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Siponimod (multiple sclerosis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Siponimod (multiple Sklerose) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 May 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.

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Table of contents

List of tables[2]

Page

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

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BICAMS	Brief International Cognitive Assessment for MS
BSC	best supportive care
BVMT-R	Brief Visuospatial Memory Test Revised
CSR	clinical study report
CYP2C9	cytochrome P450 2C9
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GCP	good clinical practice
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)
LCVA	low contrast visual acuity
MACFIMS	Minimal Assessment of Cognitive Function in MS
MMRM	mixed-effects model repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
MSWS-12	Multiple Sclerosis Walking Scale-12
PASAT	Paced Auditory Serial Addition Test
RCT	randomized controlled trial
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event
SDMT	Symbol Digit Modalities Test
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
SPMS	secondary progressive multiple sclerosis

Abbreviation	Meaning
T25-FW	Timed 25-Foot Walk
VAS	visual analogue scale

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 siponimod. 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 5 February 2020.

Research question

The aim of the present report is the assessment of the added benefit of siponimod in comparison with the appropriate comparator therapy (ACT) in adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

For the present benefit assessment of siponimod, the research questions presented in Table 2 resulted from the ACTs specified by the GB-A.

Table 2: Research questions of the benefit assessment of siponimod

Research question	**Subindication**	**ACT[a]**
Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity		
1	With superimposed relapses	Interferon (IFN)-β1a or 1b or ocrelizumab
2	Without superimposed relapses	Best supportive care (BSC)[b]
a. Presentation of the respective ACT specified by the G-BA. b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IFN: interferon; SPMS: secondary progressive multiple sclerosis		

The company followed the G-BA's specification of the 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. Longer observation periods are generally recommended, especially for studies on multiple sclerosis (MS), which primarily investigate disability progression. The chosen minimum duration of 12 months corresponds to the inclusion criteria of the company.

Results on research question 1: patients with active SPMS with superimposed relapses

Since no relevant study was identified, there were no data for the assessment of the added benefit of siponimod versus interferon (IFN)-β1a or 1b or ocrelizumab for the treatment of adult patients with active SPMS with superimposed relapses. Hence, there was no hint of an added benefit of siponimod in comparison with the ACT; an added benefit is therefore not proven.

Results on research question 2: patients with active SPMS without superimposed relapses

The EXPAND study was included in the benefit assessment for research question 2.

Study design

The EXPAND study is a randomized, double-blind, placebo-controlled multicentre study. The study consists of a randomized study phase and an optional extension phase. Only the randomized study phase is relevant for the present benefit assessment.

The study included adult SPMS patients from 18 to 60 years of age who had an Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5.

Overall, 1651 patients were randomly allocated in a 2:1 ratio either to treatment with siponimod (N = 1105) or to placebo (N = 546). All patients received supportive treatments in the sense of best supportive care (BSC).

The randomized study phase had ended at the time point of the present data cut-off from 29 April 2016. The end of the randomized study phase was planned for the time point of about 3 years after randomization of the first patient, which resulted in different observation periods for the individual patients. The available observation periods were considered sufficient to fulfil the minimum study duration of 12 months defined for the present benefit assessment, as 87% of the patients of the relevant subpopulation were observed for at least 1 year.

The primary outcome of the study was the 3-month confirmed disability progression (measured by the EDSS); secondary outcomes included 6-month confirmed disability progression, relapses, and recording of adverse events (AEs).

Patients with disability progression, confirmed over a period of at least 6 months, had the option to continue the blinded treatment with the study medication, or discontinue it and choose treatment with siponimod or another MS therapy. After the randomized study phase, the patients also had the option to participate in an extension phase, in which all patients received open-label siponimod.

Subpopulation relevant for research question 2

According to the Summary of Product Characteristics (SPC), the therapeutic indication of siponimod comprises treatment of adult patients with SPMS with active disease evidenced by

relapses or imaging features of inflammatory activity. Due to the specification of the ACT, research question 2 only includes patients without superimposed relapses.

The EXPAND study relevant for the benefit assessment included patients irrespective of whether or not they had active disease. The subpopulation that met the following criteria was used for the present benefit assessment:

- no clinical relapse in the 2 years before study inclusion, but
- imaging features of activity (magnetic resonance imaging [MRI] in the form of contrast agent (gadolinium[Gd])-enhancing lesions.

Thus, the relevant subpopulation for research question 2 comprised 128 (11.6%) patients in the siponimod + BSC arm and 61 (11.2%) patients in the placebo + BSC arm of the total population of the EXPAND study.

Approximately 3 quarters of these 189 patients had received MS therapy modifying the course of the disease before the start of the study. Since this disease-modifying MS therapy was not allowed during the study, relapses occurring during the course of the study could be relapses that had been successfully suppressed by previous MS therapy. This was taken into account in the interpretation of the result.

Risk of bias

The risk of bias at study level was rated as low.

Except for the outcome "all-cause mortality", the risk of bias for the results of all other outcomes for which usable results were available was rated as high.

Mortality

All-cause mortality

There were no event time analyses for the outcome "all-cause mortality". Due to the small proportions of events (one patient died in each of both treatment arms), a statistically significant difference can be ruled out in the present situation. This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

Morbidity

Confirmed disability progression (EDSS-based)

No statistically significant difference between both treatment arms was shown for the outcome "confirmed disability progression" (EDSS-based, confirmed over a period of at least 6 months). This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

Confirmed relapses (EDSS-based)

The annualized relapse rate was considered to be the decisive operationalization for the outcome "confirmed relapses" (EDSS-based). Here, a statistically significant difference in favour of siponimod + BSC in comparison with placebo + BSC was shown between the 2 treatment arms. A statistically significant advantage of siponimod + BSC was also shown for the operationalization of the time to first confirmed relapse presented as supplementary information. Overall, an effect in favour of siponimod + BSC can be derived from this.

However, about 3 quarters of the patients received MS therapy modifying the course of the disease before the start of the study, and it is unclear at what time before the start of the study this therapy was discontinued. A subgroup analysis of this characteristic suggests that the relapses observed in the course of the study were relapses that had been successfully suppressed by previous MS therapy. Overall, the results on the outcome "confirmed relapses" from the EXPAND study cannot be interpreted as an advantage of siponimod. On the basis of the available data, there was overall no hint of an added benefit of siponimod + BSC in comparison with BSC for the outcome "confirmed relapses"; an added benefit is therefore not proven.

Disability severity (Multiple Sclerosis Functional Composite [MSFC]), visual acuity (low contrast visual acuity [LCVA]), walking ability (Multiple Sclerosis Walking Scale-12 [MSWS-12]), physical functioning (Multiple Sclerosis Impact Scale-29 [MSIS-29]) and psychological functioning (MSIS-29)

There was no statistically significant difference between both treatment arms for these outcomes. This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for any of these outcomes; an added benefit is therefore not proven.

Cognitive functioning (recorded using the Symbol Digit Modalities Test [SDMT] as well as Brief Visuospatial Memory Test Revised [BVMT-R]) and health status (recording using the visual analogue scale [VAS] of the European Quality of Life-5 Dimensions [EQ-5D] questionnaire)

No usable analyses were available for these outcomes, since the company did not present the corrected analyses after detecting a programming error. For each of these outcomes, this resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC; an added benefit is therefore not proven.

Fatigue

The outcome "fatigue" was not recorded in the EXPAND study.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the EXPAND study.

Side effects

Serious adverse events (SAEs), discontinuation due to AEs, infections, bradycardia

There were no usable analyses for the outcomes of the category of side effects, as the analyses presented by the company did not comprise the entire documentation period, but only the period of blinded treatment. This resulted in no hint of greater or lesser harm from siponimod + BSC in comparison with BSC for any of these outcomes; greater or lesser harm is therefore not proven.

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 siponimod in comparison with the ACT are assessed as follows:

Research question 1: active SPMS with superimposed relapses

In its dossier, the company presented no data for the assessment of the added benefit of siponimod versus IFN-β1a or 1b or ocrelizumab for the treatment of adult patients with active SPMS with superimposed relapses. An added benefit of siponimod is therefore not proven for these patients.

