Official Title: An Open-Label Study to Evaluate the Efficacy and Safety of Ocrelizumab in Patients With Relapsing Remitting Multiple Sclerosis who Have a Suboptimal Response to an Adequate Course of Disease-Modifying Treatment

NCT Number: NCT02861014

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PROTOCOL TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**
PROTOCOL NUMBER:	MA30005
VERSION NUMBER:	5
EUDRACT NUMBER:	2015-005597-38
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TEST PRODUCT:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	
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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	04-Nov-2018 19:16:13

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol MA30005 has been amended with the following:

1. Updates to the safety risks associated with Ocrelizumab

Section 5.1 (Safety Plan) was updated in order to include information based on the updated core safety text and interim results of the vaccination study BN29739 (VELOCE), which evaluated the effects of ocrelizumab on the immune response in patients with relapsing forms of multiple sclerosis. This new information is considered a substantial change because it may impact the safety of the patients. The information pertaining to the risk of 'impaired immunization response' has been updated accordingly in the protocol and has been moved from 'Potential risks' to 'Identified Risks and Adverse Drug Reactions'. The Addendum to Investigators Brochure (IB) v16, dated April 2018, also includes this relevant information, and this amendment aligns the MA30005 protocol with the latest IB.

2. Clarification about the "Follow-up Period" for patients switching to commercial drug

Text was added to clarify that those patients who decide to leave the study and switch to commercially marketed ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

3. Changes in Section 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Minor changes in the text were applied to clarify the statistical approach and to align with the rest of the ocrelizumab clinical development program.

4. Clarification about the pregnancy and treatment discontinuation

Clarification was added to the study treatment discontinuation rules (Section 4.6.2): "in case of pregnancy, treatment should be interrupted, and the patient should be monitored for safety; however, the patient can be re-started with the treatment after the pregnancy and breastfeeding period. During pregnancy and breastfeeding, the patient will continue to come for regular schedule visits as per the protocol and will perform all assessments except MRI"

This does not change the existing requirement for the patients who become pregnant to discontinue study treatment, but allows the return to the study treatment after the end of pregnancy (independent of the pregnancy outcome).

5. Correction of the frequency of HBV DNA PCR test to 24 weeks instead of 12 weeks

For enrolled patients with negative HBsAg and positive total HBcAb, HBV DNA screening (by PCR) must be repeated every 24 weeks. In the previous protocol versions, it was erroneously stated the PCR test must be repeated every 12 weeks. The change to 24 weeks aligns the PCR frequency with the 24-week-frequency of the clinical visits as per Schedule of Assessment.

6. Inclusion of instructions around the optional use of a Patient Diary

Section 4.5.12 and Appendix 7 were included to provide instructions about the use of a Patient Diary and as optional additional tool to help the patient and the site with the collection and reporting of AEs and concomitant medications.

7. Correction of the start of safety follow-up for patients who discontinue study treatment early

Throughout the protocol, the change was made to clarify that the patients who discontinue treatment early will be followed up for at least 96 weeks after the Early Treatment Discontinuation Visit, and not after the last infusion of study drug.

8. Correction in the adverse event reporting period

Throughout the protocol, the inconsistencies in the adverse event reporting period was corrected from '48 weeks after the last dose of the study drug' to '96 weeks after the end of the Treatment Period' to align with the duration of the Safety Follow-up of 96 weeks.

PROTOCOL AMENDMENT, VERSION 5:
SUMMARY OF CHANGES

Substantive new information appears in italics. Deleted text is shown in strike-through mode.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

3.1 DESCRIPTION OF THE STUDY

Follow-up Period: Patients who discontinue treatment early will be followed up for at least 96 weeks after the *Early Treatment Discontinuation Visit* ~~last infusion of study drug~~. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate long-term extension (LTE) study, will be followed up for at least 96 weeks after the end of the Treatment Period. *Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.*

3.1.3 Treatment Period

Patients who discontinue treatment early will be followed up for at least 96 weeks after the *Early Treatment Discontinuation Visit* ~~last infusion of study drug~~. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate ~~long-term extension (~~LTE~~)~~ study, will be followed up for at least 96 weeks after the end of the Treatment Period (see Section 3.1.4). *Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.*

3.1.4 Follow-up Period

Patients who discontinue treatment early will be followed up for at least 96 weeks after the *Early Treatment Discontinuation Visit* ~~last infusion of study drug~~ . Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate ~~long-term extension (~~LTE~~)~~ study, will be followed up for at least 96 weeks after the end of the Treatment Period.

Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

Any patient whose peripheral blood B-cell count remains depleted after this period will continue to be monitored at 24-week intervals until the B-cell count has returned to the baseline value or to lower limit of normal (LLN) range, whichever is lower.

Figure 4 provides an overview of the Follow-up Period, which is the variable B-cell monitoring period. A schedule of assessments for the Follow-up Period is presented in Appendix 2.

During the Follow-up Period, patients will be formally assessed at clinical visits every 24 weeks and by telephone contacts every 8 weeks. If further B-cell monitoring is required and the patient is not receiving any other B-cell targeted therapy, assessments will take place at clinical visits every 24 weeks and by telephone contacts every 8 weeks until the B-cells are repleted. See Appendix 2 for further details.

After initiation of study drug, all adverse events will be reported until 96 weeks after the end of the Treatment Period but may be extended in patients whose B-cells take longer to replete.

Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

~~Unrelated SAEs must be collected and reported during the study through the end of the Safety Follow Up Period, which is at least 96 weeks after the last infusion, but may be extended in patients whose B-cells take longer to replete. Non serious adverse events have to be reported until the end of Safety Follow up Period.~~

4.5.8 Laboratory, Biomarker, and Other Biological Samples

- Viral serology and detection:
  - For enrolled patients with negative HBsAg and positive total HBcAb, Hepatitis B virus (HBV) DNA (by PCR) must be repeated every ~~12~~*24* weeks

4.5.12 Patient Diary (optional)

Due to the low frequency of study visits (every 6 months) and the structured telephone interviews (every 8 weeks between the study visits), patient diaries are proposed as an additional optional tool to help further improve the collection and documentation of Adverse Events and concomitant medications. The decision to use the patient diary is left to the discretion of each investigator. The investigator must ensure that required EC/IRB approval was obtained before implementing the patient diary at his/her site.

Additional instructions around the use of an optional Patient Diary are provided in Appendix 7.

4.6.2 Study Treatment Discontinuation

- *Ongoing* pregnancy *or breastfeeding (in case of pregnancy, treatment should be interrupted, and the patient should be monitored for safety; however, the patient can be re-started with the treatment after the pregnancy and breastfeeding period. During pregnancy and breastfeeding, the patient will continue to come for the regular schedule visits as per the protocol and will perform all assessments except MRI).*

4.6.4 End of study treatment

At the end of the study treatment the patients will be encouraged to be included in a separate ~~Long-term Extension (~~LTE~~)~~ study to further evaluate the efficacy and safety of their DMT treatment, and this is independent of the DMT. This LTE will also aim to evaluate the relationship between the primary endpoint of this study and long-term outcome.

Patients who discontinue treatment early will be followed up for at least 96 weeks after the *Early Treatment Discontinuation Visit* ~~last infusion of study drug~~. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate ~~long-term extension (~~LTE~~)~~ study, will be followed up for at least 96 weeks after the end of the Treatment Period. (see Section 3.1.4). *Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.*

Section 5.1 SAFETY PLAN

Administration of ocrelizumab will be performed in a hospital, clinic environment or doctor's office/practice under close supervision of the investigator or a medically qualified staff member with immediate availability of full resuscitation facilities. All adverse events and serious adverse events will be recorded during the study and *until* ~~at 24, and 48~~ *96* weeks after the *end of the Treatment Period*~~last dose of ocrelizumab~~ as provided through this study.

5.1.1.1 Identified Risks and Adverse Drug Reactions

Infusion-Related Reactions (IRRs)

All CD20 depleting agents administered via the intravenous route, including ocrelizumab have been associated with acute IRRs. *Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab in order to reduce frequency and severity of IRRs),* ~~S~~symptoms of IRRs may occur during any ocrelizumab infusion but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. *Across the RMS and PPMS trials, symptoms associated with IRRs included, but were not limited to:* ~~These reactions may present as~~ pruritus, rash, urticaria, erythema, throat irritation,

oropharyngeal pain, dyspnoea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea and tachycardia.

Infections

~~Peripheral B-cell depletion is an expected outcome of ocrelizumab use. Beyond the clinical trial experience of patients switching from beta interferon or glatiramer acetate to ocrelizumab, there are limited data on switching patients from other disease modifying therapies.~~

~~When switching patients from another disease modifying therapy to ocrelizumab, the half-life and mode of action of the other therapy must be considered, to take into consideration the potential for overlapping pharmacodynamic effects, whilst at the same time minimising the risk of disease reactivation.~~

In interventional clinical studies ~~T~~there were no reports of hepatitis B reactivation in MS patients treated with ocrelizumab, but it had been reported in one RA patient treated with ocrelizumab.

~~For PML see "Potential risks" below.~~Delay ocrelizumab administration in patients with an active infection until the infection is resolved.

For PML see "Potential risks" below.

Decrease in immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total immunoglobulins (Ig) over the controlled period of the studies, mainly driven by reduction in IgM, with no observed association with serious infections *during the controlled periods*. The proportion of patients with decrease in Igs below LLN increased over time and with successive dosing. Based on additional patient exposure, in cases of continuous decrease over time, a higher risk of serious infection cannot be ruled out (see below in potential risks section).

Impaired Response to Vaccination

After treatment with ocrelizumab over 2 years in pivotal clinical trials, the proportion of patients with positive antibody titers against streptococcus pneumoniae, mumps, rubella, and varicella were generally similar to the proportions at baseline.

The results of the randomized, open-label Phase IIIb study (BN29739) that assessed if ocrelizumab recipients with RMS raise adequate humoral responses to selected vaccines indicate that patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The results are summarized in the current version of the IB.

Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab. For seasonal influenza vaccines, it is still recommended to vaccinate

patients on ocrelizumab. Vaccination with live or live-attenuated vaccines are not recommended during the treatment with ocrelizumab and until B cells have returned to normal levels.

Due to the potential depletion of B-cells in neonates and infants of mothers, who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cells have recovered; therefore, measuring CD19-positive B cell level, in neonates and infants, prior to vaccination is recommended.

It is recommended that all vaccinations other than live or live-attenuated should follow the local immunization schedule and measurement of vaccine-induced response titers should be considered to check whether individuals can mount a protective immune response because the efficacy of the vaccination may be decreased.

5.1.1.2 Potential Risks

PML

PML is an important potential risk for ocrelizumab and it has only been reported with ocrelizumab where the risk for PML was preexisting, specifically *from prior immunosuppressive treatment (e.g. natalizumab or fingolimod treatment)* ~~because of prior natalizumab or fingolimod treatment~~. *In all of these PML cases, the causality with ocrelizumab was not considered plausible. Based on the available information, it is reasonable to consider that the PML started before the first administration of ocrelizumab, given new symptom onset and/or MRI changes had already occurred on the previous therapy or during the wash out period, and was related to prior immunosuppressive treatment. Physicians should be vigilant for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI, confirmatory CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently.* Please refer to Appendix 6 for guidance for diagnosis of PML. Please see the IB for more details.

Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia)

Based on additional patient exposure an apparent association between ~~sustained~~ decrease in immunoglobulins (IgA, IgG, IgM) and serious infections with ocrelizumab treatment was observed. ~~However, no pattern (e.g. type of infections, safety laboratory abnormalities beyond the decrease in Ig, latency, duration) was found that could identify a subset of patients at higher risk of serious infections.~~ *There was no difference in the pattern (type, latency, duration, outcome) of the serious infections reported in this subset of patients compared to the overall serious infections profile. In addition, risk factors for a subset of patients at higher risk of serious infections could not be identified.*

~~**Impaired Response to Vaccination**~~

~~The degree of impairment of B-cell dependent humoral response to neo-antigens and polysaccharide antigens and its clinical relevance are currently unknown in patients with MS.~~

~~After treatment with ocrelizumab over 2 years, the proportion of patients with positive antibody titers against Streptococcus pneumoniae, mumps, rubella, and varicella were generally similar to the proportions at baseline.~~

~~No data are available on the effects of vaccination in patients receiving ocrelizumab. Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab.~~

~~The safety of immunization with live or live-attenuated viral vaccines, following ocrelizumab therapy has not been studied and vaccination with live-attenuated or live vaccines is not recommended while B cells are depleted.~~

Neutropenia
In the controlled treatment period, decreased neutrophils were observed in 12 to 15% of MS patients treated with ocrelizumab, in PPMS and RMS respectively. Most were mild to moderate in severity, and approximately 1% of the patients had Grade 3 or 4 neutropenia; no temporal association with infections was identified. *Based on additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed.*

5.3.1 Adverse Event Reporting Period

After initiation of study drug, all adverse events will be reported until ~~48~~ *96* weeks after the ~~last dose of the study drug~~ *end of the Treatment Period, but may be extended in patients whose B-cells take longer to replete.*

Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

~~Unrelated SAEs must be collected and reported during the study through the end of the Safety Follow-Up Period, which is at least 96 weeks after the last infusion, but may be extended in patients whose B-cells take longer to replete.~~

Section 5.4.2.2 Events that Occur after Study Drug Initiation

After initiation of study drug, serious adverse events will be reported until ~~48~~ *96* weeks after the *end of the Treatment Period* ~~last dose of study drug~~.

Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious and non-serious adverse event that occurs after the end of the adverse event reporting period (defined as ~~48~~*96* weeks after the ~~last dose of the study drug~~ *end of the Treatment Period*), if the event is believed to be related to prior study drug treatment.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of this single-arm non-comparative study will be exploratory and primarily based on descriptive statistical methods. Unless otherwise specified, statistical tests will be two-sided and the statistical significance level will be 5%. Corresponding 95% CIs will be presented as appropriate. *Although multiple statistical tests may be conducted, no adjustments to the Type 1 error rate will be made.* ~~No correction for multiple testing will be applied.~~

6.4.4 Analysis Methods

~~Patients not completing the study will be defined as not reaching the NEDA endpoint ("NEDA=no"). More d~~*D*etails about the missing data handling, as well as sensitivity analyses ~~based on alternative imputation approaches,~~ will be specified in the statistical analysis plan.

6.7 HANDLING OF MISSING DATA

~~Patients not completing the study will be defined as not reaching the NEDA endpoint ("NEDA=no"). More d~~*D*etails about the missing data handling will be specified in statistical analysis plan

Figure 3 Overview of End of Treatment Period

Figure 3 has been revised to reflect changes to the protocol

APPENDIX 1 Schedule of Assessments: Screening through the End of Treatment Period

Appendix 1 has been revised to reflect the changes to the protocol.

APPENDIX 2 Follow-up Schedule of Assessments

Appendix 2 has been revised to reflect the changes to the protocol.

APPENDIX 7 PATIENT DIARY

Appendix 7 was included to provide instructions about the use of a Patient Diary and as optional additional tool to help the patient and the site with the collection and reporting of AEs and concomitant medications

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**
PROTOCOL NUMBER:	MA30005
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IND NUMBER:	Not applicable
TEST PRODUCT:	Ocrelizumab (RO4964913)
MEDICAL MONITOR:	TBC
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS WHO HAVE A SUBOPTIMAL RESPONSE TO AN ADEQUATE COURSE OF DISEASE-MODIFYING TREATMENT**
PROTOCOL NUMBER:	MA30005
VERSION NUMBER:	5
EUDRACT NUMBER:	2015-005597-38
IND NUMBER:	Not applicable
TEST PRODUCT:	Ocrelizumab (RO4964913)
PHASE:	Phase IIIb
INDICATION:	Relapsing remitting multiple sclerosis
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of ocrelizumab in patients with relapsing remitting multiple sclerosis (RRMS) who have a suboptimal response to an adequate course of a disease modifying treatment (DMT). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objective

The primary objective for this study is to assess the efficacy of ocrelizumab 600 mg intravenous (IV) given every 24 weeks on the basis of the following endpoint:

- Proportion of patients who have no evidence of disease activity (NEDA, as per protocol defined events) during a 96-week period. The magnetic resonance imaging (MRI) activity will be calculated on the events starting from week 8 (baseline reset) when drug is fully active.

The definition of a protocol-defined event of disease activity is the occurrence of at least one of the following while on treatment with ocrelizumab:

  - A protocol-defined relapse as defined below
  - 24 weeks confirmed disability progression based on increases in Expanded Disability Status Scale (EDSS) while on treatment with ocrelizumab
  - A T1 gadolinium (Gd)-enhanced lesion after Week 8
  - A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan

A protocol-defined multiple sclerosis (MS) relapse is an occurrence of new or worsening neurological symptoms attributable to MS that meets the following criteria:

- Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications)
- Symptoms should be preceded by neurological stability for at least 30 days
- Symptoms should be accompanied by new objective neurological worsening determined with a timely EDSS/ Functional Systems Score (FSS) assessment, consistent with an increase of at least:
  - ≥ 0.5 points on EDSS scale

- or ≥ 2 points on one of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual
- or ≥ 1 point on two or more of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual

Episodic spasms, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse (Please note: Sexual dysfunction and fatigue need not be scored).

The secondary objective for this study is to evaluate the efficacy of ocrelizumab 600 mg IV given every 24 weeks on the basis of the following endpoints:

- The proportions of patients free from a protocol-defined event of disease activity during a 24-week period and a 48-week period
- Time to first protocol-defined event of disease activity
- Change in EDSS from baseline to Week 96
- Proportion of patients who, over a 96-week period, have Confirmed Disability Improvement (CDI), Confirmed Disability Progression (CDP) or stable disability (i.e. neither CDI nor CDP)
- Annualized rate of protocol-defined relapses at Week 96
- Time to onset of first protocol-defined relapse
- Time to onset of 24 weeks CDP
- Time to onset of first new and/or enlarging T2 lesion
- Total number of T1 Gd-enhanced lesions detected by brain MRI at Weeks 24, 48 and 96
- Change in total T2 lesion volume detected by brain MRI from baseline to Week 96
- Volume and number of new and/or enlarging T2 hyperintense lesions from baseline to Weeks 24, 48 and 96
- Change in T1 hypointense lesion volume from baseline to Weeks 48 and 96
- Change in brain volume from baseline measured at Weeks 24, 48 and 96
- Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis)

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of ocrelizumab 600 mg IV given every 24 weeks on the basis of the following endpoints:

- Rate and nature of adverse events
- Changes in vital signs, physical and neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-MS central nervous system [CNS] pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration).

Exploratory Objectives

The exploratory efficacy objective for this study is to further assess the efficacy of ocrelizumab 600 mg IV given every 24 weeks by monitoring patient-reported outcomes (PROs) related to quality of life (QoL), treatment satisfaction and other endpoints and analyses as follows:

- Multiple Sclerosis Impact Scale (MSIS)-29 (MS-specific QoL questionnaire)
- Treatment satisfaction questionnaire for medication (TSQM II)
- Patient reported outcome: SymptoMScreen
- MRI and clinical outcomes at 6 months and 1 year
- Predictors of NEDA and association between NEDA and disability or other efficacy parameters
- Severity of relapses (hospitalization for MS relapse, use of corticosteroids, residual disability)
- Employment status (WPAI)

- Proportion of patients who have no evidence of disease activity (NEDA, as per protocol defined events) during a 96-week period and starting from baseline.

Study Design

Description of Study

This study is a prospective, multicenter, open-label, efficacy, and safety study in patients with RRMS who have a suboptimal response to an adequate course of a DMT. An adequate course of prior DMT is defined as a stable dose of the same DMT administered for at least 6 months. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the study duration.

Patients will be assessed for efficacy and safety every 24 weeks. The study will consist of the following periods:

- Screening period: Up to 4 weeks
- Treatment period: Open-label treatment period of 96 weeks (last dose administered at Week 72)
- A follow-up period of at least 2 years, which is independent of the DMT administered

Follow-up Period: Patients who discontinue treatment early will be followed up for at least 96 weeks after the Early Treatment Discontinuation Visit. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate long-term extension (LTE) study, will be followed up for at least 96 weeks after the end of the Treatment Period. Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

Patients whose B-cells have not been repleted after 96 weeks of Follow-up Period will continue with visits every 24 weeks, and telephone contacts every 8 weeks, until B-cell repletion (Prolonged B-cell monitoring). If the patients are receiving other B-cell targeted therapies, then the Follow-up Period will be stopped at 96 weeks regardless of their B-cell count.

A structured telephone interview will be conducted by site personnel every 8 weeks between the study visits during the treatment period and follow-up to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections.

Number of Patients

This study will enroll 750 patients with RRMS who have had a suboptimal response to an adequate course of a DMT.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent form
- Able to comply with the study protocol, in the investigator's judgment
- Age 18 – 55 years, inclusive
- Have a definite diagnosis of RRMS, confirmed as per the revised McDonald 2010 criteria (Polman et al. 2011)

- Have a length of disease duration, from first symptom, of < 10 years. If the date of first symptom is unknown, then the diagnosis of RRMS should be of $\leqslant$ 5 years
- Have received no more than two prior DMTs, and the discontinuation of the most recent DMT was due to lack of efficacy
- Suboptimal disease control while on a DMT; a suboptimal response is defined by having at least one of the following events while being on a stable dose of the same DMT for at least 6 months:
  - One or more clinically reported relapse(s)
  - OR one or more T1 Gd-enhanced lesion(s)
  - OR two or more new and/or enlarging T2 lesions on MRI

  In addition, in patients receiving stable doses of the same approved DMT for more than a year, at least one of the above events must have occurred within the last 12 months of treatment with this DMT.
- EDSS of 0.0 to 4.0, inclusive, at screening
- For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 6 months after the last dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  The following are acceptable contraceptive methods: progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, and cap, diaphragm, or sponge with spermicide. A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods) is considered acceptable

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

- Secondary progressive multiple sclerosis (SPMS) or history of primary progressive or progressive relapsing MS
- Inability to complete an MRI (contraindications for MRI include but are not restricted to pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, inability to tolerate Gadolinium-based contrast agents etc.)

- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 (HTLV-1), herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis

- History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

Exclusions Related to General Health

- Pregnancy or lactation
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- History or currently active primary or secondary immunodeficiency
- Lack of peripheral venous access
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
- Significant or uncontrolled somatic disease or any other significant disease that may preclude patient from participating in the study
- Congestive heart failure (New York Heart Association [NYHA] III or IV functional severity)
- Known active bacterial, viral, fungal, mycobacterial infection or other infection, excluding fungal infection of nail beds

  Note: Active infections should be treated and effectively controlled before possible inclusion in the study
- History of major opportunistic infections (i.e. cryptococcosis, Pneumocystis pneumonia, progressive multifocal leukoencephalopathy [PML])
- History or known presence of recurrent or chronic infection (e.g., hepatitis B or C, human immunodeficiency virus [HIV], syphilis, tuberculosis [TB])
- History of malignancy, including solid tumors and hematological malignancies, except basal cell carcinoma, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been previously completely excised with documented, clear margins
- History of alcohol or drug abuse within 24 weeks prior to baseline
- History or laboratory evidence of coagulation disorders

Exclusions Related to Medications*

- Receipt of a live vaccine or attenuated live vaccine within 6 weeks prior to the baseline visit.

  In rare cases when patient requires vaccination with a live vaccine, the screening period may be extended but cannot exceed 8 weeks
- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or five half-lives of the investigational drug (whichever is longer) or treatment with any experimental procedures for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Contraindications to or intolerance of oral or IV corticosteroids, according to the country label, including:

  a) Psychosis not yet controlled by a treatment;

  b) Hypersensitivity to any of the constituents
- Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab)
- Systemic corticosteroid therapy within 4 weeks prior to screening
- Any previous treatment with alemtuzumab (Campath/Mabcampath/Lemtrada), cladribine, mitoxantrone, daclizumab, laquinimod, total body irradiation, or bone marrow transplantation.
- Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine or methotrexate
- Previous treatment with natalizumab unless natalizumab was discontinued because of persistent anti-natalizumab antibodies
- Treatment with IV immunoglobulin (Ig) within 12 weeks prior to baseline

- Any previous treatment with an investigational MS DMT not yet approved at time of screening.
- History of recurrent aspiration pneumonia requiring antibiotic therapy
- Patients previously treated with teriflunomide, unless an accelerated elimination procedure is implemented before screening visit

  Accelerated elimination procedure after stopping treatment with teriflunomide:
  - cholestyramine 8g is administered 3 times daily for a period of 11 days, or cholestyramine 4g three times a day can be used, if cholestyramine 8g three times a day is not well tolerated,
  - alternatively, 50g of activated powdered charcoal is administered every 12 hours for a period of 11 days

  In cases where no pregnancy is expected teriflunomide plasma concentrations of 0.03-0.04 mg/ml are accepted to include the patient in study.
- Previous treatment with fingolimod or dimethyl fumarate if at baseline the lymphocyte count is below lower limit of normal (LLN). The provisions for stopping therapy as described in the respective SmPCs should be followed.
- Treatment with fampridine/dalfamipridine (Fampyra®)/Ampyra®) unless on stable dose for ⩾ 30 days prior to screening. Wherever possible, patients should remain on stable doses throughout the 96-week treatment period.

* Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.

Exclusions Related to Laboratory Findings*

- Positive serum β human chorionic gonadotropin (hCG) measured at screening
- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C (HepCAb)
- Lymphocyte count below LLN
- CD4 count<250/µL.
- Aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT)⩾ 3.0 × the upper limit of normal (ULN)
- Platelet count <100,000/µL (<100 × 10^9/L)
- Absolute neutrophil count <1.0 × 10^3/µL

*Re-testing before baseline: any abnormal screening laboratory value that is clinically relevant should be retested in order to rule out any progressive or uncontrolled underlying condition. The last value before baseline visit must meet study criteria.

Please note: based on local Ethics Committees or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or selected centers to exclude tuberculosis, Lyme disease, HTLV-1 associated myelopathy (HAM), acquire immunodeficiency syndrome (AIDS), hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the Investigator.

End of Study

The end of the study treatment period has been defined as the date on which the last patient receiving the full study treatment reached the 96-week visit. Exception will be made for patients who have EDSS change at Week 96 and need confirmation of EDSS score after a further 24 weeks.

The end of the study is defined as the last patient last visit in the B-cell monitoring of the Follow-up Period.

At the end of the study treatment, patients will be encouraged to be included in a separate LTE study to further evaluate the efficacy and safety of their DMT treatment and this is independent of the DMT administered. This LTE will also aim to evaluate the relationship between the primary endpoint of this study and long-term outcome.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years. This includes an enrollment period of approximately 12 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The first dose of ocrelizumab will be administered as two 300-mg IV infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15), followed by one 600-mg IV infusion in 500 mL 0.9% sodium chloride every subsequent dose (i.e., every 24 weeks) for a maximum of 4 doses.

Non-Investigational Medicinal Products

Premedicate with 100 mg of methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes prior to each ocrelizumab infusion, and an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab to reduce the frequency and severity of infusion-related reactions (IRRs). The addition of an antipyretic (e.g., acetaminophen/ paracetamol) may also be considered.

Statistical Methods

Primary Analysis

The primary efficacy analyses will include all enrolled patients who received any dose of ocrelizumab (intent-to-treat population). The analysis will be performed after the last CDP and CDI confirmation visit. The per-protocol population, defined as all patients who had 96 weeks of treatment and who did not have any major protocol violations that are deemed to potentially affect the efficacy and safety endpoints, will be used for supportive efficacy analyses of the primary endpoint.

The evaluation of the clinical efficacy of ocrelizumab will be based upon the events in-between the baseline visit and week 96 visit. The MRI activity is evaluated from week 8 to week 96.

The proportion of patients free from protocol-defined events up to Week 96 (i.e. patients with NEDA) will be calculated and the corresponding two-sided Clopper-Pearson 95% confidence interval (CI) will be presented. Logistic regression models will be used to identify predictors of response to treatment (freedom from protocol-defined events of disease activity). Variables that will be considered are: region, line of treatment (previous DMTs), gender, and baseline EDSS. In addition, specific efficacy endpoints, such as CDP, will be compared between patients with or without evidence of disease activity up to Week 96.

Details about the missing data handling, as well as sensitivity analyses, will be specified in the statistical analysis plan.

Determination of Sample Size

With a sample size of 750 patients, an observed NEDA rate of 30% will be estimated with a precision (half-width of the 95% CI around the estimate) of 3.3% based on the Clopper-Pearson method, i.e. the 95% CI will be (26.7%, 33.4%). Even if the NEDA rate is different from the assumed rate of 30%, with the proposed sample size the precision of the estimate will remain smaller than 3.6% (value for a NEDA rate of 50%).

The annualized relapse rate is another relevant outcome measure assessed in this study. Based on results from the pivotal Phase III studies WA21092 (OPERA I) and WA21093 (OPERA II), in

this study the adjusted annualized relapse rate assessed over two years is expected to be estimated with a precision of approximately 0.03.

Interim Analyses

No formal confirmatory efficacy interim analyses are planned. Exploratory analyses of selected endpoints may be performed during the course of the study, e.g. after all patients have completed the first 6 and 12 months of the treatment phase and the necessary data are available.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AIDS	Acquire immunodeficiency syndrome
ALT	Alanine aminotransferase
ARR	Annual relapse rate
AST	Aspartate aminotransferase
β-hCG	Beta subunit human chorionic gonadotropin
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
CDI	Confirmed disability improvement
CDP	Confirmed disability progression
CI	Confidence interval
CNS	Central nervous system
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMT	Disease modifying treatment
EC	Ethics committee
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EDSS	Expanded Disability Status Scale
EU	European Union
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion-recovery
FSH	Follicle stimulating hormone
FSS	Functional Systems Score
GA	Glatiramer acetate
GCP	Good Clinical Practice
Gd	Gadolinium
GGT	Gamma-glutamyl transpeptidase
GPA	Granulomatosis with polyangiitis
HAM	HTLV-1 associated myelopathy
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, eye, ear, nose, and throat
HepCAb	Hepatitis C antibody
HIV	Human immunodeficiency virus
HR	Hazard ratio
HTLV-1	Human T-lymphotropic virus 1
IB	Investigator's brochure

Abbreviation	Definition
ICH	International Conference on Harmonisation
IFN-β	Interferon beta
Ig	Immunoglobulin
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Infusion-related reaction
ITT	intent-to-treat
IV	Intravenous
IxRS	Interactive voice/Web response system
JCV	John Cunningham virus
LLN	Lower limit of normal
LPLV	Last patient, last visit
LTE	Long term extension
MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke
MMRM	Mixed model with repeated measure
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale (29-item scale)
NCI	National Cancer Institute
NEDA	No evidence of disease activity
NYHA	New York Heart Association
OLE	Open label extension
PCR	Polymerase chain reaction
PML	Progressive multifocal leukoencephalopathy
PP	Per-protocol
PPMS	Primary progressive multiple sclerosis
PRMS	Progressive relapsing multiple sclerosis
PRO	Patient-reported outcome
PY	Patient years
QOL	Quality of life
RA	Rheumatoid arthritis
RBC	Red blood cell
RMS	Relapsing multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of product characteristics

Abbreviation	Definition
SPMS	Secondary progressive multiple sclerosis
TB	Tuberculosis
TSQM	Treatment satisfaction questionnaire for medication
ULN	Upper limit of normal
U.S.	United States
USP	United States Pharmacopeia
WBC	White blood cell

1. BACKGROUND

1.1 BACKGROUND ON MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS) that affects approximately 400,000 people in the United States (U.S.) and 2.3million worldwide (Tullman et al. 2013). MS primarily affects young adults, with 70%–80% of patients having an age of onset (i.e., initial visit to a physician) between 20 and 40 years (Anderson et al. 1992; Noonan et al. 2002), and has a strong gender bias, with approximately 64%–70% of diagnosed patients being women (Goodin 2014).

MS is clinically subcategorized into four phenotypic disease patterns distinguished by the occurrence and timing of relapses relative to disease onset and disability progression. These include relapsing remitting MS (RRMS), primary progressive MS (PPMS), progressive relapsing MS (PRMS), and secondary progressive MS (SPMS) (Lublin et al. 1996; Lublin et al. 2014). Approximately 85% of MS patients initially present with RRMS (Confavreaux et al. 2000; Leray et al. 2015). The majority of RRMS patients will transition into SPMS within 20-25 years (Trojano et al. 2003).

The clinical signs in MS can occur in isolation or in combination, and can include weakness, spasticity, gait and coordination imbalances, sensory dysfunction, vision loss, sexual dysfunction, fatigue, depression, chronic pain, sleep disorders, and cognitive impairment (Tanasescu et al. 2015). Current diagnosis of definite MS involves both clinical (history and neurological exam) and paraclinical (for example, Magnetic Resonance Imaging [MRI], Spinal Tap, Evoked potentials) evidence.

MS treatments tackle separately the acute exacerbations and their prevention. Symptomatic management of relapses involves the use of corticosteroids, while disease-modifying treatments (DMTs) aim to decrease the clinical relapse rate and concomitant inflammation within the CNS (Tanasescu et al. 2015). DMTs, which include immunomodulatory, anti-inflammatory, and immunosuppressive drugs, are used to slow the development of MS-related neurological damage and disability progression. By providing a more effective approach to MS treatment, DMTs may improve quality of life for individuals with MS (Weinstock-Guttman 2013).

MS therapeutic landscape is changing rapidly. After several years in which first-line DMTs – glatiramer acetate (GA) and interferon beta (IFNβ) – constituted the principal treatment options, a variety of new agents for MS treatment are now approved by regulatory authorities or in phase II and III clinical trials (Tanasescu et al. 2015). In 2004 natalizumab was approved for relapsing forms of MS and in 2014, alemtuzumab and peg IFNβ-1a. Fingolimod was the first oral DMT approved by Food and Drug Administration (FDA) in 2010 for relapsing forms of MS (RMS) followed by teriflunomide in 2012 and dimethyl fumarate in 2013 (wwww.mymsaa.org).

DMTs like IFNβ and GA are often used early in the course of disease and have a favourable benefit-to-risk profile, but they are only partially effective (Freedman 2014; Ziemssen et al. 2015) and up to 40% of patients continue to show disease activity on these treatments (Tanasescu et al. 2015), indicating the need for an alternative therapeutic strategy (Ziemssen et al. 2015). Possible treatment strategies for patients who have a suboptimal response to these DMT include switching to either another IFNβ/GA or switching to a more effective DMT, namely fingolimod, natalizumab or alemtuzumab (Freedman 2014).). Switching patients early to a high-efficacy therapy that targets both focal and diffuse damage may impact the course of the disease and achieve long-term disease control (Ziemssen et al. 2015).

Suppression of disease activity and disability progression as early as possible remains an important goal of therapy in MS. With the emergence of more efficacious therapies and a better understanding of the consequences of subclinical disease activity in recent years, physicians have a lower tolerance for allowing disease activity to persist because what is lost in MS cannot typically be regained. The potential risk of irreversible disease progression is therefore an important factor in the therapeutic decision making of patients and their physicians. Although there are now several approved therapies for RMS, some lack sufficient efficacy to quell progression of disability, while more effective therapies are often reserved for later use because of serious risks. Thus there remains a need for highly effective therapies with a benefit-risk profile that supports its expeditious use at any time during the course of disease to preserve CNS tissue and neurological function, stem accrual of irreversible disability, and improve the quality of life for people living with MS.

1.2 BACKGROUND ON OCRELIZUMAB

Ocrelizumab is a recombinant humanized anti-human monoclonal antibody that selectively targets CD20-expressing B cells (Klein et al. 2013), which are believed to play a critical role in MS. It then interacts with the body's immune system to eliminate CD20-positive B-cells.

CD20 is a cell surface antigen found on pre-B cells, mature B cells, and memory B cells, but it is not expressed on lymphoid stem cells and plasma cells (Stashenko et al. 1980; Loken et al. 1987; Tedder and Engel 1994). While ocrelizumab selectively depletes CD20-expressing B cells (Kappos et al. 2011), the capacity of B-cell reconstitution and pre-existing humoral immunity are preserved (Martin and Chan 2006; DiLillo et al. 2008). In addition, innate immunity and total T-cell numbers are not affected (WA21493 Clinical Study Report).

See the Ocrelizumab Investigator's Brochure (IB) for additional details on nonclinical and clinical studies.

