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Siponimod (multiple sclerosis) –

Addendum to Commission A20-10[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
BVMT-R	Brief Visuospatial Memory Test Revised
DMT	disease-modifying therapy
EQ-5D	European Quality of Life-5 Dimensions
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)
MMRM	mixed-effects model repeated measures
MS	multiple sclerosis
SAE	serious adverse event
SC	subcutaneous
SDMT	Symbol Digit Modalities Test
SPMS	secondary progressive multiple sclerosis
VAS	visual analogue scale

1 Background

On 23 June 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-10 (Siponimod – Benefit assessment according to §35a Social Code Book V) [1].

For the assessment of the added benefit, the therapeutic indication of siponimod, secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity [2], was divided into 2 research questions, differentiating between patients with superimposed relapses and patients without superimposed relapses. In its dossier [3], the pharmaceutical company (hereinafter referred to as "the company") presented results of a subpopulation of the EXPAND study [4-12], which it considered to comprise the patients with SPMS without superimposed relapses (see Section 2.4.1.2 of the dossier assessment), for the assessment of the added benefit of siponimod in comparison with the appropriate comparator therapy (ACT) of research question 2 (active SPMS without superimposed relapses). Before the start of the study, about 3 quarters of these patients had received disease-modifying therapy (DMT) for the treatment of multiple sclerosis (MS), which had been discontinued before the start of the study. The time point of discontinuation remained unclear for the dossier assessment. A subgroup analysis on the characteristic "prior DMT" (yes versus no) in the dossier showed that the relapses observed in the subpopulation of the EXPAND study presented by the company were almost exclusively observed in patients who had received such MS therapy before the start of the study. This suggested that these relapses were relapses that had been successfully suppressed by previous MS therapy. Thus, the results for the outcome "confirmed relapses" were not interpreted as an advantage of siponimod.

In the commenting procedure, the company presented information on research question 2 that went beyond the information provided in the dossier. The G-BA commissioned IQWiG with the assessment of the data subsequently submitted regarding the following aspects:

- analysis of the subgroup analysis on the outcome "confirmed relapses" in dependence on the discontinuation of prior therapy > 1 year versus < 1 year before the start of the study
- analysis of the annualized relapse rate of confirmed relapses under exclusion of the patients with prior DMT (only interferon [IFN]-β1a and 1b) in the 2 years before the start of the study
- analysis of adverse events (AEs) since start of the study under consideration of the events after treatment switch
- analysis of the corrected analysis regarding the programming error in the morbidity outcomes of Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test Revised (BVMT-R) and European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS)

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 assessment comprises data from the EXPAND study subsequently submitted by the company in the commenting procedure for the population used by the company for the benefit assessment of siponimod in patients with active SPMS without superimposed relapses (research question 2 of dossier assessment A20-10).

Overall, the data subsequently submitted by the company for the outcome "confirmed relapses" in the subgroup analyses on the characteristic "discontinuation of prior DMT" (> 12 months versus ≤ 12 months before study start) showed that the subpopulation of the EXPAND study presented by the company in the dossier for research question 2 comprised an important proportion of patients for whom it can be assumed that pretreatment had successfully suppressed relapses before study entry. Thus, these patients do not represent the relevant subpopulation of the research question on active SPMS without superimposed relapses.

In the commenting procedure, the company subsequently submitted only selective analyses for the outcome "confirmed relapses" for the relevant population. Thus, results for all other patient-relevant outcomes of the EXPAND study are missing for the population of patients who can be used for research question 2. It is therefore not possible to draw a conclusion on the added benefit of siponimod for patients with active SPMS without superimposed relapses.

Regardless of this, the company again did not submit any usable data also for the subpopulation of the EXPAND study used by the company in the dossier with the subsequently submitted data on AE outcomes. Thus, no data are available for the weighing of benefit and harm to derive a conclusion on the added benefit of siponimod also for the subpopulation on research question 2 considered relevant by the company.

