EUnetHTA Joint Action 3 2016-2020

# 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***

## Project description and planning

INFARMED, Portugal

NCPE, Ireland



Template Version 2, December 2018

## Version Log

| Version number | Date | Modification | Reason for the modification |
|---|---|---|---|
| V1 | 07/05/2019 | First draft of the project plan | Developed PICO for survey and incorporated feedback from Member States |
| V2 | 28/05/2019 | Second draft of the project plan | Incorporated feedback from dedicated reviewers |
| Final version | 19/11/2019 | Third draft of the project plan | Final, after positive CHMP opinion release |

# Contents



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## List of abbreviations

| | |
|---|---|
| BVMT-R | Brief Visuospatial Memory Test Revised |
| CHMP | Committee for Medicinal Products for Human Use |
| CNS | Central Nervous System |
| CSR | Clinical Study Report |
| DMT | Disease Modifying Therapy |
| DOICU | Declaration of Interest and Confidentiality Undertaking |
| DR | Dedicated Reviewers |
| EAN | European Academy of Neurology |
| ECTRIMS | European Committee for Treatment and Research in Multiple Sclerosis |
| EPAR | European Public Assessment Report |
| EDSS | Expanded Disability Status Scale |
| EQ-5D | 5-Dimension European Quality of Life Questionnaire |
| EUnetHTA | European Network for Health Technology Assessment |
| F2F | Face to Face meeting |
| HRQoL | Health-Related Quality of Life |
| IV | Intravenous Therapy |
| MRI | Magnetic Resonance Imaging |
| MS | Multiple Sclerosis |
| MSIS-29 | Multiple Sclerosis Impact Scale |
| MSFC | Multiple Sclerosis Functional Composite |
| MSWS-12 | 12-Item Multiple Sclerosis Walking Scale |
| NEDA | No Evidence of Disease Activity |
| NICE | National Institute for Health and Care Excellence |
| PASAT | Progression of Paced Auditory Serial Addition Test |
| PICO | Patient, Intervention, Comparator and Outcome |
| pMAH | prospective Marketing Authorisation Holder |
| PMS | Progressive Multiple Sclerosis |
| PPMS | Primary Progressive Multiple Sclerosis |
| RCT | Randomized Controlled Trials |
| RRMS | Relapsing-Remitting Multiple Sclerosis |
| S1P | Sphingosine-1-phosphate |
| SDMT | Symbol Digit Modalities Test |
| SPMS | Secondary Progressive Multiple Sclerosis |

# 1 Introduction

On 13/3/2019, EUnetHTA and the prospective Marketing Authorisation Holder (pMAH) of siponimod (*Novartis)* agreed that EUnetHTA will perform a joint relative effectiveness assessment of siponimod for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS). Once finalised this assessment is made publicly available and can be used by European HTA bodies for their national processes supporting reimbursement and pricing decisions.

***Background***

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system (CNS) characterized by inflammation, demyelination, and degenerative changes including neuroaxonal loss and progressive atrophy (Compston & Coles, 2008). The exact etiology of MS remains unknown, although a number of factors have been identified that are associated to the risk of developing MS, both genetic and environmental (Compston & Coles, 2008).

Among studies that provided standardized estimations, the prevalence of MS in Europe varied from 170.5 per $10^5$ population in the Swedish county of Värmland (Boström, Callander, Kurtzke, & Landtblom, 2009), 154.5 per $10^5$ in Denmark (Bentzen, Meulengracht Flachs, Stenager, Brønnum-Hansen, & Koch-Henriksen, 2010) and 163 per $10^5$ in Seinäjoki, a district of Finland (Sarasoja, Wikström, Paltamaa, Hakama, & Sumelahti, 2004), to 70.6 per $10^5$ inhabitants in Las Palmas in the Canary Islands (Aladro et al., 2005). As for incidence, estimates varied from 7.6 per $10^5$ population in Oppland County, Norway, during 1994–98 (Risberg et al., 2011) and 11.6 per $10^5$ in Seinäjoki during 1979–93 to 4.1 per $10^5$ during 1998–2002 in Las Palmas (Aladro et al., 2005). These results seem to suggest a north to south gradient in the northern hemisphere (Leray, Moreau, Fromont, & Edan, 2016).