Summary of Clinical Studies of Ocrelizumab in MS

In two double-blind, double-dummy Phase III global RMS trials (Studies WA21092 and WA21093), ocrelizumab 600 mg demonstrated superior efficacy over subcutaneous IFNβ-1a 44 μg (Hauser et al. 2015). Efficacy outcomes were consistent between trials and across the primary and key clinical and imaging secondary endpoints. Ocrelizumab 600 mg demonstrated statistically significant superiority compared with IFNβ-1a on each of the following major efficacy endpoints:

- Relative reductions of 46% and 47% (both $p < 0.0001$) in the protocol-defined annual relapse rate (ARR) in Studies WA21092 and WA21093, respectively (primary endpoint)

- A 40% relative reduction in both the 12-week confirmed disability progression [CDP] (Hazards ratio [HR] 0.60 [95% confidence interval [CI]: 0.45, 0.81], $p = 0.0006$) and 24-week CDP (HR 0.60 [95% CI: 0.43, 0.84], p=0.0025) in the pooled analysis of Studies WA21092 and WA21093. Each individual trial also demonstrated a significant relative risk reduction of 12-week CDP and 24-week CDP (43% reduction for both 12- and 24-week CDP in Study WA21092 and 37% reduction for both 12- and 24-week CDP in Study WA21093)

- Relative reductions of 94% and 95% (both p<0.0001) in the number of T1- gadolinium (Gd)-enhancing lesions per scan at Weeks 24, 48 and 96 in Study WA21092 and Study WA21093, respectively

- Relative reductions of 77% and 83% (both $p < 0.0001$) in the total number of new and/or enlarging T2 hyperintense lesions per scan at Weeks 24, 48 and 96 in Study WA21092 and Study WA21093, respectively

In a Phase III global PPMS trial (Study WA25046), ocrelizumab 600 mg demonstrated statistically significant superiority compared with placebo on each of the following major efficacy endpoints (Montalban et al. 2015)

- A 24% relative risk reduction in 12-week CDP, the primary endpoint ($HR = 0.76$ [95% CI: 0.59, 0.98], $p = 0.0321$)
- A 25% relative risk reduction in 24-week CDP ($HR = 0.75$ [95% CI: 0.58, 0.98], $p = 0.0365$)
- Relative reduction of 29% in the progression rate of timed 25-foot walk from baseline to Week 120 ($p = 0.0404$)
- A decrease in the volume of T2 lesions by 3.4% over 120 weeks, compared with the placebo group in which the T2 lesion volume increased by 7.4% ($p < 0.0001$)
- Relative reduction of 17.5% in whole brain volume loss from Week 24 to Week 120 ($p = 0.0206$).

Clinical Safety

The safety data included are from the three Phase III studies in RMS (Studies WA21092 and WA21093) and PPMS (Study WA25046); safety data from the Phase II study in RRMS (Study WA21493) is described in the IB.

All four studies WA21092, WA21093, WA25046, and WA21493 have completed the controlled treatment period and are in open-label extension phase.

In the two double-blind, double-dummy RMS Phase III studies (pooled data of Studies WA21092 and WA21093) during the 96-week controlled treatment period, ocrelizumab was well tolerated with lower rates of treatment discontinuations for adverse events (AEs) in patients treated with ocrelizumab 600 mg (3.5%) than in patients receiving IFNβ-1a (6.2%). The proportion of patients with AEs (83.3% in both groups) as well as the total number of AEs were similar in the ocrelizumab and the IFNβ -1a treatment groups over the 96-week treatment period. The proportion of patients reporting infections was higher in the ocrelizumab group compared with the IFNβ-1a group, (58.4% vs. 52.4%, respectively). In addition, there were more events of infection in the ocrelizumab group (1224 events) compared with the IFNβ -1a group (948 events) and the majority of the events were of Grade 1 or 2 intensity. The difference was primarily driven by more patients with upper respiratory tract infections in Ocrelizumab group. The proportion of patients with serious adverse events (SAEs) was lower in the ocrelizumab treatment group than in the IFNβ -1a treatment group (6.9% in the ocrelizumab treatment group versus 8.7% in the IFNβ-1a treatment group). Overall, the proportion of patients with serious infections was lower in the ocrelizumab group (1.3%) than in the IFNβ-1a group (2.9%). Two serious infusion-related reactions (IRRs) were reported; one in the IFNβ -1a group (Grade 3) and one in the ocrelizumab group (Grade 4). As expected, the proportion of patients experiencing IRRs were increased in the ocrelizumab group (34.3%) compared with the active control group (9.7%) who received dummy infusions. During the 96-week controlled treatment period, a total of 6 malignancies were reported, 2 events (1 mantle cell lymphoma and 1 squamous cell carcinoma) occurred in 2 patients (0.2%) in the IFNβ -1a treatment group and 4 events (2 invasive ductal breast carcinoma, 1 renal cancer and 1 malignant melanoma) occurred in 4 patients (0.5%) in the ocrelizumab treatment group. Three deaths occurred in Studies WA21092 and WA21093; 2 patients (suicide and mechanical ileus) in the IFNβ -1a treatment group and 1 patient (suicide) in the ocrelizumab treatment group.

In the PPMS Phase III double blind placebo controlled Study WA25046, ocrelizumab was well tolerated with a similar proportion of patients with AEs leading to discontinuation from treatment (4.1%) compared with the placebo group (3.3%). The proportion of patients who experienced at least one AE was 90% in the placebo group compared with 95% in the ocrelizumab group. Taking into account that twice as many patients were randomized to ocrelizumab than placebo, the number of AEs experienced

by patients with an AE was similar (1762 events in the placebo group and 3690 events in the ocrelizumab group). The proportion of patients who experienced an infection was 69.8% in the ocrelizumab group compared with 67.8% in the placebo group. The proportion of patients with serious infections was similar in both groups: 5.9% in the placebo group compared with 6.2% in the ocrelizumab group. As expected, the proportion of patients who reported IRRs was higher in the ocrelizumab group (39.9%) compared with placebo (25.5%). Overall, 5 patients (1.0%) experienced a serious IRR in the ocrelizumab group. A total of 15 malignancies in 13 patients were reported: 2 events (basal cell carcinoma and adenocarcinoma of the cervix) occurred in 2 patients (0.8%) in the placebo group and 13 events (5 basal cell carcinoma, 2 invasive ductal breast carcinoma, 1 anaplastic large-cell lymphoma, 1 breast cancer, 1 endometrial cancer, 1 invasive breast carcinoma, 1 malignant fibrous histiocytoma, 1 pancreatic carcinoma metastatic) occurred in 11 patients (2.3%) in the ocrelizumab group. The proportion of patients with SAEs (22.2% in the placebo group compared with 20.4% in the ocrelizumab group), was similar in both groups. There were 5 deaths during the controlled treatment period, one in the placebo group (road traffic accident) and 4 in the ocrelizumab group (pulmonary embolism, pneumonia, pancreatic carcinoma, pneumonia aspiration).

For more detailed information, see IB.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Over the past two decades, there has been an increase in the number and type of available treatments for RMS. Yet, despite an adequate course of treatment with a DMT, a significant proportion of treated patients with RMS will show signs of disease activity (Freedman 2014; Ziemssen et al. 2015, Tanasescu et al. 2015). Suboptimal responses defined as relapse, confirmed disability progression, and/or new Gd-enhancing or T2 lesion(s) on brain MRI, are reported in approximately one-third of patients receiving IFN-β therapy (Bergvall et al. 2014; Durelli et al. 2008; Fernández et al. 2005; Waubant et al. 2003). Disease activity while receiving DMT is associated with poorer long-term outcomes (Bermel et al. 2013), thus subsequent treatment with a more effective therapy may be warranted in patients with breakthrough disease. Consequently, reported rates of treatment switching for suboptimal responses range from 20% to 35% of patients (Rio et al. 2012; Gajofatto et al. 2009; Teter et al. 2014).

While clinical experience and retrospective studies suggest that better disease control is obtained by escalating to higher efficacy therapy, few prospective studies have been conducted. In one prospective, observational study, Prosperini and colleagues evaluated outcomes of patients who failed first-line treatment with IFN-β or GA and switched to a different IFN-β formulation or GA (switching group) or escalated to natalizumab (escalating group) (Prosperini et al. 2012). At 1 year, no significant differences between the two groups were observed in disease activity (i.e., relapse,

disability progression, MRI activity, and combined activity). However, after 2 years, significantly greater proportions of patients who had escalated to natalizumab than those who switched between IFN-β and GA were free from all disease activity measures. In the Phase III CARE MS II trial, patients with ≥1 relapse while receiving IFN-β or GA therapy were randomized to IFN-β or alemtuzumab treatment. Significant improvements in relapse rate and accumulation of disability were reported with alemtuzumab versus IFN-β at 1 year (Coles et al. 2012).

Assessing efficacy and safety in patients who switch to ocrelizumab after a suboptimal response to an adequate course of a DMT represents an important question for clinicians. Efficacy and safety data in patients who have switched to ocrelizumab are limited. The Phase II study provided initial evidence that ocrelizumab could be effective at further reducing MS disease activity following initial IFN-β therapy and demonstrated the efficacy in reducing the disease activity as measured by T1 Gd enhancement already after 8 weeks as shown in the figure below.

Figure 1 Gd-enhancing lesions by week in each study group in Phase II study of ocrelizumab

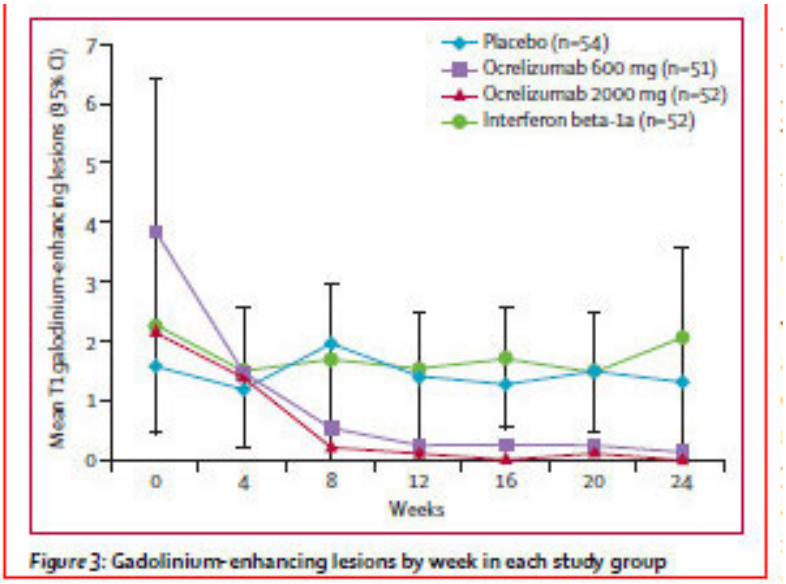


Figure 3: Gadolinium-enhancing lesions by week in each study group

Additional data will also be available on previously treated patients in two completed Phase III studies (Studies WA21092 [OPERA I], n=106 and WA21093 [OPERA II], n=113), but in a limited number of patients.

It is important to underline that the vast majority of the subjects included in OPERA I and OPERA II continue the safety and efficacy follow-up in an open label extension (OLE) phase of the study. Patients included in the IFN arm have been given the opportunity to be treated with ocrelizumab in the OLE phase of the study. This setting enables efficacy and safety data collection on subjects switching from IFN to ocrelizumab. Information on

switching from other DMTs, such as teriflunomide, fingolimod or dimethyl fumarate, is currently not available.

The benefit-risk profile of ocrelizumab appears to be favorable based on the results of the pivotal Phase III studies as described in Section 1.2. However, more data from patients who switch to higher efficacy therapies from large scale, prospective studies are needed. Therefore, a dedicated prospective study to specifically evaluate the efficacy and safety of ocrelizumab in patients who have a suboptimal response to an adequate course of a DMT is needed to address this important clinical question.

Based upon the Phase II data, and to allow the real evaluation of the treatment effect, the MRI activity should be evaluated starting from week 8. By introducing a MRI 8 weeks after baseline visit might also enable exclusion, from a safety point of view, of a possible progressive multifocal leukoencephalopathy (PML) infection carried over from a previous DMT treatment (i.e. fingolimod, dimethyl fumarate or natalizumab).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of ocrelizumab in patients with RRMS who have a suboptimal response to an adequate course of DMT.

A suboptimal response is defined by having one or more clinically reported MS relapse(s), OR one or more T1 Gd-enhanced lesion(s), OR two or more new or enlarging T2 lesions on MRI while being on a stable dose of the same DMT for at least 6 months. In addition, in patients receiving stable doses of the same approved DMT for more than a year, the event of suboptimal response must have occurred within the last 12 months of treatment with this DMT.

Patients will be encouraged to enter a long-term follow-up of at least 2 years to allow the evaluation and possible contribution of the primary outcome measure of no evidence of disease activity (NEDA) or its sub-elements on the longer term evolution of the disease.

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary objective for this study is to assess the efficacy of ocrelizumab 600 mg intravenous (IV) given every 24 weeks on the basis of the following endpoint:

- Proportion of patients who have NEDA, as per protocol defined events during a 96-week period. The MRI activity will be calculated on the events starting from week 8 (baseline reset) when drug is fully active.

The definition of a protocol-defined event of disease activity is the occurrence of at least one of the following while on treatment with ocrelizumab:

  - A protocol-defined relapse as defined in Section 4.5.4
  - 24 weeks confirmed disability progression based on increases in EDSS while on treatment with ocrelizumab
  - A T1 Gd-enhanced lesion after Week 8
  - A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan

2.1.2 Secondary Efficacy Objectives

The secondary objective for this study is to evaluate the efficacy of ocrelizumab 600 mg IV given every 24 weeks on the basis of the following endpoints:

- The proportions of patients free from a protocol-defined event of disease activity during a 24-week period and a 48-week period
- Time to first protocol-defined event of disease activity
- Change in EDSS from baseline to Week 96
- Proportion of patients who, over a 96-week period, have Confirmed Disability Improvement (CDI) Confirmed Disability Progression (CDP) or stable disability (i.e. neither CDI nor CDP).
- Annualized rate of protocol-defined relapses at Week 96
- Time to onset of first protocol-defined relapse
- Time to onset of 24 weeks CDP
- Time to onset of first new and/or enlarging T2 lesion
- Total number of T1 Gd-enhanced lesions detected by brain MRI at Weeks 24, 48 and 96
- Change in total T2 lesion volume detected by brain MRI from baseline to Week 96
- Volume and number of new and/or enlarging T2 hyperintense lesions from baseline to Weeks 24, 48 and 96
- Change in T1 hypointense lesion volume from baseline to Weeks 48 and 96
- Change in brain volume from baseline measured at Weeks 24, 48 and 96
- Change from baseline in cognitive performance at Week 48 and Week 96 as measured by the BICAMS (Brief International Cognitive Assessment for Multiple Sclerosis)

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to further assess the efficacy of ocrelizumab 600 mg IV given every 24 weeks by monitoring patient-reported outcomes (PROs) related to quality of life (QoL), treatment satisfaction and other endpoints or analyses as follows:

- Multiple Sclerosis Impact Scale (MSIS)-29 (MS-specific QoL questionnaire)
- Treatment satisfaction questionnaire for medication (TSQM II)
- Patient reported outcome: SymptoMScreen
- MRI and clinical outcomes at 6 months and 1 year
- Predictors of NEDA and association between NEDA and disability or other efficacy parameters
- Severity of relapses (hospitalization for MS relapse, use of corticosteroids, residual disability)
- Employment status (WPAI)
- Proportion of patients who have NEDA, as per protocol defined events during a 96-week period and starting from baseline

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of ocrelizumab 600 mg IV given every 24 weeks on the basis of the following endpoints:

- Rate and nature of adverse events
- Changes in vital signs, physical and neurological examinations, clinical laboratory results, locally reviewed MRI for safety (non-MS CNS pathology) and concomitant medications (including pre-medications and medications used during and following ocrelizumab administration).

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This study is a prospective, multicenter, open-label, efficacy and safety study in patients with RRMS who have had a suboptimal response to an adequate course of a DMT. An adequate course of prior DMT is defined as a stable dose of the same DMT administered for at least 6 months. The first dose of ocrelizumab will be administered as an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride

each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the remainder of the study duration.

This study will enroll 750 patients. Patients will be assessed for efficacy and safety every 24 weeks as described in the Schedule of Assessments presented in Appendix 1.

The study will consist of the following periods:

- Screening period: Up to 4 weeks
- Treatment period: Open-label treatment period of 96 weeks (last dose administered at Week 72)
- A follow-up period of at least 2 years, which is independent of the DMT administered

Follow-up Period: Patients who discontinue treatment early will be followed up for at least 96 weeks after the Early Treatment Discontinuation Visit. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate long-term extension (LTE) study, will be followed up for at least 96 weeks after the end of the Treatment Period. Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

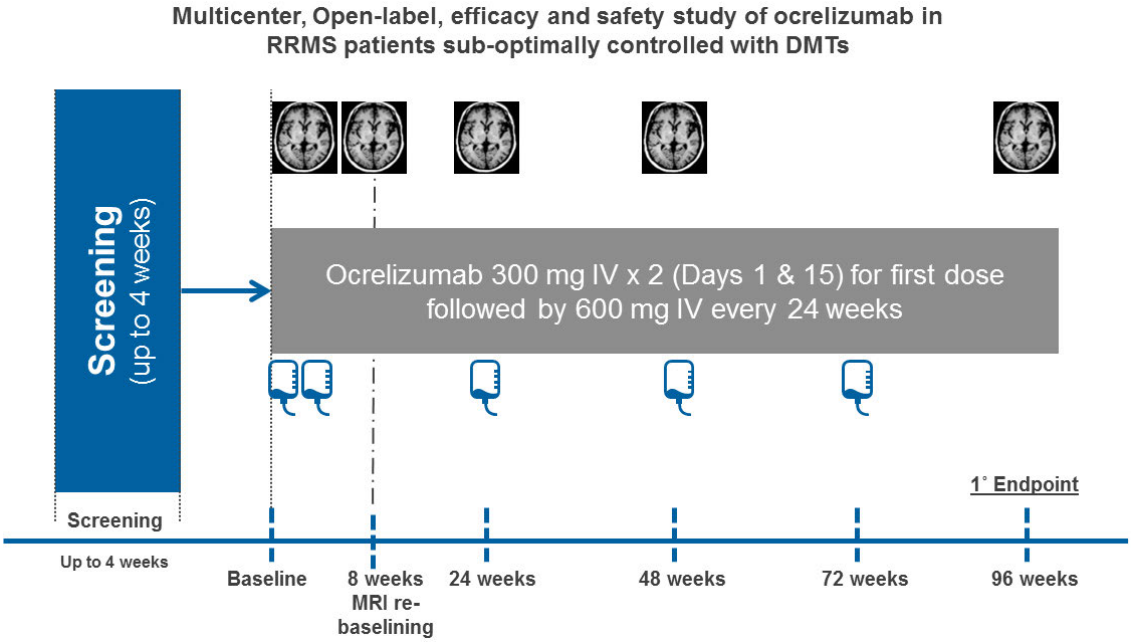
Patients whose B-cells have not been repleted after 96 weeks of Follow-up Period will continue with visits every 24 weeks, and telephone contacts every 8 weeks, until B-cell repletion (Prolonged B-cell monitoring). If the patients are receiving other B-cell targeted therapies, then the Follow-up Period will be stopped at 96 weeks regardless of their B-cell count.

A structured telephone interview will be conducted by site personnel every 8 weeks between the study visits during the treatment period and follow-up to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections.

3.1.1 Overview of Study Design

Figure 2 presents an overview of the study procedures. A schedule of assessments is provided in Appendix 1.

Figure 2 Overview of Study Procedures



DMTs = disease modifying treatments; IV = intravenous; RRMS = relapsing remitting multiple sclerosis.

3.1.2 Screening

Patients screened for this study should not be withdrawn from DMT therapies for the sole purpose of meeting eligibility for the trial. Patients who discontinue their current therapy for non-medical reasons should be informed of treatment options before deciding to enroll in the study. Investigators should refer to the local label for discontinuation/wash out of previous DMTs. The summary of product characteristics (SmPCs) of DMTs for EMEA countries are provided in Appendix 8.

After providing written informed consent, patients will enter a screening period (up to 4-weeks) to be evaluated for eligibility.

Re-screening of patients is allowed in this protocol. In case a patient needs to be re-screened there is no need to sign a new ICF if the re-screening is done within 2 months after signing the ICF; the patients should only be asked to re-sign and re-date the previously signed ICF to confirm that they are still willing to participate in the study.

3.1.3 Treatment Period

Eligible patients will be treated with an initial dose of two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15) followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks for the remainder of study duration.

Laboratory samples can be taken up to 2 weeks prior to the scheduled study visit. Results should be available prior dosing, except for John Cunningham virus (JCV) and immunoglobulins (Ig) (plasma samples collected and stored centrally), which will be analyzed upon request and CD8 and CD19 (no interference with re-treatment).

For patients presenting with EDSS change at Week 96, the EDSS score will be confirmed after a further 24 weeks.

Criteria for Re-Treatment with Ocrelizumab

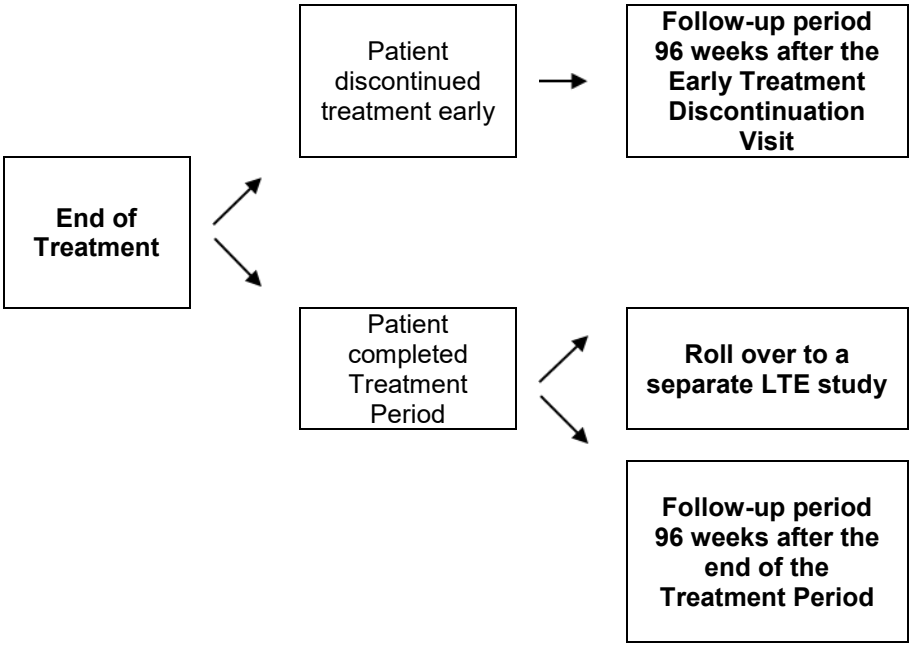
Prior to re-treatment with ocrelizumab, patients will be evaluated for the following conditions and laboratory abnormalities. If any of these are present prior to re-dosing, further administration of ocrelizumab should be suspended until these are resolved or held indefinitely:

- Life threatening (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4) infusion-related event that occurred during a previous ocrelizumab infusion
- Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Active infection other than a fungal nailbed infection. The re-treatment should be delayed until the active infection is treated, and patient fully recovered
- CD4 cell count < 250/µL
- Ongoing pregnancy

At the end of the study treatment the patients will be encouraged to be included in a separate LTE study to further evaluate the efficacy and safety of their DMT treatment and this is independent of the DMT. This LTE will also aim to evaluate the relationship between the primary endpoint of this study and long-term outcome.

Patients who discontinue treatment early will be followed up for at least 96 weeks after the Early Treatment Discontinuation Visit. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate LTE study, will be followed up for at least 96 weeks after the end of the Treatment Period (see Section 3.1.4). Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

Figure 3 Overview of End of Treatment Period



3.1.4 Follow-up Period

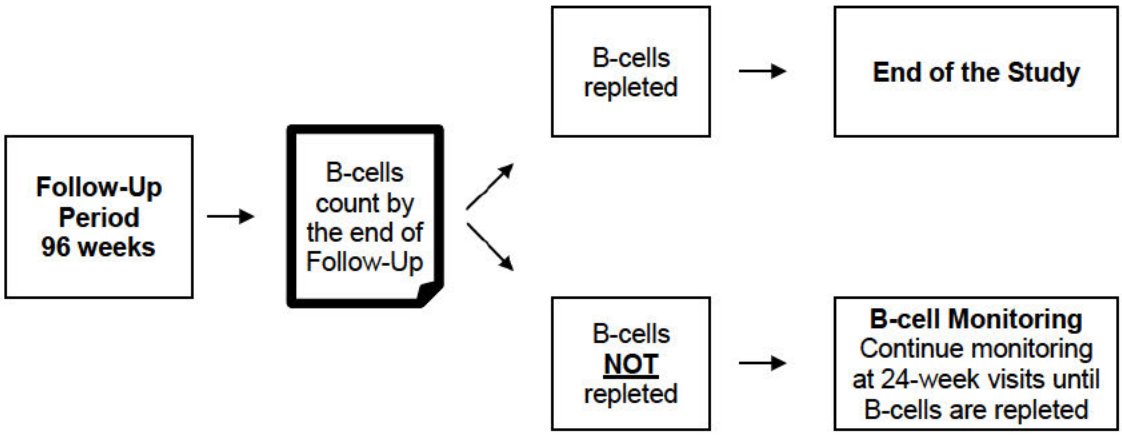
Patients who discontinue treatment early will be followed up for at least 96 weeks after the Early Treatment Discontinuation Visit. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate LTE study, will be followed up for at least 96 weeks after the end of the Treatment Period.

Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

Any patient whose peripheral blood B-cell count remains depleted after this period will continue to be monitored at 24-week intervals until the B-cell count has returned to the baseline value or to lower limit of normal (LLN) range, whichever is lower.

Figure 4 provides an overview of the Follow-up Period, which is the variable B-cell monitoring period. A schedule of assessments for the Follow-up Period is presented in Appendix 2.

Figure 4 Follow-up: Variable B-Cell Monitoring Period



During the Follow-up Period, patients will be formally assessed at clinical visits every 24 weeks and by telephone contacts every 8 weeks. If further B-cell monitoring is required and the patient is not receiving any other B-cell targeted therapy, assessments will take place at clinical visits every 24 weeks and by telephone contacts every 8 weeks until the B-cells are repleted. See Appendix 2 for further details.

After initiation of study drug, all adverse events will be reported until 96 weeks after the end of the Treatment Period but may be extended in patients whose B-cells take longer to replete.

Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

For patients withdrawing from treatment early, every effort should be made to complete the Follow-up Period and all related assessments regardless of whether or not they receive alternative treatment for MS.

A dedicated (scheduled or unscheduled) follow-up clinic visit directly prior to the start of an alternative MS treatment is required in order to assess the patient's clinical status and safety parameters (assessments to be performed as per Appendix 2, Schedule of Assessments: Follow-up including further B-cell monitoring period).

Patients who receive alternative MS therapies that may decrease B-cell levels will only be followed up for 96 weeks; they will not be entered into the prolonged B-cell Monitoring period thereafter.

A structured telephone interview will be conducted by site personnel every 8 weeks between the study visits during the treatment period and follow-up to identify and collect information on any changes in the patient's health status that warrant an unscheduled

visit (including new or worsening neurological symptoms) and possible events or infections.

3.1.5 Planned Total Sample Size

This study will enroll approximately 750 patients. Please refer to the Section 6.1 for more details.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study treatment period has been defined as the date on which the last patient receiving the full study treatment reached the 96-week visit. Exception will be made for patients that have EDSS change at Week 96 and need confirmation of EDSS score after a further 24 weeks.

The end of the study is defined as the last patient last visit in the B-cell monitoring of the Follow-Up period. At the end of the study treatment, patients will be encouraged to be included in a separate LTE study to further evaluate the efficacy and safety of their DMT treatment, and this is independent of the DMT. This LTE will also aim to evaluate the relationship between the primary endpoint of this study and long-term outcome.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5 years. This includes an enrollment period of approximately 12 months.

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase IIIb, prospective, multicenter, open-label, study to assess the efficacy and safety of ocrelizumab in patients with RRMS who have a suboptimal response to an adequate course of a DMT. The efficacy and safety of ocrelizumab has been studied in three randomized, double-blind, parallel group, controlled Phase III studies (WA21092 and WA21093 in relapsing MS and WA25046 in PPMS) with further follow-up ongoing in OLE phase. As there are limited data in patients who have switched to ocrelizumab after a suboptimal response to an adequate course of a DMT, a single-arm study is considered appropriate given the aims of this study. As the aim of the study is to evaluate the efficacy of ocrelizumab in this setting, the MRI results will be evaluated starting from week 8, as demonstrated in the Phase II clinical trial.

3.3.1 Rationale for Ocrelizumab Dose and Schedule

The dose level of ocrelizumab administered in this study is 600 mg. The first dose will be administered as two 300-mg IV infusions in 250 mL 0.9% sodium chloride each separated by 14 days in order to lower the amount of ocrelizumab administered upon first exposure. The remaining doses will be administered as single 600-mg infusion in 500 mL 0.9% sodium chloride every 24 weeks to assess the tolerability of the intended administration regimen.

This dosing regimen is anticipated to be well-tolerated and is consistent with the dosing regimen used in Studies WA21092 and WA21093 in patients with RMS.

3.3.2 Rationale for Patient Population

This study will be conducted in RRMS patients who show a suboptimal response to an adequate course of a DMT. RRMS is the most common type of MS, approximately 85% of MS patients present initially with RRMS (Confavreaux et al. 2000; Leray et al. 2015). Despite an adequate course of treatment with a DMT, a significant proportion of treated patients with RRMS will show signs of disease activity (Freedman 2014; Ziemssen et al. 2015; Tanasescu et al. 2015). Suboptimal responses are reported in approximately one-third of patients receiving DMT and therefore this population is considered to be appropriate to study the efficacy and safety of ocrelizumab.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 750 patients with RRMS who fulfill the eligibility criteria listed below will be enrolled in the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed informed consent form
- Able to comply with the study protocol, in the investigator's judgment
- Age 18 – 55 years, inclusive
- Have a definite diagnosis of RRMS, confirmed as per the revised McDonald 2010 criteria (Polman et al. 2011)
- Have a length of disease duration, from first symptom, of < 10 years. If the date of first symptom is unknown, then the diagnosis of RRMS should be of $\leqslant$ 5 years
- Have received no more than two prior DMTs, and the discontinuation of the most recent DMT was due to lack of efficacy
- Suboptimal disease control while on a DMT; a suboptimal response is defined by having at least one of the following events while being on a stable dose of the same DMT for at least 6 months:
  - One or more clinically reported relapse(s)
  - OR one or more T1 Gd-enhanced lesion(s)
  - OR two or more new and/or enlarging T2 lesions on MRI

  In addition, in patients receiving stable doses of the same approved DMT for more than a year, at least one of the above events must have occurred within the last 12 months of treatment with this DMT.
- EDSS of 0.0 to 4.0, inclusive, at screening

- For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 6 months after the last dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  The following are acceptable contraceptive methods: progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, and cap, diaphragm, or sponge with spermicide. A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods) is considered acceptable

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- SPMS or history of primary progressive or progressive relapsing MS
- Inability to complete an MRI (contraindications for MRI include but are not restricted to pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, inability to tolerate Gadolinium-based contrast agents etc.)
- Known presence of other neurological disorders, including but not limited to, the following:
  - History of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - History or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)
  - History or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
  - History or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus 1 (HTLV-1), herpes zoster myelopathy)
  - History of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; MELAS [mitochondrial myopathy, encephalopathy, lactic acidosis, stroke] syndrome)
  - Neuromyelitis optica
  - History or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behçet's disease)
  - History or known presence of sarcoidosis

- History of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)

Exclusions Related to General Health

- Pregnancy or lactation.
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study.
- History or currently active primary or secondary immunodeficiency.
- Lack of peripheral venous access.
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies.
- Significant or uncontrolled somatic disease or any other significant disease that may preclude patient from participating in the study.
- Congestive heart failure (New York Heart Association [NYHA] III or IV functional severity).
- Known active bacterial, viral, fungal, mycobacterial infection or other infection, excluding fungal infection of nail beds.
  Note: Active infections must be treated and effectively controlled before possible inclusion in the study
- History of major opportunistic infections (i.e. cryptococcosis, Pneumocystis pneumonia, PML)
- History or known presence of recurrent or chronic infection (e.g., hepatitis B or C, human immunodeficiency virus [HIV], syphilis, tuberculosis [TB])
- History of malignancy, including solid tumors and hematological malignancies, except basal cell carcinoma, in situ squamous cell carcinoma of the skin, and in situ carcinoma of the cervix of the uterus that have been previously completely excised with documented, clear margins.
- History of alcohol or drug abuse within 24 weeks prior to baseline.
- History or laboratory evidence of coagulation disorders.

Exclusions Related to Medications*

- Receipt of a live vaccine or attenuated live vaccine within 6 weeks prior to the baseline visit.

  In rare cases when patient requires vaccination with a live vaccine, the screening period may be extended but cannot exceed 8 weeks.
- Treatment with any investigational agent within 24 weeks of screening (Visit 1) or five half-lives of the investigational drug (whichever is longer) or treatment with any experimental procedures for MS (e.g., treatment for chronic cerebrospinal venous insufficiency).

- Contraindications to or intolerance of oral or IV corticosteroids, according to the country label, including:

  a) Psychosis not yet controlled by a treatment;

  b) Hypersensitivity to any of the constituents.
- Previous treatment with B-cell targeted therapies (i.e., rituximab, ocrelizumab, atacicept, belimumab, or ofatumumab).
- Systemic corticosteroid therapy within 4 weeks prior to screening.
- Any previous treatment with alemtuzumab (Campath/Mabcampath/Lemtrada), cladribine, mitoxantrone, daclizumab, laquinimod, total body irradiation, or bone marrow transplantation.
- Treatment with cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine or methotrexate.
- Previous treatment with natalizumab unless natalizumab was discontinued because of persistent anti-natalizumab antibodies.
- Treatment with IV Ig within 12 weeks prior to baseline.
- Any previous treatment with an investigational MS DMT not yet approved at time of screening.
- History of recurrent aspiration pneumonia requiring antibiotic therapy.
- Patients previously treated with teriflunomide, unless an accelerated elimination procedure is implemented before screening visit.

  Accelerated elimination procedure after stopping treatment with teriflunomide:

  - cholestyramine 8g is administered 3 times daily for a period of 11 days, or cholestyramine 4g three times a day can be used, if cholestyramine 8g three times a day is not well tolerated,
  - alternatively, 50g of activated powdered charcoal is administered every 12 hours for a period of 11 days.
- Previous treatment with fingolimod or dimethyl fumarate if at baseline the lymphocyte count is below lower limit of normal (LLN). The provisions for stopping therapy as described in the respective SmPCs should be followed.
- Treatment with fampridine/dalfamipridine (Fampyra®)/Ampyra®) unless on stable dose for $\geqslant$ 30 days prior to screening. Wherever possible, patients should remain on stable doses throughout the 96-week treatment period.

* Patients screened for this study should not be withdrawn from therapies for the sole purpose of meeting eligibility for the trial.

<u>Exclusions Related to Laboratory Findings*</u>

- Positive serum β human chorionic gonadotropin (hCG) measured at screening.

- Positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA polymerase chain reaction [PCR]) or hepatitis C (HepCAb).
- Lymphocyte count below LLN
- CD4 count<250/µL.
- Aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT) /serum glutamic pyruvic transaminase (SGPT)≥ 3.0 × ULN
- Platelet count <100,000/ µ L (<100 × 10^9/L).
- Absolute neutrophil count <1.0 × 10^3/µL.

*Re-testing before baseline: any abnormal screening laboratory value that is clinically relevant should be retested in order to rule out any progressive or uncontrolled underlying condition. The last value before baseline visit must meet study criteria.

Please note: based on local Ethics Committees or National Competent Authority requirements, additional diagnostic testing may be required for selected patients or selected centers to exclude tuberculosis, Lyme disease, HTLV-1 associated myelopathy (HAM), acquire immunodeficiency syndrome (AIDS), hereditary disorders, connective tissue disorders, or sarcoidosis. Other specific diagnostic tests may be requested when deemed necessary by the Investigator.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study in which all patients will receive the 600-mg dose of ocrelizumab following the 24-week regimen. Therefore, no randomization or blinding will be used in this study.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is ocrelizumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Ocrelizumab

Ocrelizumab will be supplied by the Sponsor as a liquid formulation containing 30-mg/mL ocrelizumab in 20 mM sodium acetate at pH 5.3, with 106 mM trehalose dihydrate and 0.02% polysorbate 20. The drug product is provided as a single-use liquid formulation in a 15-cc, type I USP, glass vial fitted with a 20-mm, fluoro-resin, laminated stopper and an aluminum seal with a flip-off plastic cap. The vial contains 300 mg ocrelizumab. No preservative is used as each vial is designed for single use.

The ocrelizumab drug product must be diluted before administration. Solutions of ocrelizumab for IV administration are prepared by dilution of the drug product into an

infusion bag containing 0.9% sodium chloride to a final drug concentration of 1 to 2 mg/mL.

Ocrelizumab may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter. The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of up to 0.2 µm).

For information on the formulation and handling of ocrelizumab, see the Ocrelizumab IB and Drug Preparation Guidelines.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Ocrelizumab

The first dose of ocrelizumab will be administered as two 300-mg infusions (600 mg total) in 250 mL 0.9% sodium chloride each separated by 14 days (i.e., Days 1 and 15), followed by one 600-mg infusion in 500 mL 0.9% sodium chloride every subsequent dose (i.e., every 24 weeks) for a maximum of 4 doses.