Research question 2: active SPMS without superimposed relapses

An advantage of siponimod versus BSC was shown for confirmed relapses. The company did not present analyses on the severity grade of the relapses. As no advantage or disadvantage of siponimod versus BSC was shown for the outcomes on disability progression and disability severity, it cannot be assumed per se that the majority of relapses were severe. In addition, subgroup analyses on the characteristic "prior MS therapy modifying the course of disease" suggest that the relapses observed in the course of the study were relapses that had been successfully suppressed by previous MS therapy.

The analyses presented by the company on the outcomes of the category of side effects were not usable, as they did not comprise the entire documentation period and were therefore incomplete with regard to content. Data on further key outcomes, such as health-related quality of life or fatigue, were also not available.

[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].

In summary, the data presented provided no hint of an added benefit of siponimod in comparison with the ACT BSC for adult patients with active SPMS without superimposed relapses.

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

Table 3: Siponimod – probability and extent of added benefit

Research question	**Subindication**	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity			
1	With superimposed relapses	Interferon (IFN)-β1a or 1b or ocrelizumab	Added benefit not proven
2	Without superimposed relapses	Best supportive care (BSC)[b]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IFN: interferon; SPMS: secondary progressive 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 the assessment of the added benefit of siponimod in comparison with the ACT in adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity.

For the present benefit assessment of siponimod, the research questions presented in Table 4 resulted from the ACTs specified by the GB-A.

Table 4: Research questions of the benefit assessment of siponimod

Research question	**Subindication**	**ACT**[a]
Adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity		
1	With superimposed relapses	Interferon (IFN)-β1a or 1b or ocrelizumab
2	Without superimposed relapses	Best supportive care (BSC)[b]

a. Presentation of the respective ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IFN: interferon; SPMS: secondary progressive multiple sclerosis

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

- Research question 1: active SPMS with superimposed relapses (referred to by the company as “subpopulation A”)
- Research question 2: active SPMS without superimposed relapses (referred to by the company as “subpopulation B”)

The company followed the G-BA’s specification of the 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. Longer observation periods are generally recommended, especially for studies on MS, which primarily investigate disability progression [3,4].

The chosen minimum duration of 12 months corresponds to the inclusion criteria of the company.

2.3 Research question 1: active SPMS with superimposed relapses

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 siponimod (status: 1 December 2019)
- bibliographical literature search on siponimod (last search on 18 November 2019)
- search in trial registries/trial results databases for studies on siponimod (last search on 25 November 2019)
- search on the GB-A website for siponimod (last search on 25 November 2019)

To check the completeness of the study pool:

- search in trial registries for studies on siponimod (last search on 13 February 2020)

No relevant study was identified from the check.

The company also identified no relevant study for this research question.

2.3.2 Results on added benefit

There were no data for the assessment of the added benefit of siponimod versus IFN-β1a or 1b or ocrelizumab for the treatment of adult patients with active SPMS with superimposed relapses. Hence, there was no hint of an added benefit of siponimod in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

In its dossier, the company presented no data for the assessment of the added benefit of siponimod versus IFN-β1a or 1b or ocrelizumab for the treatment of adult patients with active SPMS with superimposed relapses. An added benefit of siponimod is therefore not proven for these patients.

This concurs with the company’s assessment.

2.4 Research question 2: active SPMS without superimposed relapses

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 siponimod (status: 1 December 2019)
- bibliographical literature search on siponimod (last search on 18 November 2019)
- search in trial registries/trial results databases for studies on siponimod (last search on 25 November 2019)
- search on the GB-A website for siponimod (last search on 25 November 2019)

To check the completeness of the study pool:

- search in trial registries for siponimod (last search on 13 February 2020)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

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 and other sources[c] (yes/no [citation])
CBAF312A2304 (EXPAND[d])	Yes	Yes	No	Yes [5-8]	Yes [9-12]	Yes [13]

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. Other sources: documents from the search on the G-BA website.
d. In the following tables, the study is referred to with this abbreviated form.

BSC: best supportive care; CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial; vs.: versus

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EXPAND	RCT, double-blind, parallel	Adults[b] (18–60 years) with SPMS[c] ▪ EDSS 3.0–6.5 ▪ documented progression in the EDSS[d] in the last 2 years ▪ no relapse or corticosteroid treatment within 3 months prior to randomization	Siponimod + BSC (N = 1105) placebo + BSC (N = 546) Relevant subpopulation thereof[e]: siponimod + BSC (n = 128) placebo + BSC (n = 61)	Screening: ≤ 45 days Treatment: until disability progression (EDSS)[f], withdrawal of consent, loss to follow-up, or end of study Observation: until withdrawal of consent, loss to follow-up, or end of study[g]	294 study centres in Argentina, Australia, Austria, Belgium, Bulgaria, Canada, China, Czech Republic, Estonia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, United Kingdom, USA 12/2012–04/2016[h]	Primary: disability progression (EDSS) Secondary: morbidity, 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. Each patient's CYP2C9 genotype was determined at screening. Patients with CYP2C9*3*3 genotype could not participate in the study.
c. Defined by ≥ 6 month disability progression in the absence of relapses or independent of relapses. In addition, the patients had to have a prior history of RRMS according to the 2010 Revised McDonald criteria [14].
d. ≥ 1 point for patients with EDSS < 6.0 at baseline, ≥ 0.5 point for patients with EDSS ≥ 6.0 at baseline; if documented progression in the EDSS was not available, retrospective assessment of disease progression was to be submitted for central review.
e. Patients without relapses in the last 2 years, but with ≥ 1 Gd-enhancing lesion at baseline.
f. During the course of the study, patients with disability progression, confirmed over a period of at least 6 months, had the option to continue the blinded treatment, or to discontinue the blinded treatment and, with continued blinding regarding the medication already received, start open-label siponimod treatment or another MS therapy. Patients who decided to have treatment with another MS therapy continued the study on an abbreviated visit schedule with the following examinations being no longer performed: ECG, ophthalmological examination, lung function tests, dermatological examination, HRCT, sampling for pharmacokinetic investigation.
g. Observation was independent from the administration of the blinded study medication, the start of open-label siponimod treatment or another MS therapy until the end of the randomized study phase (core part). The end of the randomized study phase was defined as a time point of about 3 years after randomization of the first patient, since it was assumed that at this time point ≥ 374 patients had a disability progression confirmed after 3 months and more than 95% of the patients had participated in the study for ≥ 1 year. The patients then had the option to participate in an extension phase, in which all patients received open-label siponimod.
h. The information refers to the randomized study phase (core part).

AE: adverse event; BSC: best supportive care; CYP2C9: cytochrome P450 2C9; ECG: electrocardiogram; EDSS: Expanded Disability Status Scale; Gd: gadolinium; HRCT: high-resolution computed tomography; MS: multiple sclerosis; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