The 1996 US National Multiple Sclerosis Society Advisory Committee on Clinical Trials in Multiple Sclerosis defined four clinical subtypes of MS: relapsing-remitting, secondary progressive, primary progressive and progressive relapsing (Fred D Lublin & Reingold, 1996). The relapsing-remitting MS (RRMS) phenotype is the most common, as approximately 85% of those with MS initially experience relapses and remissions of neurological symptoms, with relapses often associated with new areas of CNS inflammation. The remaining patients diagnosed with MS, approximately 15%, have a gradual accrual of disability from disease onset, which is independent of relapses over time, known as primary progressive MS (PPMS). Progressive-relapsing (PR) MS was defined as a progressive disease from onset, with clear acute relapses, with or without full recovery, with periods between relapses characterized by continuing progression. One-half of those with RRMS may evolve into secondary progressive MS (Fred D Lublin & Reingold, 1996).

SPMS occurs after an initial relapsing course of the disease and a large proportion of subjects with RRMS will eventually go on to develop SPMS. In SPMS this gradual worsening can occur with or without additional inflammatory events. In most clinical contexts, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course. To date, there are no clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point when RRMS converts to SPMS; the transition is usually gradual (F.D. Lublin, 2014). The transition from relapsing-remitting MS to secondary progressive MS usually occurs within 10 to 20 years following disease onset (Eriksson, Andersen, & Runmarker, 2003).

In 2013, an international expert panel (International MS Phenotype Group) proposed a revision of the prior classification criteria to further characterize the clinical course of progressive MS (PMS). These changes included categorization of disease course in PMS as either having active inflammation (so-called “active”) or not having active inflammation (so-called “non-active”) based upon the presence or absence of clinical relapses, assessed at least annually, and/or magnetic resonance imaging (MRI) signs of activity (contrast-enhancing lesions or new and unequivocally enlarging T2 lesions) (F.D. Lublin, 2014). The

expert panel also recommended classifying PMS based on the presence or absence of gradual clinical disease progression, measured by clinical evaluation, assessed at least annually. Thus, disease "progression" is a measure of disability, and it is independently quantified from relapses; it is characteristic of PPMS and SPMS. The phenotype of progressive disease (PPMS and SPMS) can be characterized as one of the following:

- Active and with progression
- Active but without progression
- Not active but with progression
- Not active and without progression (stable disease)

So, for example, according with this classification, a patient with SPMS who has gradually worsened and has gadolinium-enhancing lesions on MRI is classified as active and progressing SPMS.

More recently, the term relapsing MS (RMS) has also been used to describe both RRMS and SPMS patients with superimposed relapses (EMA, 2015). Patients with RMS, whether or not they suffer from neurologic progression in the absence of relapses, have a common, inflammatory pathophysiology and, therefore, constitute a common target for treatment.

To evaluate the efficacy of a product in preventing disability progression in SPMS, it is recommended to target only SPMS patients without a recent relapse and no MRI activity suggestive of active inflammation, and with evidence of recent progression independently of relapses (EMA, 2015).

The most commonly used metric to assess disability progression over time in MS patients is the Expanded Disability Status Scale (EDSS). It is an ordinal scale ranging from 0 to 10 in 0.5 point increments (Kurtzke, 1983)(Kurtzke, 1983). The Multiple Sclerosis Functional Composite (MSFC) is another quantitative measure of MS related disability that includes arm, leg, visual, and cognitive components (Fischer, Rudick, Cutter, & Reingold, 1999).