It is anticipated that the patient will need to stay at the hospital or clinic for a full day for the infusion visits. Ocrelizumab infusions should be initiated and supervised by an experienced professional with access to appropriate medical support to manage severe reactions such as serious IRRs. Each ocrelizumab infusion should be given as a slow IV infusion over approximately 150 minutes (2.5 hours) for the 300 mg dose and approximately 215 minutes (3.6 hours) for the 600 mg dose. To reduce potential IRRs, all patients will receive prophylactic treatment with 100 mg of methylprednisolone, or equivalent, administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab. Additional premedication is recommended, see Section 4.3.3.

Hypotension, as a symptom of IRR, may occur during ocrelizumab IV infusions. Therefore, withholding antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

Ocrelizumab must not be administered as an IV push or bolus. Well-adjusted infusion pumps should be used to control the infusion rate, and ocrelizumab should be infused through a dedicated line. It is important not to use evacuated glass containers, which require vented administration sets, to prepare the infusion because this causes foaming as air bubbles pass through the solution.

The patient will need to remain at the clinic at every visit for at least 1 hour after the completion of the infusion for observation. After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs

intravenously, if necessary, in the event of a delayed reaction. If no adverse events occur during this period of time, the IV cannula may be removed, and the patient may be discharged.

See the Ocrelizumab IB and Drug Preparation Guidelines for detailed instructions on drug preparation, storage, and administration.

An overview of the ocrelizumab dosing is presented in Table 1.

Table 1 Overview of Ocrelizumab Dosing

Group	1st Dose [a,c] (Weeks 1 – 24)		2nd Dose [b,c] (Weeks 24 – 48)	3rd Dose [b,c] (Weeks 48 – 72)	4th Dose [b,c] (Weeks 72 – 96)
	Day 1 Infusion	Day 15 Infusion	Week 24 Infusion	Week 48 Infusion	Week 72 Infusion
Ocrelizumab	300 mg IV in 250 mL 0.9% sodium chloride	300 mg IV in 250 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride	600 mg IV in 500 mL 0.9% sodium chloride

IV = intravenous.

Note: Before each infusion of ocrelizumab, 100 mg of methylprednisolone IV and an antihistaminic drug will be administered to reduce the potential for infusion-related reactions. Each dose has a duration of 24 weeks. The open-label treatment period consists of 96 weeks of treatment; patients will receive a maximum of 4 doses.

[a] The first dosing will consist of two IV infusions separated by 14 days (i.e., Days 1 and 15).

[b] Beginning with the second dose, a single infusion of ocrelizumab will be administered.

[c] Prior to the next infusion, a clinical evaluation will be performed to ensure that the patient remains eligible for retreatment.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF.

4.3.3 Prophylactic Treatment

Premedicate with 100 mg of methylprednisolone (or an equivalent), administered by slow IV infusion, to be completed approximately 30 minutes prior to each ocrelizumab infusion and an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each ocrelizumab infusion to reduce the frequency and severity of IRRs. The addition of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered.

Any overdose or incorrect administration of methylprednisolone should be noted on the Pre-Infusion Prophylactic Treatment eCRF. Adverse events associated with an overdose or incorrect administration of methylprednisolone and antihistaminic drug should be recorded on the Adverse Event eCRF.

Patients administered a sedating antihistamine for the treatment or prevention of IRRs should be given appropriate warnings concerning drowsiness and potential impairment of ability to drive or operate machinery.

4.3.4 Investigational Medicinal Product Accountability

The IMP required for completion of this study (ocrelizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMP, using the interactive voice/Web response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any unused IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Post-Trial Access to Ocrelizumab

Patients who completed the study and decided, in agreement with their treating neurologist, to continue on ocrelizumab treatment can be rolled-over in a separate ocrelizumab LTE study.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient within 6 weeks prior to the screening visit to the study completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

No formal drug-drug interaction studies have been conducted with ocrelizumab, as no drug-drug interactions are expected via the Cytochromes P450, other metabolizing enzymes or transporters.

Ocrelizumab is a monotherapy and has not been studied in combination with other DMTs. As with other immunomodulatory therapies, exercise caution when initiating ocrelizumab after an immunosuppressive therapy, and when initiating another therapy after ocrelizumab, taking into consideration the potential for overlapping pharmacodynamic effects.

Immunosuppressants, lymphocyte-depleting agents, or lymphocyte-trafficking blockers should NOT be administered while patient is B-cell depleted.

Hypotension, as a symptom of IRR, may occur during ocrelizumab IV infusions. Therefore, withholding antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

See the Ocrelizumab IB for a more detailed safety profile. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments to be performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed by the investigator to confirm that patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Patients' demographics (age, gender, self-reported race) and neurological examination will be collected. Medical History will include clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 6 weeks prior to the screening visit:

MS disease history:
First MS symptom: date, symptoms, severity, MRI.
Diagnosis of MS: Date, disease status, (EDSS, relapses, MRI) and, when available, criteria on which the diagnosis is based.

Baseline disease status:
EDSS, Number of relapses in the previous year, MRI lesions

Treatment history:
DMT: name, dose, start date (EDSS, relapses), stop date with disease status and reasons for discontinuation

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. The following assessments will also be conducted: neurological examination (see Section 4.5.4), relapse description, EDSS (see Section 4.5.6), and MRI (see Section 4.5.7). Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF. Height and weight will be measured at screening only. See Appendix 1 (Schedule of Assessments) for the timing of these assessments.

4.5.4 Neurological Examinations

Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. MS relapses should be recorded throughout the treatment period on a dedicated MS relapse eCRF page. See Appendix 1 (Schedule of Assessments) for the timing of these assessments.

A protocol-defined MS relapse is an occurrence of new or worsening neurological symptoms attributable to MS that meets the following criteria:

- Symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to medications)
- Symptoms should be preceded by neurological stability for at least 30 days
- Symptoms should be accompanied by new objective neurological worsening determined with a timely EDSS/ Functional Systems Score (FSS) assessment, consistent with an increase of at least:
  - ≥ 0.5 points on EDSS scale
  - or ≥ 2 points on one of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual
  - or ≥ 1 point on two or more of the following FSS scales: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual

Episodic spasms, sexual dysfunction, fatigue, mood change or bladder or bowel urgency or incontinence will not suffice to establish a relapse (Please note: Sexual dysfunction and fatigue need not be scored).

All patients with new neurological symptoms suggestive of a relapse should have an EDSS/FSS assessment performed **as soon as possible, ideally within 7 days of the onset of symptoms**. EDSS/FSS data is needed to allow the Sponsor to confirm whether the reported clinical relapse meets the criteria for a Protocol-defined relapse.

Please note: All MS relapses (i.e., regardless of whether they may meet criteria for a protocol-defined relapse which will be adjudicated by the Sponsor based on the above criteria) will be recorded on a pre-specified eCRF "MS relapse" form.

As infection is a potentially serious complication of B cell-depleting therapy, investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study. PML should be reported as a serious adverse event (with all available information) with immediate notification of the Medical Monitor. Please refer to Appendix 6 for guidance for diagnosis of PML.

Cognitive status: The cognitive status of the patient will be evaluated at baseline, and further yearly for the full duration of the trial with the use of BICAMS components.

4.5.5 Vital Signs

Vital signs will include measurements of heart rate, systolic and diastolic blood pressures, and oral or auricular temperature while the patient is in a seated position.

Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone (or an equivalent) infusion. In addition, vital signs should be obtained prior to the ocrelizumab infusion then every 15 minutes (± 5 minutes) for the first hour, followed by every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion.

Vital sign measurements will be performed as outlined in the schedule of assessments (see Appendix 1). Record abnormalities observed before enrollment on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF (as presented in Section 5.3.5.6).

4.5.6 Assessment of Disability

Disability in MS will be measured by the EDSS. See Appendix 1 (Schedule of Assessments) for the timing of these assessments.

The EDSS is based on a standard neurological examination, incorporating seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental], plus "other") rated and scored as FSSs. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death) (see Appendix 3).

4.5.7 Brain Magnetic Resonance Imaging

MRI will be used to monitor CNS lesions and potentially other pathophysiology, such as inflammation and neurodegeneration. Brain MRI scans will be obtained at study visits as shown in the Schedule of Assessments (see Appendix 1). All efforts should be made to obtain the brain MRI scans before the next ocrelizumab infusion and the scans should be reviewed locally for the presence of any non-MS pathology, including PML, before the next infusion is administered.

If patients receive corticosteroids for a treatment of an MS relapse, every effort should be made to obtain the scan prior to the first steroid dose if the pre-steroid scan is within 1 week of the scheduled visit. In patients already receiving corticosteroids for an MS relapse, there should be an interval of at least 3 weeks between the last dose of corticosteroids and the scan, to allow for normalization of blood-brain barrier.

MRI scans will be read by a centralized reading center for efficacy endpoints. Further details on scanning acquisition sequences, methods, handling, transmission of the scans, and certification of site MRI radiologist/technicians are described in a separate MRI technical manual.

Assessments will include T1-weighted scans before and after injection of gadolinium contrast, and may also include, but may not be limited to: fluid-attenuated inversion-recovery (FLAIR), proton density-weighted, and T2-weighted scans. The MRI activity will be based upon the MRI scan taken on week 8 when the drug has reached its anti-inflammatory activity.

The total brain volume and the different white and grey matter structures will be measured over the full duration of the study and follow-up period.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples can be taken up to 2 weeks prior to the scheduled study visit. Results should be available prior to dosing, except for anti-JCV antibodies (plasma samples

collected and stored centrally), which will be analyzed upon request, and CD8 and CD19 (no interference with re-treatment).

Pre-infusion laboratory samples should be drawn so that routine laboratory test results are available for review before the infusion, unless otherwise specified.

Routine laboratory assessments (performed in local laboratory) will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, red blood cell [RBC] count, white blood cell [WBC] count, percent and absolute differential count [neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells]).
- Serum chemistries (AST, ALT, gamma-glutamyl transpeptidase [GGT], total bilirubin, creatinine, random glucose, potassium, sodium)
- Urine dipstick at site
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. A urine pregnancy test should be performed prior to methylprednisolone infusion in subsequent doses. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. The follicle-stimulating hormone (FSH) test is only applicable to confirm postmenopausal status in female patients.
- Viral serology and detection:
  - Hepatitis B (HBsAg and HBcAb confirmed, if positive, by positive viral DNA PCR)
  - For enrolled patients with negative HBsAg and positive total HBcAb, Hepatitis B virus (HBV) DNA (by PCR) must be repeated every 24 weeks
  - Hepatitis C virus (HCV) antibody
- Lymphocytes subtypes
  - Whole-blood samples will be collected to determine the duration of B-cell depletion and recovery ($CD19^+$) and T-cell counts ($CD4^+$, $CD8^+$)

Additional laboratory samples will be collected:

- Plasma samples for anti-JCV antibody assessments at baseline, 1 year and end of study. Samples will be stored in a central laboratory until one year after last patient last visit (LPLV) for further analysis upon request.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Per local Institutional Review Board (IRB)/Ethics Committee (EC) requirements, additional testing may be required for selected patients or selected centers to exclude tuberculosis, Lyme disease, HAM, AIDS, hereditary disorders, connective tissue disorders, or sarcoidosis.

4.5.9 Patient-Reported Outcomes

PRO data will be elicited from patients in this study to better characterize patient quality of life and treatment satisfaction while on ocrelizumab.

MSIS-29 is a 29-item questionnaire designed to measure the physical and psychological impact of MS from the patient's perspective.

TSQM II is a 14-item subject assessed evaluation of treatment medication using a 7-point Likert-type scale rated as follows: 1=Extremely Dissatisfied to 7= Extremely Satisfied. Domain scores range from 0–100, with higher scores representing higher satisfaction. TSQM has been validated using a national panel study of chronic disease (Atkinson et al. 2004).

SymptoMScreen: composite score based upon a battery of seven-point Likert scales for 11 distinct domains commonly affected by MS: mobility, dexterity, vision, fatigue, cognition, bladder function, sensation, spasticity, body pain, depression and anxiety. Total score and subscale scores are assessed over the study duration (Green et al. 2015).

Employment Status WPAI: questionnaire that assesses the effect of MS on ability to work and perform regular activities.

Please refer to Appendix 5 for detailed information on the PROs.

The PRO instruments, translated as required in the local language, will be distributed by the investigator staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigator site prior to the completion of other study assessments and the administration of study drug. Patients must complete these measures prior to the patient having any tests and prior to any discussion of the patient's progress with their physician or any other healthcare personnel at the site. PRO assessments will be performed as outlined in the schedule of assessments (see Appendix 1)

4.5.10 BICAMS

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery includes the following tests of mental processing speed and memory:

- Symbol Digit Modalities Test (SDMT)
- California Verbal Learning Test 2 (CVLT-II)
- Brief Visuospatial Memory Test Revised (BVMT-R)

Since CVLT-II is not yet available in all the languages of the countries participating in this study, the patients will not be assessed with this portion of the BICAMS. The patients will only need to complete the two components of the BICAMS test battery (Symbol Digit Modalities Test and Brief Visuospatial Memory Test Revised).

Please note that the BICAMS should be administered only after the patient has completed all the PRO assessments. The recommended order of administration is first the SDMT, followed by the BVMT-R. The BICAMS will be scored centrally by a global reader and the results will be provided to the sites to be recorded in the eCRF.

4.5.11 Telephone Interviews

The telephone interview will be conducted by site personnel familiar with the patient(s) every 8 weeks (± 3 days) between the study visits during the treatment period and follow-up. The purpose of this semi-structured interview is to identify new or worsening neurological symptoms that warrant an unscheduled visit and collect information on possible events of infections. The site will record in the eCRF the telephone interview as "Done" or "Not Done" and documentation of the interview will be maintained in the patient's study file. Please refer to Appendix 4 for detailed information.

4.5.12 Patient Diary (optional)

Due to the low frequency of study visits (every 6 months) and the structured telephone interviews (every 8 weeks between the study visits), patient diaries are proposed as an additional optional tool to help further improve the collection and documentation of Adverse Events and concomitant medications. The decision to use the patient diary is left to the discretion of each investigator. The investigator must ensure that required EC/IRB approval was obtained before implementing the patient diary at his/her site.

Additional instructions around the use of an optional Patient Diary are provided in Appendix 7.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

- Patient non-compliance, defined as failure to follow dosing instructions or to complete study visits

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Ongoing pregnancy or breastfeeding (in case of pregnancy, treatment should be interrupted, and the patient should be monitored for safety; however, the patient can be re-started with the treatment after the pregnancy and breastfeeding period. During pregnancy and breastfeeding, the patient will continue to come for the regular schedule visits as per protocol and will perform all assessments except MRI).
- Life-threating IRR or serious hypersensitivity reaction
- Active hepatitis B infection
- PML
- Active tuberculosis, either new onset or reactivation

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patient discontinuing the study treatment prematurely will be further monitored in a safety follow-up (see Section 3.1.4).

Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

4.6.4 End of study treatment

At the end of the study treatment the patients will be encouraged to be included in a separate LTE study to further evaluate the efficacy and safety of their DMT treatment, and this is independent of the DMT. This LTE will also aim to evaluate the relationship between the primary endpoint of this study and long-term outcome.

Patients who discontinue treatment early will be followed up for at least 96 weeks after the Early Treatment Discontinuation Visit. Patients who complete the 96 weeks Treatment Period and, in agreement with their treating neurologist, decide not to continue in a separate LTE study, will be followed up for at least 96 weeks after the end of the Treatment Period. (see Section 3.1.4). Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ocrelizumab is currently in clinical development for the treatment of MS. Identified and potential risks associated with ocrelizumab treatment will continue to be closely monitored throughout the clinical program. Patient safety during the ocrelizumab program is ensured by targeting the most appropriate patient population, stringent safety monitoring by the Sponsor, and protocol-specified ocrelizumab treatment interruption criteria. Patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and standard laboratory measurements. Adverse events will be graded according to the National Cancer Institute (NCI) CTCAE v4.0.

Administration of ocrelizumab will be performed in a hospital, clinic environment or doctor's office/practice under close supervision of the investigator or a medically qualified staff member with immediate availability of full resuscitation facilities. All adverse events and serious adverse events will be recorded during the study and until 96 weeks after the end of the Treatment Period as provided through this study. Safety assessments will include the incidence, nature, and severity of (serious) adverse events graded per the NCI CTCAE v4.0. Safety assessments will be conducted per the schedule of assessments in Appendix 1.

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize these issues, are outlined in the following sections.

5.1.1 Risks Associated with Ocrelizumab

5.1.1.1 Identified Risks and Adverse Drug Reactions

Infusion-Related Reactions (IRRs)

All CD20 depleting agents administered via the intravenous route, including ocrelizumab have been associated with acute IRRs. Following the approved administration regimen (which includes the use of premedication prior to treatment with ocrelizumab in order to reduce frequency and severity of IRRs), symptoms of IRRs may occur during any ocrelizumab infusion but have been more frequently reported during the first infusion. Physicians should alert patients that IRRs can occur within 24 hours of the infusion. Across the RMS and PPMS trials, symptoms associated with IRRs included, but were not limited to: pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea and tachycardia.

Patients should be observed for at least one hour after the completion of the infusion for any symptom of IRR. They will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Hypotension, as a symptom of IRR, may occur during ocrelizumab infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each ocrelizumab infusion.

Infections

Infection is an identified risk associated with ocrelizumab treatment, predominantly involving mild to moderate respiratory tract infections. Non-disseminated herpes virus-associated infections, mostly mild to moderate, were also reported more frequently with ocrelizumab (approximately 5 to 6%, simplex and zoster) than with comparators (approximately 3%).

During the controlled period of the pivotal trials, the proportion of patients with serious infections in RMS was lower in the ocrelizumab group (1.3%) than in the interferon beta-1a group (2.9%); in PPMS, the proportion of patients with serious infections, was similar in both groups: 6.7% in the placebo group compared with 6.2% in the ocrelizumab group

Serious, opportunistic and fatal infections have occurred in patients with lupus and rheumatoid arthritis (RA) treated with ocrelizumab in Phase III clinical trials. Data from completed studies regarding infection risks with ocrelizumab treatment in these patient populations are provided in the Ocrelizumab IB.

No opportunistic infections were reported by any MS patient treated with ocrelizumab during the controlled period of the pivotal trials.

In interventional clinical studies there were no reports of hepatitis B reactivation in MS patients treated with ocrelizumab, but it had been reported in one RA patient treated with ocrelizumab. HBV screening should be performed in all patients before initiation of treatment with ocrelizumab as per local guidelines. Patients with active Hepatitis B Virus should not be treated with ocrelizumab. Patients with positive serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent Hepatitis B reactivation.

Delay ocrelizumab administration in patients with an active infection until the infection is resolved.

For PML see “Potential risks” below.

Decrease in immunoglobulins

Treatment with ocrelizumab resulted in a decrease in total immunoglobulins (Ig) over the controlled period of the studies, mainly driven by reduction in IgM, with no observed association with serious infections during the controlled periods. The proportion of patients with decrease in Igs below LLN increased over time and with successive dosing. Based on additional patient exposure, in cases of continuous decrease over time, a higher risk of serious infection cannot be ruled out (see below in potential risks section).

Delayed return of peripheral B cells

Treatment with ocrelizumab leads to rapid depletion of CD19+ B cells in blood by 14 days post treatment (first time-point of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. The longest follow up time after the last ocrelizumab infusion from Phase II Study WA21493 in 51 patients, indicates that the median time to repletion (returned to baseline/LLN whichever occurred first of B cells was 72 weeks (range 27 − 175 weeks). Patients with prolonged B-cell depletion should be monitored until their B-cells have repleted.

Impaired Response to Vaccination

After treatment with ocrelizumab over 2 years in pivotal clinical trials, the proportion of patients with positive antibody titers against streptococcus pneumoniae, mumps, rubella, and varicella were generally similar to the proportions at baseline.

The results of the randomized, open-label Phase IIIb study (BN29739) that assessed if ocrelizumab recipients with RMS raise adequate humoral responses to selected vaccines indicate that patients treated with ocrelizumab were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide,

keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. The results are summarized in the current version of the IB.

Physicians should review the immunization status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete it at least 6 weeks prior to initiation of ocrelizumab. For seasonal influenza vaccines, it is still recommended to vaccinate patients on ocrelizumab. Vaccination with live or live-attenuated vaccines are not recommended during the treatment with ocrelizumab and until B cells have returned to normal levels.

Due to the potential depletion of B-cells in neonates and infants of mothers, who have been exposed to ocrelizumab during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cells have recovered; therefore, measuring CD19-positive B cell level, in neonates and infants, prior to vaccination is recommended.

It is recommended that all vaccinations other than live or live-attenuated should follow the local immunization schedule and measurement of vaccine-induced response titers should be considered to check whether individuals can mount a protective immune response because the efficacy of the vaccination may be decreased.

5.1.1.2 Potential Risks

PML

PML is an important potential risk for ocrelizumab and it has only been reported with ocrelizumab where the risk for PML was preexisting, specifically from prior immunosuppressive treatment (e.g. natalizumab or fingolimod treatment). In all of these PML cases, the causality with ocrelizumab was not considered plausible. Based on the available information, it is reasonable to consider that the PML started before the first administration of ocrelizumab, given new symptom onset and/or MRI changes had already occurred on the previous therapy or during the wash out period, and was related to prior immunosuppressive treatment. Physicians should be vigilant for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse. If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation of PML, including MRI, confirmatory CSF testing for JC Viral DNA and repeat neurological assessments, should be considered. If PML is confirmed, ocrelizumab must be discontinued permanently. Please refer to Appendix 6 for guidance for diagnosis of PML. Please see the IB for more details.

Serious infections related to decrease in immunoglobulins (particularly in patients previously exposed to immunosuppressive/ immunomodulatory drugs or with pre-existing hypogammaglobulinaemia)

Based on additional patient exposure an apparent association between decrease in immunoglobulins (IgA, IgG, IgM) and serious infections with ocrelizumab treatment was observed. There was no difference in the pattern (type, latency, duration, outcome) of

the serious infections reported in this subset of patients compared to the overall serious infections profile. In addition, risk factors for a subset of patients at higher risk of serious infections could not be identified.

Hypersensitivity reactions

No hypersensitivity reactions to ocrelizumab were reported in the controlled clinical trials.

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated.

Malignancies including Breast Cancer

Patients should follow standard breast cancer screening guidelines.

Please see the IB for more details.

Neutropenia

In the controlled treatment period, decreased neutrophils were observed in 12 to 15% of MS patients treated with ocrelizumab, in PPMS and RMS respectively. Most were mild to moderate in severity, and approximately 1% of the patients had Grade 3 or 4 neutropenia; no temporal association with infections was identified. Based on additional patient exposure, an association between neutropenia and serious infections with ocrelizumab treatment was not observed.

Additional information can be found in the current IB.

5.1.2 Risks Associated with Corticosteroids

The adverse reactions of corticosteroids may result from unwanted glucocorticoid actions, or from inhibition of the hypothalamic-pituitary-adrenal axis. Please refer to local Prescribing Information.

5.1.3 Risks Associated with Antihistamines

The adverse reactions depend on the sedating properties of the antihistamine and include but are not limited to nausea, drowsiness, headaches, dry mouth, and allergic reactions such as rash. Please refer to local Prescribing Information.

5.1.4 Management of Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 2. Additional guidelines are provided in the subsections below.

Table 2 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Mild to moderate IRR	• If the event that a patient experiences is a mild to moderate IRR (e.g. headache), the infusion rate should be reduced to half the rate at the time of the event. • This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion schedule.
Severe IRR (or complex of flushing, fever, and throat pain)	• If a patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately, and the patient should receive symptomatic treatment. • The infusion should be re-started only after all symptoms have resolved. • The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction.
Life-threatening or disabling IRR (e.g., anaphylaxis)	• Immediately stop ocrelizumab if there are signs of a life-threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. • The patient should receive appropriate treatment. • Permanently discontinue ocrelizumab in these patients.

hr = hour; IRR = infusion-related reaction

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4

5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7).
- Suspected transmission of an infectious agent by the study drug, as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5 and Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive

procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 96 weeks after the end of the Treatment Period, but may be extended in patients whose B-cells take longer to replete.

Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for infusion related reactions and adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for IRRs and Other Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF.

Investigators should consider a local IRR for any symptoms affecting the skin and localized to only one place. Any other IRR should be considered as systemic.

If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs

and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of RRMS.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of RRMS, "RRMS progression" should be recorded on the Adverse Event eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Relapsing Remitting Multiple Sclerosis

Events that are clearly consistent with the expected pattern of progression of the underlying disease, such as MS relapses or disability worsening should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on EDSS score. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

Occasional isolated symptoms that according to the investigator are caused by MS, but do not constitute a full MS relapse, should be reported as an AE, with the causality “Disease under study" (see Section 5.3.4).

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.
- Elective hospitalizations or surgical procedures that are a result of a patient's pre-existing condition(s) that have not worsened since receiving trial medication. Examples may include, but are not limited to, cholecystectomy for gallstones, and diagnostic testing. Such events should still be recorded as medical procedures in the "Surgeries and therapies" eCRF.
- Hospitalization to receive trial medication such as infusions of ocrelizumab unless this is prolonged (more than 24 hours).
- Hospitalization following an MS relapse as long as the reason for hospitalization is to receive standard treatment with i.v. methylprednisolone.

For a list of serious ADRs that are considered expected, kindly refer to the current IB.

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Adverse events associated with an overdose of ocrelizumab in previous clinical studies include IRRs and infection.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report

such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events will be reported until 96 weeks after the end of the Treatment Period. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

For pregnancies occurring in female patients who have been exposed to Ocrelizumab at any time during pregnancy or within six months prior to conception, pregnancy outcome and the health status of the child will be followed until the child is one year of age. Data collection is voluntary only; it does not include any interventions or invasive procedures. A Pregnancy Outcome and Infant Health Information on First Year of Life questionnaire will be submitted to Health Authorities and IRB/IECs for their approval, along with the infant data release consent form. The data will be reported on dedicated pregnancy

outcome and infant health information paper form, hence will not be entered in the eCRF.

5.4.3.2 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported in patients during the study should be followed with a Pregnancy Outcome and Infant Health Information on First Year of life questionnaire.

5.5.2 Sponsor Follow-Up

For serious adverse events, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious and non-serious adverse event that occurs after the end of the adverse event reporting period (defined as 96 weeks after the end of the Treatment Period), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Ocrelizumab IB

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Infection
- Infusion related reactions

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of this single-arm non-comparative study will be exploratory and primarily based on descriptive statistical methods. Unless otherwise specified, statistical tests will be two-sided and the statistical significance level will be 5%. Corresponding 95% CIs will be presented as appropriate. Although multiple statistical tests may be conducted, no adjustments to the Type 1 error rate will be made.

For continuous variables, descriptive statistics (e.g., mean, median, standard deviation [SD], n, 25^{th} and 75^{th} percentiles, minimum, and maximum) will be calculated and summarized. For categorical variables, the number and percentage in each category will be displayed. Full details of all statistical issues and planned statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the locking of the study database and may include further exploratory analyses not

explicitly described in this section, as well as analyses of data from the study phase beyond the main 96-week study period.

Analysis populations

The efficacy and safety analyses will be performed using the intent-to-treat (ITT) population. The per-protocol (PP) population will be used for supportive efficacy analyses of the primary endpoint and selected secondary endpoints in order to evaluate the influence of major protocol violators on key efficacy endpoints.Intent-to-Treat Population

All enrolled patients who received any dose of ocrelizumab will be included in the ITT population. Patients who prematurely withdrew from the study for any reason and who did not perform any assessment for any reason will still be included in the ITT population.

Per-Protocol Population

The per-protocol population will consist of the subset of the ITT population defined as all patients who had 96 weeks of treatment and who did not have any major protocol violations that are deemed to potentially affect the efficacy and safety endpoints. The list of criteria leading to exclusion from the per-protocol population will be finalized prior to database closure and documented in the SAP.

6.1 DETERMINATION OF SAMPLE SIZE

With a sample size of 750 patients, an observed NEDA rate of 30% will be estimated with a precision (half-width of the 95% CI around the estimate) of 3.3% based on the Clopper-Pearson method, i.e. the 95% CI will be (26.7%, 33.4%). Even if the NEDA rate is different from the assumed rate of 30%, with the proposed sample size the precision of the estimate will remain better than 3.6% (value for a NEDA rate of 50%).

The annualized relapse rate is another relevant outcome measure assessed in this study. Based on results from the pivotal Phase III studies WA21092 (Opera I) and WA21093 (Opera II), in this study the adjusted annualized relapse rate assessed over two years is expected to be estimated with a precision of approximately 0.03.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, ocrelizumab administration, and discontinuations from the study will be summarized. Patient disposition and the incidence of treatment discontinuation for reasons other than disease progression will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will also be summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patients' demographics (age, gender, and self-reported race), medical history and neurological examination will be summarized. The following will also be summarized: MS disease history (duration since first MS symptoms, duration of MS since diagnosis, relapses in the past year) and MS treatment history, baseline measures of MRI, EDSS and other important variables.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of patients who have no evidence of disease activity (NEDA), as per protocol defined events during a 96-week period. The 8 weeks MRI scan will be the baseline for MRI activity.

The definition of a protocol-defined event of disease activity is the occurrence of at least one of the following while on treatment with ocrelizumab:

- A protocol-defined relapse as defined in Section 4.5.4
- 24 weeks confirmed disability progression based on increases in EDSS while on treatment with ocrelizumab
- A T1 Gd-enhanced lesion after Week 8
- A new and/or enlarging T2 hyperintense lesion on MRI after Week 8 compared to the Week 8 MRI scan.

6.4.2 Secondary Efficacy Endpoints

The secondary objective for this study is to evaluate the efficacy of ocrelizumab 600 mg IV given every 24 weeks on the basis of the endpoints and analyses listed in Section 2.1.2.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy objective for this study is to further assess the efficacy of ocrelizumab 600 mg IV given every 24 weeks by monitoring PROs related to QoL, treatment satisfaction, and other endpoints and analyses as listed in Section 2.1.3.

6.4.4 Analysis Methods

The analysis will be performed after the last CDP and CDI confirmation visit. The per-protocol population will be used for supportive efficacy analyses of the primary endpoint.

The evaluation of the clinical efficacy of ocrelizumab will be based upon the events in-between baseline visit and week 96. The MRI activity is evaluated from week 8 to week

96. The proportion of patients free from protocol-defined events up to Week 96 (i.e. patients with NEDA) will be calculated and the corresponding two-sided Clopper-Pearson 95% CI will be presented. Logistic regression models will be used to identify predictors of response to treatment (freedom from events). Variables that will be considered include: region, line of treatment (previous DMTs), gender, and baseline EDSS. In addition, specific efficacy endpoints, such as CDP, will be compared between patients with or without evidence of disease activity up to Week 96.

Details about the missing data handling, as well as sensitivity analyses, will be specified in the statistical analysis plan.

The proportion of patients free from a protocol-defined event up to Week 24, 48, and 96 will be calculated and the corresponding two-sided Clopper-Pearson 95% CI will be presented. Logistic regression models will be used to identify predictors of response to treatment (freedom from events). Variables that will be considered include: region, line of treatment (previous DMTs), gender, and baseline EDSS.

The annualized relapse rate by Week 96 will be analyzed using regression based on a negative binomial model, adjusting for factors that may include region, baseline EDSS (<4.0 vs ≥ 4.0), line of treatment (previous DMTs), with the log-transformed drug exposure time in years as an “offset” variable. The adjusted annualized relapse rate will be presented.

EDSS and its change from baseline, as well as other continuous variables such as the change in total T2 lesion volume and the key PROs, will be summarized descriptively at each assessment visit. The time course of these variables will be described using techniques such as linear mixed models for repeated measures (MMRM) adjusting for covariates such as the respective baseline score, geographical region, and baseline EDSS.

The Kaplan–Meier method will be used to estimate the survival function for time-to-event data (e.g., time to onset of first relapse; time to onset of sustained disability progression for at least 12 weeks) and Cox proportional hazards regression will be used to identify predictors of survival. Variables to be included in the regression model will be the same as those used in the logistic regression described above. Further details will be specified in the SAP.

The total number of T1 Gd-enhanced lesions will be calculated as the sum of the individual number of T1 Gd-enhanced lesions at Weeks 24, 48 and 96. Data from unscheduled assessments will not be included in this summary or analysis. A negative binomial model will be used to estimate the rate of lesion occurrence.

6.5 SAFETY ANALYSES

6.5.1 Safety Outcome Measures

The safety outcome measures comprise the following: the incidence and nature of all adverse events, including findings on vital sign measurements, physical and neurological examinations, clinical laboratory tests, locally reviewed MRI for safety (non-MS CNS pathology), and concomitant medications.

6.5.2 Safety Analyses

Safety will be assessed through summaries of adverse events (including rates/incidence rates and corresponding 95% CIs) and clinical laboratory abnormalities.

All adverse events occurring on or after treatment on Day 1 will be coded, summarized by NCI CTCAE v4.0 grade, and tabulated by body system and Preferred Term for individual adverse events within each body system. Grade 3 to 5 adverse events, serious adverse events, adverse events leading to treatment discontinuation, time to withdrawal from the study due to an adverse event, first adverse event leading to infusion adjustment, and time to first selected treatment-related adverse event will be summarized. In addition, all serious adverse events and deaths will be listed.

Associated laboratory parameters, such as hepatic function, renal function, and hematology values, will be grouped and presented together.

Ocrelizumab exposure will be summarized, including duration and dosage.

6.6 SUBGROUP ANALYSIS

Subgroup analysis will be done based upon

- First or second switch
- Previous treatments
- Age of subjects ($\leqslant$ 40 years, > 40 years)
- Disease severity at inclusion and in disease history:
    - EDSS at baseline (< EDSS 2.5, $\geqslant$ EDSS 2.5)
    - Number of relapses over the year prior to inclusion ($\leqslant$ 1, >1)
    - MRI activity at baseline (number of T1 Gd+, $\leqslant$ 2, > 2)

6.7 HANDLING OF MISSING DATA

Details about the missing data handling will be specified in statistical analysis plan

6.8 INTERIM ANALYSIS

No formal confirmatory efficacy interim analyses are planned. Exploratory analyses of selected endpoints may be performed during the course of the study, e.g. after all patients have completed the first 6 and 12 months of the treatment phase and the necessary data are available.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data. Central imaging review data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the PRO questionnaires as well as the BICAMS scoring data received from the central reader will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the CRO.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States (U.S.) or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit [LPLV]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Roche and will be managed by Roche and CROs. CROs will provide clinical operations management, data management, biostatistics, and medical monitoring.

An IxRS will be used to assign patient numbers, monitor enrollment and patient status, and to manage study treatment requests and study drug shipments.

Patient data will be recorded via an EDC system using eCRFs.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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APPENDICES

Appendix 1: Schedule of Assessments: Screening through the End of Treatment Period

Visit	Screening	Treatment Period							Early study treatment discon-tinuation evaluation[q]	Follow-Up[a] Refer to Appendix 2
	1	2 (Baseline)	3	4	5	6	7	8		
Week	–4 to –1 weeks	1	2 (±2 days)	8 (±3 days)	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
Informed consent [b]	X									
Medical history and demographic data [c]	X									
Review inclusion & exclusion criteria	X	X								
Physical examination [d]	X	X	X		X	X	X	X	X	
Height and weight	X									
Vital signs [e]	X	X	X		X	X	X	X	X	
Laboratory Assessments										
Hematology, chemistry, urinalysis [f]	X	X	X		X	X	X	X	X	
Pregnancy test [g]	X	X	X		X	X	X	X		
Hepatitis screening [h]	X									
Hepatitis B virus DNA test [h]	X									
Lymphocytes subtypes sample [i]		X	X		X	X	X	X	X	
Plasma anti-JCV antibodies sample [j]		X				X		X	X	
EDSS score [k]	X	X			X	X	X	X	X	
Brain MRI [r]	X [s]			X	X	X		X	X	
Neurological examination [l]	X	X	X		X	X	X	X	X	
Recording of potential relapses		X	X		X	X	X	X	X	
Adverse event assessment [m]		X	X		X	X	X	X	X	
Patient Reported Outcomes		X			X	X		X	X	
BICAMS assessment [t]		X				X		X		

Visit	Screening	Treatment Period							Early study treatment discon-tinuation evaluation[q]	Follow-Up[a] Refer to Appendix 2
	1	2 (Baseline)	3	4	5	6	7	8		
Week	–4 to –1 weeks	1	2 (±2 days)	8 (±3 days)	24 (±14 days)	48 (±14 days)	72 (±14 days)	96 (±14 days)		
Concomitant treatment review		X	X		X	X	X	X		
Methylprednisolone and antihistaminic drug premedication [n]		X	X		X	X	X			
Ocrelizumab administration [o]		X	X		X	X	X			
Telephone contact every 8 weeks[p]				X					(X)	

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BICAMS= Brief International Cognitive Assessment for Multiple Sclerosis; eCRF = electronic Case Report Form; EDSS = Expanded Disability Status Scale; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HepCAb = hepatitis C; IV = intravenous; JCV = John Cunningham virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PCR = polymerase chain reaction; PML = progressive multifocal leukoencephalopathy; RBC = red blood cell; WBC = white blood cell.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] The follow-up period will begin when the patient discontinues from the study for any reason. Patients should remain in follow-up for 96 weeks following the Early Treatment Discontinuation Visit (if discontinued early) or after the end of the Treatment Period. Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

[b] Written informed consent will be obtained from all patients during screening in order to be eligible for the study. ICF signature needs to be obtained before any study related procedure; the screening visit date is the date of the first screening procedure (e.g. lab sampling, neurological exam, etc.).