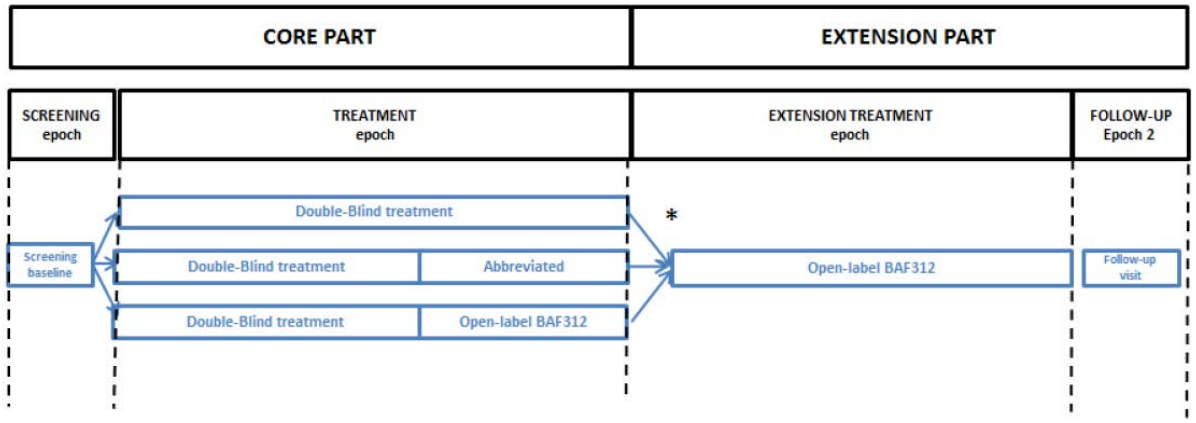
Study	Intervention	Comparison
EXPAND	Siponimod, orally, once daily ▪ initial titration phase: 0.25 mg to 2 mg for 6 days in the beginning of treatment ▪ maintenance dose: 2 mg[a]	Placebo for siponimod, orally, once daily ▪ initial titration phase: for 6 days in the beginning of treatment
	▪ single dose reduction to 1 mg/day, and interruption of treatment in case of persistent reduction in total blood lymphocyte count[b]	
	Non-permitted pretreatment: ▪ fingolimod within 2 months prior to randomization, or for > 6 months ▪ immunoglobulin IV or dimethyl fumarate within 2 months prior to randomization ▪ live or live-attenuated vaccines within 2 months prior to randomization ▪ natalizumab or immunosuppressive/chemotherapeutic medications within 6 months prior to randomization ▪ cyclophosphamide within 1 year prior to randomization ▪ rituximab, ofatumumab, ocrelizumab or cladribine within 2 years prior to randomization ▪ mitoxantrone during 2 years before start of the study or evidence of cardiotoxicity following mitoxantrone or a cumulative mitoxantrone dose of ≥ 60 mg/m^2 ▪ teriflunomide within 2 years prior to randomization (unless teriflunomide plasma concentration is zero or without relevant biological significance) or within 2 weeks prior to randomization following successful accelerated elimination procedure as described in the SPC ▪ alemtuzumab **Permitted concomitant treatment:** ▪ IV corticosteroids (up to 1000 mg/day methylprednisolone for 3-5 days) for the treatment of relapse ▪ therapies for symptom control ▪ fampridine for patients on a stable dose before start of the study **Non-permitted concomitant treatment:** ▪ immunosuppressive/chemotherapeutic medications ▪ immunomodulatory monoclonal antibodies (natalizumab, rituximab, ofatumumab, ocrelizumab and alemtuzumab) ▪ other immunomodulatory MS therapeutics or MS therapeutics modifying the course of disease ▪ live or live-attenuated vaccines up to 1 week after discontinuation of treatment with the study medication ▪ strong CYP2C9 inducers from 4 weeks before the initial dose of the study treatment	

a. The SPC recommends a maintenance dose of 1 mg for patients with CYP2C9*2*3 or *1*3 genotype. This was not mandated in the study.
b. In case of confirmed reduction of the total blood lymphocyte count < 0.2x10^9/L, the dose was reduced to 1 mg; if the reduction was persistent, treatment was interrupted; from a value of 0.6x10^9/L, a renewed administration of the reduced dose could be considered; in case of ≥ 4 day interruptions renewed titration should be performed.

BSC: best supportive care; CYP2C9: cytochrome P450 2C9; IV: intravenous; MS: multiple sclerosis; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; SPMS: secondary progressive multiple sclerosis; vs.: versus

Description of the study design

The EXPAND study is a randomized, double-blind, placebo-controlled multicentre study consisting of a randomized study phase and an optional extension phase (see Figure 1).



According to the protocol, patients with disability progression in the course of the study, confirmed over a period of at least 6 months, could continue the blinded treatment or discontinue the blinded treatment and start a therapy with siponimod (referred to as "BAF123" in the figure) or another MS therapy (referred to as "abbreviated" in the figure, as this meant that individual examinations were omitted in the study visits).

Figure 1: Design of the EXPAND study (figure from the clinical study report, adapted)

The study included adult SPMS patients from 18 to 60 years of age who had an EDSS score of 3.0 to 6.5. The patients had to have a prior history of relapsing remitting multiple sclerosis (RRMS) according to the 2010 Revised McDonald criteria [14]. Presence of SPMS was defined by disability progression over a period of at least 6 months in the absence of relapses or independent of relapses. In addition, patients had to have documented progression in the EDSS over a period of 2 years before the start of the study (≥ 1 point for patients with EDSS < 6.0 at baseline, ≥ 0.5 point for patients with EDSS ≥ 6.0 at baseline), and the patients were not allowed to have had relapse or corticosteroid treatment within 3 months prior to randomization. The cytochrome P450 2C9 (CYP2C9) genotype was determined for each patient at screening. In compliance with the recommendations of the SPC [15] patients with CYP2C9*3*3 genotype, which slows down the metabolism of siponimod, could not participate in the study.

Overall, 1651 patients were included in the study and randomly allocated in a 2:1 ratio either to treatment with siponimod (N = 1105) or to placebo (N = 546). Randomization was stratified by countries. The patients were treated in compliance with the regimen described in Table 7. Deviating from the recommendations in the SPC [15], which recommends a maintenance dose of 1 mg once daily for patients with CYP2C9*2*3 or *1*3 genotype, these patients also received 2 mg siponimod once daily in the study. According to the information provided in Module 4 A, this applies to about 14% of the subpopulation relevant for research question 2 (for the definition of this subpopulation, see the section on the subpopulation relevant for research question 2 below). The company did not provide information on the proportions in

each of the 2 treatment arms, however. All patients received supportive treatments in the sense of BSC (see the section on the implementation of the ACT below).

The primary outcome of the study was the 3-month confirmed disability progression, defined as a sustained increase in EDSS score from baseline of ≥ 1 point in patients with a baseline EDSS score of 3.0 to 5.0, or of ≥ 0.5 point in patients with a baseline EDSS score of 5.5 to 6.5. Secondary outcomes included disability progression, confirmed over a period of at least 6 months, relapses, and recording of AEs, among others. According to the study protocol patients with disability progression during the course of the study, confirmed over a period of at least 6 months, had the option to continue the blinded treatment, or to discontinue the blinded treatment and, with continued blinding regarding the medication already received, start treatment with siponimod (referred to as "BAF123" in Figure 1) or another MS therapy. Patients who decided to have treatment with another MS therapy continued the study on an abbreviated visit schedule (referred to as "abbreviated" in Figure 1), in which individual examinations, e.g. electrocardiogram (ECG) and lung function test, were no longer performed. Patients with more than 2 confirmed relapses or 1 confirmed severe relapse were informed about treatment options for relapsing forms of the disease and had to consent to further participation. An increase of ≥ 0.5 point on the EDSS score, or a change of 1 point in 2 different Functional Systems or of 2 points in 1 Functional System (except bowel/bladder or cerebral Functional System) was rated as confirmation. A relapse was rated as severe if it exceeded the criteria for a moderate relapse. The criteria for rating a relapse as moderate were as follows: increase of 1 to 2 points on the EDSS score, or change of 2 points in 1 or 2 Functional Systems, or change of 1 point in ≥ 4 Functional Systems.

The randomized study phase had ended at the time point of the present data cut-off from 29 April 2016. The end of the randomized study phase was planned for the time point of about 3 years after randomization of the first patient. This resulted in different observation periods for the individual patients, although for the majority of patients the end of the study was more than 1 year after randomization (see the section on observation and treatment duration below). After the randomized study phase, the patients had the option to participate in an extension phase, in which all patients received open-label siponimod (see Figure 1). The benefit assessment was based exclusively on data of the randomized study phase. This concurs with the company's approach.

Subpopulation relevant for research question 2 (active SPMS without superimposed relapses)

The EXPAND study included SPMS patients irrespective of whether or not they had active disease. According to the SPC [15], however, the therapeutic indication of siponimod only comprises treatment of adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity. With regard to disease activity, Section 5.1 of the SPC explains that features characteristic of inflammatory activity in SPMS can be relapse- or imaging-related (i.e. contrast agent-enhancing T1 lesions or active [new or enlarging] T2

lesions). With regard to this, however, research question 2 only comprises patients who do not have any superimposed relapses.

Correspondingly, the company defined the following selection criteria to select the relevant subpopulation (active SPMS without superimposed relapses) from the EXPAND study:

- no clinical relapse in the 2 years before study inclusion, but
- imaging features of activity (MRI in the form of contrast agent [Gd]-enhancing lesions).

The company stated that it was unable to consider T2 changes in the selection of the relevant subpopulation, as a reference MRI, standardized according to the study criteria, from at least 1 year prior to the start of the study would have had to be available already at the start of the study. This was not available, however.

