Input from manufacturer on the 2nd draft assessment
"SIPONIMOD FOR THE TREATMENT OF ADULT PATIENTS WITH SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS (SPMS) WITH ACTIVE DISEASE EVIDENCED BY RELAPSES OR IMAGING FEATURES OF INFLAMMATORY ACTIVITY"

Project ID: PTJA08

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA JA3 WP4 - Pharmaceuticals, PTJA08

Comments on the draft rapid assessment on siponimod for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity

The objective of this reviewer form is to standardise the process of the factual accuracy check of the rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment of siponimod for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity was open to review by the manufacturer [Novartis] between **28/01/2020 and 01/02/2020**.

Comments received from:

Market Authorisation Holder
Novartis

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments from Market Authorisation Holder [Novartis]

Page	Line	Comment	Character of comment[i]	Reply from author
22	Lines 16 to 19 inclusive	The line: "Overall, in the global SPMS population, siponimod in comparison with natalizumab, interferon -1a 22 and 44 µg three times weekly, interferon β-1b 250 µg every other day, or inter feron β-1a 60 µg once a week, did not show a statistically significant difference, in relation to disease progression or clinical relapses." We suggest that proper context is provided. Statistical significance is not expected when conducting analyses on sub-groups for which the trial was not powered to evaluate (e.g., as in the MAICs). While this discussion is present in later sections (e.g., Page 80, lines 22-26), the current statement on Page 22 (lines 16-19) regarding MAICs and STCs in the global population may suggest misleading implications without this context. Although it is correct that there was no statistically significant difference, there is a numerical difference that can affect health technology assessment and pricing processes. The lack of statistical significance may be reflective of drawing conclusions from a subgroup, not necessarily a lack of difference in efficacy between products. As such, the statement's wording may lead to misleading interpretations. <u>Proposed amendment</u>: "Overall, in the global SPMS population, siponimod in comparison with natalizumab, interferon -1a 22 and 44 µg three times weekly, interferon β-1b 250 µg every other day, or interferon β-1a 60 µg once a week, showed a numerical but not statistically significant difference in favour of siponimod, in relation to disease progression or clinical relapses."	3	This comment is outside of the scope of the factual accuracy check.
81	Lines 9 to 12 inclusive	The line: "Therefore, the authors requested that comparisons be made between siponimod and comparators using Bucher ITC and NMA, with MAIC and STC provided as supporting analysis where considered feasible and valid. Of note, for each pairwise comparison, the treatment effect on CDP and ARR, using different methodologies (whether coming from Bucher ITC, NMA, STC or MAIC), generally gave consistent results" After adjusting for cross-trial differences using either MAIC or STC, the results were consistently more in favor than analyses based on summary data such as Bucher ITC or NMA. <u>Proposed amendment</u>: "Therefore, …..(whether coming from Bucher ITC, NMA, STC or MAIC), generally gave consistent results, although results were more pronounced and in favor of siponimod after adjusting for cross-trial differences using MAIC or STC."	3	This comment is outside of the scope of the factual accuracy check.
155	Table 56, Row "CDP-6",	The value "0,43" should be corrected <u>Proposed amendment</u>:	3	Thank you, we made changes needed