[c] Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 6 weeks prior to the screening visit. Demographic data will include age, sex, and self-reported race/ethnicity.

[d] A complete physical examination should be performed at the screening and baseline visits and at all dosing visits during treatment. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities not related to MS should be recorded as adverse events on the Adverse Event eCRF.

[e] Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, and oral or auricular temperature while the patient is in a seated position. Vital signs should be taken within 45 minutes prior to the premedication methylprednisolone infusion. In addition, vital signs should be obtained prior to the ocrelizumab infusion then every 15 minutes (±5 minutes) for the first hour, followed by every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. Record abnormalities observed before enrollment on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Hematology will include hemoglobin, hematocrit, RBCs, WBC absolute and differential, ANC, and quantitative platelet count. Chemistry will include AST, ALT, GGT, creatinine, total bilirubin, random glucose, potassium and sodium. Urine dipstick will be done at site locally.

[g] Serum b-hCG must be performed at screening in women of childbearing potential. Subsequently, urine β-hCG (sensitivity ≥25 mIU/mL) must be collected. On infusion visits, the urine pregnancy test should be performed prior to methylprednisolone infusion in all women of childbearing potential. If positive, ocrelizumab should be withheld. The FSH test is only applicable to confirm postmenopausal status in female patients.

[h] All patients must have negative HBsAg result and negative HepCAb screening tests prior to enrollment. If total HBcAb is positive at screening, HBV DNA measured by PCR must be negative in order for a patient to be eligible for the study. For enrolled patients with negative HBsAg and positive total HBcAb, HBV DNA (by PCR) must be repeated every 24 weeks.

[i] Lymphocytes subtypes samples should be collected prior to ocrelizumab infusion to screen for CD19+ and T-cell counts (CD4+, CD8+) at a local laboratory.

[j] Plasma samples for anti-JCV antibodies should be taken at baseline and repeated yearly and end of study for storage in a central laboratory. Samples will be analyzed upon request.

[k] Patients must have an EDSS score of 0.0 to 4.0 points, inclusive at screening to be eligible. EDSS needs to be confirmed after 24 weeks if EDSS changes from baseline to Week 96

[l] Neurological examinations will be used to distinguish relapse in MS from another neurological (non-MS) disorder. Potential relapses should be recorded throughout the treatment period. Investigators will also screen patients for signs and symptoms of PML by evaluating neurological deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychological alteration, retrochiasmal visual defects, hemiparesis, cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination). Patients with suspected PML should be withheld from ocrelizumab treatment until PML is ruled out by complete clinical evaluation and appropriate diagnostic testing. A patient with confirmed PML should be withdrawn from the study.

[m] After initiation of study drug, all adverse events should be reported until 96 weeks after the end of the Treatment Period but may be extended in patients whose B-cells take longer to replete. After this period, the investigator should report any serious and non-serious adverse events that are believed to be related to prior study drug treatment (see Sections 5.3.1 and 5.6).

[n] All patients must receive prophylactic treatment with 100 mg methylprednisolone, administered by slow IV infusion, to be completed approximately 30 minutes before the start of each ocrelizumab infusion, and an antihistaminic drug (e.g., diphenhydramine) approximately 30 – 60 minutes before each infusion of ocrelizumab.

[o] Ocrelizumab will be administered as two 300-mg IV infusions in 250 mL 0.9% sodium chloride each on Days 1 and 15 and one 600-mg infusion in 500 mL 0.9% sodium chloride every subsequent dose (i.e., every 24 weeks) for a maximum of 72 weeks. It is anticipated that the patient will need to stay at the hospital or clinic for a full day for the infusion visits.

[p] A structured telephone interview will be conducted by site personnel every 8 weeks (± 3 days) to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections. No telephone contact is needed in weeks where patient is performing on-site visits (week 24, 48, 72 and 96).

[q] If the subject discontinues treatment early, all efforts should be made to perform the Early study treatment discontinuation evaluation visit as soon as possible after discontinuation from treatment period. Otherwise, reasons for discontinuation will be captured via telephone call.

[r] All efforts should be made to obtain the brain MRI scans before the next ocrelizumab infusion and the scans should be reviewed locally for the presence of any non-MS pathology, including PML, before the next infusion is administered.

[s] In case of re-screening, MRI does not need to be repeated if the MRI scan obtained at first screening is not older than 3 months.

[t] Since CVLT-II is not yet available in all the languages of the countries participating in this study, the patients will not be assessed with this portion of the BICAMS. The patients will only need to complete the two components of the BICAMS test battery (Symbol Digit Modalities Test and Brief Visuospatial Memory Test Revised).

Note: Lab samples can be taken up to 2 weeks prior to the scheduled study visit. Results should be available prior dosing, except for anti-JCV antibodies (plasma samples collected and stored centrally) which will be analyzed upon request, and CD8 and CD19 (no interference with re-treatment)

Appendix 2: Follow-up Schedule of Assessments

(Including Additional B-Cell Monitoring, if required)

Patients who decide to leave the study and switch to commercially marketed Ocrelizumab, either after completion of the 96 weeks Treatment Period or after early discontinuation of the 96 weeks Treatment Period, will not enter the safety Follow-up Period.

	Follow Up	**Prolonged B-Cell Monitoring [a]**
Assessment	Visits Every 24 Weeks (± 14 days) [b]	Visits Every 24 Weeks (± 14 days)
Routine safety laboratory tests [c]	X	X
Lymphocytes subtypes [d]	X	X
Plasma anti-JCV antibodies sample [e]	X	X
Vital signs	X	X
EDSS score [f]	X	
Potential relapses recorded	X	X
Adverse events [g]	X	X
BICAMS assessment [h]	X	X
Concomitant medication	X	X
MRI [i]	X	X
Telephone contact every 8 weeks [j]	X	X

BICAMS= Brief International Cognitive Assessment for Multiple Sclerosis; EDSS = Expanded Disability Status Scale; JCV = John Cunningham virus; MRI = Magnetic resonance imaging; MS = Multiple sclerosis

[a] Patients whose B-cells have not been repleted after 96 weeks of Follow-up Period will continue with visits every 24 weeks (± 14 days) and telephone contacts every 8 weeks until B-cell repletion (Prolonged B-cell monitoring). If the patients are receiving other B-cell targeted therapies, then the Follow-up Period is only 96 weeks regardless of their B-cell count.

[b] Visits will be performed at 24-week intervals following the Early Treatment Discontinuation Visit (if discontinued early) or after the end of the Treatment Period

[c] Routine safety lab: hematology, chemistry and urinalysis.

[d] Lymphocytes subtypes samples for CD19+ and T-cell counts (CD4+, CD8+)

[e] Plasma sampling for anti-JCV antibodies will be repeated yearly. Samples will be analyzed upon request.

[f] EDSS assessment needs to be performed only once, at the first follow-up visit

[g] After initiation of study drug, all adverse events must be reported until 96 weeks after the end of the Treatment Period, but may be extended in patients whose B-cells take longer to replete. Related SAEs must be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed (see Sections 5.3.1 and 5.6).

[h] BICAMS will be assessed yearly. Since CVLT-II is not yet available in all the languages of the countries participating in this study, the patients will not be assessed with this portion of the BICAMS. The patients will only need to complete the other two components of the BICAMS test battery (Symbol Digit Modalities Test and Brief Visuospatial Memory Test Revised).

[l] MRIs will be performed yearly

[j] A structured telephone interview will be conducted by site personnel every 8 weeks (± 3 days) to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms) and possible events or infections. No telephone contact is needed in weeks where patient is performing on-site visits.

Patients who receive alternative MS therapies that may decrease B-cell levels will not be entered into the prolonged B-cell Monitoring period thereafter.

A dedicated (scheduled or unscheduled) follow-up visit directly prior to the start of an alternative MS treatment is required for patients who begin an alternative treatment for MS while in follow-up in order to assess the patient's clinical status and safety parameters (assessments to be performed as per schedule of assessments: follow-up or prolonged B-cell monitoring visits, depending on the study period in which the patient was in when the alternative treatment began).

Appendix 3: Expanded Disability Status Scale (EDSS)

Kurtzke Expanded Disability Status Scale (EDSS)

- ❑ 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- ❑ 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
- ❑ 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
- ❑ 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- ❑ 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- ❑ 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- ❑ 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- ❑ 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- ❑ 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- ❑ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- ❑ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- ❑ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

❑ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).

❑ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).

❑ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).

❑ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).

❑ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).

❑ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).

❑ 10.0 - Death due to MS.

---

*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52.

Haber A, LaRocca NG. eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society; 1985.

Source: http://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Functional-Systems-Scores-(FSS)-and-Expanded-Disab

Appendix 4: Telephone Interviews

The purpose of this interview is to identify and collect information on any changes in the patient's health status that warrant an unscheduled visit (including new or worsening neurological symptoms). Telephone interviews should be performed by study personnel every 8 weeks between clinic visits (see also Section 4.5.11)

Please ask the following questions and record patient's answers during the Telephone Interview:

Questions	No	Yes
1. Since your last visit or telephone interview, have you had any new or worsening medical problems (such as sudden changes in your thinking, alterations in your behavior, visual disturbances, extremity weakness, limb coordination problems, or gait abnormalities) that have persisted over more than one day?		
2. Since your last visit or telephone interview, have you had any signs of an infection?		
3. Since your last visit or telephone interview, have you had any other new or worsening medical problems or conditions (including pregnancy)?		
4. Since your last visit or telephone interview, have you taken any new medicines (including medicines to treat cancer or MS, any other new medicines that weaken your immune system, or steroid medicines other than for the treatment of a recent relapse)?		

If the patient answered YES to any question, contact the Treating Investigator and review the patient's answers. The Investigator can determine if an unscheduled visit is required.

Please report all relevant information in the eCRF as well.

Record any pertinent comments made by the patient during the interview:

_____

_____

_____

_____

NAME:_____ Date:_____

Name of person completing the telephone interview

APPENDIX 4: TELEPHONE INTERVIEWS (cont.)

Below is a sample list of medications that can weaken the immune system. This list does not include all drugs that can suppress the immune system.

Approved MS Therapies:

Glatiramer acetate (Copaxone®)
Interferon β-1a (Rebif®, AVONEX®)
Interferon β-1b (Betaseron®)
Mitoxantrone (Novantrone®)
Natalizumab (Tysabri®)
Fingolimod (Gilenya®) – if relevant

Immunosuppressants/Antineoplastics:

Azathioprine (Imuran®, Azasan®)
Cladribine (Leustatin®)
Cyclophosphamide (Cytoxan®, Neosar®)
Cyclosporine (Sandimmune®, Neoral®)
Fludarabine phosphate (Fludara®)
Leflunomide (Arava®)
Mercaptopurine (Purinethol®)
Methotrexate (Methotrex®, Rheumatrex®, Trexall®)
Mycophenolate mofetil (CellCept®)
Pemetrexed (Alimta®)

Additional Immunomodulators and Immunosuppressants:

Other interferons (Actimmune®, Infergen®, Intron® A,
Pegasys®, PEG-Intron®, Rebetron®, Roferon®-A)
Adalimumab (Humira®)
Alefacept (Amevive®)
Alemtuzumab (Campath®)
Anakinra (Kineret®)
Daclizumab (Zenapax®)
Etanercept (Enbrel®)
Infliximab (Remicade®)
Intravenous immunoglobulin (IVIG)
Ofatumumab (Arzerra®)
Rituximab (Rituxan/MabThera®)
Trastuzumab (Herceptin®)

Appendix 5: Patient Reported Outcomes

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2)

UK original of MSIS-29 v2

- The following questions ask for your views about the impact of MS on your day-to-day life during **the past two weeks**.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions.

In the past two weeks, how much has your MS limited your ability to …	Not at all	A little	Moderate-ly	Extreme-ly
1. Do physically demanding tasks?	1	2	3	4
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4
3. Carry things?	1	2	3	4

In the past two weeks, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
4. Problems with your balance?	1	2	3	4
5. Difficulties moving about indoors?	1	2	3	4
6. Being clumsy?	1	2	3	4
7. Stiffness?	1	2	3	4
8. Heavy arms and/or legs?	1	2	3	4
9. Tremor of your arms or legs?	1	2	3	4
10. Spasms in your limbs?	1	2	3	4
11. Your body not doing what you want it to do?	1	2	3	4
12. Having to depend on others to do things for you?	1	2	3	4

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2) continued

In the past two weeks, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
13. Limitations in your social and leisure activities at home?	1	2	3	4
14. Being stuck at home more than you would like to be?	1	2	3	4
15. Difficulties using your hands in everyday tasks?	1	2	3	4
16. Having to cut down the amount of time you spent on work or other daily activities?	1	2	3	4
17. Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4
18. Taking longer to do things?	1	2	3	4
19. Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4
20. Needing to go to the toilet urgently?	1	2	3	4
21. Feeling unwell?	1	2	3	4
22. Problems sleeping?	1	2	3	4
23. Feeling mentally fatigued?	1	2	3	4
24. Worries related to your MS?	1	2	3	4
25. Feeling anxious or tense?	1	2	3	4
26. Feeling irritable, impatient, or short-tempered?	1	2	3	4
27. Problems concentrating?	1	2	3	4
28. Lack of confidence?	1	2	3	4
29. Feeling depressed?	1	2	3	4

TSQM *(Version II)*

Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Dissatisfied
☐$_4$ Somewhat Satisfied
☐$_5$ Satisfied
☐$_6$ Very Satisfied
☐$_7$ Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐$_1$ Yes
☐$_0$ No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

☐$_1$ Extremely Dissatisfied
☐$_2$ Very Dissatisfied
☐$_3$ Somewhat Dissatisfied
☐$_4$ Slightly Dissatisfied
☐$_5$ Not at all Dissatisfied
☐$_{(5)}$ Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied
☐(5) Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

Work Productivity and Activity Impairment Questionnaire:
Specific Health Problem V2.0 (WPAI:SHP)

The following questions ask about the effect of your PROBLEM on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your PROBLEM? *Include hours you missed on sick days, times you went in late, left early, etc., because of your PROBLEM. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your PROBLEM affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If PROBLEM affected your work only a little, choose a low number. Choose a high number if PROBLEM affected your work a great deal.

Consider only how much PROBLEM affected productivity while you were working.

PROBLEM had no effect on my work — 0 1 2 3 4 5 6 7 8 9 10 — PROBLEM completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your PROBLEM affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If PROBLEM affected your activities only a little, choose a low number. Choose a high number if PROBLEM affected your activities a great deal.

Consider only how much PROBLEM affected your ability to do your regular daily activities, other than work at a job.

PROBLEM had no effect on my daily activities — 0 1 2 3 4 5 6 7 8 9 10 — PROBLEM completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5):353-365.

SYMPTOM SCREEN

Please circle **one number that best describes how MS has affected each function.** For example, if it takes you longer to type or text, you might rate your hand function as 'mildly limited' (circle '2'), but if you gave up typing completely, you might rate your hand function as 'very limited' (circle '4').

	0 – not affected at all	1 – very mild limitation/ I make minor adjustments	2 – mild limitation/ I make frequent adjustments	3 – moderate limitation/ I reduced my daily activities	4 – severe limitation/ I gave up some activities	5- very severe limitation/ I'm unable to do many daily activities	6 – total limitation/ I'm unable to do most daily activities
Walking	0	1	2	3	4	5	6
Hand function/Dexterity Poor hand coordination, tremors	0	1	2	3	4	5	6
Spasticity & Stiffness Muscle cramping or muscle tightness	0	1	2	3	4	5	6
Bodily Pain Achiness, tenderness	0	1	2	3	4	5	6
Sensory symptoms Numbness, tingling, or burning	0	1	2	3	4	5	6
Bladder control Urinary urgency, frequency	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Vision Blurry vision, double vision	0	1	2	3	4	5	6
Dizziness Feeling off balance, 'spinning'/vertigo	0	1	2	3	4	5	6
Cognitive function Memory, concentration problems	0	1	2	3	4	5	6
Depression Depressed thoughts, low mood	0	1	2	3	4	5	6
Anxiety Feelings of stress; panic attacks	0	1	2	3	4	5	6

Appendix 6: Guidance for Diagnosis of Progressive Multifocal Leukoencephalopathy

Action Steps if Progressive Multifocal Leukoencephalopathy (PML) is Suspected

- If the clinical presentation is suggestive of PML, further investigations should include brain MRI evaluation as soon as possible. If MRI evaluation reveals lesions suspicious for PML (see Figure 5), a lumbar puncture with evaluation of the cerebrospinal fluid (CSF) for the detection of JC virus (JCV) DNA using a validated sensitive assay should be undertaken. A diagnosis of PML can potentially be made by evaluating clinical and MRI findings plus the identification of JCV in the CSF.
- There is no known treatment or cure for PML. Treatment considerations are discussed in the medical literature (Calabrese et al. 2007)

MRI Assessment

- Although there are no pathognomonic findings that differentiate PML from MS, a brain MRI scan that includes fluid-attenuated inversion recovery (FLAIR) and T2-weighted and T1-weighted sequences, with and without gadolinium, should be performed to assess patients with neurological changes suggestive of PML (see Figure 5).
- Comparison with a baseline scan may assist with interpretation of the findings on the newly acquired MRI (see Table 5 for differences in lesion characteristics that may help differentiate between PML and MS).

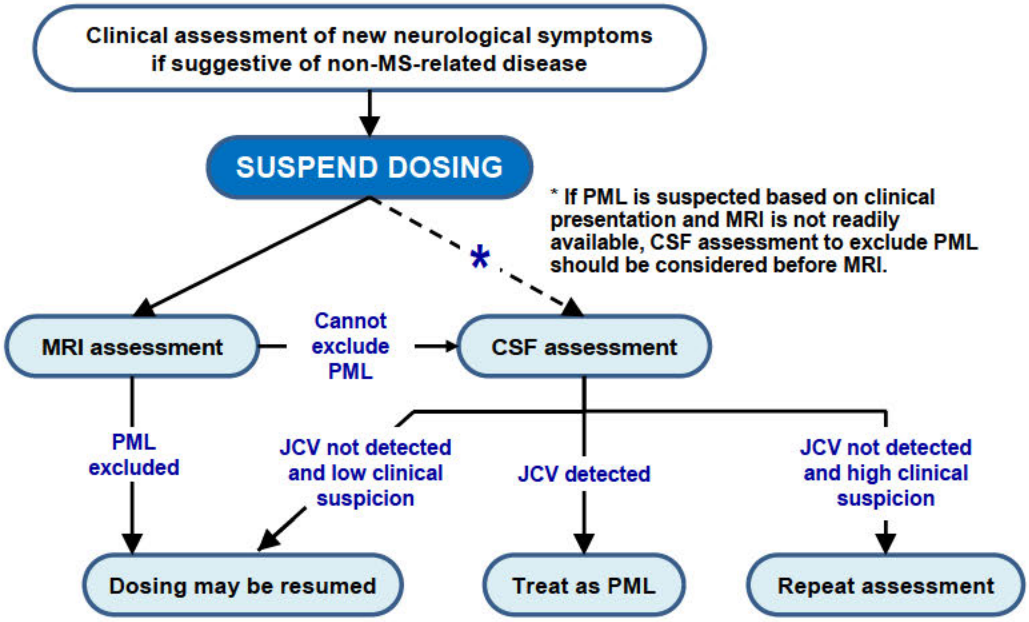
CSF Assessment

- The detection of JCV DNA in the CSF of a patient with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in CSF and if clinical suspicion of PML remains high, a repeat lumbar puncture should be performed.
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

APPENDIX 6:
GUIDANCE FOR DIAGNOSIS OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (Cont.)

Figure 5 Diagnostic Algorithm for PML

Suggested Diagnostic Algorithm



CSF = cerebrospinal fluid; JCV = John Cunningham virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy.

Clinical Signs and Symptoms Typical of MS and PML*		
	MS	**PML**
Onset	➢ Acute	➢ Subacute
Evolution	➢ Over hours to days ➢ Normally stabilized ➢ Resolve spontaneously even without therapy	➢ Over weeks ➢ Progressive
Clinical presentation	➢ Diplopia ➢ Paresthesia ➢ Paraparesis ➢ Optic neuritis ➢ Myelopathy	➢ Cortical symptoms/signs ➢ Behavioral and neuropsychological alteration ➢ Retrochiasmal visual defects ➢ Hemiparesis ➢ Cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination)

*Adapted from Kappos L et al. 2007

APPENDIX 6:
GUIDANCE FOR DIAGNOSIS OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (Cont.)

Table 5 MRI Lesion Characteristics Typical of PML and MS

Feature	MS (relapse)	PML
Location of new lesions	Mostly focal; affect entire brain and spinal chord, in white and possibly gray matter	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exclusively in white matter, although occasional extension to gray matter has been seen; posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; irregular in shape; confined to white matter; sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed.
Mode of extension	Initially focal; lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T2-weighted sequence	- Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure - Subacute and chronic lesions: hyperintense with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions.
On T1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious; true extension of abnormality more clearly visible than in T2-weighted images
With enhancement	- Acute lesions: dense homogeneous enhancement, sharp edges - Subacute lesions: ring enhancement - Chronic lesions: no enhancement	Usually no enhancement, even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy.

Atrophy	Focal atrophy possible due to focal white-matter degeneration; no progression	No focal atrophy

Adapted from Yousry TA et al. 2006

Appendix 7: Patient Diary

Accurate AE reporting is essential to ensure patient safety, early detection of safety signals, assess molecule benefit profile, regulatory compliance. In this study protocol the patient visits will occur every 6 months, site staff will conduct a phone interview every 8 week in between the visits at site.

Due to the low visit frequency patient diaries have been proposed as an optional tool to mitigate the risk related to AEs / concomitant medication low reporting.

The decision to use the patient diary is left to the discretion of each PI. The PI must ensure that required EC/IRB approval was obtained before implementing the patient diary at his/her site.

If you are using the patient diary, this is to be considered as patient source documentation. Please ensure the following process is followed at your site:

- The patient diary will be provided to the patient at the Baseline Visit.
- You or your site staff will explain to the patient when/how to complete it and remind him/her to bring it back at each visit at your site.
- Dispensing at Baseline and re-dispensing of patient diary at subsequent on-site visits should be documented in patient notes.
- Completed patient diaries should never be mailed to/ by patients.
- You or your site staff must review the completed patient diary at each visit and discuss the reported data with the patient.
- In between of the visit, you or your site staff should discuss the patient diary and any updates made during the 8-weeks telephone interviews.
- During each visit you or your site staff should make a copy of the completed patient diary, document your review and assessment, sign and date all pages and file it with the medical records
- In case you or your site staff cannot copy the patient diary, you would need to check the original during each patient study visits at site for any new adverse events / any new concomitant medication which occurred since last patient visit at site and document this in the patient notes (Source Data).
- When the patient early terminated or has completed the study, originals should be filed in the patient notes.
- To increase the patient compliance, please thank the patients for their time and effort and emphasize the importance of their contribution to the study to them.

Appendix 8: Summary of Product Characteristics (SmPC) for Disease Modifying Therapies for EMEA Countries

SmPC for Aubagio

1. NAME OF THE MEDICINAL PRODUCT

AUBAGIO 14 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 14 mg of teriflunomide.

Excipient with known effect: Each tablet contains 72 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale blue to pastel blue, pentagonal film-coated tablets with imprint on one side ('14') and engraved with a corporate logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUBAGIO is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). (please refer to section 5.1 for important information on the population for which efficacy has been established).

4.2 Posology and method of administration

The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis.

Posology
The recommended dose of AUBAGIO is 14 mg once daily.

Special populations
Elderly population
AUBAGIO should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy.

Renal impairment
No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment not undergoing dialysis.
Patients with severe renal impairment undergoing dialysis were not evaluated. Teriflunomide is contraindicated in this population (see section 4.3).

Hepatic impairment
No dosage adjustment is necessary for patients with mild and moderate hepatic impairment.
Teriflunomide is contraindicated in patients with severe hepatic impairment (see section 4.3).

Paediatric population
The safety and efficacy of AUBAGIO in children aged from 10 to less than 18 years has not yet been established. There is no relevant use of teriflunomide in children aged from birth to less than 10 years for the treatment of multiple sclerosis.
No data are available.

Method of administration
The film-coated tablets are for oral use. The tablets should be swallowed whole with some water. AUBAGIO can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with severe hepatic impairment (Child-Pugh class C).
Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with teriflunomide and thereafter as long as its plasma levels are above 0.02 mg/l (see section 4.6). Pregnancy must be excluded before start of treatment (see section 4.6).

Breast-feeding women (see section 4.6).

Patients with severe immunodeficiency states, e.g. AIDS.

Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia.

Patients with severe active infection until resolution (see section 4.4).

Patients with severe renal impairment undergoing dialysis, because insufficient clinical experience is available in this patient group.

Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.

4.4 Special warnings and precautions for use

Monitoring
Before treatment
Before starting treatment with teriflunomide the following should be assessed:
- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell count including differential white blood cell and platelet count.

During treatment
During treatment with teriflunomide the following should be monitored:
- Blood pressure
- Alanine aminotransferase (ALT/SGPT)
- Complete blood cell counts should be performed based on signs and symptoms (e.g. infections) during t reatment.

Accelerated elimination procedure
Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide (see section 4.6 and 5.2 for procedural details).

Hepatic effects
Elevations of liver enzymes have been observed in patients receiving teriflunomide (see section 4.8). These elevations occurred mostly within the first 6 months of treatment.
Liver enzymes should be assessed before initiation of teriflunomide therapy - every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly. Teriflunomide therapy should be discontinued if liver injury is suspected; consider discontinuing teriflunomide therapy if elevated liver enzymes (greater than 3-fold ULN) are confirmed. Patients with pre- existing liver disease may be at increased risk of developing elevated liver enzymes when taking teriflunomide and should be closely monitored for signals of liver disease.

The medicinal product should be used with caution in patients who consume substantial quantities of alcohol.

Since teriflunomide is highly protein bound and as the binding is dependent upon the concentrations of albumin, unbound plasma teriflunomide concentrations are expected to be increased in patients with hypoproteinaemia, e.g. in nephrotic syndrome. Teriflunomide should not be used in patients with conditions of severe hypoproteinaemia.

Blood pressure
Elevation of blood pressure may occur during treatment with teriflunomide (see section 4.8). Blood pressure must be checked before the start of teriflunomide treatment and periodically thereafter. Blood pressure elevation should be appropriately managed before and during treatment with teriflunomide.

Infections
Initiation of treatment with teriflunomide should be delayed in patients with severe active infection until resolution.
In placebo-controlled studies, no increase in serious infections was observed with teriflunomide (see section 4.8). However, based on the immunomodulatory effect of AUBAGIO, if a patient develops a serious infection, suspending treatment with AUBAGIO should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Due to the prolonged half-life, accelerated elimination with cholestyramine or charcoal may be considered.
Patients receiving AUBAGIO should be instructed to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment with AUBAGIO until the infection(s) is resolved.
The safety of AUBAGIO in individuals with latent tuberculosis infection is unknown, as tuberculosis screening was not systematically performed in clinical studies. For patients testing positive in tuberculosis screening, treat by standard medical practice prior to therapy with AUBAGIO.

Respiratory reactions
No cases of interstitial lung diseases (ILD) have been reported with teriflunomide in the clinical trials. However, ILD, which is a potentially fatal disorder, has been reported during treatment with leflunomide, the parent compound. ILD may occur acutely during therapy; the risk is increased in patients who had a history of ILD when treated with leflunomide.
Pulmonary symptoms, such as persistent cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate.

Haematological effects
A mean decrease less than 15% from baseline affecting white blood cell count has been observed (see section 4.8). As a precaution, a recent complete blood cell count, including differential white blood cell count and platelets, should be available before the initiation of treatment with AUBAGIO and the complete blood cell count should be assessed during AUBAGIO therapy as indicated by clinical signs and symptoms (e.g., infections).

In patients with pre-existing anaemia, leucopenia, and /or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of bone marrow suppression, the risk of haematological disorders is increased. If such effects occur, the accelerated elimination procedure (see above) to reduce plasma levels of teriflunomide should be considered.
In cases of severe haematological reactions, including pancytopenia, AUBAGIO and any concomitant myelosuppressive treatment must be discontinued and a teriflunomide accelerated elimination procedure should be considered.

Skin reactions
Cases of severe skin reactions have been reported postmarketing (including Stevens-Johnson syndrome and toxic epidermal necrolysis).

In patients treated with leflunomide, the parent compound, very rare cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported.

In case of ulcerative stomatitis, teriflunomide administration should be discontinued. If skin and /or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome), teriflunomide and any

other possibly associated treatment must be discontinued, and an accelerated procedure initiated immediately. In such cases patients should not be re-exposed to teriflunomide (see section 4.3).

Peripheral neuropathy
Cases of peripheral neuropathy have been reported in patients receiving AUBAGIO (see section 4.8). Most patients improved after discontinuation of AUBAGIO. However, there was a wide variability in final outcome, i.e. in some patients the neuropathy resolved and some patients had persistent symptoms. If a patient taking AUBAGIO develops a confirmed peripheral neuropathy, consider discontinuing AUBAGIO therapy and performing the accelerated elimination procedure.

Vaccination
Two clinical studies have shown that vaccinations to inactivated neoantigen (first vaccination), or recall antigen (reexposure) were safe and effective during AUBAGIO treatment. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.

Immunosuppressive or immunomodulating therapies
As leflunomide is the parent compound of teriflunomide, co-administration of teriflunomide with leflunomide is not recommended.
Co-administration with antineoplastic or immunosuppressive therapies used for treatment of MS has not been evaluated. Safety studies, in which teriflunomide was concomitantly administered with interferon beta or with glatiramer acetate for up to one year did not reveal any specific safety concerns, but a higher adverse reaction rate as compared to teriflunomide monotherapy was observed. The long term safety of these combinations in the treatment of multiple sclerosis has not been established.

Switching to or from AUBAGIO
Based on the clinical data related to concomitant administration of teriflunomide with interferon beta or with glatiramer acetate, no waiting period is required when initiating teriflunomide after interferon beta or glatiramer acetate or when starting interferon beta or glatiramer acetate, after teriflunomide.

Due to the long half-life of natalizumab, concomitant exposure, and thus concomitant immune effects, could occur for up to 2-3 months following discontinuation of natalizumab if AUBAGIO was immediately started. Therefore, caution is required when switching patients from natalizumab to AUBAGIO.

Based on the half-life of fingolimod, a 6-week interval without therapy is needed for clearance from the circulation and a 1 to 2 month period is needed for lymphocytes to return to normal range following discontinuation of fingolimod. Starting AUBAGIO during this interval will result in concomitant exposure to fingolimod. This may lead to an additive effect on the immune system and caution is, therefore, indicated.

In MS patients, the median $t_{1/2z}$ was approximately 19 days after repeated doses of 14 mg. If a decision is made to stop treatment with AUBAGIO, during the interval of 5 half-lives (approximately 3.5 months although may be longer in some patients), starting other therapies will result in concomitant exposure to AUBAGIO. This may lead to an additive effect on the immune system and caution is, therefore, indicated.

Lactose
Since AUBAGIO tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions of other substances on teriflunomide
The primary biotransformation pathway for teriflunomide is hydrolysis, with oxidation being a minor pathway.
Potent cytochrome P450 (CYP) and transporter inducers: Co-administration of repeated doses (600 mg once daily for 22 days) of rifampicin (a CYP2B6, 2C8, 2C9, 2C19, 3A inducer), as well as an inducer of the efflux transporters P-glycoprotein [P-gp] and breast cancer resistant protein [BCRP] with teriflunomide (70 mg single dose) resulted in an approximately 40% decrease in teriflunomide exposure. Rifampicin and other known potent CYP and transporter inducers such as carbamazepine,

phenobarbital, phenytoin and St John's Wort should be used with caution during the treatment with teriflunomide.

Cholestyramine or activated charcoal
It is recommended that patients receiving teriflunomide are not treated with cholestyramine or activated charcoal because this leads to a rapid and significant decrease in plasma concentration unless an accelerated elimination is desired. The mechanism is thought to be by interruption of enterohepatic recycling and/or gastrointestinal dialysis of teriflunomide.

Pharmacokinetic interactions of teriflunomide on other substances
Effect of teriflunomide on CYP2C8 substrate: repaglinide
There was an increase in mean repaglinide C_{max} and AUC (1.7- and 2.4-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 *in vivo*. Therefore, medicinal products metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during treatment with teriflunomide.

Effect of teriflunomide on oral contraceptive: 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel
There was an increase in mean ethinylestradiol C_{max} and AUC_{0-24} (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC_{0-24} (1.33- and 1.41-fold, respectively) following repeated doses of
teriflunomide. While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, it should be considered when selecting or adjusting oral contraceptive treatment used in combination with teriflunomide.

Effect of teriflunomide on CYP1A2 substrate: caffeine
Repeated doses of teriflunomide decreased mean C_{max} and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 *in vivo*. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetin, alosetron, theophylline and tizanidine) should be used with caution during treatment with teriflunomide, as it could lead to the reduction of the efficacy of these products.

Effect of teriflunomide on warfarin
Repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin, indicating that teriflunomide is not an inhibitor or an inducer of CYP2C9. However, a 25% decrease in peak international normalised ratio (INR) was observed when teriflunomide was coadministered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered with teriflunomide, close INR follow-up and monitoring is recommended.

Effect of teriflunomide on organic anion transporter 3 (OAT3) substrates:
There was an increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of OAT3 *in vivo*. Therefore, when teriflunomide is coadministered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.

Effect of teriflunomide on BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates:
There was an increase in mean rosuvastatin C_{max} and AUC (2.65- and 2.51-fold, respectively), following repeated doses of teriflunomide. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. For rosuvastatin, a dose reduction by 50% is recommended for coadministration with teriflunomide. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration of teriflunomide should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

4.6 Fertility, pregnancy and lactation

Use in males
The risk of male-mediated embryo-foetal toxicity through teriflunomide treatment is considered low (see section 5.3).

Pregnancy
There are limited amount of data from the use of teriflunomide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Teriflunomide may cause serious birth defects when administered during pregnancy. Teriflunomide is contraindicated in pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception during treatment and after treatment as long as teriflunomide plasma concentration is above 0.02 mg/l. During this period women should discuss any plans to stop or change contraception with the treating physician.

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing, and if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of teriflunomide, by instituting the accelerated elimination procedure described below, at the first delay of menses, may decrease the risk to the foetus.
For women receiving teriflunomide treatment, who wish to become pregnant, the medicine should be stopped and an accelerated elimination procedure is recommended in order to more rapidly achieve concentration below 0.02 mg/l (see below):

If an accelerated elimination procedure is not used, teriflunomide plasma levels can be expected to be above
0.02 mg/l for an average of 8 months, however, in some patients it may take up to 2 years to reach plasma concentration below 0.02 mg/l. Therefore, teriflunomide plasma concentrations should be measured before a woman begins to attempt to become pregnant. Once the teriflunomide plasma concentration is determined to be below 0.02 mg/l, the plasma concentration must be determined again after an interval of at least 14 days. If both plasma concentrations are below 0.02 mg/l, no risk to the foetus is to be expected.
For further information on the sample testing please contact the Marketing Authorisation Holder or its local representative (see section 7).

Accelerated elimination procedure

After stopping treatment with teriflunomide:
- cholestyramine 8 g is administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated,
- alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days.

However, also following either of the accelerated elimination procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation is required.
Both cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the accelerated elimination procedure with cholestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Breast-feeding
Animal studies have shown excretion of teriflunomide in breast milk. Breast-feeding women must, therefore, not receive teriflunomide.

Fertility
Results of studies in animals have not shown an effect on fertility (see section 5.3). Although human data are lacking, no effect on male and female fertility is anticipated.

4.7 Effects on ability to drive and use machines

AUBAGIO has no or negligible influence on the ability to drive and use machines.
In the case of adverse reactions such as dizziness, which has been reported with leflunomide, the parent compound, the patient's ability to concentrate and to react properly may be impaired. In such cases, patients should refrain from driving cars and using machines.

4.8 Undesirable effects

Summary of the safety profile

A total of 2267 patients were exposed to teriflunomide (1155 on teriflunomide 7 mg and 1112 on teriflunomide 14 mg) once daily for a median duration of about 672 days in four placebo-controlled studies (1045 and 1002 patients for teriflunomide 7 mg and 14 mg, respectively) and one active comparator study (110 patients in each of the teriflunomide treatment groups) in patients with relapsing forms of MS (Relapsing Multiple Sclerosis, RMS).
Teriflunomide is the main metabolite of leflunomide. The safety profile of leflunomide in patients suffering from rheumatoid arthritis or psoriatic arthritis may be pertinent when prescribing teriflunomide in MS patients.