The assessments summarized above are explained in detail below.

2.1 Subpopulation from the EXPAND study for research question 2 (active SPMS without superimposed relapses)

Based on the data presented by the company for the subpopulation from the EXPAND study, the dossier assessment on commission A20-10 showed an effect in favour of siponimod + best supportive care (BSC) versus placebo + BSC for research question 2 for the outcome "confirmed relapses". As described in the dossier assessment, about 3 quarters of the total of 189 patients of this subpopulation had been pretreated with MS therapy modifying the course of disease. This therapy was not allowed during the study and was discontinued in the patients before study entry. It was therefore possible that the relapses observed in the course of the study were relapses that had been successfully suppressed by the previous MS therapy. Since the relapses observed in the course of the study were almost exclusively observed in patients who had been pretreated with such MS therapy before the start of the study (see dossier assessment A20-10, Appendix C) and the time point of discontinuation of these therapies before the start of the study was unclear, the observed effect on the outcome "confirmed relapses" from the

EXPAND study could not be interpreted as an advantage of siponimod for research question 2 of the dossier assessment.

The company subsequently submitted the following analyses in the commenting procedure:

1) Analysis of the annualized relapse rate of confirmed relapses in the subpopulation from the EXPAND study considered by the company without patients pretreated with subcutaneous (SC) IFN-β1a and SC IFN-β1b in the 2 years before study start
2) Subgroup analyses on the outcome "confirmed relapses" regarding the characteristic "discontinuation of prior DMT" (> 12 months versus ≤ 12 months before study start). The company presented analyses under inclusion and under exclusion of patients who had not received such a pretreatment before study entry (DMT-naive).

Analyses without patients with pretreatment with SC IFN-β1a and SC IFN-β1b in the 2 years before study start

In its comments [13], the company presented an analysis that excluded patients with pretreatment with SC IFN-β1a and SC IFN-β1b in the 2 years before the start of the study. This analysis is not appropriate to determine whether the confirmed relapses observed in the EXPAND study were mainly those that had been successfully suppressed by previous MS therapy. For instance, the information on pretreatment also provided in the comments showed that about 42% of the patients with relapse events in the study had received glatiramer acetate. It was therefore not appropriate to exclude only the patients with SC IFN-β1a and SC IFN-β1b. This analysis presented by the company was therefore not considered further.

Subgroup analyses on the characteristic "discontinuation of prior DMT" (> 12 months versus ≤ 12 months before study start) on the outcome "confirmed relapses"

The company presented analyses including also DMT-naive patients and analyses excluding these patients for the characteristic "discontinuation of prior DMT" (> 12 months versus ≤ 12 months before study start). The exclusion of these patients from the analysis is inadequate, as patients without prior DMT without superimposed relapses before the start of the study are explicitly comprised by the present research question 2. For this reason, the analyses under exclusion of these patients were not considered further.

It can be inferred from the data subsequently submitted that the subgroup analyses on the characteristic "discontinuation of prior DMT" (> 12 months versus ≤ 12 months before study start) under consideration of the DMT-naive patients include these patients in the subgroup "DMT-free > 12 months before study start". This approach was adequate. These analyses subsequently submitted by the company (see Table 2, Appendix A) show that 13 of the total of 25 patients with confirmed relapse in the course of the study had discontinued their DMT only within 12 months before study entry. At about 18%, the relative proportion of the patients with relapse in the course of the study in the group that had been DMT-free for ≤ 12 months before study start was almost twice as large as the relative proportion of about 10% in the group that

had been DMT-free for more than 12 months before study start. For patients who had been DMT-free for ≤ 12 months before study start, the analyses subsequently submitted support the assumption from the dossier assessment that the relapses observed in the course of the study were relapses that had been successfully suppressed by prior DMT.