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	Column "MAIC"	"0.43" (the comma appears to be a typo) to prevent misinterpretation of the results.		
12	36-37	The phase 3 study met its primary endpoint disease progression in the overall population.The effects independent of relapses or without MRI activity were less profound but not absent. Proposed amendment: The phase 3 study met its primary endpoint disease progression in the overall population. The drug was approved for active SPMS as efficacy was more pronounced in patients with active disease evidenced by relapses or focal MRI activity.	1	This comment is outside of the scope of the factual accuracy check.
12	30-31	S1P1 and S1P5 and prevents egress of lymphocytes from lymph 30 nodes Proposed amendment: S1P1 and S1P5. Only S1P1 prevents egress of lymphocytes from lymph nodes. S1P1 and S1P5 receptors are implicated for effects of siponimod in the CNS as evidenced by preclinical data which are potentially useful in SPMS.	2	Thank you, we made changes needed
16	33-34	In the case of EXPAND, this was due to deviation from blinding procedures for EDSS raters which resulted in temporary access to potentially unblinding information. Proposed amendment: The unintended database access granted does not mean unblinding (unless access was used). It is important to note that out of 568 EDSS raters, only 3 EDSS raters were granted access to the first dose database in error. The number of patients that could potentially have been impacted, (no evidence of this), is 13. Excluding these patients from the data set showed no impact on the primary disability outcome. The sensitivity analysis of EDSS raters with access to the cardiac database was provided and can be found in the EXPAND CSR (section 11.4.1.1 subsection Sensitivity analyses, Table 14.2-1.16. - Interim Clinical Study Report. CBAF312A2304). Novartis has conducted extensive investigations into this issue and have found no evidence of unblinding or that potential unblinding due to inappropriate database access had biased the trial outcomes. Novartis concludes that the EXPAND study data are valid. After reviewing all data, the FDA and the TGA approved siponimod based on the study data. This conclusion was also supported by the CHMP/EMA. - The U.S. Food and Drug Administration (FDA). Sipomimod: Summary Review. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209884Orig1s000SumR.pdf - European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Summary of opinion: Mayzent (siponimod) 2019 Nov 14. Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-	1	This comment is outside of the scope of the factual accuracy check. However, regarding the quality of evidence, the following text was added: While sensitivity analyses, excluding patients affected by potential unblinding, were reassuring, the potential for bias cannot be completely excluded.

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		mayzent_en.pdf - Austrailan Government, Department of Health, Therapeutic Goods Administration (TGA). Australian prescription medicine decision summaries: Mayzent 2019 Dec 13. Available from: https://www.tga.gov.au/apm-summary/mayzent Novartis requests that the Authors account for the extensive investigation that found no evidence of unblinding or that possible unblinding due to inappropriate database access had biased Expand outcomes. Importantly, upon investigation, the FDA and CHMP acknowledge that important aspects of the EXPAND trial argue strongly against false-positive findings.		
54	13-18	The risk of bias for participants (blinding of participants) was therefore considered 13 to be low. However, blinding procedures were potential not followed for 15.7% of the patients in the 14 siponimod group, and 15.8% in the placebo group. The potential unblinding resulted from temporary 15 incorrect access rights for site staff (EDSS raters and investigators) to the different databases, lead-16 ing to potential unblinding of some cases. Therefore the risk of bias was considered unclear for the 17 outcome assessors. Proposed amendment: In Amendment 1 of the CSR, the %s referring to blinding procedures potentially not followed have been updated. The correct numbers are: 11.3% (not 15.7%) of the patients in the siponimod group and 11.5% (not 15.8%) of the patients in the placebo group. These protocol deviations refer to instances where access rights were granted to treating physicians/team member in error to a database containing potentially unblinding heart rate data. The treating physicians/team member do not however rate the primary endpoint EDSS scores and had no access the EDSS scoring database. There could therefore not have been a direct impact on the primary endpoint due to this deviation. (The primary endpoint EDSS scores are obtained by the independent EDSS raters).	1	Thank you, we made changes needed regarding the values of potential blinding procedures not followed. The text was also changed into: While sensitivity analyses, excluding patients affected by potential unblinding, were reassuring, the potential for bias cannot be completely excluded
54	28-30	Comparison: Given the pooled information on both studies in the comparison, it was considered that there was a serious risk of bias associated with the domain 'blinding'. Therefore, it was decided to rate down the evidence quality by one level due to lack of blinding. Proposed amendment : It should be clarified that the "blinding procedures potentially not followed as explained in the previous comment, did not concern the EDSS primary endpoint. There were however a total of 3 EDSS raters who were in error granted access to the database containing potentially unblinding heart rate data. These 3 EDSS raters rated 13 patients in total. There was no actual unblinding or evidence that access to the database had been made. Excluding these patients in a sensitivity analysis on the 3mCDP EDSS-based primary endpoint showed statistically significant results in line with the primary analysis.	1	This comment is outside of the scope of the factual accuracy check.