The company's approach to form the relevant subpopulation was considered adequate for the present benefit assessment. Disease activity at baseline was shown by the presence of relapses in the last 2 years and the presence of Gd-enhancing T1 lesions at baseline. Both characteristics were predefined as subgroup analyses in the statistical analysis plan. With regard to the characteristic of relapses, it should be noted that the assessment of superimposed relapses was retrospective and that patients without superimposed relapses may still have relapses in the further course of the disease. Concurring with research question 2, the company considered only those patients with active SPMS who had no relapses, but Gd-enhancing T1 lesions. This comprised 128 (11.6%) patients in the siponimod + BSC arm and 61 (11.2%) patients in the placebo + BSC arm of the total population of the EXPAND study.

Approximately 3 quarters of these 189 patients had received MS therapy modifying the course of the disease before the start of the study (see description of the patient characteristics below). Since this disease-modifying MS therapy was not allowed during the study, relapses occurring during the course of the study could be relapses that had been successfully suppressed by previous MS therapy. This was taken into account in the interpretation of the result.

Implementation of the appropriate comparator therapy

The G-BA specified BSC as ACT for research question 2 (active SPMS without superimposed relapses). Although the study protocol of the EXPAND study did not contain any concrete instructions on the use of supportive therapies, all concomitant drug and non-drug therapies, including physiotherapy and blood transfusions, had to be recorded. For the total population, the documentation of these therapies in the clinical study report (CSR) showed that supportive therapies were used and were comparable in both treatment arms. No separate data were available for the relevant subpopulation. The supportive therapies administered in the EXPAND study were considered to be a sufficient implementation of the ACT BSC.

Patient characteristics

Table 8 shows the characteristics of the relevant subpopulation in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses) (multipage table)

Study **Characteristics** **Category**	**Siponimod + BSC** **N[a] = 127**	**Placebo + BSC** **N[a] = 61**
EXPAND		
Age [years], mean (SD)	47 (7)	48 (9)
Age groups, n (%)		
18–30	3 (2)	2 (3)
31–40	15 (12)	11 (18)
41–55	95 (75)	33 (54)
> 55	14 (11)	15 (25)
Sex [F/M], %	60/40	61/39
Family origin, n (%)		
White	126 (99)	57 (93)
Other[b]	1 (1)	4 (7)
Region, n (%)		
Europe	106 (83[c])	52 (85[c])
Other	21 (17[c])	9 (15[c])
EDSS at baseline, n (%)		
< 3.0	1 (1)	0 (0)
3.0–4.5	29 (23)	16 (26)
5.0–5.5	15 (12)	9 (15)
6.0–6.5	82 (65)	36 (59)
> 6.5	0 (0)	0 (0)
Gd-enhancing T1 lesions		
Mean (SD)	3.0 (3.2)	3.1 (8.4)
Median [min; max]	2.0 [1; 18]	1.0 [1; 65]
Number of relapses in the 2 years before baseline, n (%)		
0	127 (100)	61 (100)
≥ 1	0 (0)	0 (0)
Time between first symptoms and randomization [years], mean (SD)	17.1 (7.5)	15.8 (7.9)
Time between first diagnosis and randomization [years], mean (SD)	13.2 (6.8)	12.0 (6.7)
Time between SPMS conversion and randomization [years], mean (SD)	4.4 (3.8)	4.0 (3.0)
Pretreatment with disease-modifying MS therapy, n (%)		
Yes	107 (84[c])	44 (72[c])
No	20 (16[c])	17 (28[c])

Table 8: Characteristics of the study population – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses) (multipage table)

Study **Characteristics** **Category**	**Siponimod + BSC** **N[a] = 127**	**Placebo + BSC** **N[a] = 61**
Treatment discontinuation (blinded treatment), n (%)	45 (35)	25 (41)
Continued treatment after discontinuation of blinded treatment		
Open-label siponimod treatment	14 (11)	9 (15)
Continued participation on abbreviated visit schedule (with or without other MS therapy)[d]	ND[e]	ND[e]
Complete discontinuation of the treatment phase	ND[f]	ND[f]
Study discontinuation, n (%)	24 (19)	16 (26)

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, including the following categories: Asian, black or African American, other, and unknown.
c. Institute's calculation.
d. The following examinations were not performed: ECG, ophthalmological examination, lung function tests, dermatological examination, HRCT, sampling for pharmacokinetic investigation.
e. Discrepant information in Module 4 A of the dossier and the study documents; it remains unclear whether the information on the relevant subpopulation in Module 4 A refers to all patients who continued participation in the study on the abbreviated visit schedule. It can be inferred from the CSR that the corresponding information for the total population in Module 4 A only refers to patients who completed the study. According to this information, a total of 135 (12.2%) patients in the siponimod + BSC arm and 57 (10.4%) patients in the placebo + BSC arm continued to participate in the study under the abbreviated visit schedule. Of these, n = 64 and n = 25 completed the study, and n = 71 and n = 32 discontinued the study prematurely. For the relevant subpopulation, it is unclear whether the information in Module 4 A (N = 7 [5.5%] in the siponimod + BSC arm and N = 2 [3.3%] in the placebo + BSC arm) refers to all patients who continued to participate in the study on the abbreviated visit schedule after discontinuation of the blinded treatment, or whether, in analogy to the total population, only to the subset of those who completed the study.
f. Discrepant information in Module 4 A of the dossier and the study documents. For the total population, the CSR shows that, deviating from the information in Module 4 A, 112 (10.1%) of the patients in the siponimod + BSC arm and 73 (13.4%) of the patients in the placebo + BSC arm also discontinued the study when they discontinued the blinded treatment. Module 4 A provides the following information, however: 188 [17.0%] of the patients in the siponimod + BSC arm and 105 [19.2%] of the patients in the placebo + BSC arm. For the relevant subpopulation, it is unclear what the information in Module 4 A (24 [18.8%] patients in the siponimod + BSC arm and 14 [23.0%] in the placebo + BSC arm) refers to.

BSC: best supportive care; CSR: clinical study report; ECG: electrocardiogram; EDSS: Expanded Disability Status Scale; F: female; Gd: gadolinium; HRCT: high-resolution computed tomography; M: male; max: maximum; min: minimum; MS: multiple sclerosis; n: number of patients in the category; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SPMS: secondary progressive multiple sclerosis; vs.: versus

The demographic and clinical characteristics of the patients in both treatment arms were largely comparable. On average, the patients were 47 and 48 years old, mostly female, and the majority had an EDSS score of 6.0 to 6.5 at baseline. Patients with a higher EDSS score or older than 60 years could not participate in the study, however. Concurring with the selection criteria to form the relevant subpopulation, none of the patients had had a relapse in the last 2 years before baseline, but all had at least 1 Gd-enhancing T1 lesion.

84% of the patients in the siponimod + BSC arm and 72% of the patients in the placebo + BSC arm had received MS therapy modifying the course of the disease before baseline. A list of the therapies received was not available for the relevant subpopulation. In addition, it is unclear at which time point before baseline the MS therapy modifying the course of the disease had been discontinued.

As already described in the section on the study design, patients with disability progression during the course of the study, confirmed over a period of at least 6 months, had the option to continue the blinded, randomly allocated treatment, or to choose treatment with siponimod or another MS therapy (on an abbreviated visit schedule). Overall, 35% of the patients of the relevant subpopulation in the siponimod + BSC arm and 41% in the placebo + BSC arm had discontinued blinded treatment prematurely. 11% and 15% then continued treatment with open-label siponimod. The proportion of those who, after discontinuation of the blinded treatment, continued to participate in the study on the abbreviated visit schedule, with or without another MS therapy, or who discontinued the study altogether, was unclear due to discrepant information between Module 4 A and the study documents (see information on treatment discontinuation provided in Table 8). The subsequent therapies modifying the course of the disease that were administered to patients after discontinuation of the study medication are listed in Appendix A of the full dossier assessment. This information refers to the total population, however, as no information was available for the relevant subpopulation.

The total number of patients who discontinued the study was 19% in the siponimod + BSC arm, compared with 26% in the placebo + BSC arm.

Observation period and treatment duration

In the EXPAND study, the end of the randomized study phase was not based on a fixed observation period, resulting in different observation times for individual patients.

Originally, the end of the randomized study phase was planned for the time point at which 374 patients showed 3-month confirmed disability progression. It was estimated that the majority of patients would have been treated for at least 24 months at this time point. However, as the events occurred more quickly than expected and the initial inclusion of patients in the study was slower than expected, it was assumed that only a small proportion of patients would have been treated for at least 24 months at the originally planned end of the study phase. Therefore, the end of the randomized study phase was adjusted by means of a protocol change and defined as a point in time of approximately 3 years after randomization of the first patient. It was assumed that at this time point ≥ 374 patients would have 3-month confirmed disability progression and more than 95% of the patients would have participated in the study for ≥ 1 year.