Interferon beta-1b was the first disease modifying therapy (DMT) for MS to receive regulatory approval. Since then, significant advances were made and several DMTs have been approved for the treatment of MS. Most approved therapies target various immune cells that contribute to the inflammatory cascade identified in MS. However, overall, the efficacy of MS treatments seems to be higher in the earlier stages of RRMS and decrease over time. The following therapies are indicated in the treatment of relapsing multiple sclerosis: glatiramer acetate, Interferon beta preparations, cladribine, dymethyl-fumarate, fingolimod, teriflunomide, alentuzumab, mitoxantrone, natalizumab, ocrelizumab. According to surveys of clinical practice, these drugs are often also used in patients with SPMS with evidence of disease activity, but there is no agreement on the treatment choice (Fernández et al., 2018) (Khan, Miller, Tornatore, Theodore Phillips, & Barnes, 2012). These surveys also acknowledge the difficulties in detecting when patients transition from RRMS to SPMS and in incorporating the recent revisions of the classification of disease course (into active and non-active forms of progressive MS) into clinical practice.

Only one therapy (ocrelizumab) has recently been shown to reduce the risk of progression in PPMS (Montalban et al., 2017).

***The technology***

Siponimod is a selective sphingosine-1-phosphate (S1P) receptor modulator that prevents egress of lymphocytes from secondary lymph organs and their entry into the CNS. Siponimod also crosses the blood brain barrier and may have direct neuroprotective effects in the CNS by directly interfering with ongoing S1P1-mediated astroglial inflammatory processes and/or stimulating S1P5-mediated pro-remyelination repair mechanisms. It is similar in activity to fingolimod, which is another S1P receptor modulator that is approved for RRMS (Dumitrescu, Constantinescu, & Tanasescu, 2019). Fingolimod

phosphate also binds to S1P receptor located on lymphocytes and also readily crosses the blood-brain barrier.

***Current clinical management***

In the European trial of Betaferon® in SPMS (EUSP), interferon beta-1b was associated with lengthened time to onset of sustained progression of disability as measured by the EDSS. This treatment effect, independent of baseline EDSS score and previous relapses, led to the approval of interferon beta-1b for patients with SPMS in Europe and Canada (Kappos et al., 2004). However, similar benefits were not found in the other phase III trials: the North American trial of interferon beta-1b (Betaseron®), the Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in Multiple Sclerosis (SPECTRIMS) trial of interferon beta-1a (Rebif®) (Francis, 2001), and the International Multiple Sclerosis Secondary Progressive Avonex Controlled Trial (IMPACT) of interferon beta-1a (Avonex®) (Cohen et al., 2002) (Montalban et al., 2018). Some investigators have suggested that different treatment effects measured by the EDSS in these clinical trials reflect fundamental differences in the cohorts of patients. Patients in the European trial were, on average, younger and less likely to be free of exacerbations for 2 years before study enrolment than those in the other trials (Kappos et al., 2004). Consistent with this interpretation, the National Institute for Health and Care Excellence (NICE) in the UK recommended withdrawal of approval for interferon beta1b for patients with SPMS without superimposed relapses. According to the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) / European Academy of Neurology (EAN) guidelines on the pharmacological treatment of MS, treatment with interferon beta-1a (subcutaneously) or interferon beta-1b should be considered in patients with active secondary progressive MS taking into account, in discussion with the patient, the uncertain efficacy, as well as the safety and tolerability profile of these drugs (Montalban et al., 2018).

Mitoxantrone is an anthracycline analogue that is used as a chemotherapeutic agent for some cancers. Small randomized controlled trials (RCT) found that mitoxantrone is effective for patients with worsening RRMS or SPMS, particularly in patients with superimposed relapses. However, the risks of cardiotoxicity and potential for the development of leukaemia with mitoxantrone limit its utility. The largest trial of mitoxantrone in MS was a single multicentre, double-blind trial of 194 patients with worsening RRMS or SPMS (worsening defined as 1·0 or more EDSS points during the 18 months before enrolment) (Hartung et al., 2018). Patients were randomly assigned to treatment with Intravenous therapy (IV) mitoxantrone or placebo every three months for two years. Treatment with mitoxantrone was associated with significant clinical benefits compared with placebo on multivariate analysis, reducing progression of disability and clinical exacerbations. According to the ECTRIMS/EAN guidelines, treatment with mitoxantrone should be considered in patients with active SPMS taking into account, in discussion with the patient, the efficacy and specifically the safety and tolerability profile of this agent.

