Table 9: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–12 months, study SUNBEAM) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Ozanimod N = 383**	**IFN-β1a N = 358**
PT		
Alanine aminotransferase increased	15 (3.9)	4 (1.1)
Pyrexia	5 (1.3)	25 (7.0)
Gamma-glutamyltransferase increased	12 (3.1)	2 (0.6)
Influenza like illness	16 (4.2)	188 (52.5)
Urinary tract infection	12 (3.1)	7 (2.0)
Headache	31 (8.1)	20 (5.6)
Nasopharyngitis	23 (6.0)	30 (8.4)
Back pain	13 (3.4)	6 (1.7)
Upper respiratory tract infection	15 (3.9)	14 (3.9)
Virus infection of the respiratory tract	12 (3.1)	3 (0.8)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 18.1.

AE: adverse event; IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; vs.: versus

Table 10: Common SAEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–12 months, study SUNBEAM)

Study	**Patients with event n (%)**	
	Ozanimod N = 383	**IFN-β1a N = 358**
SUNBEAM		
Overall SAE rate[b]	10 (2.6)	8 (2.2)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

A.2.2 – Results at the 24-month data cut-off (RADIANCE B) or end of treatment (SUNBEAM)

A.2.2.1 – Results from the RADIANCE B study

Table 11: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–24 months, study RADIANCE B) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ozanimod** **N = 371**	**IFN-β1a** **N = 366**
RADIANCE B		
Overall AE rate	278 (74.9)	304 (83.1)
SOC		
General disorders and administration site conditions	59 (15.9)	224 (61.2)
Eye disorders	25 (6.7)	27 (7.4)
Endocrine disorders	10 (2.7)	9 (2.5)
Respiratory, thoracic and mediastinal disorders	33 (8.9)	37 (10.1)
Reproductive system and breast disorders	22 (5.9)	22 (6.0)
Skin and subcutaneous tissue disorders	23 (6.2)	29 (7.9)
Blood and lymphatic system disorders	7 (1.9)	14 (3.8)
Gastrointestinal disorders	50 (13.5)	58 (15.8)
Nervous system disorders	79 (21.3)	81 (22.1)
Ear and labyrinth disorders	13 (3.5)	10 (2.7)
Vascular disorders	49 (13.2)	40 (10.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (2.7)	11 (3.0)
Cardiac disorders	16 (4.3)	11 (3.0)
Infections and infestations	152 (41.0)	161 (44.0)
Psychiatric disorders	36 (9.7)	39 (10.7)
Musculoskeletal and connective tissue disorders	48 (12.9)	49 (13.4)
Metabolism and nutrition disorders	16 (4.3)	15 (4.1)
Investigations	70 (18.9)	49 (13.4)
Injury, poisoning and procedural complications	31 (8.4)	33 (9.0)

Table 11: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–24 months, study RADIANCE B) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ozanimod** **N = 371**	**IFN-β1a** **N = 366**
PT		
Abdominal pain upper	13 (3.5)	6 (1.6)
Alanine aminotransferase increased	23 (6.2)	18 (4.9)
Arthralgia	11 (3.0)	3 (0.8)
Aspartate aminotransferase increased	8 (2.2)	11 (3.0)
Back pain	16 (4.3)	12 (3.3)
Bronchitis	12 (3.2)	10 (2.7)
Depression	9 (2.4)	12 (3.3)
Fatigue	11 (3.0)	10 (2.7)
Gamma-glutamyltransferase increased	23 (6.2)	8 (2.2)
Headache	39 (10.5)	49 (13.4)
Hypertension	18 (4.8)	13 (3.5)
Influenza like illness	22 (5.9)	192 (52.5)
Insomnia	11 (3.0)	13 (3.5)
Nasopharyngitis	60 (16.2)	43 (11.8)
Oropharyngeal pain	2 (0.5)	11 (3.0)
Orthostatic hypotension	23 (6.2)	24 (6.6)
Pain in extremity	8 (2.2)	10 (2.7)
Pharyngitis	16 (4.3)	15 (4.1)
Pyrexia	9 (2.4)	26 (7.1)
Respiratory tract infection	7 (1.9)	15 (4.1)
Sinusitis	8 (2.2)	15 (4.1)
Upper respiratory tract infection	27 (7.3)	31 (8.5)
Urinary tract infection	18 (4.8)	16 (4.4)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 18.1.