All outcomes of the study, regarding both benefit and harm, were to be observed until the end of the randomized study phase, regardless of whether the patient received the blinded study medication or switched to another MS therapy or siponimod treatment after discontinuation.

Table 9 shows the mean/median observation period of the patients. According to these data, the median observation periods of the patients in the relevant subpopulation were 1.8 and 1.7 years. The proportion of those who were observed for more than 1 year was 87%. This proportion of patients fulfilled the minimum study duration of 12 months defined for the present benefit assessment. Fewer than half of the patients in the relevant subpopulation were observed for at least 2 years. Hence, no long-term data were available.

There was no information on the treatment duration for the relevant subpopulation.

Table 9: Information on the course of the study – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

Study **Duration of the study phase**	**Siponimod + BSC** **N = 127**	**Placebo + BSC** **N = 61**
EXPAND		
Observation period [years]		
Median [min; max]	1.8 [0.0; 3.0][a]	1.7 [0.1; 3.0][a]
Mean (SD)	1.8 (0.7)[a]	1.7 (0.7)[a]
Proportion ≥ 1 year in study, n (%)	111 (87)	53 (87)
Proportion < 1 year in study, n (%)	16 (13)	8 (13)
Proportion ≥ 2 years in study, n (%)	54 (43)	22 (36)
Proportion < 2 years in study, n (%)	73 (58)	39 (64)
Treatment duration [years]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. Institute's calculation (days in years).

BSC: best supportive care; max: maximum; min: minimum; n: number of patients in the category; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SPMS: secondary progressive multiple sclerosis; vs.: versus

Risk of bias across outcomes (study level)

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

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

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			
EXPAND	Yes	Yes	Yes	Unclear[a]	Yes	No[b]	Low

a. Treating staff and outcome assessors had potential knowledge of the patients' group allocation.
b. 14.8% of the patients in the placebo + BSC arm switched to siponimod after discontinuation of the blinded treatment with the study medication.

BSC: best supportive care; RCT: randomized controlled trial; SPMS: secondary progressive multiple sclerosis; vs.: versus

It can be inferred from the study documents and the European Public Assessment Report (EPAR [16]) that due to the incorrect granting of access rights to several of the existing databases, part of the study staff – in particular the person who carried out the assessment of disability progression using the EDSS – had potential knowledge of the patients' group allocation. According to the EPAR, complete blinding of the treating staff and the outcome assessors may not have been guaranteed in 213 (12.9%) patients of the total population of the EXPAND study. According to the EPAR, analyses in this subpopulation of 213 patients showed a notably higher effect estimation for the primary outcome of the study (time to disability progression, confirmed over a period of 3 months) than in the total population.

No information was available on the proportion of patients in the relevant subpopulation for whom the treating staff and/or the outcome assessors had knowledge of the group allocation. According to the CSR, the majority of the patients affected by this potential unblinding were included in the list of protocol deviations under the category "other good clinical practice (GCP) deviation". Module 4 A provides corresponding information, which are based on uncorrected numbers, however. According to Amendment 1 (19 July 2018) to the CSR, the number of those who were included in this category of protocol deviation was corrected upwards. The company did not address this issue in Module 4 A, however. The corrected numbers cannot be inferred from the dossier.

When assessing the outcome-specific risk of bias, the present benefit assessment takes the aspect of the potential lack of blinding into account for outcomes recorded by the treating staff and especially by the EDSS raters. This deviates from the approach of the company, which did not address the potentially biasing aspect from the potential unblinding in the recording of outcomes.

Furthermore, patients with disability progression during the course of the study, confirmed over a period of at least 6 months, had the option to discontinue the blinded treatment with the study medication and continue treatment with siponimod. Overall, about 15% of the patients of the relevant subpopulation in the placebo + BSC arm switched to treatment with siponimod. Switching from the control to the experimental intervention can have a potentially biasing effect on the results of the benefit assessment, however. This aspect was therefore taken into account in the assessment of the outcome-specific risk of bias for outcomes where the switch of treatment may have affected the results.

Nonetheless, the risk of bias across outcomes was rated as low for the EXPAND study. Regarding the result, this corresponds to the assessment of the company, which did not mention the above-mentioned aspects regarding the potential lack of blinding and the switch of treatment from the control to the experimental intervention, however.

Transferability of the study results to the German health care context

From the company's point of view, the study population as well as the subpopulation relevant for research question 2, referred to by the company as "subpopulation B", are largely structurally equal to the population with SPMS or SPMS with active disease in Germany in terms of their demographic and other characteristics at baseline, diagnosis and pretreatment. The company referred to an analysis based on the German MS registry [17]. According to the company, the results of the study and especially the results on the relevant subpopulation, referred to by the company as "subpopulation B", are thus transferable to the German health care context.

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

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - confirmed disability progression (EDSS-based, confirmed over a period of 6 months)
  - disability severity (recorded using the MSFC)
  - confirmed relapses (EDSS-based)
  - fatigue
  - cognitive functioning (recorded using the SDMT and the BVMT-R)
  - visual acuity (recorded using the LCVA)
  - walking ability (recorded using the MSWS-12)
  - physical functioning (recorded using the MSIS-29, physical functioning scales)
  - psychological functioning (recorded using the MSIS-29, psychological functioning scales)
  - health status (recorded using the EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections
  - bradycardia
  - if applicable, further specific AEs

The cognitive tests mentioned above can be used independently, but are also part of common test batteries for assessing cognitive functioning, such as the Brief International Cognitive Assessment for MS (BICAMS) and the Minimal Assessment of Cognitive Function in MS (MACFIMS). In these test batteries, additional tests are used to cover other core domains of cognitive functioning.

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 brain volume) as supplementary information.

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

Table 11: Matrix of outcomes – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

Study	Outcomes																	
	All-cause mortality	Confirmed disability progression[a] (EDSS)	Disability severity (MSFC)	Confirmed relapses (EDSS-based)	Fatigue	Cognitive functioning (SDMT)	Cognitive functioning (BVMT-R)	Visual acuity (LCVA)	Walking ability (MSWS-12)	Physical functioning (MSIS-29)	Psychological functioning (MSIS-29)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Infections	Bradycardia	Further specific AEs
EXPAND	Y	Y	Y	Y	No[b]	No[c]	No[c]	Y	Y	Y	Y	No[c]	No[b]	No[d]	No[d]	No[d]	No[d]	No[d]

a. Disability progression confirmed over a period of 6 months.
b. Outcome not recorded.
c. No usable analyses available, as there are no corrected analyses available after correction of a programming error.
d. No usable analyses available, as the available analyses do not comprise the entire documentation time.

AE: adverse event; BSC: best supportive care; BVMT-R: Brief Visuospatial Memory Test Revised; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; LCVA: low contrast visual acuity; MSFC: Multiple Sclerosis Functional Composite; MSIS-29: Multiple Sclerosis Impact Scale-29; MSWS-12: Multiple Sclerosis Walking Scale-12; RCT: randomized controlled trial; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test; SPMS: secondary progressive multiple sclerosis; VAS: visual analogue scale; vs.: versus; Y: yes

No usable analyses were available for the outcomes “cognitive functioning” (recorded using SDMT and BVMT-R) and “health status” (EQ-5D VAS), or for the outcomes of the category of side effects. This is justified below.

With Amendment 1 (19 July 2018) to the CSR, a programming error regarding the analyses of SDMT, BVMT-R and EQ-5D VAS was corrected. The dossier presented the results of the analysis using the mixed-effects model repeated measures (MMRM) before the correction of the programming error for the total population. It was therefore assumed for the present benefit assessment that the results of SDMT, BVMT-R and EQ-5D VAS for the relevant subpopulation were also based on the analyses without correction. The possible influence of the correction on the presented results of the relevant subpopulation remained unclear, so that the available analyses on the outcomes “cognitive functioning” (recorded using SDMT and BVMT-R) and “health status” (EQ-5D VAS) were rated as not usable.

This deviates from the assessment of the company, which provided the results before the correction of the programming error for the outcomes mentioned and did not address this programming error in Module 4 A.