The placebo-controlled pooled analysis was based on 2047 patients with Relapsing Multiple Sclerosis treated with teriflunomide once daily. Within this safety population, the most commonly reported adverse reactions in the teriflunomide treated patients were: headache, diarrhoea, increased ALT, nausea, and alopecia. In general, headache, diarrhoea, nausea and alopecia, were mild to moderate, transient and infrequently led to treatment discontinuation.

Tabulated list of adverse reactions

Adverse reactions reported with AUBAGIO in placebo-controlled studies, reported for teriflunomide 7 mg or 14 mg at ⩾ 1% higher rate than for placebo, are shown below. Frequencies were defined using the following convention: very common (⩾1/10); common (⩾1/100 to <1/10); uncommon (⩾1/1,000 to <1/100); rare (⩾1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations (see section 4.4)		Influenza, Upper respiratory tract infection, Urinary tract infection, Bronchitis, Sinusitis, Pharyngitis, Cystitis, Gastroenteritis viral, Oral herpes, Tooth infection, Laryngitis, Tinea pedis				Severe infections including sepsis[a]
Blood and lymphatic system disorders		Neutropenia, (see section 4.4) Anaemia	Mild thrombocytopenia (platelets <100G/l)			
Immune system disorders		Mild allergic reactions				Hyper-sensitivity reactions (immediate or delayed) including anaphylaxis and angioedema
Psychiatric disorders		Anxiety				
Nervous system disorders	Headache	Paraesthesia, Sciatica, Carpal tunnel syndrome	Hyperaesthesia, Neuralgia, Peripheral neuropathy			

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Cardiac disorders		Palpitations				
Vascular disorders		Hypertension (see section 4.4)				
Respiratory, thoracic and mediastinal disorders					Interstitial lung disease*	
Gastrointestinal disorders	Diarrhoea, Nausea	Abdominal pain upper, Vomiting, Toothache				Pancreatitis, Stomatitis
Skin and subcutaneous tissue disorders	Alopecia	Rash, Acne				Severe skin reactions[a]
Musculoskeletal and connective tissue disorders		Musculoskeletal pain, Myalgia, Arthralgia				
Renal and urinary disorders		Pollakiuria				
Reproductive system and breast disorders		Menorrhagia				
General disorders and administration site conditions		Pain				
Investigations	Alanine aminotransferase (ALT) increase (see section 4.4)	Gamma-glutamyltransferase (GGT) increase (see section 4.4), Aspartate aminotransferase increase (see section 4.4), Weight decrease, Neutrophil count decrease (see section 4.4), White blood cell count decrease (see section 4.4), Blood creatine phosphokinase increased				
Injury, poisoning and procedural complications			Post-traumatic pain			

*: Based on leflunomide data only
a: please refer to the detailed description section

Description of selected adverse reactions

Alopecia

Alopecia was reported as hair thinning, decreased hair density, hair loss, associated or not with hair texture change, in 13.9% of patients treated with 14 mg teriflunomide versus 5.1% in patients treated with placebo. Most cases were described as diffuse or generalised over the scalp (no

complete hair loss reported) and occurred most often during the first 6 months and with resolution in 121 of 139 (87.1%) patients treated with teriflunomide 14 mg. Discontinuation because of alopecia was 1.3% in the teriflunomide 14 mg teriflunomide group, versus 0.1% in the placebo group.

Hepatic effects
During placebo-controlled studies the following was detected:

ALT increase (based on laboratory data) according to baseline status - Safety population in placebo- controlled studies

	Placebo (N=997)	**Teriflunomide 14 mg (N=1002)**
>3 ULN	66/994 (6.6%)	80/999 (8.0%)
>5 ULN	37/994 (3.7%)	31/999 (3.1%)
>10 ULN	16/994 (1.6%)	9/999 (0.9%)
>20 ULN	4/994 (0.4%)	3/999 (0.3%)
ALT >3 ULN and TBILI >2 ULN	5/994 (0.5%)	3/999 (0.3%)

Mild increases in transaminase, ALT below or equal to 3-fold ULN were more frequently seen in teriflunomide-treated groups as compared to placebo. The frequency of elevations above 3-fold ULN and higher was balanced across treatment groups. These elevations in transaminase occurred mostly within the first 6 months of treatment and were reversible after treatment cessation. The recovery time varied between months and years.

Blood pressure effects
In placebo-controlled studies the following was established:
- systolic blood pressure was >140 mm Hg in 19.9% of patients receiving 14 mg/day teriflunomide as compared to 15.5% receiving placebo;
- systolic blood pressure was >160 mm Hg in 3.8% of patients receiving 14 mg/day teriflunomide as compared to 2.0% receiving placebo;

diastolic blood pressure was >90 mm Hg in 21.4% of patients receiving 14 mg/day teriflunomide as c ompared to 13.6% receiving placebo.

Infections
In placebo-controlled studies, no increase in serious infections was observed with teriflunomide 14 mg (2.7%) as compared to placebo (2.2%). Serious opportunistic infections occurred in 0.2% of each group. Severe infections including sepsis, sometimes fatal have been reported postmarketing.

Haematological effects
A mean decrease affecting white blood cell (WBC) count (<15% from baseline levels, mainly neutrophil and lymphocytes decrease) was observed in placebo-controlled trials with AUBAGIO, although a greater decrease was observed in some patients. The decrease in mean count from baseline occurred during the first 6 weeks then stabilised over time while on-treatment but at decreased levels (less than a 15% decrease from baseline). The effect on red blood cell (RBC) (<2%) and platelet counts (<10%) was less pronounced.

Peripheral neuropathy
In placebo-controlled studies, peripheral neuropathy, including both polyneuropathy and mononeuropathy (e.g., carpal tunnel syndrome), was reported more frequently in patients taking teriflunomide than in patients taking placebo. In the pivotal, placebo-controlled studies, the incidence of peripheral neuropathy confirmed by nerve conduction studies was 1.9% (17 patients out of 898) on 14 mg of teriflunomide, compared with 0.4% (4 patients out of 898) on placebo. Treatment was discontinued in 5 patients with peripheral neuropathy on teriflunomide 14 mg. Recovery following treatment discontinuation was reported in 4 of these patients.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
There does not appear to be an increased risk of malignancy with teriflunomide in the clinical trial experience. The risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some other agents that affect the immune system (class effect).

Severe skin reactions
Cases of severe skin reactions have been reported with teriflunomide post-marketing (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily was administered up to 14 days in healthy subjects. The adverse reactions were consistent with the safety profile for teriflunomide in MS patients.

Management
In the event of relevant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination. The recommended elimination procedure is cholestyramine 8 g three times a day for 11 days. If this is not well tolerated, cholestyramine 4 g three times a day for 11 days can be used.
Alternatively, when cholestyramine is not available, activated charcoal 50 g twice a day for 11 days may also be used. In addition, if required for tolerability reasons, administration of cholestyramine or activated charcoal does not need to occur on consecutive days (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC Code: L04AA31.
Mechanism of action
Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. As a consequence teriflunomide reduces the proliferation of dividing cells that need de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.

Pharmacodynamic effects

Immune system
Effects on immune cell numbers in the blood: In the placebo-controlled studies, teriflunomide 14 mg once a day led to a mild mean reduction in lymphocyte count, of less than 0.3 x 10^9/l, which occurred over the first 3 months of treatment and levels were maintained until the end of the treatment.

Potential to prolong the QT interval
In a placebo-controlled thorough QT study performed in healthy subjects, teriflunomide at mean steady-state concentrations did not show any potential for prolonging the QTcF interval compared with placebo: the largest time matched mean difference between teriflunomide and placebo was 3.45 ms with the upper bound of the 90% CI being 6.45 ms.

Effect on renal tubular functions
In the placebo-controlled studies, mean decreases in serum uric acid at a range of 20 to 30% were observed in patients treated with teriflunomide compared to placebo. Mean decrease in serum phosphorus was around 10% in the teriflunomide group compared to placebo. These effects are considered to be related to increase in renal tubular excretion and not related to changes in glomerular functions.

Clinical efficacy and safety

The efficacy of AUBAGIO was demonstrated in two placebo-controlled studies, the TEMSO and the TOWER study, that evaluated once daily doses of teriflunomide 7 mg and 14 mg in patients with RMS.

A total of 1088 patients with RMS were randomised in TEMSO to receive 7 mg (n=366) or 14 mg (n=359) of teriflunomide or placebo (n= 363) for 108 weeks duration. All patients had a definite diagnosis of MS (based on McDonald criteria (2001)), exhibited a relapsing clinical course, with or without progression, and experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ⩽5.5.
The mean age of the study population was 37.9 years. The majority of patients had relapsing–remitting multiple sclerosis (91.5%), but a subgroup of patients had secondary progressive (4.7%) or progressive relapsing multiple sclerosis (3.9%). The mean number of relapses within the year before study inclusion was
1.4 with 36.2% of patients having gadolinium-enhancing lesions at baseline. The median EDSS score at baseline was 2.50**;** 249 patients (22.9%) had an EDSS score › 3.5 at baseline. The mean duration of disease, since first symptoms, was 8.7 years. A majority of patients (73%) had not received disease-modifying therapy during the 2 years before study entry. The study results are shown in Table 1.

A total of 1169 patients with RMS were randomised in TOWER to receive 7 mg (n=408) or 14 mg (n=372) of teriflunomide or placebo (n= 389) for a variable treatment duration ending at 48 weeks after last patient randomised. All patients had a definite diagnosis of MS (based on McDonald criteria (2005)), exhibited a relapsing clinical course, with or without progression, and experienced at least 1 relapse over the year preceding the trial or at least 2 relapses over the 2 years preceding the trial. At entry, patients had an Expanded Disability Status Scale (EDSS) score ⩽5.5.
The mean age of the study population was 37.9 years. The majority of patients had relapsing–remitting multiple sclerosis (97.5%), but a subgroup of patients had secondary progressive (0.8%) or progressive relapsing multiple sclerosis (1.7%). The mean number of relapses within the year before study inclusion was
1.4. Gadolinium-enhancing lesions at baseline: no data. The median EDSS score at baseline was 2.50; 298 patients (25.5%) had an EDSS score › 3.5 at baseline. The mean duration of disease, since first symptoms, was 8.0 years. A majority of patients (67.2%) had not received disease-modifying therapy during the 2 years before study entry. The study results are shown in Table 1.

Table 1 - Main Results (for the approved dose, ITT population)

	TEMSO-study		**TOWER-study**	
	Teriflunomide 14 mg	**Placebo**	**Teriflunomide 14 mg**	**Placebo**
N	**358**	**363**	**370**	**388**
Clinical Outcomes				
Annualised relapse rate	0.37	0.54	0.32	0.50
Risk difference (CI95%)	-0.17 (-0.26, -0.08)***		-0.18 (-0.27, -0.09)****	
Relapse-free week 108	56.5%	45.6%	57.1%	46.8%
Hazard ratio (CI95%)	0.72, (0.58, 0.89)**		0.63, (0.50, 0.79)****	
3-month Sustained Disability Progression week 108	20.2%	27.3%	15.8%	19.7%
Hazard ratio (CI95%) 6-month Sustained Disability Progression week 108	0.70 (0.51, 0.97)*		0.68 (0.47, 1.00)*	
Hazard ratio (CI95%) **MRI endpoints**	13.8%	18.7%	11.7%	11.9%
Change in BOD week 10 (1)	0.75 (0.50, 1.11)		0.84 (0.53, 1.33)	
8	0.72	2.21		
Change relative to placebo	67%***			
Mean Number of Gd-enhancing lesions at week 108	0.38	1.18	Not measured	

Change relative to placebo (CI95%)	-0.80 (-1.20, -0.39)****	
Number of unique active lesions /scan	0.75 2.46	
Change relative to placebo (CI95%)	69%, (59%; 77%)****	

**** p<0.0001 *** p<0.001 ** p<0.01 * p<0.05 compared to placebo
(1) BOD: burden of disease: total lesion volume (T2 and T1 hypointense) in ml

Efficacy in patients with high disease activity:
A consistent treatment effect on relapses and time to 3-month sustained disability progression in a subgroup of patients in TEMSO (n= 127) with high disease activity was observed. Due to the design of the study, high disease activity was defined as 2 or more relapses in one year, and with one or more Gd-enhancing lesion on brain MRI. No similar subgroup analysis was performed in TOWER as no MRI data were obtained.
No data are available in patients who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or patients having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years.

TOPIC was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg for up to 108 weeks in patients with first clinical demyelinating event (mean age 32.1 years). The primary endpoint was time to a second clinical episode (relapse). A total of 618 patients were randomized to receive 7 mg (n=205) or 14 mg (n=216) of teriflunomide or placebo (n=197). The risk of a second clinical attack over 2 years was 35.9% in the placebo group and 24.0% in the teriflunomide 14 mg treatment group (hazard ratio: 0.57, 95% confidence interval: 0.38 to 0.87, p=0.0087). The results from the TOPIC study confirmed the efficacy of teriflunomide in RRMS (including early RRMS with first clinical demyelinating event and MRI lesions disseminated in time and space).

Teriflunomide effectiveness was compared to that of a subcutaneous interferon beta-1a (at the recommended dose of 44 µg three times a week) in 324 randomised patients in a study (TENERE) with minimum treatment duration of 48 weeks (maximum 114 weeks). The risk of failure (confirmed relapse or permanent treatment discontinuation whichever came first) was the primary endpoint. The number of patients with permanent treatment discontinuation in the teriflunomide 14 mg group was 22 out of 111 (19.8%), the reasons being adverse events (10.8%), lack of efficacy (3.6%), other reason (4.5%) and lost to follow-up (0.9%). The number of patients with permanent treatment discontinuation in the subcutaneous interferon beta-1a group was 30 out of 104 (28 .8%), the reasons being adverse events (21.2%), lack of efficacy (1.9%), other reason (4.8%) and poor compliance to protocol (1%). Teriflunomide 14 mg/day was not superior to interferon beta- 1a on the primary endpoint: the estimated percentage of patients with treatment failure at 96 weeks using the Kaplan-Meier method was 41.1% versus 44.4% (teriflunomide 14 mg versus interferon beta-1a group, p=0.595).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with AUBAGIO in children from birth to less than 10 years in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).
The European Medicines Agency has deferred the obligation to submit the results of studies with AUBAGIO in one or more subsets of the paediatric population in multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Median time to reach maximum plasma concentrations occurs between 1 to 4 hours post-dose following repeated oral administration of teriflunomide, with high bioavailability (approximately 100%).

Food does not have a clinically relevant effect on teriflunomide pharmacokinetics.

From the mean predicted pharmacokinetic parameters calculated from the population pharmacokinetic (PopPK) analysis using data from healthy volunteers and MS patients, there is a slow approach to steady- state concentration (i.e., approximately 100 days (3.5 months) to attain 95% of steady-state concentrations) and the estimated AUC accumulation ratio is approximately 34-fold.

Distribution
Teriflunomide is extensively bound to plasma protein (>99%), probably albumin and is mainly distributed in plasma. The volume of distribution is 11 l after a single intravenous (IV) administration. However, this is most likely an underestimation since extensive organ distribution was observed in rats.

Biotransformation
Teriflunomide is moderately metabolised and is the only component detected in plasma. The primary biotransformation pathway for teriflunomide is hydrolysis with oxidation being a minor pathway. Secondary pathways involve oxidation, N-acetylation and sulfate conjugation.

Elimination
Teriflunomide is excreted in the gastrointestinal tract mainly through the bile as unchanged medicinal product and most likely by direct secretion. Teriflunomide is a substrate of the efflux transporter BCRP, which could be involved in direct secretion. Over 21 days, 60.1% of the administered dose is excreted via feces (37.5%) and urine (22.6%). After the rapid elimination procedure with cholestyramine, an additional 23.1% was recovered (mostly in feces). Based on individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, median $t_{1/2z}$ was approximately 19 days after repeated doses of 14 mg. After a single IV administration, the total body clearance of teriflunomide is 30.5 ml/h.

Accelerated Elimination Procedure: Cholestyramine and activated charcoal
The elimination of teriflunomide from the circulation can be accelerated by administration of cholestyramine or activated charcoal, presumably by interrupting the reabsorption processes at the intestinal level.
Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 8 g cholestyramine three times a day, 4 g cholestyramine three times a day or 50 g activated charcoal twice a day following cessation of teriflunomide treatment have shown that these regimens were effective in accelerating teriflunomide elimination, leading to more than 98% decrease in teriflunomide plasma concentrations, with cholestyramine being faster than charcoal. Following discontinuation of teriflunomide and the administration of cholestyramine 8 g three times a day, the plasma concentration of teriflunomide is reduced 52% at the end of day 1, 91% at the end of day 3, 99.2% at the end of day 7, and 99.9% at the completion of day 11. The choice between the 3 elimination procedures should depend on the patient's tolerability. If cholestyramine 8 g three times a day is not well-tolerated, cholestyramine 4 g three times a day can be used. Alternatively, activated charcoal may also be used (the 11 days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly).

Linearity/non-linearity
Systemic exposure increases in a dose proportional manner after oral administration teriflunomide from 7 to 14 mg.

Characteristics in specific groups of patients
Gender, Elderly, Paediatric patients
Several sources of intrinsic variability were identified in healthy subjects and MS patients based on the PopPK analysis: age, body weight, gender, race, and albumin and bilirubin levels. Nevertheless, their impact remains limited (≤31%).

Hepatic impairment
Mild and moderate hepatic impairment had no impact on the pharmacokinetic of teriflunomide. Therefore no dose adjustment is anticipated in mild and moderate hepatic-impaired patients. However, teriflunomide is contraindicated in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Renal impairment

Severe renal impairment had no impact on the pharmacokinetic of teriflunomide. Therefore no dose adjustment is anticipated in mild, moderate and severe renal-impaired patients.

5.3 Preclinical safety data

Repeated oral administration of teriflunomide to mice, rats and dogs for up to 3, 6, and 12 months, respectively, revealed that the major targets of toxicity were the bone marrow, lymphoid organs, oral cavity/ gastro intestinal tract, reproductive organs, and pancreas. Evidence of an oxidative effect on red blood cells was also observed. Anemia, decreased platelet counts and effects on the immune system, including leukopenia, lymphopenia and secondary infections, were related to the effects on the bone marrow and/or lymphoid organs. The majority of effects reflect the basic mode of action of the compound (inhibition of dividing cells). Animals are more sensitive to the pharmacology, and therefore toxicity, of teriflunomide than humans. As a result, toxicity in animals was found at exposures equivalent or below human therapeutic levels.

Teriflunomide was not mutagenic *in vitro* or clastogenic *in vivo*. Clastogenicity observed *in vitro* was considered to be an indirect effect related to nucleotide pool imbalance resulting from the pharmacology of DHO-DH inhibition. The minor metabolite TFMA (4-trifluoromethylaniline) caused mutagenicity and clastogenicity *in vitro* but not *in vivo*.

No evidence of carcinogenicity was observed in rats and mice.

Fertility was unaffected in rats despite adverse effects of teriflunomide on male reproductive organs, including reduced sperm count. There were no external malformations in the offspring of male rats administered teriflunomide prior to mating with untreated female rats. Teriflunomide was embryotoxic and teratogenic in rats and rabbits at doses in the human therapeutic range. Adverse effects on the offspring were also seen when teriflunomide was administered to pregnant rats during gestation and lactation. The risk of male-mediated embryo-fetal toxicity through teriflunomide treatment is considered low. The estimated female plasma exposure via the semen of a treated patient is expected to be 100 times lower than the plasma exposure after 14 mg of oral teriflunomide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
lactose monohydrate
maize starch
microcrystalline cellulose
sodium starch glycolate (Type A)
hydroxypropylcellulose
magnesium stearate

Tablet coating
hypromellose
titanium dioxide (E171)
talc
macrogol 8000
indigo carmine aluminum lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-aluminium blisters inserted in wallets (14 and 28 film-coated tablets) and packed in cartons containing 14, 28, 84 (3 wallets of 28), and 98 (7 wallets of 14) film-coated tablets.
Each wallet is placed in a protective sleeve.

Aluminium-aluminium perforated unit-dose blister packs in cartons containing 10x1 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis groupe
54, rue La Boétie
F-75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/838/001
EU/1/13/838/002
EU/1/13/838/003
EU/1/13/838/004
EU/1/13/838/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu..

SmPC for Copaxone

Copaxone 20mg/ml, Solution For Injection, Pre-Filled Syringe

Summary of Product Characteristics Updated 21-Apr-2016 | Teva Pharmaceuticals Ltd

1. Name of the medicinal product

Copaxone ® 20 mg/ml Solution for Injection, Pre-filled Syringe

2. Qualitative and quantitative composition

1 ml of solution for injection contains 20 mg glatiramer acetate *, equivalent to 18 mg of glatiramer base per pre-filled syringe

* The average molecular weight of glatiramer acetate mixture is in the range of 5,000-9,000 daltons. Due to its compositional complexity, no specified polypeptide can be fully characterized in terms of amino acid sequence, although the final glatiramer acetate composition is not entirely random.

For full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for Injection, Pre-filled Syringe Clear solution free of visible particles

The solution for injection has a pH of 5.5 - 7.0 and an osmolarity of about 265 mOsmol/L.

4. Clinical particulars

4.1 Therapeutic indications

Copaxone is indicated for the treatment of relapsing forms of multiple sclerosis (MS) (see section 5.1 for important information on the population for which efficacy has been established).

Copaxone is not indicated in primary or secondary progressive MS.

4.2 Posology and method of administration Posology

The recommended dosage in adults is 20 mg of glatiramer acetate (one pre-filled syringe), administered as a subcutaneous injection once daily.

At the present time, it is not known for how long the patient should be treated.

A decision concerning long term treatment should be made on an individual basis by the treating physician.

Paediatric population

Children and adolescents: No prospective, randomized, controlled clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 18 years of age receiving Copaxone 20 mg subcutaneously every day is similar to that seen in adults.

There is not enough information available on the use of Copaxone in children below 12 years of age to make any recommendation for its use. Therefore, Copaxone should not be used in this population.

Elderly patients

Copaxone has not been specifically studied in the elderly.

Patients with renal impairment

Copaxone has not been specifically studied in patients with renal impairment (see section 4.4).

Method of administration

Patients should be instructed in self-injection techniques and should be supervised by a health-care professional the first time they self-inject and for 30 minutes after.

A different site for injection should be chosen every day, so this will reduce the chances of any irritation or pain at the site of the injection. Sites for self-injection include the abdomen, arms, hips and thighs.

4.3 Contraindications

Copaxone is contraindicated under the following conditions:

- Hypersensitivity to glatiramer acetate or mannitol.
- Pregnant women

4.4 Special warnings and precautions for use

Copaxone should only be administered subcutaneously. Copaxone should not be administered by intravenous or intramuscular routes.
The initiation of Copaxone treatment should be supervised by a neurologist or a physician experienced in the treatment of MS.
The treating physician should explain to the patient that a reaction associated with at least one of the following symptoms may occur within minutes of a Copaxone injection: vasodilatation (flushing), chest pain, dyspnoea, palpitations or tachycardia. The majority of these symptoms is short-lived and resolves spontaneously without any sequelae. Should a severe adverse event occur, the patient must immediately stop Copaxone treatment and contact his/her physician or any emergency doctor. Symptomatic treatment may be instituted at the discretion of the physician.
There is no evidence to suggest that any particular patient groups are at special risk from these reactions. Nevertheless, caution should be exercised when administering Copaxone to patients with pre-existing cardiac disorders. These patients should be followed up regularly during treatment.
Convulsions and/or anaphylactoid or allergic reactions have been reported rarely.
Serious hypersensitivity reactions (e.g. bronchospasm, anaphylaxis or urticaria) may rarely occur. If reactions are severe, appropriate treatment should be instituted and Copaxone should be discontinued.
Glatiramer acetate-reactive antibodies were detected in patients' sera during daily chronic treatment with Copaxone. Maximal levels were attained after average treatment duration of 3-4 months and, thereafter, declined and stabilised at a level slightly higher than baseline.
There is no evidence to suggest that these glatiramer acetate-reactive antibodies are neutralising or that their formation is likely to affect the clinical efficacy of Copaxone.
In patients with renal impairment, renal function should be monitored while they are treated with Copaxone. Whilst there is no evidence of glomerular deposition of immune complexes in patients, the possibility cannot be excluded.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction between Copaxone and other medicinal products have not been formally evaluated. Observations from existing clinical trials and post-marketing experience do not suggest any significant interactions of Copaxone with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days.
In vitro work suggests that glatiramer acetate in blood is highly bound to plasma proteins but that it is not displaced by, and does not itself displace, phenytoin or carbamazepine. Nevertheless, as Copaxone has, theoretically, the potential to affect the distribution of protein bound substances, concomitant use of such medicinal products should be monitored carefully.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of glatiramer acetate in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Copaxone is contraindicated during pregnancy.
A contraceptive cover should be considered whilst using this medicinal product.
Breastfeeding
Data regarding excretion of glatiramer acetate, its metabolites or antibodies in human milk are unavailable. Caution should be exercised when Copaxone is administered to a nursing mother. The relative risk and benefit to the mother and child should be taken into consideration.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In all clinical trials, injection-site reactions were seen to be the most frequent adverse reactions and were reported by the majority of patients receiving Copaxone. In controlled studies, the proportion of patients reporting these reactions, at least once, was higher following treatment with Copaxone (70%) than placebo injections (37%). The most commonly reported injection-site reactions, in

clinical trials and in post marketing experience, were erythema, pain, mass, pruritus, oedema, inflammation and hypersensitivity, and rare occurrences of lipoatrophy and skin necrosis.
A reaction, associated with at least one or more of the following symptoms, has been described as the Immediate Post-Injection Reaction: vasodilatation(flushing), chest pain, dyspnoea, palpitation or tachycardia. This reaction may

occur within minutes of a Copaxone injection. At least one component of this Immediate Post-Injection Reaction was reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo.
All adverse reactions, which were more frequently reported in Copaxone vs. placebo-treated patients, are presented in the table below. This data was derived from four pivotal, double-blind, placebo-controlled clinical trials with a total of 512 patients treated with Copaxone and 509 patients treated with placebo for up to 36 months. Three trials in relapsing-remitting MS (RRMS) included a total of 269 patients treated with Copaxone and 271 patients treated with placebo for up to 35 months. The fourth trial in patients who have experienced a first clinical episode and were determined to be at high risk of developing clinically definite MS included 243 patients treated with Copaxone and 238 patients treated with placebo for up to 36 months.

System Organ Class (SOC)	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Infections and infestations	Infection, Influenza	Bronchitis, Gastroenteritis, Herpes Simplex, Otitis Media, Rhinitis, Tooth Abscess, Vaginal Candidiasis*	Abscess, Cellulitis, Furuncle, Herpes Zoster, Pyelonephritis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Benign Neoplasm Of Skin, Neoplasm	Skin Cancer
Blood and lymphatic system disorders		Lymphadenopathy*	Leukocytosis, Leukopenia, Splenomegaly Thrombocytopenia, Lymphocyte Morphology Abnormal
Immune system disorders		Hypersensitivity	
Endocrine disorders			Goitre, Hyperthyroidism
Metabolism and nutrition disorders		Anorexia, Weight Increased*	Alcohol Intolerance, Gout, Hyperlipidaemia, Blood Sodium Increased, Serum Ferritin Decreased
Psychiatric disorders	Anxiety*, Depression	Nervousness	Abnormal Dreams, Confusional State, Euphoric Mood, Hallucination, Hostility, Mania, Personality Disorder, Suicide Attempt
Nervous system disorders	Headache,	Dysgeusia, Hypertonia, Migraine, Speech Disorder, Syncope, Tremor*	Carpal Tunnel Syndrome, Cognitive Disorder, Convulsion, Dysgraphia, Dyslexia, Dystonia, Motor Dysfunction, Myoclonus, Neuritis, Neuromuscular Blockade, Nystagmus, Paralysis, Peroneal Nerve Palsy, Stupor, Visual Field Defect
Eye disorders		Diplopia, Eye Disorder*	Cataract, Corneal Lesion, Dry Eye, Eye Haemorrhage, Eyelid Ptosis, Mydriasis, Optic Atrophy
Ear and labyrinth disorders		Ear Disorder	
Cardiac disorders		Palpitations*, Tachycardia*	Extrasystoles, Sinus Bradycardia, Tachycardia Paroxysmal
Vascular disorders	Vasodilatation*		Varicose Vein

System Organ Class (SOC)	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Respiratory, thoracic and mediastinal disorders	Dyspnoea*	Cough, Rhinitis Seasonal	Apnoea, Epistaxis, Hyperventilation, Laryngospasm, Lung Disorder, Choking Sensation
Gastrointestinal disorders	Nausea*	Anorectal Disorder, Constipation, Dental Caries, Dyspepsia, Dysphagia, Faecal Incontinence, Vomiting*	Colitis, Colonic Polyp, Enterocolitis, Eructation, Oesophageal Ulcer, Periodontitis Rectal Haemorrhage, Salivary Gland Enlargement
Hepatobiliary disorders		Liver Function Test Abnormal	Cholelithiasis, Hepatomegaly
Skin and subcutaneous tissue disorders	Rash*	Ecchymosis, Hyperhidrosis, Pruritus, Skin Disorder*, Urticaria	Angioedema, Dermatitis Contact, Erythema Nodosum, Skin Nodule
Musculoskeletal and connective tissue disorders	Arthralgia, Back Pain*	Neck Pain	Arthritis, Bursitis, Flank Pain, Muscle Atrophy, Osteoarthritis
Renal and urinary disorders		Micturition Urgency, Pollakiuria, Urinary Retention	Haematuria, Nephrolithiasis, Urinary Tract Disorder, Urine Abnormality
Pregnancy, puerperium and perinatal Conditions			Abortion
Reproductive system and breast disorders			Breast Engorgement, Erectile Dysfunction, Pelvic Prolapse, Priapism, Prostatic Disorder, Smear Cervix Abnormal, Testicular Disorder, Vaginal Haemorrhage, Vulvovaginal Disorder
General disorders and administration site conditions	Asthenia, Chest Pain*, Injection Site Reactions*§, Pain*	Chills*, Face Oedema*, Injection Site Atrophy♣, Local Reaction*, Oedema Peripheral, Oedema, Pyrexia	Cyst, Hangover, Hypothermia, Immediate Post-Injection Reaction, Inflammation, Injection Site Necrosis, Mucous Membrane Disorder
Injury, poisoning and procedural complications			Post Vaccination Syndrome

* More than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group. Adverse reaction without the * symbol represents a difference of less than or equal to 2%.
§ The term 'Injection site reactions' (various kinds) comprises all adverse events occurring at the injection site excluding injection site atrophy and injection site necrosis, which are presented separately within the table.
♣ Includes terms which relate to localized lipoatrophy at the injection sites.
In the fourth trial noted above, an open-label treatment phase followed the placebo-controlled period (see section 5.1). No change in the known risk profile of Copaxone was observed during the open-label follow-up period of up to 5 years.
The following adverse reaction reports were collected from MS patients treated with Copaxone in uncontrolled clinical trials and from post-marketing experience with Copaxone: hypersensitivity reactions (including rare occurrence of anaphylaxis, >1/10000, < 1/1000.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

A few cases of overdose with Copaxone (up to 300 mg glatiramer acetate) have been reported. These cases were not associated with any adverse reactions other than those mentioned in section 4.8.
In case of overdose, patients should be monitored and the appropriate symptomatic and supportive therapy instituted.

5. Pharmacological properties
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, Other Immunostimulants ATC code: L03AX13
The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in several animal species through immunisation against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and in MS patients suggest that upon its administration, glatiramer acetate- specific suppressor T cells are induced and activated in the periphery.

RRMS:
A total of 269 patients have been treated with Copaxone in three controlled trials. The first was a two-year study involving 50 patients (Copaxone n=25, placebo n=25) who were diagnosed with relapsing-remitting MS by the then- applicable standard criteria, and who had at least two attacks of neurological dysfunction (exacerbations) during the preceding two years. The second study applied the same inclusion criteria and included 251 patients treated for up to 35 months (Copaxone n=125, placebo n=126). The third study was a nine-month study involving 239 patients (Copaxone n=119, placebo n=120) where inclusion criteria were similar to those in the first and second studies with the additional criterion that patients had to have at least one gadolinium-enhancing lesion on the screening MRI.
In clinical trials in MS patients receiving Copaxone, a significant reduction in the number of relapses, compared with placebo, was seen.
In the largest controlled study, the relapse rate was reduced by 32% from 1.98 under placebo to 1.34 under glatiramer acetate.
Exposure data are available for up to twelve years in 103 patients treated with Copaxone.
Copaxone has also demonstrated beneficial effects over placebo on MRI parameters relevant to relapsing-remitting MS.
Copaxone had, however, no beneficial effect on progression of disability in relapsing-remitting MS patients. There is no evidence that Copaxone treatment has an effect on relapse duration or severity.
There is currently no evidence for the use of Copaxone in patients with primary or secondary progressive disease.

Single clinical event suggestive of MS:
One placebo-controlled study involving 481 patients (Copaxone n=243, placebo n=238) was performed in patients with a well-defined, single, unifocal neurological manifestation and MRI features highly suggestive of MS (at least two cerebral lesions on the T2-weighted MRI above 6 mm diameter). Any disease other than MS that could better explain signs and symptoms of the patient had to be excluded. The placebo-controlled period was followed by an open label treatment: Patients who either presented with MS symptoms or were asymptomatic for three years, whichever came first, were assigned to active drug treatment in an open-label phase for an additional period of two years, not exceeding a maximal total treatment duration of 5 years. Of the 243 patients initially randomized to Copaxone, 198 continued Copaxone treatment in the open-label phase. Of the 238 patients initially randomized to placebo, 211 switched to Copaxone treatment in the open-label phase.
During the placebo-controlled period of up to three years, Copaxone delayed the progression from the first clinical event to clinically definite multiple sclerosis (CDMS) according to Poser criteria in a statistically significant and clinically meaningful manner, corresponding to a risk reduction of 45% (Hazard Ratio = 0.55; 95% CI [0.40; 0.77],
p-value=0.0005). The proportion of patients who converted to CDMS was 43% for the placebo group and 25% in the Copaxone group.

The favourable effect of treatment with Copaxone over placebo was also demonstrated in two secondary MRI endpoints, i.e. number of new T2 lesions and T2 lesion volume.
Post-hoc subgroup analyses were performed in patients with various baseline characteristics to identify a population at high risk to develop the second attack. For subjects with baseline MRI with at least one T1 Gd-enhancing lesion and 9 or more T2 lesions, conversion to CDMS was evident for 50% of the placebo subjects vs. 28% of the Copaxone subjects in 2.4 years. For subjects with 9 or more T2 lesions at baseline, conversion to CDMS was evident for 45% of the placebo subjects vs. 26% on Copaxone in 2.4 years. However, the impact of early treatment with Copaxone on the long term evolution of the disease is unknown even in these high-risk subgroups as the study was mainly designed to assess the time to the second event. In any case, treatment should only be considered for patients classified at high risk.

The effect shown in the placebo-controlled phase was sustained in the long-term follow-up period of up to 5 years. The time progression from the first clinical event to CDMS was prolonged with earlier Copaxone treatment as compared to delayed treatment, reflecting a 41% risk reduction with earlier versus later treatment (Hazard Ratio = 0.59; 95% CI [0.44; 0.80], p-value=0.0005). The proportion of subjects in the Delayed Start group who progressed was higher (49.6%) compared to those in the Early Start group (32.9%).
A consistent effect in favour of early treatment over delayed treatment across time was shown for the annualized number of lesions over the entire study period in new T1 Gd-enhancing lesions (reduced by 54%; p<0.0001), new T2 lesions (reduced by 42%; p<0.0001) and new T1 hypointense lesions (reduced by 52%; p<0.0001). An effect in reductions in favour of early versus delayed treatment was also observed for the total number of new T1 Gd- enhancing lesions (reduced by 46%; p=0.001), T1 Gd-enhancing lesion volume (a mean difference of -0.06 ml; p<0.001), as well as the total number of new T1 hypointense lesions (reduced by 46%; p<0.001) measured over the entire study period.
No appreciable differences between the Early Start and Delayed Start cohorts were observed for either hypointense T1 lesion volume or brain atrophy over 5 years. However, analysis of brain atrophy at last observed value (adjusted to treatment exposure) showed a reduction in favour of early treatment with GA (the mean difference of percent change in brain volume was 0.28%; p=0.0209).