AE: adverse event; IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; vs.: versus

Table 12: Common SAEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0–24 months, study RADIANCE B)

Study	Patients with event n (%)	
	Ozanimod N = 371	IFN-β1a N = 366
RADIANCE B		
Overall SAE rate[b]	24 (6.5)	25 (6.8)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

A.2.2.2 – Results from the SUNBEAM study

Table 13: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0 until end of treatment, study SUNBEAM) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ozanimod** **N = 383**	**IFN-β1a** **N = 358**
SUNBEAM		
Overall AE rate	232 (60.6)	270 (75.4)
SOC		
General disorders and administration site conditions	39 (10.2)	214 (59.8)
Eye disorders	14 (3.7)	18 (5.0)
Respiratory, thoracic and mediastinal disorders	14 (3.7)	11 (3.1)
Reproductive system and breast disorders	15 (3.9)	12 (3.4)
Skin and subcutaneous tissue disorders	13 (3.4)	16 (4.5)
Blood and lymphatic system disorders	11 (2.9)	12 (3.4)
Gastrointestinal disorders	29 (7.6)	19 (5.3)
Nervous system disorders	49 (12.8)	34 (9.5)
Vascular disorders	16 (4.2)	7 (2.0)
Infections and infestations	107 (27.9)	89 (24.9)
Psychiatric disorders	25 (6.5)	24 (6.7)
Musculoskeletal and connective tissue disorders	40 (10.4)	32 (8.9)
Metabolism and nutrition disorders	20 (5.2)	14 (3.9)
Investigations	56 (14.6)	32 (8.9)
Injury, poisoning and procedural complications	12 (3.1)	13 (3.6)

Table 13: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0 until end of treatment, study SUNBEAM) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ozanimod** **N = 383**	**IFN-β1a** **N = 358**
PT		
Alanine aminotransferase increased	19 (5.0)	6 (1.7)
Back pain	14 (3.7)	8 (2.2)
Gamma-glutamyltransferase increased	15 (3.9)	2 (0.6)
Headache	32 (8.4)	20 (5.6)
Influenza like illness	16 (4.2)	188 (52.5)
Nasopharyngitis	25 (6.5)	32 (8.9)
Pharyngitis	10 (2.6)	3 (0.8)
Pyrexia	5 (1.3)	25 (7.0)
Virus infection of the respiratory tract	12 (3.1)	3 (0.8)
Upper respiratory tract infection	15 (3.9)	16 (4.5)
Urinary tract infection	15 (3.9)	9 (2.5)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 18.1.

AE: adverse event; IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; vs.: versus

Table 14: Common SAEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (treatment-naive patients and pretreated patients with non-highly active RRMS, period 0 until end of treatment, study SUNBEAM)

Study	**Patients with event n (%)**	
	Ozanimod **N = 383**	**IFN-β1a** **N = 358**
SUNBEAM		
Overall SAE rate[b]	10 (2.6)	10 (2.8)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

A.3 – Research question 2: pretreated patients with highly active RRMS for whom a change within the basic therapy is an option

A.3.1 – Results for the 12-month data cut-off

A.3.1.1 – Results from the RADIANCE B study

Table 15: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option, period 0–12 months, study RADIANCE B)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Ozanimod** **N = 47**	**IFN-β1a** **N = 56**
RADIANCE B		
Overall AE rate	29 (61.7)	42 (75.0)
SOC		
General disorders and administration site conditions	7 (14.9)	21 (37.5)
Skin and subcutaneous tissue disorders	5 (10.6)	4 (7.1)
Gastrointestinal disorders	7 (14.9)	4 (7.1)
Nervous system disorders	4 (8.5)	12 (21.4)
Vascular disorders	6 (12.8)	5 (8.9)
Infections and infestations	14 (29.8)	13 (23.2)
Psychiatric disorders	5 (10.6)	3 (5.4)
Musculoskeletal and connective tissue disorders	5 (10.6)	3 (5.4)
Investigations	7 (14.9)	5 (8.9)
PT		
Influenza like illness	3 (6.4)	15 (26.8)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 18.1.