Ocrelizumab is a recombinant human anti-CD20 monoclonal antibody that binds to a different, but overlapping, CD20 epitope from that of rituximab. Evidence from large randomized trials have shown that, in patients with relapsing MS, with at least 2 documented clinical relapses within the last 2 years prior to screening or one clinical relapses in the year prior to screening, ocrelizumab was more effective than interferon beta1a for reducing relapses and, in the pooled analysis, disability progression. This trial did not specifically include patients with SPMS (Hauser et al., 2016). Ocrelizumab was also the first drug approved in the EU for the treatment of adult patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity (Montalban et al., 2017).

Natalizumab is a recombinant monoclonal antibody directed against the alpha-4 sub-unit of integrin molecules, thereby blocking integrin association with vascular receptors and limiting adhesion and transmigration of leukocytes. Natalizumab is a highly effective drug for the treatment of RRMS. However, in a phase III placebo-controlled trial in patients with SPMS for at least 2 years and disability progression unrelated to relapses in the previous year (ASCEND), Natalizumab did not significantly reduce disability progression as assessed by the primary multicomponent endpoint and secondary endpoints. However,

progression of the upper limb component of the primary disability endpoint was reduced (Kapoor et al., 2018).

Cladribine is a nucleoside analogue of deoxyadenosine that selectively depletes dividing and non-dividing T and B cells implicated in the pathogenesis of MS. Cladribine is approved in RMS. Controlled trials of cladribine have not shown consistent benefit specifically for patients with progressive forms of MS, although some data suggest benefit for patients with SPMS. Cladribine was associated with a reduction of the signs of imaging activity in two trials of patients with progressive forms of MS (Sipe et al., 1994) (Rice, Filippi, & Comi, 2000). No significant treatment effects were found, however, for cladribine in terms of disability progression.

Fingolimod is a sphingosine analogue that modulates the S1P receptor and thereby alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes. There is evidence from several RCT that fingolimod is effective in reducing the relapse rate in patients with RRMS. In a trial of patients with PPMS (INFORMS trial), fingolimod compared with placebo failed to slow disease progression (Fred D Lublin & Reingold, 1996) (F. Lublin et al., 2016). No studies have accessed the efficacy of fingolimod in SPMS.

Although treatment with Rituximab in patients with PPMS was not associated with delayed time to confirmed disease progression in the OLYMPUS trial (Hawker et al., 2009) the available information on treatment practices for MS in Europe suggests that rituximab is occasionally used in the treatment of SPMS (Fernández et al., 2018).

The study of dimethyl fumarate in SPMS (INSPIRE) was terminated early by the sponsor for business reasons. Efficacy, patient-reported outcomes, and pharmacodynamic data were not analysed (in Clinicaltrials.gov, accessed 29th March 2019). Teriflunomide and alemtuzumab have not been studied in SPMS. A Cochrane review concluded that glatiramer acetate is not effective in progressive MS patients (Loredana La Mantia, Munari, & Lovati, 2010). The available information on treatment practices for MS in Europe, suggests that dimethyl fumarate, teriflunomide and glatiramer acetate are seldom used in the treatment of SPMS (Fernández et al., 2018).

Older immunomodulators, including steroids (Goodkin et al., 1998), azathioprine (Casetta, Iuliano, & Filippini, 2010) , methotrexate (Gray, McDonnell, & Forbes, 2006) and cyclophosphamide (L. La Mantia, Milanese, Mascoli, D'Amico, & Weinstock-Guttman, 2007), have also been studied in patients with MS and results have not showed a convincing benefit on progression.

Finally, in a trial, a synthetic peptide analogue of myelin basic protein (MBP8298) was found to be ineffective in SPMS (Freedman et al., 2011).

According to a recent survey of diagnostic and treatment practices for MS in Europe, most respondents agreed that in RRMS patients converting to a clinically apparent progressive course with evidence of MRI activity, treatment with ongoing injectable DMT should be changed. However, there was no agreement on what the new treatment should be. Second-line treatments (fingolimod and natalizumab) received the highest proportion of responses (≈30% for each). Furthermore, as a general rule, treatment with DMT was only initiated in patients with SPMS who experience Gadolinium positive lesions or exacerbations (Fernández et al., 2018).