Assuming that the 12-month cut-off value is adequate to differentiate patients with active SPMS without superimposed relapses from those with superimposed relapses, the population for research question 2 presented by the company in the dossier included a total of about 38% patients for whom SPMS without superimposed relapses cannot be assumed (49 patients in the siponimod + BSC arm, 22 in the placebo + BSC arm). This population was therefore unsuitable for the assessment of research question 2.

However, the company presented analyses for the population from the EXPAND study, for which on the basis of the available data an SPMS without superimposed relapses can be assumed (i.e. DMT-free > 12 months before study start or DMT-naive), only selectively for the outcome "confirmed relapses". There were no corresponding analyses for all other patient-relevant outcomes of the EXPAND study. For this reason, the results on the outcome "confirmed relapses" (see Table 2, Appendix A) were not interpreted further, as an overall conclusion on the added benefit of siponimod for patients without superimposed relapses is not possible.

2.2 Results on the outcomes "cognitive functioning" (recorded using SDMT and BVMT-R), health status (recorded using EQ-5D VAS)

There were no usable analyses for the outcomes "cognitive functioning" (recorded using SDMT and BVMT-R) and "health status" (EQ-5D VAS) for the benefit assessment, as it was assumed that the available results were based on analyses with a programming error. In its written comments, the company confirmed the error in the data in the dossier and subsequently submitted analyses using the mixed-effects model repeated measures (MMRM) for these outcomes, correcting the programming error. As was the case in the dossier assessment, there were no effect estimations over the total study period, but only at months 12 and 24, for the analyses subsequently submitted.

The analyses subsequently submitted by the company on the outcomes mentioned above were based on the subpopulation it considered relevant. As described in Section 2.1, this subpopulation included an important proportion of patients for whom it cannot be assumed that they had active SPMS without superimposed relapses at study start and who were therefore not to be considered for research question 2. Hence, the analyses corrected by the company are presented only as supplementary information in Table 3 (Appendix A), showing the analyses at month 12 (see dossier assessment, Section 2.4.2.3, for reasons). There was a high risk of bias for the results of SDMT, BVMT-R and EQ-5D VAS, as 14.8% of the patients in the placebo + BSC arm switched to siponimod after discontinuation of the blinded treatment with the study medication (see also dossier assessment, Section 2.4.2.2). An additional factor for the results of the BVMT-R was that a large proportion of patients was not included in the analysis (> 10%).

Overall, the results subsequently submitted by the company did not show a statistically significant or relevant difference between the treatment groups for any of the outcomes.

2.3 Results on adverse events

As described in Section 2.4.2.1 of the dossier assessment A20-10, the analyses presented by the company in its dossier were not usable for the benefit assessment for the following reasons. In the EXPAND study, side effect outcomes were 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. However, there were no analyses for any of the AE outcomes over the total study period, but only for the period of the blinded treatment with the randomly allocated study medication, for the dossier (for the population presented by the company). Another reason why the analyses were not usable was the company's handling of disease-specific events in the analysis. Besides events that can be clearly allocated to the disease (e.g. "multiple sclerosis relapse"), the company subtracted also events that can be both symptoms and side effects (e.g. "abdominal pain" and "pain") for the dossier. As already described in the dossier assessment, the study protocol of the EXPAND study specified that relapses as well as disability progression were generally not to be recorded as serious adverse events (SAEs), unless they were unusually severe or occurred unexpectedly. This approach for the overall rate of SAEs specified for the study was considered as sufficiently adequate for the benefit assessment already in the dossier assessment.

With its comments, the company subsequently submitted analyses on AEs in which it considered the total study period. However, it did not address how it had handled events that can be both symptoms and side effects in these analyses. In the oral hearing [14], the company confirmed that it had chosen the approach as in the dossier. For this reason, the analyses on AEs subsequently submitted with the comments are also not usable. Furthermore, these analyses again referred to the subpopulation from the EXPAND study considered relevant by the company for research question 2, which was unsuitable for the assessment.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of siponimod from dossier assessment A20-10.

The following Table 1 shows the result of the benefit assessment of siponimod under consideration of dossier assessment A20-10 and the present addendum.