5.2 Pharmacokinetic properties

Pharmacokinetic studies in patients have not been performed. *In vitro* data and limited data from healthy volunteers indicate that with subcutaneous administration of glatiramer acetate, the active substance is readily absorbed and that a large part of the dose is rapidly degraded to smaller fragments already in subcutaneous tissue.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction, genotoxicity or carcinogenicity, beyond the information included in other sections of the SPC. Due to the lack of pharmacokinetic data in humans, margins of exposure between humans and animals can not be established.
Immune complex deposition in the glomeruli of the kidney was reported in a small number of rats and monkeys treated for at least 6 months. In a 2 years rat study, no indication of immune complex deposition in the glomeruli of the kidney was seen.
Anaphylaxis after administration to sensitised animals (guinea pigs or mice) was reported. The relevance of these data for humans is unknown.
Toxicity at the injection site was a common finding after repeated administration in animals.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the pre-filled syringes in the outer carton, in order to protect from light. Store in a refrigerator (2°C – 8°C).
Do not freeze.
If the pre-filled syringes cannot be stored in a refrigerator, they can be stored between 15°C and 25°C, once for up to one month.
After this one month period, if the Copaxone 20 mg/ml pre-filled syringes have not been used and are still in their original packaging, they must be returned to storage in a refrigerator (2°C to 8°C).

6.5 Nature and contents of container

A pre-filled syringe containing Copaxone solution for injection consists of a 1 ml long colourless type I glass syringe barrel with staked needle, a polypropylene (optional polystyrene) plunger rod, a rubber plunger stopper and a needle shield.
Copaxone is available in packs containing 7, 28 or 30 pre-filled syringes of 1 ml solution for injection or a multipack containing 90 (3 packs of 30) pre-filled syringes of 1 ml solution for injection.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Any unused product or waste material must be discarded.

7. Marketing authorisation holder
Teva Pharmaceuticals Ltd.
Ridings Point
Whistler Drive
Castleford
West Yorkshire
WF10 5HX United Kingdom

8. Marketing authorisation number(s)
PL 10921/0023

9. Date of first authorisation/renewal of the authorisation
Date of first authorization: 7 April 2003

10. Date of revision of the text
17/03/2016

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SmPC for Gilenya

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg fingolimod (as hydrochloride). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Capsule of 16 mm with bright yellow opaque cap and white opaque body; imprint with black ink, "FTY0.5 mg" on cap and two radial bands imprinted on the body with yellow ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1).

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.2 Posology and method of administration

The treatment should be initiated and supervised by a physician experienced in multiple sclerosis. Posology
The recommended dose of Gilenya is one 0.5 mg capsule taken orally once daily. Gilenya can be taken with or without food.

The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:

- 1 day or more during the first 2 weeks of treatment.
- more than 7 days during weeks 3 and 4 of treatment.
- more than 2 weeks after one month of treatment.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned (see section 4.4).

Special populations
Elderly population
Gilenya should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy (see section 5.2).

Renal impairment
Gilenya was not studied in patients with renal impairment in the multiple sclerosis pivotal studies. Based on clinical pharmacology studies, no dose adjustments are needed in patients with mild to severe renal impairment.

Hepatic impairment

Gilenya must not be used in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3). Although no dose adjustments are needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment in these patients (see sections 4.4 and 5.2).

Diabetic patients
Gilenya has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. Gilenya should be used with caution in these patients due to a potential increase in the risk of macular oedema (see sections 4.4 and 4.8). Regular ophthalmological examinations should be conducted in these patients to detect macular oedema.

Paediatric population
The safety and efficacy of Gilenya in children aged 0 to 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

Known immunodeficiency syndrome.
Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies).
Severe active infections, active chronic infections (hepatitis, tuberculosis). Known active malignancies.
Severe liver impairment (Child-Pugh class C).
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Bradyarrhythmia
Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block (see sections 4.8 and 5.1).

After the first dose, the decline in heart rate starts within one hour, and is maximal within 6 hours. This post-dose effect persists over the following days, although usually to a milder extent, and usually abates over the next weeks. With continued administration, the average heart rate returns towards baseline within one month. However individual patients may not return to baseline heart rate by the end of the first month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. If necessary, the decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline.

All patients should have an ECG and blood pressure measurement performed prior to and 6 hours after the first dose of Gilenya. All patients should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6 hour period is recommended.

Should post-dose bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. Should a patient require pharmacological intervention during the first-dose monitoring, overnight monitoring in a medical facility should be instituted and the first-dose monitoring should be repeated after the second dose of Gilenya.

If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), monitoring should be extended by at least 2 hours and until heart rate increases again. Additionally, if after 6 hours, the heart rate is <45 bpm, or the ECG shows new onset second degree or higher grade AV block or a QTc interval $\geqslant$500 msec, extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring (at least overnight monitoring).

Very rare cases of T-wave inversion have been reported in patients treated with fingolimod. In case of T-wave inversion, the prescriber should ensure that there are no associated myocardial ischaemia signs or symptoms. If myocardial ischaemia is suspected, it is recommended to seek advice from a cardiologist.

Due to the risk of serious rhythm disturbances, Gilenya should not be used in patients with second degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope, or in patients with significant QT prolongation (QTc>470msec (female) or >450msec (male)). Since significant bradycardia may be poorly tolerated in patients with known ischaemic heart disease (including angina pectoris), cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea, Gilenya should not be used in these patients. In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring, at least overnight extended monitoring is recommended for treatment initiation (see also section 4.5).

Gilenya has not been studied in patients with arrhythmias requiring treatment with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Class Ia and class III antiarrhythmic medicinal products have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of Gilenya treatment results in decreased heart rate, Gilenya should not be used concomitantly with these medicinal products.

Experience with Gilenya is limited in patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).
Since the initiation of Gilenya treatment is also associated with slowing of the heart rate (see also section 4.8, Bradyarrhythmia), concomitant use of these substances during Gilenya initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment with Gilenya should not be initiated in patients who are concurrently treated with these substances (see also section 4.5). In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment with Gilenya is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products prior to initiation of treatment. If the heart-rate-lowering medication cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended (see also section 4.5).

The effects on heart rate and atrioventricular conduction may recur on re-introduction of Gilenya treatment depending on duration of the interruption and time since start of Gilenya treatment. The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:

- 1 day or more during the first 2 weeks of treatment.
- more than 7 days during weeks 3 and 4 of treatment.
- more than 2 weeks after one month of treatment.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

QT interval
In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper limit of the 90% CI $\leqslant$13.0 ms. There is no dose- or exposure-response relationship of fingolimod and QTcI prolongation. There is no consistent signal of increased incidence of QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment.

The clinical relevance of this finding is unknown. In the multiple sclerosis studies, clinically relevant effects on prolongation of the QTc-interval have not been observed but patients at risk for QT prolongation were not included in clinical studies.

Medicinal products that may prolong QTc interval are best avoided in patients with relevant risk factors, for example, hypokalaemia or congenital QT prolongation.

Infections
A core pharmacodynamic effect of Gilenya is a dose-dependent reduction of the peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see section 5.1).

Before initiating treatment with Gilenya, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended

periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection.

Absolute lymphocyte count <$0.2x10^9$/l, if confirmed, should lead to treatment interruption until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count <$0.2x10^9$/l.

Initiation of treatment with Gilenya should be delayed in patients with severe active infection until resolution.

Patients need to be assessed for their immunity to varicella (chickenpox) prior to Gilenya treatment. It is recommended that patients without a health care professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating Gilenya therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with Gilenya (see section 4.8). Initiation of treatment with Gilenya should be postponed for 1 month to allow full effect of vaccination to occur.

The immune system effects of Gilenya may increase the risk of infections, including opportunistic infections (see section 4.8). Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. During treatment, patients receiving Gilenya should be instructed to report symptoms of infection to their physician.

Suspension of Gilenya should be considered if a patient develops a serious infection and consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

Isolated cases of cryptococcal meningitis (a fungal infection) have been reported in the post- marketing setting (see section 4.8). Patients with symptoms and signs consistent with cryptococcal meningitis (e.g. headache accompanied by mental changes such as confusion, hallucinations, and/or personality changes) should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, fingolimod should be suspended and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of fingolimod is warranted.

Progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod treatment since marketing authorisation (see section 4.8). PML is an opportunistic infection caused by John Cunningham virus (JCV), which may be fatal or result in severe disability. PML can only occur in the presence of a JCV infection. If JCV testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of anti-JCV antibody testing has not been studied in fingolimod-treated patients. It should also be noted that a negative anti-JCV antibody test does not preclude the possibility of subsequent JCV infection. Before initiating treatment with fingolimod, a baseline MRI should be available (usually within 3 months) as a reference. During routine MRI (in accordance with national and local recommendations), physicians should pay attention to PML suggestive lesions.
MRI may be considered as part of increased vigilance in patients considered at increased risk of PML. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded.

Elimination of fingolimod following discontinuation of therapy may take up to two months and vigilance for infection should therefore be continued throughout this period. Patients should be instructed to report symptoms of infection up to 2 months after discontinuation of fingolimod.

Macular oedema
Macular oedema with or without visual symptoms has been reported in 0.5% of patients treated with fingolimod 0.5 mg, occurring predominantly in the first 3-4 months of therapy (see section 4.8). An ophthalmological evaluation is therefore recommended at 3-4 months after treatment initiation. If patients report visual disturbances at any time while on therapy, evaluation of the fundus, including the macula, should be carried out.

Patients with history of uveitis and patients with diabetes mellitus are at increased risk of macular oedema (see section 4.8). Gilenya has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. It is recommended that multiple sclerosis patients with diabetes mellitus or a history of uveitis undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy.

Continuation of Gilenya in patients with macular oedema has not been evaluated. It is recommended that Gilenya be discontinued if a patient develops macular oedema. A decision on whether or not Gilenya therapy should be re-initiated after resolution of macular oedema needs to take into account the potential benefits and risks for the individual patient.

Liver function

Increased hepatic enzymes, in particular alanine aminotransaminase (ALT) but also gamma glutamyltransferase (GGT) and aspartate transaminase (AST) have been reported in multiple sclerosis patients treated with Gilenya. In clinical trials, elevations 3-fold the upper limit of normal (ULN) or greater in ALT occurred in 8.0% of patients treated with fingolimod 0.5 mg compared to 1.9% of placebo patients. Elevations 5-fold the ULN occurred in 1.8% of patients on fingolimod and 0.9% of patients on placebo. In clinical trials, fingolimod was discontinued if the elevation exceeded 5 times the ULN. Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod.

Gilenya has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and should not be used in these patients (see section 4.3).

Due to the immunosuppressive properties of fingolimod, initiation of treatment should be delayed in patients with active viral hepatitis until resolution.

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with Gilenya. In the absence of clinical symptoms, liver transaminases should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with Gilenya should be interrupted and only re-commenced once liver transaminase values have normalised.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes checked and Gilenya should be discontinued if significant liver injury is confirmed (for example liver transaminase levels greater than 5-fold the ULN and/or serum bilirubin elevations). Resumption of therapy will be dependent on whether or not another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction.

Although there are no data to establish that patients with pre-existing liver disease are at increased risk of developing elevated liver function tests when taking Gilenya, caution in the use of Gilenya should be exercised in patients with a history of significant liver disease.

Interference with serological testing

Since fingolimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

Blood pressure effects

Patients with hypertension uncontrolled by medication were excluded from participation in premarketing clinical trials and special care is indicated if patients with uncontrolled hypertension are treated with Gilenya.

In MS clinical trials, patients treated with fingolimod 0.5 mg had an average increase of approximately 3 mmHg in systolic pressure, and approximately 1 mmHg in diastolic pressure, first detected approximately 1 month after treatment initiation, and persisting with continued treatment. In the two-year placebo-controlled study, hypertension was reported as an adverse event in 6.5% of patients on fingolimod 0.5 mg and in 3.3% of patients on placebo. Therefore, blood pressure should be regularly monitored during treatment with Gilenya.

Respiratory effects

Minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were observed with Gilenya treatment starting at Month 1 and remaining stable thereafter. Gilenya should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (see also section 4.8).

Posterior reversible encephalopathy syndrome
Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported at the 0.5 mg dose in clinical trials and in the post-marketing setting (see section 4.8). Symptoms reported included sudden onset of severe headache, nausea, vomiting, altered mental status, visual disturbances and seizure. Symptoms of PRES are usually reversible but may evolve into ischaemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, Gilenya should be discontinued.

Prior treatment with immunosuppressive or immunomodulatory therapies
There have been no studies performed to evaluate the efficacy and safety of Gilenya when switching patients from teriflunomide, dimethyl fumarate or alemtuzumab treatment to Gilenya. When switching patients from another disease modifying therapy to Gilenya, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A CBC is recommended prior to initiating Gilenya to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Gilenya can generally be started immediately after discontinuation of interferon or glatiramer acetate.

For dimethyl fumarate, the washout period should be sufficient for CBC to recover before treatment with Gilenya is started.

Due to the long half-life of natalizumab, elimination usually takes up to 2-3 months following discontinuation. Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide summary of product characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to Gilenya.

Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with Gilenya after alemtuzumab is not recommended unless the benefits of such treatment clearly outweigh the risks for the individual patient.

A decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.

Co-administration with potent CYP450 inducers
The combination of fingolimod with potent CYP450 inducers should be used with caution. Concomitant administration with St John's wort is not recommended (see section 4.5).

Basal cell carcinoma
Basal cell carcinoma (BCC) has been reported in patients receiving Gilenya (see section 4.8). Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, after at least one year and then at least yearly taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected.

Stopping therapy
If a decision is made to stop treatment with Gilenya a 6 week interval without therapy is needed, based on half-life, to clear fingolimod from the circulation (see section 5.2). Lymphocyte counts progressively return to normal range within 1-2 months of stopping therapy (see section 5.1). Starting other therapies during this interval will result in concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of Gilenya may lead to an additive effect on the immune system and caution is therefore indicated.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-neoplastic, immunomodulatory or immunosuppressive therapies

Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects (see sections 4.3 and 4.4).

Caution should also be exercised when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone (see section 4.4). In multiple sclerosis clinical studies the concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection.

Vaccination
During and for up to two months after treatment with Gilenya vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided (see sections 4.4 and 4.8).

Bradycardia-inducing substances
Fingolimod has been studied in combination with atenolol and diltiazem. When fingolimod was used with atenolol in an interaction study in healthy volunteers, there was an additional 15% reduction of heart rate at fingolimod treatment initiation, an effect not seen with diltiazem. Treatment with Gilenya should not be initiated in patients receiving beta blockers, or other substances which may decrease heart rate, such as class Ia and III antiarrhythmics, calcium channel blockers (such as ivabradine, verapamil or diltiazem), digoxin, anticholinesteratic agents or pilocarpine because of the potential additive effects on heart rate (see sections 4.4 and 4.8). If treatment with Gilenya is considered in such patients, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended, if the heart-rate-lowering medication cannot be stopped.

Pharmacokinetic interactions of other substances on fingolimod
Fingolimod is metabolised mainly by CYP4F2. Other enzymes like CYP3A4 may also contribute to its metabolism, notably in the case of strong induction of CYP3A4. Potent inhibitors of transporter proteins are not expected to influence fingolimod disposition. Co-administration of fingolimod with ketoconazole resulted in a 1.7-fold increase in fingolimod and fingolimod phosphate exposure (AUC) by inhibition of CYP4F2. Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).

Co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of fingolimod 2 mg reduced the AUC of fingolimod and its metabolite by approximately 40%. Other strong CYP3A4 enzyme inducers, for example rifampicin, phenobarbital, phenytoin, efavirenz and St. John's Wort, may reduce the AUC of fingolimod and its metabolite at least to this extent. As this could potentially impair the efficacy, their co-administration should be used with caution.
Concomitant administration with St. John's Wort is however not recommended (see section 4.4).

Pharmacokinetic interactions of fingolimod on other substances
Fingolimod is unlikely to interact with substances mainly cleared by the CYP450 enzymes or by substrates of the main transporter proteins.

Co-administration of fingolimod with ciclosporin did not elicit any change in the ciclosporin or fingolimod exposure. Therefore, fingolimod is not expected to alter the pharmacokinetics of medicinal products that are CYP3A4 substrates.

Co-administration of fingolimod with oral contraceptives (ethinylestradiol and levonorgestrel) did not elicit any change in oral contraceptive exposure. No interaction studies have been performed with oral contraceptives containing other progestagens, however an effect of fingolimod on their exposure is not expected.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females
Before initiation of Gilenya treatment, women of childbearing potential should be counselled regarding the potential for serious risk to the foetus and the need for effective contraception during treatment with Gilenya. Since it takes approximately two months to eliminate fingolimod from the body on stopping treatment (see section 4.4), the potential risk to the foetus may persist and contraception should be continued during that period.

Pregnancy

Before initiation of treatment in women of childbearing potential a negative pregnancy test result needs to be available. While on treatment, women should not become pregnant and active contraception is recommended. If a woman becomes pregnant while taking Gilenya, discontinuation of Gilenya is recommended.

Animal studies have shown reproductive toxicity including foetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect (see section 5.3). Furthermore, the receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. There are very limited data from the use of fingolimod in pregnant women. There are no data on the effects of fingolimod on labour and delivery.

Breast-feeding

Fingolimod is excreted in milk of treated animals during lactation at concentrations 2-3-fold higher than that found in maternal plasma (see section 5.3). Due to the potential for serious adverse reactions to fingolimod in nursing infants, women receiving Gilenya should not breastfeed.

Fertility

Data from preclinical studies do not suggest that fingolimod would be associated with an increased risk of reduced fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Gilenya has no or negligible influence on the ability to drive and use machines.

However, dizziness or drowsiness may occasionally occur when initiating therapy with Gilenya. On initiation of Gilenya treatment it is recommended that patients be observed for a period of 6 hours (see section 4.4, Bradyarrhythmia).

4.8 Undesirable effects

Summary of the safety profile

The safety population of Gilenya is derived from two Phase III placebo-controlled clinical studies and one Phase III active-controlled clinical study in patients with relapsing remitting multiple sclerosis. It includes a total of 2,431 patients on Gilenya (0.5 or 1.25 mg). Study D2301 (FREEDOMS) was a 2- year placebo-controlled clinical study in 854 patients treated with fingolimod (placebo: 418). Study D2309 (FREEDOMS II) was a 2-year placebo-controlled clinical study in 728 multiple sclerosis patients treated with fingolimod (placebo: 355). In the pooled data from these two studies the most serious adverse reactions on Gilenya 0.5 mg were infections, macular oedema and transient atrioventricular block at treatment initiation. The most frequent adverse reactions (incidence ⩾10%) on Gilenya 0.5 mg were influenza, sinusitis, headache, diarrhoea, back pain, hepatic enzyme increased and cough. The most frequent adverse reaction reported for Gilenya 0.5 mg leading to treatment interruption was ALT elevations (2.2%). The adverse reactions in Study D2302 (TRANSFORMS), a 1-year study in 849 patients treated with fingolimod which used interferon beta-1a as comparator, were generally similar to placebo-controlled studies, taking into account the differences in study duration.

Adverse reactions reported with Gilenya 0.5 mg in Studies D2301 (FREEDOMS) and D2309 (FREEDOMS II) are shown below. Frequencies were defined using the following convention: very common (⩾1/10); common (⩾1/100 to <1/10); uncommon (⩾1/1,000 to <1/100); rare (⩾1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Tabulated list of adverse reactions

Infections and infestations

Very common:	Influenza Sinusitis
Common:	Herpes viral infections Bronchitis Tinea versicolor
Uncommon:	Pneumonia
Not known**:	Progressive multifocal leukoencephalopathy (PML) Cryptococcal infections

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Common:	Basal cell carcinoma
Rare***:	Lymphoma
Blood and lymphatic system disorders	
Common:	Lymphopenia Leucopenia
Not known***:	Peripheral oedema
Immune system disorders	
Not known***:	Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation
Psychiatric disorders	
Common:	Depression
Uncommon:	Depressed mood
Nervous system disorders	
Very common:	Headache
Common:	Dizziness Migraine
Rare*:	Posterior reversible encephalopathy syndrome (PRES)
Eye disorders	
Common:	Vision blurred
Uncommon:	Macular oedema
Cardiac disorders	
Common:	Bradycardia Atrioventricular block
Very rare***:	T-wave inversion
Vascular disorders	
Common:	Hypertension
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough
Common:	Dyspnoea
Gastrointestinal disorders	
Very common:	Diarrhoea
Uncommon***:	Nausea
Skin and subcutaneous tissue disorders	
Common:	Eczema Alopecia Pruritus
Musculoskeletal and connective tissue disorders	
Very common:	Back pain
General disorders and administration site conditions	
Common:	Asthenia
Investigations	
Very common:	Hepatic enzyme increased (increased ALT, Gamma glutamyltransferase, Aspartate transaminase)
Common:	Blood triglycerides increased
Uncommon:	Neutrophil count decreased

* Not reported in Studies FREEDOMS, FREEDOMS II and TRANSFORMS. The frequency category was based on an estimated exposure of approximately 10, 000 patients to fingolimod in all clinical trials.

** PML and cryptococcal infections (including isolated cases of cryptococcal meningitis) have been reported in the post-marketing setting (see section 4.4).

*** Adverse drug reactions from spontaneous reports and literature

Description of selected adverse reactions

Infections

In multiple sclerosis clinical studies the overall rate of infections (65.1%) at the 0.5 mg dose was similar to placebo. However, lower respiratory tract infections, primarily bronchitis and to a lesser extent herpes infection and pneumonia were more common in Gilenya-treated patients.

Some cases of disseminated herpes infection, including fatal cases, have been reported even at the 0.5 mg dose.

In the post-marketing setting, cases of infections with opportunistic pathogens, such as viral (e.g. varicella zoster virus [VZV], John Cunningham virus [JCV] causing Progressive Multifocal Leukoencephalopathy, herpes simplex virus [HSV]), fungal (e.g. cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported (see section 4.4).

Macular oedema

In multiple sclerosis clinical studies macular oedema occurred in 0.5% of patients treated with the recommended dose of 0.5 mg and 1.1% of patients treated with the higher dose of 1.25 mg. The majority of cases occurred within the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmological examination. The macular oedema generally improved or resolved spontaneously after discontinuation of Gilenya. The risk of recurrence after re-challenge has not been evaluated.

Macular oedema incidence is increased in multiple sclerosis patients with a history of uveitis (17% with a history of uveitis vs. 0.6% without a history of uveitis). Gilenya has not been studied in multiple sclerosis patients with diabetes mellitus, a disease which is associated with an increased risk for macular oedema (see section 4.4). In renal transplant clinical studies in which patients with diabetes mellitus were included, therapy with fingolimod 2.5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular oedema.

Bradyarrhythmia

Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays. In multiple sclerosis clinical studies the maximal decline in heart rate was seen within 6 hours after treatment initiation, with declines in mean heart rate of 12-13 beats per minute for Gilenya 0.5 mg. Heart rate below 40 beats per minute was rarely observed in patients on Gilenya 0.5 mg. The average heart rate returned towards baseline within 1 month of chronic treatment. Bradycardia was generally asymptomatic but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue and/or palpitations, which resolved within the first 24 hours after treatment initiation (see also sections 4.4 and 5.1).

In multiple sclerosis clinical studies first-degree atrioventricular block (prolonged PR interval on ECG) was detected after treatment initiation in 4.7% of patients on fingolimod 0.5 mg, in 2.8% of patients on intramuscular interferon beta-1a, and in 1.6% of patients on placebo. Second-degree atrioventricular block was detected in less than 0.2% patients on Gilenya 0.5 mg. In the post- marketing setting, isolated reports of transient, spontaneously resolving complete AV block have been observed during the six hour monitoring period following the first dose of Gilenya. The patients recovered spontaneously. The conduction abnormalities observed both in clinical trials and post- marketing were typically transient, asymptomatic and resolved within the first 24 hours after treatment initiation. Although most patients did not require medical intervention, one patient on Gilenya 0.5 mg received isoprenaline for asymptomatic second-degree Mobitz I atrioventricular block.

In the post-marketing setting, isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These cases have been confounded by concomitant medicinal products and/or pre-existing disease. The relationship of such events to Gilenya is uncertain.

Blood pressure

In multiple sclerosis clinical studies Gilenya 0.5 mg was associated with an average increase of approximately 3 mmHg in systolic pressure and approximately 1 mmHg in diastolic pressure, manifesting approximately 1 month after treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.5% of patients on fingolimod 0.5 mg and in 3.3% of patients on placebo. In the post-marketing setting, cases of hypertension have been reported within the first month of treatment

initiation and on the first day of treatment that may require treatment with antihypertensive agents or discontinuation of Gilenya (see also section 4.4, Blood pressure effects).

Liver function
Increased hepatic enzymes have been reported in multiple sclerosis patients treated with Gilenya. In clinical studies 8.0% and 1.8% of patients treated with Gilenya 0.5 mg experienced an asymptomatic elevation in serum levels of ALT of ⩾3x ULN (upper limit of normal) and ⩾5x ULN, respectively. Recurrence of liver transaminase elevations has occurred upon re-challenge in some patients, supporting a relationship to the medicinal product. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. ALT levels returned to normal within approximately 2 months after discontinuation of Gilenya. In a small number of patients (N=10 on 1.25 mg, N=2 on 0.5 mg) who experienced ALT elevations ⩾5x ULN and who continued on Gilenya therapy, the ALT levels returned to normal within approximately
5 months (see also section 4.4, Liver function).

Nervous system disorders
In clinical studies, rare events involving the nervous system occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg) including ischaemic and haemorrhagic strokes and neurological atypical disorders, such as acute disseminated encephalomyelitis (ADEM)-like events.

Vascular disorders
Rare cases of peripheral arterial occlusive disease occurred in patients treated with fingolimod at higher doses (1.25 mg).

Respiratory system
Minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were observed with Gilenya treatment starting at Month 1 and remaining stable thereafter. At Month 24, the reduction from baseline values in percentage of predicted FEV_1 was 2.7% for fingolimod 0.5 mg and 1.2% for placebo, a difference that resolved after treatment discontinuation. For DLCO the reductions at Month 24 were 3.3% for fingolimod 0.5 mg and 2.7% for placebo.

Lymphomas
There have been cases of lymphoma of different varieties, in both clinical studies and the post- marketing setting, including a fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma. The incidence of lymphoma (B-cell and T-cell) cases was higher in clinical trials than expected in the general population.

Haemophagocytic syndrome
Very rare cases of haemophagocytic syndrome (HPS) with fatal outcome have been reported in patients treated with fingolimod in the context of an infection. HPS is a rare condition that has been described in association with infections, immunosuppression and a variety of autoimmune diseases.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 80 times the recommended dose (0.5 mg) were well tolerated in healthy volunteers. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

Fingolimod can induce bradycardia upon treatment initiation. The decline in heart rate usually starts within one hour of the first dose, and is steepest within 6 hours. The negative chronotropic effect of Gilenya persists beyond 6 hours and progressively attenuates over subsequent days of treatment (see section 4.4 for details). There have been reports of slow atrioventricular conduction, with isolated reports of transient, spontaneously resolving complete AV block (see sections 4.4 and 4.8).

If the overdose constitutes first exposure to Gilenya, it is important to monitor patients with a continuous (real time) ECG and hourly measurement of heart rate and blood pressure, at least during the first 6 hours (see section 4.4).

Additionally, if after 6 hours the heart rate is <45 bpm or if the ECG at 6 hours after the first dose shows second degree or higher AV block, or if it shows a QTc interval ⩾500 msec, monitoring should be extended at least for overnight and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring including overnight monitoring.

Neither dialysis nor plasma exchange results in removal of fingolimod from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA27 Mechanism of action

Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. Animal studies have shown that this redistribution reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 cells, into the CNS, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also act via interaction with S1P receptors on neural cells.

Pharmacodynamic effects

Within 4-6 hours after the first dose of fingolimod 0.5 mg, the lymphocyte count decreases to approximately 75% of baseline in peripheral blood. With continued daily dosing, the lymphocyte count continues to decrease over a two-week period, reaching a minimal count of approximately 500 cells/microlitre or approximately 30% of baseline. Eighteen percent of patients reached a minimal count below 200 cells/microlitre on at least one occasion. Low lymphocyte counts are maintained with chronic daily dosing. The majority of T and B lymphocytes regularly traffic through lymphoid organs and these are the cells mainly affected by fingolimod. Approximately 15-20% of T lymphocytes have an effector memory phenotype, cells that are important for peripheral immune surveillance. Since this lymphocyte subset typically does not traffic to lymphoid organs it is not affected by fingolimod. Peripheral lymphocyte count increases are evident within days of stopping fingolimod treatment and typically normal counts are reached within one to two months. Chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline. Monocytes are unaffected by fingolimod.

Fingolimod causes a transient reduction in heart rate and decrease in atrioventricular conduction at treatment initiation (see sections 4.4 and 4.8). The maximal decline in heart rate is seen within 6 hours post dose, with 70% of the negative chronotropic effect achieved on the first day. With continued administration heart rate returns to baseline within one month. The decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline. Inhaled salmeterol has also been shown to have a modest positive chronotropic effect. With initiation of fingolimod treatment there is an increase in atrial premature contractions, but there is no increased rate of atrial fibrillation/flutter or ventricular arrhythmias or ectopy. Fingolimod treatment is not associated with a decrease in cardiac output. Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise are not affected by fingolimod treatment.

Fingolimod treatment with single or multiple doses of 0.5 and 1.25 mg for two weeks is not associated with a detectable increase in airway resistance as measured by FEV_1 and forced expiratory flow rate (FEF) 25-75. However, single fingolimod doses ⩾5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. Fingolimod treatment with multiple doses of 0.5, 1.25, or 5 mg is not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment have a normal bronchodilator response to inhaled beta-agonists.

Clinical efficacy and safety

The efficacy of Gilenya has been demonstrated in two studies which evaluated once-daily doses of fingolimod 0.5 mg and 1.25 mg in patients with relapsing-remitting multiple sclerosis (RRMS). Both studies included patients who had experienced ⩾2 relapses in the prior 2 years or ⩾1 relapse during the prior year. Expanded Disability Status Score (EDSS) was between 0 and 5.5. A third study targeting the same patient population was completed after registration of Gilenya.

Study D2301 (FREEDOMS) was a 2-year randomised, double-blind, placebo-controlled Phase III study of 1,272 patients (n=425 on 0.5 mg, 429 on 1.25 mg, 418 on placebo). Median values for baseline characteristics were: age 37 years, disease duration 6.7 years, and EDSS score 2.0. Outcome results are shown in Table 1. There were no significant differences between the 0.5 mg and the 1.25 mg doses as regards either endpoint.

Table 1: Study D2301 (FREEDOMS): Main results

	Fingolimod 0.5 mg	**Placebo**
Clinical endpoints		
Annualised relapse rate (primary endpoint)	0.18**	0.40
Percentage of patients remaining relapse-free at 24 months	70%**	46%
Proportion with 3-month Confirmed Disability Progression† Hazard ratio (95% CI)	17% 0.70 (0.52, 0.96)*	24%
MRI endpoints		
Median (mean) number of new or enlarging T2 lesions over 24 months	0.0 (2.5)**	5.0 (9.8)
Median (mean) number of Gd-enhancing lesions at Month 24	0.0 (0.2)**	0.0 (1.1)
Median (mean) % change in brain volume over 24 months	-0.7 (-0.8)**	-1.0 (-1.3)
† Disability progression defined as 1-point increase in EDSS confirmed 3 months later ** p<0.001, *p<0.05 compared to placebo All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.		

Patients who completed the 24-month core FREEDOMS study could enter a dose-blinded extension study (D2301E1) and receive fingolimod. In total, 920 patients entered (n=331 continued on 0.5 mg, 289 continued on 1.25 mg, 155 switched from placebo to 0.5 mg and 145 switched from placebo to 1.25 mg). After 12 months (month 36), 856 patients (93%) were still enrolled. Between months 24 and 36, the annualised relapse rate (ARR) for patients on fingolimod 0.5 mg in the core study who remained on 0.5 mg was 0.17 (0.21 in the core study). The ARR for patients who switched from placebo to fingolimod 0.5 mg was 0.22 (0.42 in the core study).

Comparable results were shown in a replicate 2-year randomised, double-blind, placebo-controlled Phase III study on fingolimod in 1,083 patients (n=358 on 0.5 mg, 370 on 1.25 mg, 355 on placebo) with RRMS (D2309; FREEDOMS 2). Median values for baseline characteristics were: age 41 years, disease duration 8.9 years, EDSS score 2.5.

Table 2: Study D2309 (FREEDOMS 2): Main results

	Fingolimod 0.5 mg	**Placebo**
Clinical endpoints		
Annualised relapse rate (primary endpoint)	0.21**	0.40
Percentage of patients remaining relapse-free at 24 months	71.5%**	52.7%
Proportion with 3-month Confirmed Disability Progression† Hazard ratio (95% CI)	25% 0.83 (0.61, 1.12)	29%
MRI endpoints		

Median (mean) number of new or enlarging T2 lesions over 24 months	0.0 (2.3)**	4.0 (8.9)
Median (mean) number of Gd-enhancing lesions at Month 24	0.0 (0.4)**	0.0 (1.2)
Median (mean) % change in brain volume over 24 months	-0.71 (-0.86)**	-1.02 (-1.28)
† Disability progression defined as 1-point increase in EDSS confirmed 3 months later ** p<0.001 compared to placebo All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.		

Study D2302 (TRANSFORMS) was a 1-year randomised, double-blind, double-dummy, active (interferon beta-1a)-controlled Phase III study of 1,280 patients (n=429 on 0.5 mg, 420 on 1.25 mg, 431 on interferon beta-1a, 30 µg by intramuscular injection once weekly). Median values for baseline characteristics were: age 36 years, disease duration 5.9 years, and EDSS score 2.0. Outcome results are shown in Table 3. There were no significant differences between the 0.5 mg and the 1.25 mg doses as regards study endpoints.

Table 3: Study D2302 (TRANSFORMS): Main results

	Fingolimod 0.5 mg	**Interferon beta-1a, 30 µg**
Clinical endpoints		
Annualised relapse rate (primary endpoint)	0.16**	0.33
Percentage of patients remaining relapse-free at 12 months	83%**	71%
Proportion with 3-month Confirmed Disability Progression† Hazard ratio (95% CI)	6% 0.71 (0.42, 1.21)	8%
MRI endpoints		
Median (mean) number of new or enlarging T2 lesions over 12 months	0.0 (1.7)*	1.0 (2.6)
Median (mean) number of Gd-enhancing lesions at 12 months	0.0 (0.2)**	0.0 (0.5)
Median (mean) % change in brain volume over 12 months	-0.2 (-0.3)**	-0.4 (-0.5)
† Disability progression defined as 1-point increase in EDSS confirmed 3 months later. * p<0.01,** p<0.001, compared to interferon beta-1a All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.		

Patients who completed the 12-month core TRANSFORMS study could enter a dose-blinded extension (D2302E1) and receive fingolimod. In total, 1,030 patients entered, however, 3 of these patients did not receive treatment (n=356 continued on 0.5 mg, 330 continued on 1.25 mg, 167 switched from interferon beta-1a to 0.5 mg and 174 from interferon beta-1a to 1.25 mg). After 12 months (month 24), 882 patients (86%) were still enrolled. Between months 12 and 24, the ARR for patients on fingolimod 0.5 mg in the core study who remained on 0.5 mg was 0.20 (0.19 in the core study). The ARR for patients who switched from interferon beta-1a to fingolimod 0.5 mg was 0.33 (0.48 in the core study).

Pooled results of Studies D2301 and D2302 showed a consistent and statistically significant reduction in annualised relapse rate compared to comparator in subgroups defined by gender, age, prior multiple sclerosis therapy, disease activity or disability levels at baseline.

Further analyses of clinical trial data demonstrate consistent treatment effects in highly active subgroups of relapsing remitting multiple sclerosis patients.

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The European Medicines Agency has deferred the obligation to submit the results of studies with Gilenya in one or more subsets of the paediatric population in multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetic data were obtained in healthy volunteers, in renal transplant patients and in multiple sclerosis patients.
The pharmacologically active metabolite responsible for efficacy is fingolimod phosphate. Absorption
Fingolimod absorption is slow (t_{max} of 12-16 hours) and extensive ($\geqslant$85%). The apparent absolute oral bioavailability is 93% (95% confidence interval: 79-111%). Steady-state-blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Food intake does not alter C_{max} or exposure (AUC) of fingolimod. Fingolimod phosphate C_{max} was slightly increased by 34% but AUC was unchanged. Therefore, Gilenya may be taken without regard to meals (see section 4.2).

Distribution
Fingolimod highly distributes in red blood cells, with the fraction in blood cells of 86%. Fingolimod phosphate has a smaller uptake in blood cells of <17%. Fingolimod and fingolimod phosphate are highly protein bound (>99%).

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1,200±260 litres. A study in four healthy subjects who received a single intravenous dose of a radioiodolabelled analogue of fingolimod demonstrated that fingolimod penetrates into the brain. In a study in 13 male multiple sclerosis patients who received Gilenya 0.5 mg/day, the mean amount of fingolimod (and fingolimod phosphate) in seminal ejaculate, at steady-state, was approximately 10,000 times lower than the oral dose administered (0.5 mg).

Biotransformation
Fingolimod is transformed in humans by reversible stereoselective phosphorylation to the pharmacologically active (S)-enantiomer of fingolimod phosphate. Fingolimod is eliminated by oxidative biotransformation catalysed mainly via CYP4F2 and possibly other isoenzymes and subsequent fatty acid-like degradation to inactive metabolites. Formation of pharmacologically inactive non-polar ceramide analogues of fingolimod was also observed. The main enzyme involved in the metabolism of fingolimod is partially identified and may be either CYP4F2 or CYP3A4.