Additionally, in this survey, there was general agreement that treatment with a DMT should only be initiated in patients with SPMS who experience contrast-enhancing lesions or exacerbations (Fernández et al., 2018).

Thus, considering the lack of a European-wide agreed reference comparator, and following the EUnetHTA guidelines for comparators and comparisons, interventions routinely used in clinical practice were chosen as comparators.

# 2 Research question and scope

The aim of this project is to compare the clinical effectiveness and safety of siponimod in the target patient populations with relevant comparators. The target patient populations and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope below.

One agency requested RRMS as an additional population in the PICO, due to the national reimbursement system. The authors acknowledge that different systems may have valid requirements for the PICO, however in this case RRMS is considered out of the scope of both the EMA and the EUnetHTA submission and is therefore not included.

The following table provides the scope identified for the assessment of siponimod.

*Table 2-1: Assessment scope: relevant PICO(s) identified for the planned assessment*

| **Description** | **Assessment scope** | | |
|---|---|---|---|
| **PICO 1** | | | |
| **Population** | Adult patients with SPMS, classified as active, evidenced by relapses and/or MRI signs of activity (contrast-enhancing lesions or new and unequivocally enlarging T2 lesions): | | |
| **Intervention** | Siponimod in combination with best supportive care* | | |
| **Comparison** | - Interferon beta-1a and 1b plus best supportive care*<br>- Mitoxantrone plus best supportive care*<br>- Ocrelizumab plus best supportive care*<br>- Natalizumab plus best supportive care*<br>- Fingolimod plus best supportive care*<br>- Cladribine plus best supportive care*<br>- Rituximab plus best supportive care* | | |
| **Outcomes** | **Clinical effectiveness** | **Rate [b]** | **Relative importance** |
| | Confirmed Disability Progression at 6 months [a] | 9 | critical |
| | Other measures of Disability Progression [a] (e.g., Confirmed disability progression at 3 months, Time to confirmed disability progression (CDP), Timed 25-foot walk test, and 9-hole peg test, Multiple Sclerosis Walking Scale (MSWS-12), rate of patients that become confined to wheelchair use, time to wheelchair, progression of Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT) or Brief Visuospatial Memory Test Revised (BVMT-R). | 8 | critical |
| | Symptoms [a] (e.g., fatigue, cognitive, bowel and bladder dysfunction) | 7 | critical |
| | Clinical Relapse (e.g. annualized relapse rate, proportion of patients relapse-free) | 7 | critical |
| | Mortality | 9 | critical |
| | Health-Related Quality Of Life [a] (HRQoL) (e.g. 5-dimension European Quality of Life questionnaire (EQ-5D), Multiple Sclerosis Impact Scale (MSIS-29) | 9 | critical |
| | MRI Inflammatory measured disease activity and burden of disease (T1 Gd-enhancing lesions, new or enlarging T2 lesions, brain volume) | 5 | important |

| | | | |
|---|---|---|---|
| | No evidence of disease activity (NEDA - absence of progression, relapses and MRI-activity) | 5 | important |
| | **Safety** | | |
| | Adverse events [a] | 6 | important |
| | Serious adverse events | 8 | critical |
| | Adverse events leading to treatment discontinuation | 7 | critical |
| | Treatment-related mortality | 9 | critical |

** Best supportive care defined as symptomatic management through targeted physical therapy and symptomatic pharmacological interventions as fampridine for gait difficulties, and baclofen or tizanidine for spasticity. DMTs are excluded from best supportive care.*

[a] *Outcomes that are related to issues particularly emphasised by patient organisations.*

[b] *According to the GRADE methodology, authors of a drug assessment must, as a first step in a drug assessment process, make a preliminary classification of the importance of the selected outcomes.*
*The outcomes were rated on a 1-9 scale, in which critical outcomes were scored 7-9, important outcomes were scored 4-6, and non-important outcomes were scored 1-3.*
*Each author scored separately each outcome, and the final score was the arithmetic mean (the average of the set of numerical values, as calculated by adding them together and dividing by the number of terms in the set) of the scores attributed by 3 authors.*
*Authors have also taken into account patients' perspective expressed during the scoping phase.*

# 3 Methods

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, will be consulted throughout the assessment process.