In the EXPAND study, the side effect outcomes, like other outcomes, were also to be recorded until the end of the study, regardless of whether the patient opted for treatment with siponimod or another MS therapy after discontinuation of the blinded treatment. For the relevant subpopulation, however, only analyses over the period of the blinded treatment with the randomly allocated study medication were available for all AE outcomes. Thus, the available analyses on AEs did not allow any conclusion to be made about the entire documentation time, unless the patient had discontinued the study itself when discontinuing the blinded treatment (see Table 8). The available analyses on the outcomes of the category of side effects were therefore not usable in the present situation.

Regarding the overall rates of AEs, SAEs and discontinuation due to AEs, the company provided analyses excluding events rated as disease-specific by the company as further operationalization. The selection of the events rated by the company as disease-specific, which the company subtracted from the respective overall rates, was made for the dossier. It also subtracted events that are not immediately obvious as symptoms of the underlying disease (for example: “abdominal pain” and “pain”). The EXPAND study protocol had already stipulated that relapses and disability progression should not be regularly recorded as SAEs unless they were unusually severe or unexpected. For the present benefit assessment, the approach in the study itself was considered sufficiently adequate for the overall rate of SAEs.

It is not clear from the study documents how the specific AEs considered by the company were defined or whether they had been prespecified.

2.4.2.2 Risk of bias

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

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

Study		Outcomes																
	Study level	All-cause mortality	Confirmed disability progression (EDSS-based)	Disability severity (MSFC)	Confirmed relapses (EDSS-based)	Fatigue	Cognitive functioning (SDMT)	Cognitive functioning (BVMT-R)	Visual acuity (LCVA)	Walking ability (MSWS-12)	Physical functioning (MSIS-29)	Psychological functioning (MSIS-29)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Infections	Bradycardia
EXPAND	L	L	H[a]	H[a, b, c]	H[a, b]	–[d]	–[e]	–[e]	H[a, b, c]	H[b]	H[b, f]	H[b, f]	–[e]	–[d]	–[e]	–[e]	–[e]	–[e]

a. Unclear proportion of patients in the relevant subpopulation for whom the outcome assessor had potential knowledge of the group allocation.
b. 14.8% of the patients in the placebo + BSC arm switched to siponimod after discontinuation of the blinded treatment with the study medication.
c. Large proportion of patients not included in the analysis (> 10%); for patients included in the analysis, a large proportion of values was missing as of the second documentation time after start of the study (month 12); this proportion additionally differed notably between the treatment groups for the outcome "disability severity".
d. Outcome not recorded.
e. No usable data available; for reasons, see Section 2.4.2.1.
f. Proportions of patients with missing values at the second documentation time after the start of the study (month 12) differed notably between the treatment groups (> 10 percentage points).

AE: adverse event; BSC: best supportive care; BVMT-R: Brief Visuospatial Memory Test Revised; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; H: high; LCVA: low contrast visual acuity; L: low; MSFC: Multiple Sclerosis Functional Composite; MSIS-29: Multiple Sclerosis Impact Scale-29; MSWS-12: Multiple Sclerosis Walking Scale-12; RCT: randomized controlled trial; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test; SPMS: secondary progressive multiple sclerosis; VAS: visual analogue scale; vs.: versus

Except for the outcome "all-cause mortality", the risk of bias for the results of all other outcomes for which usable results were available was rated as high. This is explained below.

For all outcomes with usable results, except for the outcome "confirmed disability progression", one reason for the high risk of bias was at least the treatment switch from the control to the experimental intervention. After the blinded treatment with placebo + BSC, almost 15% of the patients switched to siponimod. Further causes of bias are described below.

Due to unclear proportions of patients whose group allocations were potentially known by the outcome assessors, the risk of bias was rated as high for the results of the following outcomes: confirmed disability progression (EDSS-based), disability severity (MSFC), confirmed relapses (EDSS-based), and visual acuity (LCVA). Details are described in Section 2.4.1.2 on the risk of bias across outcomes. Furthermore, a large proportion of values not included in the analysis, which for the outcome "disability severity" additionally differed notably between the treatment groups, also contributed to the high risk of bias for the 2 outcomes "disability severity" (MSFC) and "visual acuity" (LCVA).

Besides the aspect of treatment switching from the control to the experimental intervention described above, a notable difference between the treatment groups regarding the proportions of patients with missing values also contributed to the high risk of bias for the results of the outcomes "physical functioning" and "psychological functioning".

No usable analyses were available for the outcomes on cognitive functioning (SDMT and BVMT-R) and health status (EQ-5D VAS), and for the side effect outcomes (see Section 2.4.2.1); the risk of bias was therefore not assessed. The outcomes "fatigue" and "health-related quality of life" were not recorded in the EXPAND study.

These assessments partly deviate from those of the company, which rated the risk of bias of the results of the relevant subpopulation as low for all outcomes except disability severity (MSFC) and physical/psychological functioning (MSIS-29).

2.4.2.3 Results

Table 13, Table 14 and Table 15 summarize the results of the comparison of siponimod + BSC with placebo + BSC in patients with active SPMS without superimposed relapses. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves for the outcome "confirmed disability progression" as well as for the analysis of the time to first confirmed relapse presented as additional information can be found in Appendix B of the full dossier assessment. Tables on common AEs are not presented, as the available AE analyses were not usable because they did not comprise the entire documentation time (see Section 2.4.2.1).

Table 13: Results (mortality, morbidity, side effects, time to event) – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

Study **Outcome category**	**Siponimod + BSC**		**Placebo + BSC**		**siponimod + BSC vs. placebo + BSC**
Outcome	**N**	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in weeks [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
EXPAND					
Mortality					
All-cause mortality	127	ND 1 (0.8)	61	ND 1 (1.6)	ND
Morbidity					
Confirmed disability progression (EDSS-based)	127	NA 24 (18.9)	61	NA 16 (26.2)	0.57 [0.28; 1.16]; 0.121
Fatigue	Outcome not recorded				
Side effects					
AEs (supplementary information)	No usable analyses[b]				
SAEs					
Discontinuation due to AEs					
Infections					
Bradycardia					

a. Cox proportional hazards model adjusted for country and EDSS at baseline.
b. No usable analyses available; for reasons, see Section 2.4.2.1.

AE: adverse event; BSC: best supportive care; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SPMS: secondary progressive multiple sclerosis; vs.: versus

Table 14: Results (morbidity, confirmed relapses) – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses)

Study **Outcome category** **Outcome**	**Siponimod + BSC**			**Placebo + BSC**			**Siponimod + BSC vs. placebo + BSC**
	N	**n/exposure**	**Annualized relapse rate [95% CI][a]**	**N**	**n/exposure**	**Annualized relapse rate [95% CI][a]**	**Rate ratio [95% CI]; p-value[a]**
EXPAND							
Morbidity							
Confirmed relapses (EDSS-based)							
Annualized relapse rate	127	14/ND	0.06 [0.03; 0.10]	61	15/ND	0.14 [0.08; 0.26]	0.41 [0.18; 0.92]; 0.031
		Median time to event in weeks [95% CI] **Patients with event n (%)**			**Median time to event in weeks [95% CI]** **Patients with event n (%)**		**HR [95% CI]; p-value[b]**
Time to first confirmed relapse (supplementary information)	*127*	*NA* *13 (10.2[c])*		*61*	*NA* *12 (19.7[c])*		*0.38 [0.16; 0.89]; 0.026*

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 for EDSS at baseline; time a patient was in the study (logarithm of time in years) as offset.
b. Cox proportional hazards model adjusted for country as well as EDSS and number of T1 lesions at baseline.
c. Institute's calculation.