Table 1: 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 G-BA decides on the added benefit.

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Appendix A – Analyses subsequently submitted by the company

Table 2: Subgroups (morbidity, confirmed relapses) – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (population considered by the company for research question 2, active SPMS without superimposed relapses)

Study Outcome Characteristic Subgroup	Siponimod + BSC N	n/exposure	Annualized relapse rate [95% CI][a]	Placebo + BSC N	n/exposure	Annualized relapse rate [95% CI][a]	Siponimod + BSC vs. placebo + BSC Rate ratio [95% CI][a]	p-value[a]
EXPAND								
Morbidity								
Confirmed relapses (EDSS-based)								
Annualized relapse rate								
DMT-free before study start								
> 12 months	78	5/ND	0.03 [0.01; 0.08]	39	8/ND	0.11 [0.05; 0.25]	0.29 [0.09; 0.94]	0.039
≤ 12 months	49	9/ND	0.10 [0.05; 0.21]	22	7/ND	0.19 [0.08; 0.44]	0.54 [0.18; 1.59]	0.262
Total							Interaction:	0.451
		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][b]**	**p-value[b]**
Time to first confirmed relapse (supplementary information)								
DMT-free before study start								
> 12 months	*78*	*NA* *5 (6.4[c])*		*39*	*NA* *7 (17.9[c])*		*0.35 [0.11; 1.12]*	*0.078*
≤ 12 months	*49*	*NA* *8 (16.3[c])*		*22*	*NA* *5 (22.7[c])*		*0.62 [0.20; 1.93]*	*0.411*
Total							Interaction:	*0.498*

a. No exact information on the statistical model, presumably analogous to the dossier: adjusted annualized relapse rate and CI (per treatment arm) as well as rate ratio with CI and p-value (group comparison, interaction testing): negative binomial model adjusted for EDSS at baseline; time a patient was in the study (logarithm of time in years) as offset; including subgroup and corresponding interaction term.
b. Cox proportional hazards model; no exact information on the statistical model, presumably adjusted for country and EDSS and number of T1 lesions at baseline; including subgroup and corresponding interaction term.
c. Institute's calculation.

BSC: best supportive care; CI: confidence interval; DMT: disease-modifying therapy; 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 3: Results (morbidity, continuous) – RCT, direct comparison: siponimod + BSC vs. placebo + BSC (population considered by the company for research question 2, active SPMS without superimposed relapses)

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							
Cognitive functioning							
SDMT[c]	118	36.5 (13.9)	−0.3 (0.9)	57	37.1 (12.1)	−3.0 (1.2)	2.73 [0.17; 5.29]; 0.037 Hedges' g: 0.34 [0.02; 0.65][d]
BVMT-R[c]							
Total recall[e]	113	20.3 (8.9)	−0.7 (0.7)	56	18.2 (7.9)	−0.2 (1.0)	−0.52 [−2.55; 1.52]; 0.616
Delayed recall[e]	113	7.9 (3.3)	−0.5 (0.3)	56	7.2 (3.3)	0.4 (0.4)	−0.85 [−1.75; 0.05]; 0.064
Health status (EQ-5D VAS)[c]	117	58.8 (19.0)	−2.2 (1.7)	58	56.5 (20.2)	−0.2 (2.5)	−2.02 [−7.93; 3.89]; 0.501

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 outcome "cognitive 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. Institute's calculation based on the mean difference and CI of the MMRM.
e. Total recall: summarized result of 3 consecutive learning tests in which patients were shown the same sheet of paper with a geometric shape for 10 seconds. The patients were asked to reproduce the shape as accurately as possible and where it was located on the paper. Delayed recall: There was a recall after 25 minutes.

BSC: best supportive care; BVMT-R: Brief Visuospatial Memory Test Revised; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SDMT: Symbol Digit Modalities Test; SE: standard error; VAS: visual analogue scale; vs.: versus