## 3.1 Inclusion criteria

During the assessment, the inclusion criteria applied by the pMAH will be checked to evaluate if they capture the PICO defined for the assessment. In addition, the following criteria are considered relevant for study inclusion:

- Study design: Randomized controlled trials

## 3.2 Information retrieval

The assessment will be based on a submission dossier submitted by the pMAH. To allow for a meaningful assessment, the submission dossier has to be complete with regard to the available evidence relevant for the research question(s). This requires the systematic identification of all published and unpublished studies relevant to the assessment according to the research question and scope defined in Section 2. The assessment will investigate whether these requirements are met and thus whether the evidence base for the assessment is complete.

The cut-off date for the pMAH's list of sponsored studies and the searches should be a maximum of three months before submission (of the submission dossier). This cut-off date will also be relevant for the assessment. There will be no updates of searches beyond this cut-off by the authors of the assessment.

During the assessment, the evidence base with regard to the drug under assessment provided by the pMAH will be reviewed. Search strategies will be checked for appropriateness and the results of information retrieval included in the pMAH's submission dossier will be checked for completeness against a search in study registries and against the studies included in the regulatory assessment report. If there are major flaws in the search conducted by the manufacturer, further supplementary searches, as appropriate, will be conducted to check for possible incompleteness of the study pool. The search date, complete search strategies and the results of these searches will be reported in the assessment.

If the evidence provided in the submission dossier is incomplete it will not be supplemented by own searches and analyses by the authors of the assessment. The incompleteness and its consequences for the conclusions of the report will be described in the assessment report.

## 3.3 Data analysis and synthesis

The assessment will be based on the data and analyses included in the submission dossier prepared by the pMAH. During the assessment, the completeness of data and analyses in the submission dossier will be verified. Furthermore, the methods for data analysis and synthesis applied by the pMAH will be checked against the requirements of the submission dossier and applicable EUnetHTA Guidelines and assessed with regard to scientific validity. The results of this assessment and the results of the included studies, as appropriate, will be presented in the assessment report according to the research questions defined in Section 2.

### 3.3.1 Data extraction

Information used for the assessment of benefits and harms will be extracted from the submission dossier and verified against the Clinical Study Reports (CSR) or other original documentation provided in the submission dossier.

### 3.3.2 Assessment of risk of bias

The quality of the body of evidence of pairwise meta-analysis will be assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology. The assessment of risk of bias will follow the criteria described in the two EUnetHTA guidelines on the internal validity of randomised controlled trials and non-randomised studies on interventions. The risk of bias of the results will be described separately for each patient-relevant outcome.

Rating the confidence in treatment effect estimates from network meta-analysis, will be based on threshold analysis (Phillippo et al., 2019), and evaluation of the network meta-analysis will be based on the principles described in the EUnetHTA Guideline on Direct and indirect comparisons.

During the assessment, the methods and outcome of the risk-of-bias assessment presented in the submission dossier will be evaluated. Risk-of-bias will be assessed by the authors only for outcomes (and studies) that are included based on the research question(s) (PICO). The result of the risk-of-bias assessment will be presented in the assessment report.

### 3.3.3 Description of design and results of individual studies

During the assessment, the information in the submission dossier on the study design, study methods, populations, endpoints (patient relevance, validity, and operationalization) and study results will be evaluated. The results of this evaluation will be presented, used for identification of relevant analyses and considered for the conclusions of the assessment report.

### 3.3.4 Synthesis of study results

#### Meta-analyses

If several studies are available for the same PICO, they will be quantitatively pooled in a meta-analysis if they are sufficiently comparable from a clinical (e.g. patient groups) and methodological (e.g. study design) point of view.

During the assessment, the methods applied for the meta-analyses presented in the submission dossier, and, if applicable, the justification for deviations from the procedures described above will be evaluated. The meta-analyses relevant for the research questions (see Section 2) will be presented in the assessment report.