BSC: best supportive care; CI: confidence interval; EDSS: Expanded Disability Status Scale; HR: hazard ratio; N: number of analysed patients; n: number of relapses (in relation to annualized relapse rate) or number of patients with event (in relation to the event time analysis); NA: not achieved; ND: no data; RCT: randomized controlled trial; SPMS: secondary progressive multiple sclerosis; vs.: versus

Table 15: Results (morbidity, continuous) – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses) (multipage table)

Study Outcome category Outcome	Siponimod + BSC			Placebo + BSC			Siponimod + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at month 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at month 12 mean (SE)[b]	MD [95% CI]; p-value[b]
EXPAND							
Morbidity							
Disability severity							
MSFC z score[c]	113	−0.10 (0.65)	0.04 (0.04)	53	−0.11 (0.60)	0.02 (0.06)	0.02 [−0.11; 0.15]; 0.743
T25-FW[d]	121	16.45 (15.80)	6.14 (1.76)	60	14.44 (12.19)	7.90 (2.61)	−1.76 [−8.05; 4.54]; 0.579
9-HPT[d]	124	39.67 (22.21)	−1.03 (1.16)	60	34.81 (17.19)	0.00 (1.70)	−1.03 [−5.13; 3.07]; 0.620
PASAT-3[c]	115	37.80 (14.41)	3.13 (0.87)	56	34.57 (13.48)	3.44 (1.29)	−0.31 [−3.39; 2.77]; 0.842
Cognitive functioning							
SDMT	No usable analyses[e]						
BVMT-R	No usable analyses[e]						
Visual acuity (LCVA)[c]	110	0.39 (0.26)	0.00 (0.03)	55	0.39 (0.26)	−0.01 (0.03)	0.02 [−0.06; 0.09]; 0.632
Walking ability (MSWS-12)[d]	118	70.06 (24.52)	4.46 (2.32)	57	68.25 (23.57)	4.72 (3.08)	−0.26 [−6.89; 6.36]; 0.938
Physical functioning (MSIS-29)[d]	117	52.15 (21.74)	1.53 (2.28)	56	53.61 (23.26)	0.41 (3.00)	1.12 [−5.22; 7.46]; 0.727
Psychological functioning (MSIS-29)[d]	117	34.73 (21.90)	3.33 (2.39)	55	41.68 (24.26)	1.35 (3.21)	1.98 [−4.77; 8.73]; 0.563
Health status (EQ-5D VAS)	No usable analyses[e]						
Health-related quality of life	Outcome not recorded						

Table 15: Results (morbidity, continuous) – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (research question 2 – active SPMS without superimposed relapses) (multipage table)

Study Outcome category Outcome	Siponimod + BSC			Placebo + BSC			Siponimod + BSC vs. placebo + BSC
	N[a]	Values at baseline mean (SD)	Change at month 12 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at month 12 mean (SE)[b]	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. MMRM with the terms for treatment, visit, value at baseline, as well as the interaction term for treatment and visit; for the outcomes "visual acuity", "walking ability" as well as "physical and psychological functioning" with additional term for country. c. A positive change from baseline to end of study indicates improvement; a positive effect estimation indicates an advantage for siponimod. d. A negative change from baseline to end of study indicates improvement; a negative effect estimation indicates an advantage for siponimod. e. No usable analyses available due to a programming error in the analysis of the data; see Section 2.4.2.1 for details. BSC: best supportive care; BVMT-R: Brief Visuospatial Memory Test Revised; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; 9-HPT: 9-Hole Peg Test; LCVA: low contrast visual acuity; MD: mean difference; MMRM: mixed-effects model repeated measures; MSFC: Multiple Sclerosis Functional Composite; MSIS-29: Multiple Sclerosis Impact Scale-29; N: number of analysed patients; PASAT: Paced Auditory Serial Addition Test; RCT: randomized controlled trial; SD: standard deviation; SDMT: Symbol Digit Modalities Test; SE: standard error; SPMS: secondary progressive multiple sclerosis; T25-FW: Timed 25-Foot Walk; VAS: visual analogue scale; vs.: versus						

On the basis of the available data, at most an indication, e.g. of an added benefit, can be derived for the outcome "all-cause mortality", and at most hints for all other outcomes due to the high risk of bias.

The company did not draw separate conclusions on the probability and extent of the added benefit for each outcome, but derived an advantage or disadvantage of siponimod + BSC in comparison with BSC for the individual outcomes based on the statistical significance of the results. Furthermore, the company considered the results of the total population for all outcomes as supplementary information. The following comments on the company's approach are limited to the results of the relevant subpopulation for research question 2, referred to by the company as "subpopulation B" (see the section on the subpopulation relevant for research question 2 above).

Mortality

All-cause mortality

There were no event time analyses for the outcome "all-cause mortality". Due to the small proportions of events (one patient died in each of both treatment arms), a statistically significant difference can be ruled out in the present situation. This resulted in no hint of an added benefit

of siponimod + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This concurs with the approach of the company insofar as the company also derived no added benefit based on the results of this outcome.

Morbidity

Confirmed disability progression (EDSS-based)

The analyses on confirmed disability progression over a period of 6 months were used for the outcome "confirmed disability progression" (EDSS-based). No statistically significant difference was shown between the 2 treatment arms. This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This concurs with the approach of the company insofar as the company also derived no added benefit based on the results of this outcome. The company additionally considered the analysis of 3-month confirmed disability progression as well as analyses of the proportion of patients with event, however.

Confirmed relapses (EDSS-based)

The annualized relapse rate was considered to be the decisive operationalization for the outcome "confirmed relapses". An increase of ≥ 0.5 point on the EDSS score, or a change of 1 point in 2 different Functional Systems or of 2 points in 1 Functional System (except bowel/bladder or cerebral Functional System) was rated as confirmation in the EXPAND study. A statistically significant difference in favour of siponimod + BSC in comparison with placebo + BSC was shown between the 2 treatment arms in annualized relapse rate. A statistically significant advantage of siponimod + BSC was also shown for the operationalization of the time to first confirmed relapse presented as supplementary information. Overall, an effect in favour of siponimod + BSC can be derived from this.

As described in Section 2.4.1.2 on patient characteristics, however, about 3 quarters of the patients received MS therapy modifying the course of the disease before the start of the study, and it is unclear at what time before the start of the study this therapy was discontinued. A subgroup analysis on this characteristic showed that the relapses observed in the EXPAND study were almost exclusively observed in patients who had received MS therapy modifying the course of the disease before the start of the study (see Figure 4 in Appendix C of the full dossier assessment). This suggests that the relapses observed in the course of the study were relapses that had been successfully suppressed by previous MS therapy. Overall, the results on the outcome "confirmed relapses" from the EXPAND study cannot be interpreted as an advantage of siponimod. On the basis of the available data, there was overall no hint of an added benefit of siponimod + BSC in comparison with BSC for the outcome "confirmed relapses"; an added benefit is therefore not proven.

This deviates from the approach of the company, which used both operationalizations (annualized relapse rate and time to first confirmed relapse) for the derivation of the added benefit, and derived an added benefit in favour of siponimod + BSC based on this.

Disability severity (MSFC), cognitive functioning (recorded using SMDT and BVMT-R), visual acuity (LCVA), walking ability (MSWS-12), physical functioning (MSIS-29), psychological functioning (MSIS-29), health status (EQ-5D VAS)

For these outcomes, there were no effect estimations on analyses over the entire study period for the relevant subpopulation, but only at month 12 and month 24. With regard to the outcomes for which usable analyses were available, the analyses at month 12 were used, as the response rate to questionnaires in both treatment arms was sufficiently high at this time point (about 77 to 82%) compared with month 24. In principle, however, the analysis that takes into account the course over the entire period of the study would be preferable. The company did not justify why, deviating from the reporting of results for the total population in the CSR, it did not present this analysis for the relevant subpopulation. In each case, the company used the results at month 12 also for the derivation of the added benefit. Deviating from the present benefit assessment, it presented the results at month 24 as supplementary information in each case.

Disability severity (MSFC)

There was no statistically significant difference between the 2 treatment arms for the outcome "disability severity" (recorded using the MSFC z score). This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This concurs with the approach of the company insofar as the company also derived no added benefit based on the results of this outcome. Besides the MSFC z score, however, it also considered the individual results from the Timed 25-Foot Walk (T25-FW), the 9-Hole Peg Test (9-HPT) and the Paced Auditory Serial Addition Test (PASAT) on the change from baseline, as well as analyses on the proportion of patients with confirmed deterioration by at least 20% in the T25-FW, as well as the corresponding event time analysis.

Cognitive functioning (recorded using SDMT and BVMT-R)

There were no usable analyses for the outcome "cognitive functioning" recorded using the SDMT and the BVMT-R (see Section 2.4.2.1). This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This deviates from the approach of the company insofar as the company used the available analyses and derived an added benefit in favour of siponimod + BSC based on the results of the SDMT on the change from baseline. Regarding the corresponding analyses using the BVMT-R as well as the analyses on the proportion of patients with improvement/deterioration by more than 4 points in the SDMT additionally considered by the company, the company stated that there was no statistically significant difference between the treatment groups.