Following single oral administration of [^{14}C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 34 days post dose of total radiolabelled components, are fingolimod itself (23%), fingolimod phosphate (10%), and inactive metabolites (M3 carboxylic acid metabolite (8%), M29 ceramide metabolite (9%) and M30 ceramide metabolite (7%)).

Elimination
Fingolimod blood clearance is 6.3±2.3 l/h, and the average apparent terminal half-life ($t_{1/2}$) is 6-9 days. Blood levels of fingolimod and fingolimod phosphate decline in parallel in the terminal phase, leading to similar half-lives for both.

After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod phosphate are not excreted intact in urine but are the major components in the faeces, with amounts representing less than 2.5% of the dose each. After 34 days, the recovery of the administered dose is 89%.

Linearity
Fingolimod and fingolimod phosphate concentrations increase in an apparently dose proportional manner after multiple once-daily doses of 0.5 mg or 1.25 mg.

Characteristics in specific groups of patients
The pharmacokinetics of fingolimod and fingolimod phosphate do not differ in males and females, in patients of different ethnic origin, or in patients with mild to severe renal impairment.

In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), no change in fingolimod C_{max} was observed, but fingolimod AUC was increased respectively by 12%, 44%, and 103%. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod- phosphate C_{max} was decreased by 22% and AUC was not substantially changed. The pharmacokinetics of fingolimod-phosphate were not evaluated in patients with mild or moderate hepatic impairment.
The apparent elimination half-life of fingolimod is unchanged in subjects with mild hepatic impairment, but is prolonged by about 50% in patients with moderate or severe hepatic impairment.

Fingolimod should not be used in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3). Fingolimod should be introduced cautiously in mild and moderate hepatic impaired patients (see section 4.2).

Clinical experience and pharmacokinetic information in patients aged above 65 years are limited. Gilenya should be used with caution in patients aged 65 years and over (see section 4.2).

Paediatric population
There are limited data available from a renal transplant study that included 7 children above 11 years of age (study FTY720A0115). The comparison of these data to those in adult healthy volunteers is of limited relevance and no valid conclusions can be drawn regarding the pharmacokinetic properties of fingolimod in children.

5.3 Preclinical safety data

The preclinical safety profile of fingolimod was assessed in mice, rats, dogs and monkeys. The major target organs were the lymphoid system (lymphopenia and lymphoid atrophy), lungs (increased weight, smooth muscle hypertrophy at the bronchio-alveolar junction), and heart (negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration) in several species; blood vessels (vasculopathy) in rats only at doses of 0.15 mg/kg and higher in a 2- year study, representing an approximate 4-fold margin based on the human systemic exposure (AUC) at a daily dose of 0.5 mg.

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of fingolimod up to the maximally tolerated dose of 2.5 mg/kg, representing an approximate 50-fold margin based on human systemic exposure (AUC) at the 0.5 mg dose. However, in a 2-year mouse study, an increased incidence of malignant lymphoma was seen at doses of 0.25 mg/kg and higher, representing an approximate 6-fold margin based on the human systemic exposure (AUC) at a daily dose of
0.5 mg.

Fingolimod was neither mutagenic nor clastogenic in animal studies.

Fingolimod had no effect on sperm count/motility or on fertility in male and female rats up to the highest dose tested (10 mg/kg), representing an approximate 150-fold margin based on human systemic exposure (AUC) at a daily dose of 0.5 mg.

Fingolimod was teratogenic in the rat when given at doses of 0.1 mg/kg or higher. The most common foetal visceral malformations included persistent truncus arteriosus and ventricular septum defect.
The teratogenic potential in rabbits could not be fully assessed, however an increased embryo-foetal mortality was seen at doses of 1.5 mg/kg and higher, and a decrease in viable foetuses as well as foetal growth retardation was seen at 5 mg/kg.

In rats, F1 generation pup survival was decreased in the early postpartum period at doses that did not cause maternal toxicity. However, F1 body weights, development, behaviour, and fertility were not affected by treatment with fingolimod.

Fingolimod was excreted in milk of treated animals during lactation. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Environmental Risk Assessment (ERA)
A risk for the environment due to use of Gilenya by patients with relapsing multiple sclerosis is not expected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core:
Magnesium stearate
Mannitol

Capsule shell:
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

Printing ink:
Shellac (E904)
Dehydrated alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Purified water
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Dimethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister packs containing 7, 28 or 98 hard capsules or multipacks containing 84 (3 packs of 28) hard capsules.
PVC/PVDC/aluminium perforated unit dose blister packs containing 7x 1 hard capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm
Limited Frimley Business
Park Camberley GU16
7SR United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 March 2011
Date of latest renewal: 23 November 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

SmPC for Plegridy

1. NAME OF THE MEDICINAL PRODUCT

Plegridy 63 micrograms solution for injection in pre-filled syringe.
Plegridy 94 micrograms solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 63 microgram pre-filled syringe contains 63 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.
Each 94 microgram pre-filled syringe contains 94 micrograms of peginterferon beta-1a* in 0.5 mL solution for injection.

The dose indicates the quantity of the interferon beta-1a moiety of peginterferon beta-1a without consideration of the PEG moiety attached.
*The active substance, peginterferon beta-1a, is a covalent conjugate of interferon beta-1a, produced in Chinese Hamster Ovary cells, with 20,000 Dalton (20 kDa) methoxy poly(ethyleneglycol) using an O-2-methylpropionaldehyde linker.

The potency of this medicinal product should not be compared to the one of another pegylated or non-pegylated protein of the same therapeutic class. For more information see section 5.1.

Excipients with known effect

Each syringe contains 0.13 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear and colourless solution with pH 4.5-5.1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plegridy is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis.

Efficacy of Plegridy has been demonstrated over placebo. Direct comparative data for Plegridy versus non-pegylated interferon beta or data on efficacy of Plegridy after switching from a non-pegylated interferon beta are not available. This should be considered when switching patients between pegylated and non-pegylated interferons. Please refer also to section 5.1.

Posology

The recommended dosage of Plegridy is 125 micrograms injected subcutaneously every 2 weeks (14 days).

Treatment initiation

It is generally recommended that patients start treatment with 63 micrograms at dose 1 (on day 0), increasing to 94 micrograms at dose 2 (on day 14), reaching the full dose of 125 micrograms by dose 3 (on day 28) and continuing with the full dose (125 micrograms) every 2 weeks (14 days) thereafter (see Table 1). An Initiation Pack is available containing the first 2 doses (63 micrograms and 94 micrograms).

Table 1: Titration schedule at initiation

Dose	Time*	Amount (micrograms)	Syringe label
Dose 1	Day 0	63	Orange
Dose 2	Day 14	94	Blue
Dose 3	Day 28	125 (full dose)	Grey

*Dosed every 2 weeks (14 days)

Dose titration at the initiation of treatment may help to ameliorate flu-like symptoms that can occur at treatment initiation with interferons. Prophylactic and concurrent use of anti-inflammatory, analgesic and/or antipyretic treatments may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment (see section 4.8).

If a dose is missed, it should be administered as soon as possible.

- If 7 days or more to the next planned dose: Patients should administer their missed dose immediately. Treatment can then continue with the next scheduled dose as planned.
- If less than 7 days to the next planned dose: Patients should begin a new 2 week dosing schedule starting from when they administer their missed dose. A patient should not administer two doses of Plegridy within 7 days of each other.

Special populations

Elderly population

The safety and efficacy of Plegridy in patients over the age of 65 have not been sufficiently studied due to the limited number of such patients included in clinical trials.

Renal impairment

No dosage adjustments are necessary in patients with renal impairment based on study data in mild, moderate, and severe renal impairment and end stage renal disease (see sections 4.4 and 5.2).

Hepatic impairment

Plegridy has not been studied in patients with hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of Plegridy in children and adolescents aged 0 to 18 years have not been established in multiple sclerosis. No data are available.

Method of administration

Plegridy is for subcutaneous use.

It is recommended that a healthcare professional trains patients in the proper technique for self-administering subcutaneous injections using the pre-filled syringe. Patients should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections include abdomen, arm, and thigh.

Each Plegridy pre-filled syringe is provided with the needle pre-attached. Pre-filled syringes are for single use only and should be discarded after use.

Precautions to be taken before handling or administering the medicinal product

Once removed from the refrigerator, Plegridy should be allowed to warm to room temperature (about 30 minutes) prior to injection. External heat sources such as hot water must not be used to warm Plegridy.

Plegridy pre-filled syringe must not be used if the liquid is coloured, cloudy, or contains floating particles. The liquid in the syringe must be clear and colourless.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or peginterferon or to any of the excipients listed in section 6.1.
- Initiation of treatment in pregnancy (see section 4.6).
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Hepatic injury

Elevated serum hepatic transaminase levels, hepatitis, autoimmune hepatitis and rare cases of severe hepatic failure have been reported with interferon beta medicinal products. Elevations in hepatic enzymes have been observed with the use of Plegridy. Patients should be monitored for signs of hepatic injury (see section 4.8).

Depression

Plegridy should be administered with caution to patients with previous depressive disorders (see section 4.3). Depression occurs with increased frequency in the multiple sclerosis population and in association with interferon use. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy with Plegridy should be considered (see section 4.8).

Hypersensitivity reactions

Serious hypersensitivity reactions have been reported as a rare complication of treatment with interferon beta, including Plegridy. Peginterferon beta-1a should be discontinued if serious hypersensitivity reactions occur (see section 4.8).

Injection site reactions

Injection site reactions, including injection site necrosis, have been reported with the use of subcutaneous interferon beta. To minimise the risk of injection site reactions patients should be instructed in the use of an aseptic injection technique. The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred. If the patient experiences any break in the skin, which may be accompanied by swelling or drainage of fluid from the injection site, the patient should be advised to speak with their doctor. One patient treated with Plegridy in clinical trials experienced an injection site necrosis. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis (see section 4.8).

Decreased peripheral blood counts

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and severe thrombocytopenia, have been reported in patients receiving interferon beta. Cytopenias, including rare severe neutropenia and thrombocytopenia, have been observed in patients treated with Plegridy. Patients should be monitored for symptoms or signs of decreased peripheral blood counts (see section 4.8).

Renal and urinary disorders

Nephrotic syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta

products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Plegridy should be considered.

Severe renal impairment

Caution should be used when administering Plegridy to patients with severe renal impairment.

Thrombotic microangiopathy (TMA)

Cases of TMA, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Plegridy is recommended.

Laboratory abnormalities

Laboratory abnormalities are associated with the use of interferons. In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. aspartate aminotransferase (AST), alanine aminotransaminase (ALT)), are recommended prior to initiation and at regular intervals following introduction of Plegridy therapy and then periodically thereafter in the absence of clinical symptoms.

Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Hypothyroidism and hyperthyroidism have been observed with the use of interferon beta products. Regular thyroid function tests are recommended in patients with a history of thyroid dysfunction or as clinically indicated.

Seizure

Plegridy should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see section 4.8).

Cardiac disease

Worsening of cardiac disease has been reported in patients receiving interferon beta. The incidence of cardiovascular events was similar between Plegridy (125 micrograms every 2 weeks) and placebo treatment groups (7% in each group). No serious cardiovascular events were reported in patients who received Plegridy in the ADVANCE study. Nevertheless, patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmia should be monitored for worsening of their cardiac condition, particularly during initiation of treatment.

Immunogenicity

Patients may develop antibodies to Plegridy. Data from patients treated up to 2 years with Plegridy suggests that less than 1% (5/715) developed persistent-neutralising antibodies to the interferon beta-1a portion of peginterferon beta-1a. Neutralising antibodies have the potential to reduce clinical efficacy. However, the development of antibodies against the interferon moiety of peginterferon beta-1a had no discernible impact on safety or clinical efficacy, although the analysis was limited by the low immunogenicity incidence.

3% of patients (18/681) developed persistent antibodies to the PEG moiety of peginterferon beta-1a. In the clinical study conducted, the development of antibodies against the PEG moiety of peginterferon beta-1a had no discernible impact on safety, or clinical efficacy (including annualised relapse rate, MRI lesions, and disability progression).

Hepatic impairment

Caution should be used and close monitoring considered when administering Plegridy to patients with severe hepatic impairment. Patients should be monitored for signs of hepatic injury and caution exercised when interferons are used concomitantly with other medicinal products associated with hepatic injury (see sections 4.8 and 5.2).

Sodium content

Each syringe contains less than 1 mmol (23 mg) sodium and is therefore considered essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The clinical studies indicate that multiple sclerosis patients can receive Plegridy and corticosteroids during relapses. Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Plegridy is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. some classes of antiepileptics and antidepressants.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential have to take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking Plegridy she should be informed of the potential hazards and discontinuation of therapy should be considered (see section 5.3). In patients with a high relapse rate before treatment started, the risk of a severe relapse following discontinuation of Plegridy in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Pregnancy

There is limited information on the use of Plegridy in pregnancy. Available data indicates that there may be an increased risk of spontaneous abortion. Initiation of treatment is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether peginferferon beta-1a is secreted in human milk. Because of the potential for serious adverse reactions in breast-feeding infants, a decision should be made either to discontinue breast-feeding or Plegridy therapy.

Fertility

There are no data on the effects of peginferferon beta-1a on human fertility. In animals, anovulatory effects were observed at very high doses (see section 5.3). No information is available on the effects of peginterferon beta-1a on male fertility in animals.

4.7 Effects on ability to drive and use machines

Central nervous system-related adverse events associated with the use of interferon beta might influence the patient's ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The most common adverse drug reactions (ADR) (at a higher incidence than placebo) for Plegridy

125 micrograms subcutaneously every 2 weeks were injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia. The most commonly reported adverse reaction leading to discontinuation in patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks was influenza-like illness (<1%).

Tabulated list of adverse reactions

In clinical studies 1468 patients received Plegridy for up to 177 weeks (overall exposure equivalent to 1932 person-years). 1093 patients received at least 1 year, and 415 patients have received at least 2 years of treatment with Plegridy. The experience in the randomised, uncontrolled phase (year 2) of the ADVANCE study and in the 2 year safety extension study ATTAIN was consistent with the experience in the 1 year placebo-controlled phase of the ADVANCE study.

The table summarizes ADRs (incidence above placebo and with a reasonable possibility of causality) from 512 patients treated with Plegridy 125 micrograms subcutaneously every 2 weeks and 500 patients who received placebo for up to 48 weeks.

The ADRs are presented as MedDRA preferred terms under the MedDRA System Organ Class. The incidence of the adverse reactions below are expressed according to the following categories:

Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1, 000 to <1/100)
- Rare (≥1/10, 000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Adverse reaction	Frequency category
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*	Rare
Immune system disorders	Hypersensitivity reaction	Uncommon
Nervous system disorders	Headache	Very common
	Seizure	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary arterial hypertension†	Not known
Gastrointestinal disorders	Nausea	Common
	Vomiting	
Skin and subcutaneous tissue disorders	Pruritus	Common
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	Very common
	Arthralgia	
Renal and urinary disorders	Nephrotic syndrome, glomerulosclerosis	Rare
General disorders and administration site conditions	Injection site erythema	Very common
	Influenza like illness	
	Pyrexia	
	Chills	
	Injection site pain	
	Asthenia	
	Injection site pruritus	
	Hyperthermia	Common
	Pain	
	Injection site oedema	
	Injection site warmth	
	Injection site haematoma	
	Injection site rash	
	Injection site swelling	

MedDRA System Organ Class	Adverse reaction	Frequency category
	Injection site discolouration	
	Injection site inflammation	
	Injection site necrosis	Rare
Investigations	Body temperature increased	Common
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Gamma-glutamyl-transferase increased	
	Haemoglobin decreased	
	Platelet count decreased	Uncommon
	Decreases in white blood cell counts	Common
Psychiatric disorders	Depression	Common

*Class label for interferon beta products (see section 4.4).

+ Class label for interferon products, see below *Pulmonary arterial hypertension*

Description of selected adverse reactions

Flu-like symptoms

Influenza-like illness was experienced by 47% of patients receiving Plegridy 125 micrograms every 2 weeks and 13% of patients receiving placebo. The incidence of flu-like symptoms (e.g. influenza-like illness, chills, hyperpyrexia, musculoskeletal pain, myalgia, pain, pyrexia) was highest at the initiation of treatment and generally decreased over the first 6 months. Of the patients who reported flu-like symptoms 90% reported them as mild or moderate in severity. None were considered serious in nature. Less than 1% of patients who received Plegridy during the placebo controlled phase of the ADVANCE study discontinued treatment due to flu-like symptoms.

Injection site reactions

Injection site reactions (e.g. injection site erythema, pain, pruritus, or oedema) were reported by 66% of patients who received Plegridy 125 micrograms every 2 weeks compared to 11% of patients receiving placebo. Injection site erythema was the most commonly reported injection site reaction. Of the patients who experienced injection site reactions 95% reported them as mild or moderate in severity. One patient out of 1468 patients who received Plegridy in clinical studies experienced an injection site necrosis which resolved with standard medical treatment.

Hepatic transaminase abnormalities

The incidence of hepatic transaminase increases was greater in patients receiving Plegridy compared to placebo. The majority of enzyme elevations were <3 times the upper limit of normal (ULN). Elevations of alanine aminotransferase and aspartate aminotransferase (>5 times ULN), were reported in 1% and <1% of placebo-treated patients and 2% and <1% of patients treated with Plegridy respectively. Elevations of serum hepatic transaminases combined with elevated bilirubin were observed in two patients who had pre-existing liver test abnormalities prior to receiving Plegridy in the clinical trials. Both cases resolved following discontinuation of Plegridy.

Haematological disorders

Decreases in white blood cell counts of $<3.0 \times 10^9$/L were observed in 7% of patients receiving Plegridy and in 1% receiving placebo. Mean white blood cell counts remained within normal limits in patients treated with Plegridy. Decreases in white blood cell counts were not associated with an increased risk of infections or serious infections. The incidence of potentially clinically significant decreases in lymphocyte counts
($<0.5 \times 10^9$/L) (<1%), neutrophil counts ($\leqslant 1.0 \times 10^9$/L) (<1%) and platelet counts ($\leqslant 100 \times 10^9$/L) ($\leqslant$ 1%) was similar in Plegridy-treated patients compared to placebo-treated patients. Two serious cases were reported in
patients treated with Plegridy: one patient (<1%) experienced severe thrombocytopenia (platelet count

<10 x 10^9/L), another patient (<1%) experienced severe neutropenia (neutrophil count <0.5 x 10^9/L). In both patients, cell counts recovered after discontinuation of Plegridy. Slight decreases in mean red blood cell (RBC) counts were observed in Plegridy treated patients. The incidence of potentially clinically significant decreases in RBC counts (<3.3 x 10^{12}/L) was similar in Plegridy-treated patients compared to placebo-treated patients.

Hypersensitivity reactions

Hypersensitivity events were reported in 16% of patients treated with Plegridy 125 micrograms every 2 weeks and 14% of patients who received placebo. Less than 1% of Plegridy treated patients experienced a serious hypersensitivity event (e.g. angioedema, urticaria) and they recovered promptly after treatment with anti-histamines and/or corticosteroids.

Depression and suicidal ideation

The overall incidence of adverse events related to depression and suicidal ideation was 8% for both Plegridy 125 micrograms every 2 weeks and placebo groups. The incidence of serious events related to depression and suicidal ideation were similar and low (<1%) in both Plegridy 125 micrograms every 2 weeks and placebo-treated patients.

Seizure

The incidence of seizure events was low and comparable in patients receiving Plegridy (125 micrograms every 2 weeks) and placebo (<1% in each group).

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of over-dose, patients may be hospitalized for observation and appropriate supportive treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents; immunostimulants; interferons
ATC code: L03AB13

Plegridy is an interferon beta-1a conjugated with a single, linear molecule of 20,000 Da methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde (20 kDa mPEG-O-2-methylpropionaldehyde) at a degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 44 kDa of which the protein moiety constitutes approximately 23 kDa.

Mechanism of action

A definitive mechanism of action of peginterferon beta-1a in multiple sclerosis (MS) is not known. Plegridy binds to the type I interferon receptor on the surface of cells and elicits a cascade of intracellular events leading to the regulation of interferon-responsive gene expression. Biological effects that may be mediated by Plegridy include up-regulation of anti-inflammatory cytokines (e.g. IL-4, IL-10, IL-27), down-regulation

of pro-inflammatory cytokines (e.g. IL-2, IL-12, IFN-γ, TNF-α) and inhibiting the migration of activated T cells across the blood brain barrier; however additional mechanisms may be involved. Whether the mechanism of action of Plegridy in MS is mediated by the same pathway(s) as the biological effects described above is not known because the pathophysiology of MS is only partially understood.

Pharmacodynamic effects

Plegridy is interferon beta-1a conjugated to a single, linear 20 kDa methoxy poly(ethyleneglycol) molecule at the alpha-amino group of the N-terminal amino acid residue.

Interferons are a family of naturally occurring proteins that are induced by cells in response to biological and chemical stimuli, and mediate numerous cellular responses that have been classified as antiviral, antiproliferative, and immunomodulatory in nature. The pharmacological properties of Plegridy are consistent with those of interferon beta-1a and are believed to be mediated by the protein portion of the molecule.

Pharmacodynamic responses were evaluated by measuring the induction of interferon-responsive genes including those encoding 2′,5′-oligoadenylate synthetase (2′,5′-OAS), myxovirus resistance protein A (MxA), and several chemokines and cytokines, as well as neopterin (D-erythro-1, 2, 3,- trihydroxypropylpterin), a product of the interferon-inducible enzyme, GTP-cyclohydrolase I. Gene induction in healthy human subjects was greater in terms of peak level and exposure (area under the effect curve) for Plegridy compared to non-pegylated interferon beta-1a (IM) when both were given at the same dose by activity (6 MIU). The duration of this response was sustained and prolonged for Plegridy, with elevations detected up to 15 days compared to 4 days for non-pegylated interferon beta-1a. Increased concentrations of neopterin were observed in both healthy subjects and multiple sclerosis patients treated with Plegridy, with a sustained and prolonged elevation over 10 days compared to 5 days observed for
non-pegylated interferon beta-1a. Neopterin concentrations return to baseline after the two week dosing interval.

Clinical efficacy and safety

The efficacy and safety of Plegridy was assessed from the placebo-controlled first year of a 2 year randomised, double-blind, clinical study in patients with relapsing remitting multiple sclerosis (the ADVANCE study). 1512 patients were randomised to and dosed with 125 micrograms Plegridy injected subcutaneously every 2 (n=512) or 4 (n=500) weeks versus placebo (n=500).

The primary endpoint was the annualised relapse rate (ARR) over 1 year. The study design and patient demographics are presented in Table 2.

No data are available from clinical efficacy/safety studies directly comparing pegylated with non-pegylated interferon beta-1a, or from patients switching between non-pegylated and pegylated interferon.

Table 2: Study design

Study design	
Disease history	Patients with RRMS, with at least 2 relapses within the prior 3 years, and 1 relapse in the prior year, with an EDSS score of ≤5.0
Follow-up	1 year
Study population	83% treatment-naïve patients 47% ≥2 relapses in prior year 38% at least 1 Gd+ lesion at baseline 92% ≥9 T2 lesions baseline 16% EDSS ≥4 17% previously treated
Baseline characteristics	
Mean age (years)	37
Mean/Median disease duration (years)	3.6/2.0
Mean number of relapses within the past 3 years	2.5

Mean EDSS score at baseline	2.5

EDSS: Expanded Disability Status Scale
Gd+: Gadolinium-enhancing

Plegridy every 2 weeks significantly reduced the annualized relapse rate (ARR) by 36% compared to placebo (p=0.0007) at one year (Table 3) with consistent reductions of the ARR noted in subgroups defined by demographic and baseline disease characteristics. Plegridy also significantly reduced the risk of relapse by 39% (p=0.0003), the risk of sustained disability progression confirmed at 12 weeks by 38% (p=0.0383) and
at 24 weeks (post-hoc analysis) by 54% (p=0.0069), the number of new or newly enlarging T2 lesions by 67% (p<0.0001), the number of Gd-enhancing lesions by 86% (p<0.0001) and the number of new T1 hypointense lesions compared to placebo by 53% (p<0.0001). A treatment effect was observed as early as 6 months, with Plegridy 125 micrograms every 2 weeks demonstrating a 61% reduction (p<0.0001) in new or newly enlarging T2 lesions as compared with placebo. Across relapse and MRI endpoints Plegridy
125 micrograms every two weeks showed a numerically greater treatment effect over the Plegridy every four weeks dosing regimen at year 1.

Results over 2 years confirmed that efficacy was maintained beyond the placebo controlled first year of the study. Patients exposed to Plegridy every 2 weeks showed statistically significant reductions compared to patients exposed to Plegridy every 4 weeks over 2 years in a post-hoc analysis for endpoints including ARR (24%, p=0.0209), the risk of relapse (24%, p=0.0212), the risk of disability progression with 24 week confirmation (36%, p=0.0459), and MRI endpoints (new/enlarging T2 60%, Gd+ 71%, and new T1 hypointense lesions 53%; p<0.0001 for all).

Results for this study are shown in Table 3.

Table 3: Clinical and MRI results

	Placebo	Plegridy 125 micrograms every 2 weeks	Plegridy 125 micrograms every 4 weeks
Clinical endpoints			
N	500	512	500
Annualised relapse rate	0.397	0.256	0.288
Rate ratio 95% CI P-value		0.64 0.50 – 0.83 p=0.0007	0.72 0.56 – 0.93 p=0.0114
Proportion of subjects relapsed	0.291	0.187	0.222
HR 95% CI P-value		0.61 0.47 – 0.80 p=0.0003	0.74 0.57 – 0.95 p=0.020
Proportion with 12 week confirmed disability progression*	0.105	0.068	0.068
HR 95% CI P-value		0.62 0.40 – 0.97 p=0.0383	0.62 0.40 – 0.97 p=0.0380
Proportion with 24-week confirmed disability progression*	0.084	0.040	0.058
HR 95% CI P-value		0.46 (0.26 – 0.81) p=0.0069	0.67 (0.41 – 1.10) p=0.1116
MRI endpoints			
N	476	457	462
Mean [Median] no. of new or newly enlarging T2 hyperintense lesions (range)	13.3 [6.0] (0 – 148)	4.1 [1.0] (0 – 69)	9.2 [3.0] (0 – 113)
Lesion mean ratio (95% CI) P-value		0.33 (0.27, 0.40) p⩽0.0001	0.72 (0.60, 0.87) p=0.0008
Mean [Median] no. of Gd-enhancing lesions (range)	1.4^ [0.0] (0 – 39)	0.2 [0.0] (0 – 13)	0.9 [0.0] (0 – 41)
% reduction vs placebo P-value		86 p<0.0001	36 p=0.0738

Mean [Median] no. of new T1 hypointense lesions (range)	3.8 [1.0] (0 – 56)	1.8 [0.0] (0 – 39)	3.1 [1.0] (0 – 61)
% reduction vs placebo P-value		53 p<0.0001	18 0.0815

HR: Hazard ratio
CI: Confidence interval
* Sustained disability progression was defined as at least a 1 point increase from baseline EDSS ⩾ 1 or 1.5 point increase for patients with baseline EDSS of 0, sustained for 12 / 24 weeks.
^n=477

Patients who failed previous MS treatment were not included in the study.

Subgroups of patients with higher disease activity were defined by relapse and MRI criteria as reported below, with the following efficacy results:

- For patients with ⩾1 relapse in the previous year and ⩾9 T2 lesions or ⩾1 Gd+ lesion (n=1401), the annual relapse rate at 1 year was 0.39 for placebo, 0.29 for Plegridy every 4 weeks and 0.25 for Plegridy every 2 weeks.

  Results in this subgroup were consistent with those in the overall population.

- For patients with ⩾2 relapses in the previous year and at least 1 Gd+ lesion (n=273), the annual relapse rate at 1 year was 0.47 for placebo, 0.35 for Plegridy every 4 weeks, and 0.33 for Plegridy every 2 weeks.

  Results in this subgroup were numerically consistent with those in the overall population but not statistically significant.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Plegridy in one or more subsets of the paediatric population in treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The serum half-life of peginterferon beta-1a is prolonged compared with non-pegylated interferon beta-1a. Serum concentration of peginterferon beta-1a was dose-proportional in the range of 63 to 188 micrograms as observed in a single dose and a multiple dose study in healthy subjects. Pharmacokinetics observed in multiple sclerosis patients were consistent with those seen in healthy subjects.

Absorption

Following subcutaneous administration of peginterferon beta-1a in multiple sclerosis patients, the peak concentration was reached between 1 to 1.5 days post-dose. The observed C_{max} (mean±SE) was 280 ± 79 pg/mL following repeat dosing of 125 micrograms every two weeks.
Subcutaneous peginterferon beta-1a resulted in approximately 4-, 9-, and 13-fold higher exposure (AUC_{168h}) values and approximately 2-, 3.5- and 5-fold higher C_{max}, following single doses of 63 (6 MIU),
125 (12 MIU), and 188 (18 MIU) micrograms respectively, compared to intramuscular administration of 30 (6 MIU) micrograms non-pegylated beta-1a.

Distribution

Following repeat dosing of 125 micrograms doses every two weeks by subcutaneous administration, the volume of distribution uncorrected for bioavailability (mean±SE) was 481 ± 105 L.

Biotransformation and elimination

Urinary (renal) clearance is postulated to be a major excretory pathway for Plegridy. The process of covalently conjugating a PEG moiety to a protein can alter the in vivo properties of the unmodified protein, including decreased renal clearance and decreased proteolysis thus extending the circulating half-life. Accordingly, the half-life ($t_{1/2}$) of peginterferon beta-1a is approximately 2-fold longer than non-pegylated interferon beta-1a in healthy volunteers. In multiple sclerosis patients, the $t_{1/2}$ (mean±SE) of peginterferon beta-1a was 78 ± 15 hours at steady state. The mean steady state clearance of peginterferon beta-1a was 4.1 ± 0.4 L/hr.

Special populations

Renal impairment

A single-dose study in healthy subjects and subjects with various degrees of renal impairment (mild, moderate, and severe renal impairment as well as subjects with end state renal disease) showed a fractional increase in AUC (13-62%) and C_{max} (42-71%) in subjects with mild (estimated glomerular filtration rate 50 to $\leqslant$80 mL/min/1.73m^2), moderate (estimated glomerular filtration rate 30 to <50 mL/min/1.73m^2), and severe (estimated glomerular filtration rate <30 mL/min/1.73m^2) renal impairment, compared to subjects with normal renal function (estimated glomerular filtration rate >80 mL/min/1.73m^2). Subjects with end stage renal disease requiring 2-3 times haemodialysis weekly showed similar AUC and C_{max} as compared to subjects with normal renal function. Each haemodialysis reduced peginterferon beta-1a concentration by approximately 24%, suggesting that haemodialysis partially removes peginterferon beta-1a from systemic circulation.

Hepatic function

The pharmacokinetics of peginterferon beta-1a has not been evaluated in patients with hepatic insufficiency.

Elderly patients

Clinical experience in patients aged above 65 years is limited. However, results from a population pharmacokinetic analysis (in patients up to 65 years) suggest that age does not impact peginterferon beta-1a clearance.

Gender

No gender effect on the pharmacokinetics of peginterferon beta-1a was found in a population pharmacokinetic analysis.

Race

Race had no effect on the pharmacokinetics of peginterferon beta-1a in a population pharmacokinetic analysis.

5.3 Preclinical safety data

Toxicity

Following repeated subcutaneous administration of peginterferon beta-1a in rhesus monkeys at doses up to 400-fold (based on exposure, AUC) the recommended therapeutic dose; no effects other than the known mild pharmacological responses by rhesus monkeys to interferon beta-1a were observed after the first and second weekly dose. Repeated dose toxicology studies were limited to 5 weeks as exposure was greatly diminished from 3 weeks onwards, due to the formation of anti-drug antibodies by rhesus monkeys to human interferon beta-1a. Therefore, the long-term safety of chronic administration of Plegridy to patients cannot be assessed on the basis of these studies.

Mutagenesis

Peginterferon beta-1a was not mutagenic when tested in an in vitro bacterial reverse mutation (Ames) test and was not clastogenic in an in vitro assay in human lymphocytes.

Carcinogenesis

Peginterferon beta-1a has not been tested for carcinogenicity in animals. Based on the known pharmacology of interferon beta-1a and clinical experience with interferon beta, the potential for carcinogenicity is expected to be low.

Reproductive Toxicity
Peginterferon beta-1a has not been tested for reproductive toxicity in pregnant animals. Fertility and developmental studies in rhesus monkeys have been carried out with non-pegylated interferon beta-1a. At very high doses, anovulatory and abortifacient effects were observed in animals. No information is available on the potential effects of peginterferon beta-1a on male fertility. Upon repeated dosing with peginterferon beta-1a of sexually mature female monkeys, effects on menstrual cycle length and progesterone levels were observed. Reversibility of the effects on menstrual cycle length was demonstrated. The validity of extrapolating these non-clinical data to humans is unknown.

Data from studies with other interferon beta compounds did not show teratogenic potential. The available information on the effects of interferon beta-1a in the peri- and postnatal periods is limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid, glacial
L-Arginine hydrochloride
Polysorbate 20
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Plegridy can be stored at room temperature (up to 25°C) for up to 30 days as long as it is stored away from light. If Plegridy is at room temperature for a total of 30 days, it should be used or discarded. If it is not clear if Plegridy has been stored at room temperature 30 days or more, it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C
to 8°C). Do not freeze.
Store in the original package in order to protect from light.

See section 6.3 for additional information on storage at room temperature (up to 25°C).

6.5 Nature and contents of container

1 mL pre-filled syringe made of glass (Type I) with a bromobutyl rubber stopper and thermoplastic and polypropylene rigid needle shield, containing 0.5 mL of solution.

The Plegridy Initiation Pack contains 1x 63 micrograms pre-filled syringe (orange labelled syringe, 1st dose) and 1x 94 micrograms pre-filled syringe (blue labelled syringe, 2nd dose) in sealed plastic trays.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BIOGEN IDEC LIMITED
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/934/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

SmPC for Rebif

1. NAME OF THE MEDICINAL PRODUCT

Rebif 22 micrograms solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.5 mL) contains 22 micrograms (6 MIU*) of interferon beta-1a**.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon beta-1a standard which is calibrated against the current international NIH standard (GB-23-902-531).
** produced in Chinese hamster ovary Cells (CHO-K1) by recombinant DNA technology.

Excipient with known effect: 2.5 mg benzyl alcohol
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.
Clear to opalescent solution, with pH 3.5 to 4.5 and osmolarity 250 to 450 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rebif is indicated for the treatment of relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years (see section 5.1).

Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

Rebif is available in three strengths: 8.8 micrograms, 22 micrograms and 44 micrograms. For patients initiating treatment with Rebif, Rebif 8.8 micrograms and Rebif 22 micrograms are available in a pack that corresponds to the patient needs for the first month of therapy.

Posology

The recommended posology of Rebif is 44 micrograms given three times per week by subcutaneous injection. A lower dose of 22 micrograms, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose in view of the treating specialist.

When first starting treatment with Rebif, the dose should be gradually escalated in order to allow tachyphylaxis to develop thus reducing adverse reactions. The Rebif initiation package corresponds to the patient needs for the first month of treatment.

Paediatric population
No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, a paediatric retrospective cohort study collected safety data with Rebif from medical records in children (n=52) and adolescents (n=255). The results of this study suggest that the safety profile in children (2 to 11 years old) and in adolescents (12 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms subcutaneous three times per week is similar to that seen in adults.

The safety and efficacy of Rebif in children below 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

Rebif is administered by subcutaneous injection. Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is advised to decrease flu-like symptoms associated with Rebif administration.

At the present time, it is not known for how long patients should be treated. Safety and efficacy with Rebif have not been demonstrated beyond 4 years of treatment. It is recommended that patients should be evaluated at least every second year in the 4-year period after initiation of treatment with Rebif and a decision for longer term treatment should then be made on an individual basis by the treating physician.

4.3 Contraindications

- Initiation of treatment in pregnancy (see section 4.6).
- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Patients should be informed of the most frequent adverse reactions associated with interferon beta administration, including symptoms of the flu-like syndrome (see section 4.8). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.

Thrombotic microangiopathy (TMA)

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Rebif is recommended.

Depression and suicidal ideation

Rebif should be administered with caution to patients with previous or current depressive disorders in particular to those with antecedents of suicidal ideation (see section 4.3). Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with Rebif should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Rebif and treated appropriately. Cessation of therapy with Rebif should be considered (see sections 4.3 and 4.8).

Seizure disorders

Rebif should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with antiepileptics (see sections 4.5 and 4.8).

Cardiac disease

Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation of therapy with interferon beta-1a.

Symptoms of the flu-like syndrome associated with interferon beta-1a therapy may prove stressful to patients with cardiac conditions.

Injection site necrosis

Injection site necrosis (ISN) has been reported in patients using Rebif (see section 4.8). To minimise the risk of injection site necrosis patients should be advised to:

- use an aseptic injection technique,
- rotate the injection sites with each dose.