#### Sensitivity analyses

To evaluate the robustness of results, sensitivity analyses with regard to methodological factors presented in the submission dossier and the corresponding methods applied will be evaluated. These methodological factors arise from decisions made within the framework of the retrieval and assessment of information, for example, the specification of cut-offs for the time point of data collection or the choice of effect measure. The sensitivity analysis will in particular consider the classification of the risk of bias of study results. The result of the sensitivity analysis can affect the assessment of the certainty of results.

#### Subgroup analyses and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the submission dossier and the corresponding methods applied will be evaluated. The evaluation also includes the justification for the choice of cut-offs if quantitative characteristics were categorized. If potential effect modifiers are identified, the conclusions inferred from the effects observed in the complete patient group can possibly be formulated more precisely.

### Indirect comparisons

If indirect comparisons are included in the submission dossier, the methods applied, and if applicable, the justification in the event of deviations from the required approaches will be evaluated. The indirect comparisons relevant for the research questions (see Section 2) will be presented and examined in the assessment report.

## 3.4 Patient involvement

At the start of this Joint Assessment an open call for patient input was published on the EUnetHTA website. This open call specifically asked patient organisations to answer the questions, as they have the position to collect and present patient's and care-givers' views and experiences by engaging with a wide range of patients and their careers.

The open call used by EUnetHTA asks general questions to elicit patients' views on living with the disease, important outcomes to be considered in this assessment and expectations about the drug under assessment. The questions are based on the HTAi questionnaire template. For more information on the development of the HTAi questionnaire template please see their website.

European and national patient organisations had to provide an organisational perspective on the questions in English. In all parts of the open call, the term 'patient' refers to anyone living with, or who has lived with, the condition for which the new medicine is indicated. Four patient organisations completed the survey, namely MS Society of Slovakia, Russian MS organisation, Smaragd sclerosis multiplexes betegek egyesülete (Hungary) and Združenie Sklerosis multiplex Nádej (Slovakia).

In addition, EUnetHTA reached out via email to the patient organisations who responded to the open call for input on the ranking of outcomes. None of the patient organisations responded to this additional request for information.

The information gathered from the open call was used to inform the scope of this assessment, in particular the outcomes to be considered. In the PICO table, the outcomes that are related to issues particularly emphasised by patient organisations are marked by an "a". The frequency and route of administration was also mentioned as important points to take into account.

Comments were received regarding how SPMS affects carers/unpaid care-givers. Even though this assessment will focus on patient relevant outcomes, the costs (humans and financial) of carers/unpaid care-givers may be captured at national level in an economic assessment with a society perspective.

# 4 Project organisation

## 4.1 Participants

*Table 4-1: Project participants*

| | Agency | Role in the project | Country | Distribution of work |
|---|---|---|---|---|
| Assessment team | | | | |
| 1. | National Authority of Medicines and Health Products, I.P. [INFARMED] | Author | Portugal | |
| 2. | National Centre for Pharmacoeconomics [NCPE] | Co-Author | Ireland | |
| 3. | National Authority of Medicines and Health Products, I.P. [INFARMED] | Information specialist | Portugal | Review of information retrieval, conduct of searches required for checking completeness of information retrieval in submission dossier; reporting information retrieval check in the assessment report |
| 4. | National Authority of Medicines and Health Products, I.P. [INFARMED] | Statistical specialist | Portugal | Expert review of statistical analyses presented in submission dossier, statistical support for authors |
| 5. | National Centre for Pharmacoeconomics [NCPE] | Statistical specialist | Ireland | Expert review of statistical analyses presented in submission dossier, statistical support for authors |
| 6. | Italian Medicines Agency [AIFA] | Dedicated Reviewer | Italy | |
| 7. | Directorate of the Canary Islands Health Service [SESCS/Funcanis] | Dedicated Reviewer | Spain | |
| 8. | Zorginstituut Nederland [ZIN] | Dedicated Reviewer | Netherlands | |
| 9. | Regione Emilia-Romagna [RER] | Dedicated Reviewer | Italy | |
| Contributors | | | | |
| 10. | PD Dr. med. Clemens Warnke | External expert | Germany | Answer specific question during the assessment. |