Visual acuity (LCVA)

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

This concurs with the approach of the company, which also derived no added benefit based on the results of this outcome.

Walking ability (MSWS-12)

No statistically significant difference between the 2 treatment arms was shown for the outcome "walking ability" recorded using the MSWS-12. This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This concurs with the approach of the company, which also derived no added benefit based on the results of this outcome.

Physical functioning (MSIS-29) and psychological functioning (MSIS-29)

No statistically significant difference was shown between the 2 treatment arms for the outcome "physical functioning" (MSIS-29, physical functioning scales) or for the outcome "psychological functioning" (MSIS-29, psychological functioning scales). This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for either of these 2 outcomes; an added benefit is therefore not proven.

This concurs with the approach of the company insofar as the company also derived no added benefit based on the results of the MSIS-29. The company allocated the analyses on physical and psychological functioning using the MSIS-29 to the category of health-related quality of life, however.

Health status (EQ-5D VAS)

No usable analyses were available for the outcome "health status" recorded using the EQ-5D VAS (see Section 2.4.2.1). This resulted in no hint of an added benefit of siponimod + BSC in comparison with BSC for this outcome; an added benefit is therefore not proven.

This deviates from the approach of the company insofar as the company used the analyses on this outcome and did not derive an added benefit based on this. Deviating from the present benefit assessment, the company allocated this outcome to the category of health-related quality of life.

Fatigue

The outcome "fatigue" was not recorded in the EXPAND study.

Health-related quality of life

The outcome “health-related quality of life” was not recorded in the EXPAND study.

Side effects

Serious adverse events (SAEs), discontinuation due to AEs, infections, bradycardia

There were no usable analyses for the outcomes of the category of side effects (see Section 2.4.2.1). This resulted in no hint of greater or lesser harm from siponimod + BSC in comparison with BSC for any of these outcomes; greater or lesser harm is therefore not proven.

This deviates from the approach of the company insofar as the company used the analyses on the outcomes of the category of side effects. Except for the overall rate of AEs, the company did not determine statistically significant differences between the treatment arms for the side effect outcomes it considered.

2.4.2.4 Subgroups and other effect modifiers

Age and sex (female, male) were rated as potential effect modifiers for the present benefit assessment.

Regarding the characteristic of age, the company stated that it had chosen the age categories considered (18–30 years; 31–40 years, and 18–40 years; 41–55 years; > 55 years) post hoc according to the CSR analysis of the patient characteristics. Due to the post hoc choice, event-driven reporting cannot be ruled out, so that the available analyses on age were not used for the 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 sex was identified for the outcomes for which usable analyses were available.

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 2.4.2 (see Table 16).

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

In its dossier, the company did not present any information for the relevant subpopulation that would allow an assessment of the severity of the confirmed relapses, although, according to the study protocol, the severity grade of a relapse was to be assessed using defined criteria for accompanying changes in the EDSS. An analysis of the annualized relapse rate, e.g. of relapses requiring hospitalization, was additionally mandated. Besides, the result for the outcome of disability severity using MSFC (z score) showed neither an advantage nor a disadvantage of siponimod + BSC in comparison with placebo + BSC. It cannot be deduced from this either that the majority of confirmed relapses were severe per se. Therefore, the outcome "confirmed relapses" was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 16: Extent of added benefit at outcome level: siponimod + BSC vs. BSC (research question 2 – active SPMS without superimposed relapses) (multipage table)

Outcome category **Outcome**	**Siponimod + BSC vs. BSC** **Median time to event (weeks) 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	Median: ND Proportion of events: 0.8% vs. 1.6% HR: ND	Lesser benefit/added benefit not proven[c]
Morbidity		
Confirmed disability progression (EDSS-based)	Median: NA vs. NA HR: 0.57 [0.28; 1.16] p = 0.121	Lesser benefit/added benefit not proven
Disability severity MSFC z score	Mean change: 0.04 vs. 0.02 MD: 0.02 [−0.11; 0.15] p = 0.743	Lesser benefit/added benefit not proven
Confirmed relapses (EDSS-based) Annualized relapse rate *Time to first confirmed relapse (supplementary information)*	Rate: 0.06 vs. 0.14 rate ratio: 0.41 [0.18; 0.92] p = 0.031 *Median: NA vs. NA* *HR: 0.38 [0.16; 0.89]* *p = 0.026*	Lesser benefit/added benefit not proven[d]
Fatigue	Outcome not recorded	
Cognitive functioning SDMT BVMT-R	No usable analyses[e]	Lesser benefit/added benefit not proven
Visual acuity (LCVA)	Mean change: 0.00 vs. −0.01 MD: 0.02 [−0.06; 0.09] p = 0.632	Lesser benefit/added benefit not proven
Walking ability (MSWS-12)	Mean change: 4.46 vs. 4.72 MD: −0.26 [−6.89; 6.36] p = 0.938	Lesser benefit/added benefit not proven
Physical functioning (MSIS-29)	Mean change: 1.53 vs. 0.41 MD: 1.12 [−5.22; 7.46] p = 0.727	Lesser benefit/added benefit not proven
Psychological functioning (MSIS-29)	Mean change: 3.33 vs. 1.35 MD: 1.98 [−4.77; 8.73] p = 0.563	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable analyses[e]	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: siponimod + BSC vs. BSC (research question 2 – active SPMS without superimposed relapses) (multipage table)

Outcome category **Outcome**	**Siponimod + BSC vs. BSC** **Median time to event (weeks) 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]
Health-related quality of life	Outcome not recorded	
Side effects		
SAEs	No usable analyses[f]	Greater/lesser harm not proven
Discontinuation due to AEs		
Infections		
Bradycardia		

a. Probability provided if there is a statistically significant and relevant effect.
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 the small proportions of events (one patient died in each of both treatment arms), a statistically significant difference can be ruled out in the present situation.
d. The results in the outcome "confirmed relapses" cannot be interpreted as an advantage of siponimod + BSC due to the information on prior therapies (see Section 2.4.2.3).
e. No usable analyses available, as there are no corrected analyses after correction of a programming error.
f. No usable analyses available, as the available analyses do not comprise the entire documentation time.

AE: adverse event; BSC: best supportive care; BVMT-R: Brief Visuospatial Memory Test Revised; CI: confidence interval; CI_u: upper limit of the confidence interval; EDSS: Expanded Disability Status Scale; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCVA: low contrast visual acuity; MD: mean difference; MSFC: Multiple Sclerosis Functional Composite; MSIS-29: Multiple Sclerosis Impact Scale-29; MSWS-12: Multiple Sclerosis Walking Scale-12; NA: not achieved; ND: no data; SAE: serious adverse event; SDMT: Symbol Digit Modalities Test; SPMS: secondary progressive multiple sclerosis; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

An advantage of siponimod versus BSC was shown for confirmed relapses. The company did not present analyses on the severity grade of the relapses. As no advantage or disadvantage of siponimod versus BSC was shown for the outcomes on disability progression and disability severity, it cannot be assumed per se that the majority of relapses were severe. In addition, subgroup analyses on the characteristic "prior MS therapy modifying the course of disease" suggest that the relapses observed in the course of the study were relapses that had been successfully suppressed by previous MS therapy (see Section 2.4.2.3).

The analyses presented by the company on the outcomes of the category of side effects were not usable, as they did not comprise the entire documentation period and were therefore incomplete with regard to content. Data on further key outcomes, such as health-related quality of life or fatigue, were also not available.

In summary, the data presented provided no hint of an added benefit of siponimod in comparison with the ACT BSC for adult patients with active SPMS without superimposed relapses.

This deviates from the assessment of the company, which overall derived an indication of a minor added benefit for the relevant subpopulation for research question 2, referred to by the company as “subpopulation B”.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of siponimod in comparison with the ACT is summarized in Table 17.

Table 17: Siponimod – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with SPMS with active disease evidenced by relapses or imaging features of inflammatory activity			
1	With superimposed relapses	Interferon (IFN)-β1a or 1b or ocrelizumab	Added benefit not proven
2	Without superimposed relapses	Best supportive care (BSC)[b]	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; IFN: interferon; SPMS: secondary progressive 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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