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28	Table 5	Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease. Proposed amendment: Mayzent is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.	1	Thank you, we made changes needed
113	2	Evidence Gaps: Study design, Pragmatic RCTs and prospective cohort studies Proposed amendment: Novartis is working in collaboration with eight academic MS registries across Europe, two real world evidence studies (RWE) are ongoing in SPMS to characterize the population with a clinical diagnosis of SPMS and to explore the impact of different diagnostic definitions on population characteristics and prevalence. Three further RWE studies are planned incorporating data from a number of these registries. These studies are as follows: • Untreated SPMS patients in the real world setting compared with EXPAND placebo arm and siponimod EXPAND arm • Siponimod effectiveness versus real world comparator(s) including DMTs and best supportive care • Comparison of characteristics of real world siponimod users versus EXPAND population criteria It is anticipated that, over time, these RWE studies will help to reduce the level of uncertainty associated with comparisons of DMTs in SPMS, as highlighted by EUNetHTA	1	This comment is outside of the scope of the factual accuracy check.
19 (75)	50-51 (19-20)	The Authoring team considers that MAIC is an inappropriate method for indirect treatment comparison in the setting of the current assessment. Proposed amendment: If this statement (“MAIC is inappropriate”) is meant to refer to the active/relapsing subgroup, in which MAIC is not possible due to a lack of available data, the wording should be clarified to indicate this. Context could be added by framing this with some of the same limitations discussed in the introductory sections, for instance, that the between-trial heterogeneity of the subgroup is unknown because there were no subgroup-specific patient characteristics reported; due to this lack of reporting, it was not possible to conduct MAICs for the relapsing or active subgroup. An example of relevant context can be found on Page 13: *“To adjust for any*	1	Comment received based on 3rd draft of AR. This comment is outside of the scope of the factual accuracy check. However, the following sentence was added: *The Authoring team considers that MAIC is an inappropriate method for*

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		potential imbalance in patient characteristics across studies, the feasibility of population adjustment methods such as MAIC [12] or STC [11] was assessed. However, there was insufficient information on the baseline characteristics of the relapsing population subgroups in comparator trials to allow these analyses to be carried out, as they require these characteristics for adjustment. Therefore, no population adjustment methods could be undertaken in the "relapsing" SPMS subgroup." However, if this statement refers to MAICs in the overall randomized population, it appears that the statement is not evidence-based. It is not explained on what basis MAIC is considered "inappropriate" when comparing these heterogeneous trials in which treatment effect modifiers have been demonstrated, and for which it is acknowledged that bucher ITCs are confounded by heterogeneity.		*indirect treatment comparison in the setting of the current assessment. This is due to the inherent limitations of statistical techniques like MAIC [69], which has not been shown to produce less biased estimates than would be available through standard indirect comparisons, in the target population*
19 (75)	51-52 (20-21)	Additionally, the alleged advantage of matching and adjustment by the MAIC is not clear. <u>Proposed amendment</u>: The statement is not supported. A reader would need more information to better understand what the Authors mean by "not clear". Therefore, we propose that the statement is either clarified with supporting evidence or removed from the final Assessment Report.	1	Comment received based on 3rd draft of AR. This comment is outside of the scope of the factual accuracy check.
20 (75)	4-5 (25-26)	Siponimod in comparison with interferon-β-1a 22 µg once a week showed a statistically significant difference favouring siponimod <u>Proposed amendment</u>: The statement does not specify which outcome, population, study are being referred to, nor does it include the hazard ratio and CI. We propose that the statement is clarified by the Authors in the final Assessment Report.		Comment received based on 3rd draft of AR. This comment is outside of the scope of the factual accuracy check. This information can be found on the Summary of ancillary analysis - Table 4.15.

<table>
<tr><th>Page</th><th>Line</th><th>Comment</th><th>Character of comment[i]</th><th>Reply from author</th></tr>
<tr><td>16</td><td>1</td><td>
Table 0.2. Summary of relative outcomes in the relapsing SPMS population using Bucher ITCs

<u>Proposed amendment</u>:
The table lacks columns with subgroup results versus placebo which may limit usability for decision-makers. This omission could cause confusion for readers who are intending to populate models, which will usually require the values of each therapy versus placebo. We have included the table from our analysis below, note the “Siponimod vs. Placebo” and “Comparator vs. Placebo” columns. We suggest including these columns for full context and completeness and to aid decision-makers.