| | | | | |
|---|---|---|---|---|
| 11. | MS Society of Slovakia,<br>Russian MS organisation,<br>Smaragd sclerosis multiplexes betegek egyesülete (Hungary)<br>Združenie Sklerosis multiplex Nádej (Slovakia). | Patient organisations | | Complete the EUnetHTA open call in order to inform the scope of the assessment. Rank identified outcomes on importance. |
| 12. | Nextgenediting | Medical Editor | | Responsible for the medical editing of the report |
| 13. | Zorginstituut Nederland [ZIN] | Project Manager | Netherlands | Coordination between involved parties throughout the assessment period |

## 4.2 Project stakeholders

*Table 4-2: Project stakeholders*

| **Organisation** | **Role in the project** |
|---|---|
| Novartis | Manufacturer [MAH];<br>Completing the submission dossier;<br>Fact check of the draft assessment report |

## 4.3 Milestones and deliverables

*Table 4-3: Milestones and deliverables*

| Milestones/Deliverables | Start date | End date |
|---|---|---|
| **Project duration** | **13-03-2019** | **13-02-2020** |
| Letter of Intent received | 13-03-2019 | |
| **Scoping phase** | **25-02-2019** | **14-11-2019** |
| Scoping PICO and development of first draft Project Plan | 25-02-2019 | 07-05-2019 |
| PICO survey – request relevant PICO from Member States | 05-04-2019 | 19-04-2019 |
| Adapt draft Project Plan based on PICO survey | 19-04-2019 | 07-05-2019 |
| Open call for patient input | 28-03-2019 | 26-05-2019 |
| Review of first draft Project Plan | 07-05-2019 | 15-05-2019 |
| Development of second draft Project Plan & answers to DR comments | 16-05-2019 | 28-05-2019 |
| Receive scoping F2F meeting documents from pMAH | 03-06-2019 | |
| Pre-scoping e-meeting with the assessment team | 27-06-2019 | |
| Share discussion topics for Scoping F2F Meeting | 05-07-2019 | |
| Scoping F2F meeting with manufacturer | 11-07-2019 | |
| Share action points from F2F meeting with manufacturer | 19-07-2019 | |
| **(pre-)Assessment phase** | **21-09-2019** | **14-11-2019** |
| Receive Submission Dossier from pMAH | 20-09-2019 | |
| Check formal completeness of Submission Dossier | 21-09-2019 | 01-10-2019 |
| Receive missing items and comments on the requests from the formal completeness check from pMAH | 05-10-2019 | |
| Start writing Assessment (background, methods) | 06-10-2019 | 14-11-2019 |
| CHMP opinion (expected date) | 14-11-2019 | |
| Finalize Project Plan | 15-11-2019 | |
| Optional: Grace period to revise Submission Dossier by pMAH (based on CHMP opinion) | TBD | |
| **Assessment phase** | **14-11-2019** | **13-02-2020** |
| Writing first draft Joint Assessment | 14-11-2019 | 06-01-2020 |
| Review by DRs (and if applicable include experts) | 07-01-2020 | 15-01-2020 |
| Writing second draft Joint Assessment | 16-01-2020 | 27-01-2020 |
| Medical Editing | 28-01-2020 | 01-02-2020 |

| | | |
|---|---|---|
| Fact Check by pMAH (parallel with medical editing) | 28-01-2020 | 01-02-2020 |
| Final Assessment + response Fact Check | 11-02-2020 | |
| Expected EPAR | 07-02-2020 | |
| Publication final version of rapid assessment | 12-02-2020 | 13-02-2020 |

## 4.4 Conflict of interest management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised "Declaration of Interest and Confidentiality Undertaking" (DOICU) statement.

Authors, co-authors and dedicated reviewers who declare a conflict of interest will be excluded from parts of or the whole work on this specific topic. However, they may still be included in other assessments.

For external experts and patients, conflict of interest declarations are collected with regard to the topic. External experts or patients who declare conflict of interest will be excluded from parts of or the whole work on this specific topic. However, they may still be included in other assessments.

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