AE: adverse event; IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; vs.: versus

Table 16: Common SAEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option, period 0–12 months, study RADIANCE B)

Study	Patients with event n (%)	
	Ozanimod N = 47	IFN-β1a N = 56
RADIANCE B		
Overall SAE rate[b]	0 (0)	2 (3.6)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

A.3.1.2 – Results from the SUNBEAM study

Table 17: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option, period 0–12 months, study SUNBEAM)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Ozanimod N = 44**	**IFN-β1a N = 60**
SUNBEAM		
Overall AE rate	24 (54.5)	46 (76.7)
SOC		
General disorders and administration site conditions	4 (9.1)	30 (50.0)
Gastrointestinal disorders	7 (15.9)	5 (8.3)
Nervous system disorders	4 (9.1)	7 (11.7)
Infections and infestations	14 (31.8)	20 (33.3)
Psychiatric disorders	2 (4.5)	7 (11.7)
Investigations	5 (11.4)	2 (3.3)
PT		
Influenza like illness	0 (0)	27 (45.0)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 18.1.

AE: adverse event; IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; vs.: versus

Table 18: Common SAEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option, period 0–12 months, study SUNBEAM)

Study	Patients with event n (%)	
	Ozanimod N = 44	IFN-β1a N = 60
SUNBEAM		
Overall SAE rate[b]	3 (6.8)	1 (1.7)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

A.3.2 – Results at the 24-month data cut-off (RADIANCE B) or end of treatment (SUNBEAM)

A.3.2.1 – Results from the RADIANCE B study

Table 19: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option, period 0–24 months, study RADIANCE B)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Ozanimod N = 47**	**IFN-β1a N = 56**
RADIANCE B		
Overall AE rate	33 (70.2)	48 (85.7)
SOC		
General disorders and administration site conditions	8 (17.0)	22 (39.3)
Skin and subcutaneous tissue disorders	7 (14.9)	6 (10.7)
Gastrointestinal disorders	9 (19.1)	7 (12.5)
Nervous system disorders	8 (17.0)	12 (21.4)
Vascular disorders	9 (19.1)	5 (8.9)
Infections and infestations	21 (44.7)	21 (37.5)
Psychiatric disorders	6 (12.8)	5 (8.9)
Musculoskeletal and connective tissue disorders	8 (17.0)	5 (8.9)
Investigations	9 (19.1)	7 (12.5)
PT		
Influenza like illness	3 (6.4)	15 (26.8)
Orthostatic hypotension	7 (14.9)	2 (3.6)
Upper respiratory tract infection	6 (12.8)	3 (5.4)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 18.1.

AE: adverse event; IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; vs.: versus

Table 20: Common SAEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option, period 0–24 months, study RADIANCE B)

Study	Patients with event n (%)	
	Ozanimod N = 47	IFN-β1a N = 56
RADIANCE B		
Overall SAE rate[b]	3 (6.4)	2 (3.6)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

A.3.2.2 – Results from the SUNBEAM study

Table 21: Common AEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option, period 0 until end of treatment, study SUNBEAM)

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Ozanimod N = 44**	**IFN-β1a N = 60**
SUNBEAM		
Overall AE rate	26 (59.1)	47 (78.3)
SOC		
General disorders and administration site conditions	5 (11.4)	30 (50.0)
Gastrointestinal disorders	7 (15.9)	7 (11.7)
Nervous system disorders	4 (9.1)	7 (11.7)
Infections and infestations	15 (34.1)	21 (35.0)
Psychiatric disorders	2 (4.5)	7 (11.7)
Investigations	7 (15.9)	2 (3.3)
PT		
Influenza like illness	0 (0)	27 (45.0)
Upper respiratory tract infection	3 (6.8)	6 (10.0)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 18.1.

AE: adverse event; IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SOC: System Organ Class; vs.: versus

Table 22: Common SAEs[a] – RCT, direct comparison: ozanimod vs. IFN-β1a (pretreated patients with highly active RRMS for whom a change within the basic therapy is an option, period 0 until end of treatment, study SUNBEAM)

Study	Patients with event n (%)	
	Ozanimod N = 44	IFN-β1a N = 60
SUNBEAM		
Overall SAE rate[b]	3 (6.8)	1 (1.7)

a. Events that occurred in ≥ 5% of the patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

IFN-β: interferon beta; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SAE: serious adverse event; SOC: System Organ Class; vs.: versus