Technical Report Table D.2: Summary of Subgroup Bucher ITC Results for CDP-6, CDP-3, and ARR (Relapsing Subgroup)
<table>
<tr><th rowspan="3">Comparator Intervention</th><th rowspan="3">Regimen</th><th rowspan="3">Study ID(s)</th><th rowspan="3">Assumptions</th><th colspan="2">Siponimod vs. Placebo Subgroup from EXPAND IPD (95% CI)</th><th colspan="2">Comparator vs. Placebo Subgroup from Publication (95% CI)</th><th colspan="2">Subgroup Bucher ITC Results Siponimod vs. Comparator (95% CI)</th></tr>
<tr><th>Type</th><th>Value</th><th>Type</th><th>Value</th><th>Type</th><th>Value</th></tr>
<tr><td colspan="10">Time to CDP-6 in Subgroup: Patients with Relapses in the 4 Years Before Study</td></tr>
<tr><td>Rebif®
(SC IFNβ-1a)</td><td>22 µg qw</td><td>Nordic SPMS Study</td><td>-</td><td>HR</td><td>0.71
(0.54 - 0.93)</td><td>HR</td><td>1.01
(0.68 - 1.56)</td><td>HR</td><td>0.70
(0.43 - 1.15)</td></tr>
<tr><td colspan="10">Proportion with CDP-3 (33 months) in Subgroup: Patients with Relapses in the 2 Years Before Study</td></tr>
<tr><td>Betaferon®
(SC IFNβ-1b)</td><td>250 µg q2d</td><td>European Study</td><td>Imputation of censored data for EXPAND: Last observation carried forward*</td><td>OR</td><td>0.61
(0.42 - 0.88)</td><td>OR</td><td>0.69
(0.49 - 0.98)</td><td>OR</td><td>0.88
(0.53 - 1.47)</td></tr>
<tr><td>Betaferon</td><td>250 µg q2d</td><td>European</td><td>Compared</td><td>HR</td><td>0.67</td><td>ReR</td><td>0.83</td><td>ReR</td><td>0.81</td></tr>
</table>
</td><td>1</td><td>Comment received based on 3rd draft of AR.

This comment is outside of the scope of the factual accuracy check. Results of siponimod and comparators versus placebo are presented in Table 4.13.</td></tr>
</table>

Page	Line	Comment	Character of comment[i]	Reply from author

® (SC IFNβ-1b)		Study	subgroup ReR of European Study with subgroup time-to-event HR of EXPAND**		**(0.50 - 0.91)**		**(0.69 - 0.99)**	compared to HR**	(0.57 - 1.15)
Time to CDP-3 in Subgroup: Patients with Relapses in the 2 Years Before Study									
Rebif® (SC IFNβ-1a)	44 µg tiw‡	SPECTRIMS	-	HR	**0.67** **(0.49 - 0.91)**	HR	0.76 (0.53 - 1.10)	HR	0.88 (0.55 - 1.42)
ARR in Subgroup: Patients with Relapses in the 2 Years Before Study									
Rebif® (SC IFNβ-1a)	22 µg tiw	SPECTRIMS	SPECTRIMS: Assume the RR p-value = 0.001 in order to calculate the 95% CI†	RR	**0.58** **(0.40 - 0.84)**	RR	**0.53** **(0.36 - 0.77)** †	RR	1.10 (0.65 - 1.87)
Rebif® (SC IFNβ-1a)	44 µg tiw	SPECTRIMS		RR	**0.58** **(0.40 - 0.84)**	RR	**0.62** **(0.47 - 0.82)** †	RR	0.94 (0.59 - 1.49)

Statistically significant values are bolded.

*Last observation carried forward: censored patients are assumed to have the same status at the cut-off time-point as they did on the day they were censored. Note that **Complete Case** could not be derived from the EXPAND IPD due to the volume of censoring (in complete case, censored patients are removed from the data).

**Must be interpreted with caution.

†Analysis of the ARR outcome for the relapsing subgroup in SPECTRIMS required making an assumption about the p-value (reported as "<0.001 for both doses") in order to calculate the 95% CI, which was not reported. The p-value was assumed to equal 0.001 for each dose.

‡ Time to CDP-3 subgroup results not reported for the 22 µg dose in SPECTRIMS.

Abbreviations: CI = confidence interval; HR = hazard ratio; IFN = interferon; IPD = individual patient data; NR = not reported; OR = odds ratio; ReR = relative risk; RR = rate ratio.

[i] Character of comment
- 'major'=1
- minor'= 2

'linguistic'=3