The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred.

If the patient experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the patient should be advised to consult with their physician before continuing injections with Rebif. If the patient has multiple lesions, Rebif should be discontinued until healing has occurred. Patients with single lesions may continue provided that the necrosis is not too extensive.

Hepatic dysfunction

In clinical trials with Rebif, asymptomatic elevations of hepatic transaminases (particularly alanine aminotransferase (ALT)) were common and 1-3% of patients developed elevations of hepatic transaminases above 5 times the upper limit of normal (ULN). In the absence of clinical symptoms, serum ALT levels should be monitored prior to the start of therapy, at months 1, 3 and 6 on therapy and periodically thereafter. Dose reduction of Rebif should be considered if ALT rises above 5 times the ULN, and gradually re-escalated when enzyme levels have normalized. Rebif should be initiated with caution in patients with a history of significant liver disease, clinical evidence of active liver disease, alcohol abuse or increased serum ALT (>2.5 times ULN). Treatment with Rebif should be stopped if icterus or other clinical symptoms of liver dysfunction appear.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. The mechanism for the rare symptomatic hepatic dysfunction is not known. No specific risk factors have been identified.

Renal and urinary disorders

Nephrotic syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon-beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Rebif should be considered.

Laboratory abnormalities

Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, liver enzyme monitoring and complete and differential blood cell counts and platelet counts are recommended at regular intervals (1, 3 and 6 months) following introduction of Rebif therapy and then periodically thereafter in the absence of clinical symptoms.

Thyroid disorders

Patients being treated with Rebif may occasionally develop new or worsening thyroid abnormalities. Thyroid function testing is recommended at baseline and if abnormal, every 6-12 months following initiation of therapy. If tests are normal at baseline, routine testing is not needed but should be performed if clinical findings of thyroid dysfunction appear (see section 4.8).

Severe renal or hepatic failure and severe myelosuppression

Caution should be used, and close monitoring considered when administering interferon beta-1a to patients with severe renal and hepatic failure and to patients with severe myelosuppression.

Neutralising antibodies

Serum neutralising antibodies against interferon beta-1a may develop. The precise incidence of antibodies is as yet uncertain. Clinical data suggest that after 24 to 48 months of treatment with Rebif 22 micrograms, approximately 24% of patients develop persistent serum antibodies to interferon beta-1a. The presence of antibodies has been shown to attenuate the pharmacodynamic response to interferon beta-1a (beta-2 microglobulin and neopterin). Although the clinical significance of the induction of antibodies has not been fully elucidated, the development of neutralising antibodies is associated with reduced efficacy on clinical and MRI variables. If a patient responds poorly to therapy with Rebif, and has neutralising antibodies, the treating physician should reassess the benefit/risk ratio of continued Rebif therapy.

The use of various assays to detect serum antibodies and differing definitions of antibody positivity limits the ability to compare antigenicity among different products.

Other forms of multiple sclerosis

Only sparse safety and efficacy data are available from non-ambulatory patients with multiple sclerosis. Rebif has not yet been investigated in patients with primary progressive multiple sclerosis and should not be used in these patients.

Benzyl alcohol

This medicinal product contains 2.5 mg benzyl alcohol per dose.
It must not be given to premature babies or neonates. It may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with interferon beta-1a in humans.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when administering Rebif in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. antiepileptics and some classes of antidepressants.

The interaction of Rebif with corticosteroids or adrenocorticotropic hormone (ACTH) has not been studied systematically. Clinical studies indicate that multiple sclerosis patients can receive Rebif and corticosteroids or ACTH during relapses.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking Rebif she should be informed of the potential hazards and discontinuation of therapy should be considered (see section 5.3). In patients with a high relapse rate before treatment has started, the risk of a severe relapse following discontinuation of Rebif in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Pregnancy

There is limited information on the use of Rebif in pregnancy. Available data indicates that there may be an increased risk of spontaneous abortion. Therefore initiation of treatment is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether Rebif is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, a decision should be made whether to discontinue breast-feeding or Rebif therapy.

Fertility

The effects of Rebif on fertility have not been investigated.

4.7 Effects on ability to drive and use machines

Central nervous system-related adverse events associated with the use of interferon beta (e.g. dizziness) might influence the patient's ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The highest incidence of adverse reactions associated with Rebif therapy is related to flu-like syndrome. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment. Approximately 70% of patients treated with Rebif can expect to experience the typical interferon flu-like syndrome within the first six months after starting treatment. Approximately 30% of patients will also experience reactions at the injection site, predominantly mild inflammation or erythema. Asymptomatic increases in laboratory parameters of hepatic function and decreases in white blood cells are also common.

The majority of adverse reactions observed with interferon beta-1a are usually mild and reversible, and respond well to dose reductions. In case of severe or persistent undesirable effects, the dose of Rebif may be temporarily lowered or interrupted, at the discretion of the physician.

List of adverse reactions

The adverse reactions presented have been identified from clinical studies as well as from post- marketing reports *(an asterisk [*] indicates adverse reactions identified during post-marketing surveillance)*. The following definitions apply to the frequency terminology used hereafter: very common (≥1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common:	Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare:	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon:	Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism

Immune system disorders

Rare:	Anaphylactic reactions*

Hepatobiliary disorders

Very common:	Asymptomatic transaminase
increase Common:	Severe elevations in transaminases
Uncommon:	Hepatitis with or without icterus*
Rare:	Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common:	Depression, insomnia
Rare:	Suicide attempt*

Nervous system disorders

Very common:	Headache
Uncommon:	Seizures*
Frequency not known:	Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon:	Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*

Vascular disorders

Uncommon:	Thromboembolic events*

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea*
Not known:	Pulmonary arterial hypertension* (class label for interferon beta products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common:	Diarrhoea, vomiting, nausea

Skin and subcutaneous tissue disorders

Common:	Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon:	Urticaria*
Rare:	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common:	Myalgia, arthralgia
Rare:	Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare:	Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

The administration of interferons has been associated with anorexia, dizziness, anxiety, arrhythmias, vasodilation and palpitation, menorrhagia and metrorrhagia.
An increased formation of auto-antibodies may occur during treatment with interferon beta.

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of overdose, patients should be hospitalised for observation and appropriate supportive treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Interferons, ATC code: L03AB07

Interferons are a group of endogenous glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties.

Rebif (interferon beta-1a) shares the same amino acid sequence with endogenous human interferon beta. It is produced in mammalian cells (Chinese hamster ovary) and is therefore glycosylated like the natural protein.

Regardless of the route of dosing, pronounced pharmacodynamic changes are associated with the administration of Rebif. After a single dose, intracellular and serum activity of 2'5'OAS synthetase and serum concentrations of beta-2 microglobulin and neopterin increase within 24 hours, and start to decline within 2 days. Intramuscular and subcutaneous administrations produce fully superimposable responses. After repeated subcutaneous administration every 48 hours for 4 doses, these biological responses remain elevated, with no signs of tolerance development.

Biological response markers (e.g., 2',5'-OAS activity, neopterin and beta 2-microglobulin) are induced by interferon beta-1a following subcutaneous doses administered to healthy volunteer subjects. Time to peak concentrations following a single subcutaneous injection were 24 to 48 hours for neopterin, beta-2-microglobulin and 2'5'OAS, 12 hours for MX1 and 24 hours for OAS1 and OAS2 gene expression. Peaks of similar height and time were observed for most of these markers after first and sixth administration.

The precise mechanism of action of Rebif in multiple sclerosis is still under investigation.

Relapsing-remitting multiple sclerosis

The safety and efficacy of Rebif has been evaluated in patients with relapsing-remitting multiple sclerosis at doses ranging from 11 to 44 micrograms (3-12 million IU), administered subcutaneously three times per week. At licensed posology, Rebif 22 micrograms has been demonstrated to decrease the incidence (approximately 30% over 2 years) and severity of clinical relapses in patients with at least 2 exacerbations in the previous 2 years and with an EDSS of 0-5.0 at entry. The proportion of patients with disability progression, as defined by at least one point increase in EDSS confirmed three months later, was reduced from 39% (placebo) to 30% (Rebif 22 micrograms). Over 4 years, the reduction in the mean exacerbation rate was 22% in patients treated with Rebif 22 micrograms, and 29% in patients treated with Rebif 44 micrograms group compared with a group of patients treated with placebo for 2 years and then either Rebif 22 or Rebif 44 micrograms for 2 years.

Secondary progressive multiple sclerosis

In a 3-year study in patients with secondary progressive multiple sclerosis (EDSS 3-6.5) with evidence of clinical progression in the preceding two years and who had not experienced relapses in the preceding 8 weeks, Rebif had no significant effect on progression of disability, but relapse rate was reduced by approximately 30%. If the patient population was divided into 2 subgroups (those with and those without relapses in the 2-year period prior to study entry), there was no effect on disability in patients without relapses, but in patients with relapses, the proportion with progression in disability at the end of the study was reduced from 70% (placebo) to 57% (Rebif 22 micrograms and 44 micrograms combined). These results obtained in a subgroup of patients a posteriori should be interpreted cautiously.

Primary progressive multiple sclerosis

Rebif has not yet been investigated in patients with primary progressive multiple sclerosis, and should not be used in these patients.

5.2 Pharmacokinetic properties

Absorption
In healthy volunteers after intravenous administration, interferon beta-1a exhibits a sharp multi-exponential decline, with serum levels proportional to the dose. Subcutaneous and intramuscular administrations of Rebif produce equivalent exposure to interferon beta.

Distribution
Following repeated subcutaneous injections of 22 and 44 micrograms doses of Rebif maximum concentrations were typically observed after 8 hours, but this was highly variable.

Elimination
After repeated subcutaneous doses in healthy volunteers, the main PK parameters (AUC_{tau} and C_{max}) increased proportional to the increased in dose from 22 micrograms to 44 micrograms. The estimated apparent half-life is 50 to 60 hours, which is in line with the accumulation observed after multiple dosing.

Metabolism
Interferon beta-1a is mainly metabolised and excreted by the liver and the kidneys.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, and genotoxicity.

Rebif has not been investigated for carcinogenicity.

A study on embryo/foetal toxicity in monkeys showed no evidence of reproductive disturbances. Based on observations with other alpha and beta interferons, an increased risk of abortions cannot be excluded. No information is available on the effects of the interferon beta-1a on male fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Poloxamer 188
L-methionine
Benzyl alcohol
Sodium acetate
Acetic acid for pH adjustment
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C) away from the cooling element. Do not freeze. Store in the original package in order to protect from light.

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

6.5 Nature and contents of container

One mL type 1 glass syringe, with a stainless steel needle, containing 0.5 mL solution. Rebif 22 micrograms is available as a package of 1, 3 or 12 syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution for injection in a pre-filled syringe is ready for use. It may also be administered with a suitable auto-injector.

For single use only. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Serono Europe Limited
56, Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/001
EU/1/98/063/002
EU/1/98/063/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998
Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

SmPC for Tecfidera

1. NAME OF THE MEDICINAL PRODUCT

Tecfidera 120 mg gastro-resistant hard capsules
Tecfidera 240 mg gastro-resistant hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tecfidera 120mg capsule
Each capsule contains 120 mg dimethyl fumarate.

Tecfidera 240mg capsule
Each capsule contains 240 mg dimethyl fumarate
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant hard capsule
Tecfidera 120mg capsule
Green and white gastro-resistant hard capsule printed with 'BG-12 120 mg'.

Tecfidera 240mg capsule
Green gastro-resistant hard capsule printed with 'BG-12 240 mg'

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tecfidera is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (please refer to section 5.1 for important information on the populations for which efficacy has been established).

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

Posology

The starting dose is 120 mg twice a day. After 7 days, the dose is increased to the recommended dose of 240 mg twice a day.

Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 240 mg twice a day should be resumed.

Tecfidera should be taken with food (see section 5.2). For those patients who may experience flushing or gastrointestinal adverse reactions, taking Tecfidera with food may improve tolerability (see sections 4.4, 4.5 and 4.8).

Elderly

Clinical studies of Tecfidera had limited exposure to patients aged 55 years and above, and did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients (see section 5.2). Based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly.

Renal and hepatic impairment

Tecfidera has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology studies, no dose adjustments are needed (see section 5.2). Caution should be used when treating patients with severe renal or severe hepatic impairment (see section 4.4).

Paediatric population

The safety and efficacy of Tecfidera in children and adolescents aged 10 to 18 years have not been established. No data are available. There is no relevant use of Tecfidera in children aged less than 10 years for the indication of relapsing remitting multiple sclerosis.

Method of administration

For oral use.

The capsule or its contents should not be crushed, divided, dissolved, sucked or chewed as the enteric-coating of the microtablets prevents irritant effects on the gut.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Blood/laboratory tests

Changes in renal and hepatic laboratory tests have been seen in clinical trials in subjects treated with Tecfidera (see section 4.8). The clinical implications of these changes are unknown. Assessments of renal function (e.g. creatinine, blood urea nitrogen and urinalysis) and hepatic function (e.g. ALT and AST) are recommended prior to treatment initiation, after 3 and 6 months of treatment, every 6 to 12 months thereafter and as clinically indicated.

Patients treated with Tecfidera may develop severe prolonged lymphopaenia (see section 4.8). Tecfidera has not been studied in patients with pre-existing low lymphocyte counts and caution should be exercised when treating these patients. Prior to initiating treatment with Tecfidera, a current complete blood count, including lymphocytes, must be performed. If lymphocyte count is found to be below the normal range, thorough assessment of possible causes should be completed prior to initiation of treatment with Tecfidera.

After starting therapy, complete blood counts, including lymphocytes, must be performed every 3 months.

Consider interruption of Tecfidera in patients with lymphocyte counts $<0.5x10^9$/L persisting for more than 6 months. The benefit/risk balance of the therapy should be reconsidered in discussion with the patient in the context of other therapeutic options available. Clinical factors, evaluation of any laboratory and imaging investigations could be included as part of this re-consideration. If treatment is continued despite a persistent lymphocyte count $< 0.5x10^9$/L, enhanced vigilance is recommended (see also subsection on PML).

Lymphocyte counts should be followed until recovery. Upon recovery and in the absence of alternative treatment options, decisions about whether or not to restart Tecfidera after treatment discontinuation should be based on clinical judgement.

MR imaging

Before initiating treatment with Tecfidera, a baseline MRI should be available (usually within 3 months) as a reference. The need for further MRI scanning should be considered in accordance with national and local recommendations. MRI imaging may be considered as part of increased vigilance in patients considered at increased risk of PML. In case of clinical suspicion of PML, MRI should be performed immediately for diagnostic purposes.

Progressive Multifocal Leukoencephalopathy (PML)

PML cases have occurred with Tecfidera and other products containing fumarates in the setting of severe and prolonged lymphopenia. PML is an opportunistic infection caused by John-Cunningham virus (JCV), which may be fatal or result in severe disability. PML can only occur in the presence of a JCV infection. If

JCV testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of anti-JCV antibody test has not been studied in Tecfidera treated patients. It should also be noted that a negative anti JCV antibody test (in the presence of normal lymphocyte counts) does not preclude the possibility of subsequent JCV infection.

Prior treatment with immunosuppressive or immunomodulating therapies

No studies have been performed evaluating the efficacy and safety of Tecfidera when switching patients from other disease modifying therapies to Tecfidera. The contribution of prior immunosuppressive therapy to the development of PML in Tecfidera treated patients is unknown. When switching patients from another disease modifying therapy to Tecfidera, the half-life and mode of action of the other therapy should be considered in order to avoid an additive immune effect while at the same time, reducing the risk of reactivation of MS.

A complete blood count is recommended prior to initiating Tecfidera and regularly during treatment (see Blood/laboratory tests above).

Tecfidera can generally be started immediately after discontinuation of interferon or glatiramer acetate.

Severe renal and hepatic impairment

Tecfidera has not been studied in patients with severe renal or severe hepatic impairment and caution should, therefore, be used in these patients (see section 4.2).

Severe active gastrointestinal disease

Tecfidera has not been studied in patients with severe active gastrointestinal disease and caution should, therefore, be used in these patients.

Flushing

In clinical trials, 34% of Tecfidera treated patients experienced flushing. In the majority of patients who experienced flushing, it was mild or moderate in severity.

In clinical trials, 3 patients out of a total of 2,560 patients treated with Tecfidera experienced serious flushing symptoms that were probable hypersensitivity or anaphylactoid reactions. These events were not life-threatening, but led to hospitalisation. Prescribers and patients should be alert to this possibility in the event of severe flushing reactions (see sections 4.2, 4.5 and 4.8).

Infections

In phase III placebo-controlled studies, the incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar in patients treated with Tecfidera or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts $<0.8x10^9$/L or $<0.5x10^9$/L. During treatment with Tecfidera in the MS placebo controlled trials, mean lymphocyte counts decreased by approximately 30% from baseline at one year and then plateaued (see section 4.8). Mean lymphocyte counts remained within normal limits. Patients with lymphocyte counts $<0.5x10^9$/L were observed in <1% of patients treated with placebo and 6% of patients treated with Tecfidera. In clinical studies (both controlled and uncontrolled), 2% of patients experienced lymphocyte counts $<0.5 \times 10^9$/L for at least six months. In these patients, the majority of lymphocyte counts remained $<0.5 \times 10^9$/L with continued therapy.

If therapy is continued in the presence of severe prolonged lymphopenia, the risk of an opportunistic infection, including Progressive Multifocal Leukoencephalopathy (PML) cannot be ruled out (please refer to subsection PML above for further details).

If a patient develops a serious infection, suspending treatment with Tecfidera should be considered and the benefits and risks should be reassessed prior to re-initiation of therapy. Patients receiving Tecfidera should be instructed to report symptoms of infections to a physician. Patients with serious infections should not start treatment with Tecfidera until the infection(s) is resolved.

4.5 Interaction with other medicinal products and other forms of interaction

Tecfidera has not been studied in combination with anti-neoplastic or immunosuppressive therapies and caution should, therefore, be used during concomitant administration. In multiple sclerosis clinical studies, the concomitant treatment of relapses with a short course of intravenous corticosteroids was not associated with a clinically relevant increase of infection.

Vaccination during treatment with Tecfidera has not been studied. It is not known whether treatment with Tecfidera might reduce the effectiveness of some vaccines. Live vaccines might carry an increased risk of clinical infection and should not be given to patients treated with Tecfidera unless, in exceptional cases, this potential risk is considered to be outweighed by the risk to the individual of not vaccinating.

During treatment with Tecfidera, simultaneous use of other fumaric acid derivatives (topical or systemic) should be avoided.

In humans, dimethyl fumarate is extensively metabolised by esterases before it reaches the systemic circulation and further metabolism occurs through the tricarboxylic acid cycle, with no involvement of the cytochrome P450 (CYP) system. Potential drug interaction risks were not identified from *in vitro* CYP-inhibition and induction studies, a p-glycoprotein study, or studies of the protein binding of dimethyl fumarate and monomethyl fumarate (a primary metabolite of dimethyl fumarate).

Commonly used medicinal products in patients with multiple sclerosis, intramuscular interferon beta-1a and glatiramer acetate, were clinically tested for potential interactions with dimethyl fumarate and did not alter the pharmacokinetic profile of dimethyl fumarate.

Administration of 325 mg (or equivalent) non-enteric coated acetylsalicylic acid, 30 minutes prior to Tecfidera, over 4 days of dosing, did not alter the pharmacokinetic profile of Tecfidera and reduced the occurrence and severity of flushing in a healthy volunteer study. However, long term use of acetylsalicylic acid is not recommended for the management of flushing. Potential risks associated with acetylsalicylic acid therapy should be considered prior to co-administration with Tecfidera. (see sections 4.2, 4.4 and 4.8).

Concurrent therapy with nephrotoxic medicinal products (such as aminoglycosides, diuretics, NSAIDs or lithium) may increase the potential of renal adverse reactions (e.g. proteinuria) in patients taking Tecfidera (see section 4.8).

Consumption of moderate amounts of alcohol did not alter exposure to Tecfidera and was not associated with an increase in adverse reactions. Consumption of large quantities of undiluted strong alcoholic drinks (more than 30% alcohol by volume) may lead to increased dissolution rates of Tecfidera and, therefore, may increase the frequency of gastrointestinal adverse reactions.

In vitro CYP induction studies did not demonstrate an interaction between Tecfidera and oral contraceptives. *In vivo* interaction studies have not been performed with oral contraceptives. Even though an interaction is not expected, non-hormonal contraceptive measures should be considered with Tecfidera (see section 4.6).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of dimethyl fumarate in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Tecfidera is not recommended during pregnancy and in women of childbearing potential not using appropriate contraception (see section 4.5). Tecfidera should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether dimethyl fumarate or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Tecfidera therapy. The benefit of breast-feeding for the child and the benefit of therapy for the woman should be taken into account.

Fertility

There are no data on the effects of Tecfidera on human fertility. Data from preclinical studies do not suggest that dimethyl fumarate would be associated with an increased risk of reduced fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been conducted.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (incidence ⩾10%) for patients treated with Tecfidera were flushing and gastrointestinal events (i.e. diarrhoea, nausea, abdominal pain, abdominal pain upper). Flushing and gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing and gastrointestinal events, these events may continue to occur intermittently throughout treatment with Tecfidera. The most commonly reported adverse reactions leading to discontinuation (incidence >1%) in patients treated with Tecfidera were flushing (3%) and gastrointestinal events (4%).

In placebo-controlled and uncontrolled clinical studies, a total of 2,468 patients have received Tecfidera and been followed for periods up to 4 years with an overall exposure equivalent to 3,588 person-years. Approximately 1,056 patients have received more than 2 years of treatment with Tecfidera. The experience in uncontrolled clinical trials is consistent with the experience in the placebo-controlled clinical trials.

Tabulated summary of adverse reactions

Adverse reactions, which were more frequently reported in Tecfidera versus placebo-treated patients, are presented in the table below. These data were derived from 2 pivotal Phase 3 placebo-controlled, double-blind clinical trials with a total of 1,529 patients treated with Tecfidera and for up to 24 months with an overall exposure of 2,371 person-years (see section 5.1). The frequencies described in the table below are based on 769 patients treated with Tecfidera 240 mg twice a day and 771 patients treated with placebo.

The adverse reactions are presented as MedDRA preferred terms under the MedDRA System Organ Class. The incidence of the adverse reactions below are expressed according to the following categories:

- Very common (⩾1/10)
- Common (⩾1/100 to <1/10)
- Uncommon (⩾1/1, 000 to <1/100)
- Rare (⩾1/10, 000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

MedDRA System Organ Class	Adverse reaction	Frequency category
Infections and infestations	Gastroenteritis	Common
	Progressive multifocal leukoencephalopathy (PML)	Not known
Blood and lymphatic system disorders	Lymphopenia	Common
	Leucopenia	Common
Immune system disorders	Hypersensitivity	Uncommon
Nervous system disorders	Burning sensation	Common
Vascular disorders	Flushing	Very common
	Hot flush	Common

MedDRA System Organ Class	Adverse reaction	Frequency category
Gastrointestinal disorders	Diarrhoea	Very common
	Nausea	Very common
	Abdominal pain upper	Very common
	Abdominal pain	Very common
	Vomiting	Common
	Dyspepsia	Common
	Gastritis	Common
	Gastrointestinal disorder	Common
Skin and subcutaneous tissue disorders	Pruritus	Common
	Rash	Common
	Erythema	Common
Renal and urinary disorders	Proteinuria	Common
General disorders and administration site conditions	Feeling hot	Common
Investigations	Ketones measured in urine	Very common
	Albumin urine present	Common
	Aspartate aminotransferase increased	Common
	Alanine aminotransferase increased	Common
	White blood cell count decreased	Common

Description of selected adverse reactions

Flushing

In the placebo-controlled studies, the incidence of flushing (34% versus 4%) and hot flush (7% versus 2%) was increased in patients treated with Tecfidera compared to placebo, respectively.

Flushing is usually described as flushing or hot flush, but can include other events (e.g. warmth, redness, itching, and burning sensation). Flushing events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience flushing, these events may continue to occur intermittently throughout treatment with Tecfidera. In patients with flushing, the majority had flushing events that were mild or moderate in severity. Overall, 3% of patients treated with Tecfidera discontinued due to flushing. The incidence of serious flushing, which may be characterised by generalised erythema, rash and/or pruritus, was seen in less than 1% of patients treated with Tecfidera (see sections 4.2, 4.4 and 4.5).

Gastrointestinal

The incidence of gastrointestinal events (e.g. diarrhoea [14% versus 10%], nausea [12% versus 9%], upper abdominal pain [10% versus 6%], abdominal pain [9% versus 4%], vomiting [8% versus 5%] and dyspepsia [5% versus 3%]) was increased in patients treated with Tecfidera compared to placebo, respectively. Gastrointestinal events tend to begin early in the course of treatment (primarily during the first month) and in patients who experience gastrointestinal events, these events may continue to occur intermittently throughout treatment with Tecfidera. In the majority of patients who experienced gastrointestinal events, it was mild or moderate in severity. Four per cent (4%) of patients treated with Tecfidera discontinued due to gastrointestinal events. The incidence of serious gastrointestinal events, including gastroenteritis and gastritis, was seen in 1% of patients treated with Tecfidera (see section 4.2).

Hepatic transaminases

In placebo-controlled studies, elevations of hepatic transaminases were observed. The majority of patients with elevations had hepatic transaminases that were <3 times the upper limit of normal (ULN). The increased incidence of elevations of hepatic transaminases in patients treated with Tecfidera relative to placebo was primarily seen during the first 6 months of treatment. Elevations of alanine aminotransferase and aspartate aminotransferase ⩾3 times ULN, respectively, were seen in 5% and 2% of patients treated with placebo and 6% and 2% of patients treated with Tecfidera. There were no elevations in transaminases ⩾3 times ULN with concomitant elevations in total bilirubin

>2 times ULN. Discontinuations due to elevated hepatic transaminases were <1% and similar in patients treated with Tecfidera or placebo.

Renal

In placebo-controlled studies, the incidence of proteinuria was higher in patients treated with Tecfidera (9%) compared to placebo (7%). The overall incidence of renal and urinary adverse events was similar for Tecfidera and placebo-treated patients. There were no reports of serious renal failure. On urinalysis, the percentage of patients with protein values of 1+ or greater was similar for Tecfidera (43%) and placebo-treated patients (40%). Typically, laboratory observations of proteinuria were not progressive. Compared to patients treated with placebo, estimated glomerular filtration rate (eGFR) was observed to increase in patients treated with Tecfidera, including those patients with 2 consecutive occurrences of proteinuria (⩾1+).

Haematological

In the placebo-controlled studies, most patients (>98%) had normal lymphocyte values prior to initiating treatment. Upon treatment with Tecfidera, mean lymphocyte counts decreased over the first year with a subsequent plateau. On average, lymphocyte counts decreased by approximately 30% of baseline value. Mean and median lymphocyte counts remained within normal limits. Lymphocyte counts $<0.5x10^9$/l were observed in <1% of patients treated with placebo and 6% of patients treated with Tecfidera. A lymphocyte count $<0.2x10^9$/l was observed in 1 patient treated with Tecfidera and in no patients treated with placebo.The incidence of infections (58% versus 60%) and serious infections (2% versus 2%) was similar in patients treated with placebo or Tecfidera. An increased incidence of infections and serious infections was not observed in patients with lymphocyte counts $<0.8x10^9$/l or $<0.5x10^9$/l. PML has occurred in the setting of severe and prolonged lymphopenia (please refer to section 4.4). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.

Laboratory abnormalities

In the placebo-controlled studies, measurement of urinary ketones (1+ or greater) was higher in patients treated with Tecfidera (45%) compared to placebo (10%). No untoward clinical consequences were observed in clinical trials.

Levels of 1,25-dihydroxyvitamin D decreased in Tecfidera treated patients relative to placebo (median percentage decrease from baseline at 2 years of 25% versus 15%, respectively) and levels of parathyroid hormone (PTH) increased in Tecfidera treated patients relative to placebo (median percentage increase from baseline at 2 years of 29% versus 15%, respectively). Mean values for both parameters remained within normal range.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX09

Mechanism of action
The mechanism by which dimethyl fumarate exerts therapeutic effects in multiple sclerosis is not fully understood. Preclinical studies indicate that dimethyl fumarate pharmacodynamic responses appear to be primarily mediated through activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional

pathway. Dimethyl fumarate has been shown to up regulate Nrf2-dependent antioxidant genes in patients (e.g. NAD(P)H dehydrogenase, quinone 1; [NQO1]).

Pharmacodynamic effects

Effects on the immune system

In preclinical and clinical studies, Tecfidera demonstrated anti-inflammatory and immunomodulatory properties. Dimethyl fumarate and monomethyl fumarate, the primary metabolite of dimethyl fumarate, significantly reduced immune cell activation and subsequent release of pro-inflammatory cytokines in response to inflammatory stimuli in preclinical models. In clinical studies with psoriasis patients, dimethyl fumarate affected lymphocyte phenotypes through a down-regulation of pro- inflammatory cytokine profiles (T_H1, T_H17), and biased towards anti-inflammatory production (T_H2). Dimethyl fumarate demonstrated therapeutic activity in multiple models of inflammatory and neuroinflammatory injury. In Phase 3 studies, upon treatment with Tecfidera mean lymphocyte counts decreased on average by approximately 30% of their baseline value over the first year with a subsequent plateau.

Effect on cardiovascular system

Single doses of 240 mg or 360 mg Tecfidera did not have any effect on the QTc interval when compared to placebo in a QTc study.

Clinical efficacy and safety

Two, 2-year, randomised, double-blind, placebo controlled studies [Study 1 (DEFINE) with 1234 subjects and Study 2 (CONFIRM) with 1417 subjects] of subjects with relapsing-remitting multiple sclerosis (RRMS) were performed. Subjects with progressive forms of MS were not included in these studies. Efficacy (see table below) and safety were demonstrated in subjects with Expanded Disability Status Scale (EDSS) scores ranging from 0 to 5 inclusive, who had experienced at least 1 relapse during the year prior to randomisation, or, within 6 weeks of randomisation had a brain Magnetic Resonance Imaging (MRI) demonstrating at least one gadolinium-enhancing (Gd+) lesion. Study 2 contained a rater-blinded (i.e. study physician/ investigator assessing the response to study treatment was blinded) reference comparator of glatiramer acetate.

In Study 1, patients had the following median baseline characteristics: age 39 years, disease duration 7.0 years, EDSS score 2.0. In addition, 16% of patients had an EDSS score >3.5, 28% had ⩾2 relapses in the prior year and 42% had previously received other approved MS treatments. In the MRI cohort 36% of patients entering the study had Gd+ lesions at baseline (mean number of Gd+ lesions 1.4).

In Study 2, patients had the following median baseline characteristics: age 37 years, disease duration 6.0 years, EDSS score 2.5. In addition, 17% of patients had an EDSS score >3.5, 32% had ⩾2 relapses in the prior year and 30% had previously received other approved MS treatments. In the MRI cohort 45% of patients entering the study had Gd+ lesions at baseline (mean number of Gd+ lesions 2.4).

Compared to placebo, subjects treated with Tecfidera had a clinically meaningful and statistically significant reduction on: the primary endpoint in Study 1, proportion of subjects relapsed at 2 years; and the primary endpoint in Study 2, annualised relapse rate at 2 years.

The annualised relapse rate for glatiramer acetate and placebo was 0.286 and 0.401 respectively in Study 2, corresponding to a reduction of 29% (p=0.013), which is consistent with approved prescribing information.

	DEFINE		**CONFIRM**		
	Placebo	**Tecfidera 240 mg twice a day**	**Placebo**	**Tecfidera 240 mg twice a day**	**Glatiramer acetate**
Clinical Endpoints[a]					
No. subjects	408	410	363	359	350
Annualised relapse rate	0.364	0.172***	0.401	0.224***	0.286*
Rate ratio		0.47		0.56	0.71

	DEFINE		CONFIRM		
	Placebo	**Tecfidera 240 mg twice a day**	**Placebo**	**Tecfidera 240 mg twice a day**	**Glatiramer acetate**
(95% CI)		(0.37, 0.61)		(0.42, 0.74)	(0.55, 0.93)
Proportion relapsed	0.461	0.270***	0.410	0.291**	0.321**
Hazard ratio (95% CI)		0.51 (0.40, 0.66)		0.66 (0.51, 0.86)	0.71 (0.55, 0.92)
Proportion with 12-week confirmed disability progression	0.271	0.164**	0.169	0.128#	0.156#
Hazard ratio (95% CI)		0.62 (0.44, 0.87)		0.79 (0.52, 1.19)	0.93 (0.63, 1.37)
Proportion with 24 week confirmed disability progression	0.169	0.128#	0.125	0.078#	0.108#
Hazard ratio (95% CI)		0.77 (0.52, 1.14)		0.62 (0.37, 1.03)	0.87 (0.55, 1.38)
MRI Endpoints[b]					
No. subjects	165	152	144	147	161
Mean (median) number of new or newly enlarging T2 lesions over 2 years	16.5 (7.0)	3.2 (1.0)***	19.9 (11.0)	5.7 (2.0)***	9.6 (3.0)***
Lesion mean ratio (95% CI)		0.15 (0.10, 0.23)		0.29 (0.21, 0.41)	0.46 (0.33, 0.63)
Mean (median) number of Gd lesions at 2 years	1.8 (0)	0.1 (0)***	2.0 (0.0)	0.5 (0.0)***	0.7 (0.0)**
Odds ratio (95% CI)		0.10 (0.05, 0.22)		0.26 (0.15, 0.46)	0.39 (0.24, 0.65)
Mean (median) number of new T1 hypointense lesions over 2 years	5.7 (2.0)	2.0 (1.0)***	8.1 (4.0)	3.8 (1.0)***	4.5 (2.0)**
Lesion mean ratio (95% CI)		0.28 (0.20, 0.39)		0.43 (0.30, 0.61)	0.59 (0.42, 0.82)

[a]All analyses of clinical endpoints were intent-to-treat; [b]MRI analysis used MRI cohort
*P-value < 0.05; **P-value < 0.01; ***P-value < 0.0001; #not statistically significant

Efficacy in patients with high disease activity:
Consistent treatment effect on relapses in a subgroup of patients with high disease activity was observed, whilst the effect on time to 3-month sustained disability progression was not clearly established. Due to the design of the studies, high disease activity was defined as follows:

- Patients with 2 or more relapses in one year, and with one or more Gd-enhancing lesions on brain MRI (n=42 in DEFINE; n=51 in CONFIRM) or,
- Patients who have failed to respond to a full and adequate course (at least one year of treatment) of beta-interferon, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or patients having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years (n=177 in DEFINE; n=141 in CONFIRM).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Tecfidera in one or more subsets of the paediatric population in multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Orally administered Tecfidera (dimethyl fumarate) undergoes rapid presystemic hydrolysis by esterases and is converted to its primary metabolite, monomethyl fumarate, which is also active. Dimethyl fumarate is not quantifiable in plasma following oral administration of Tecfidera. Therefore, all pharmacokinetic analyses related to dimethyl fumarate were performed with plasma monomethyl fumarate concentrations. Pharmacokinetic data were obtained in subjects with multiple sclerosis and healthy volunteers.

Absorption

The T_{max} of monomethyl fumarate is 2 to 2.5 hours. As Tecfidera gastro-resistant hard capsules contain microtablets, which are protected by an enteric coating, absorption does not commence until they leave the stomach (generally less than 1 hour). Following 240 mg twice a day administered with food, the median peak (C_{max}) was 1.72 mg/l and overall (AUC) exposure was 8.02 h.mg/l in subjects with multiple sclerosis. Overall, C_{max} and AUC increased approximately dose- proportionally in the dose range studied (120 mg to 360 mg). In subjects with multiple sclerosis, two 240 mg doses were administered 4 hours apart as part of a three times a day dosing regimen. This resulted in a minimal accumulation of exposure yielding an increase in the median Cmax of 12% compared to the twice daily dosing (1.72 mg/l for twice daily compared to 1.93 mg/l for three times daily) with no safety implications.

Food does not have a clinically significant effect on exposure of dimethyl fumarate. However, Tecfidera should be taken with food due to improved tolerability with respect to flushing or gastrointestinal adverse events (see section 4.2).

Distribution

The apparent volume of distribution following oral administration of 240 mg Tecfidera varies between 60 L and 90 L. Human plasma protein binding of monomethyl fumarate generally ranges between 27% and 40%.

Biotransformation

In humans, dimethyl fumarate is extensively metabolised with less than 0.1% of the dose excreted as unchanged dimethyl fumarate in urine. It is initially metabolised by esterases, which are ubiquitous in the gastrointestinal tract, blood and tissues, before it reaches the systemic circulation. Further metabolism occurs through the tricarboxylic acid cycle, with no involvement of the cytochrome P450 (CYP) system. A single 240 mg ^{14}C-dimethyl fumarate dose study identified glucose as the predominant metabolite in human plasma. Other circulating metabolites included fumaric acid, citric acid and monomethyl fumarate. The downstream metabolism of fumaric acid occurs through the tricarboxylic acid cycle, with exhalation of CO_2 serving as a primary route of elimination.

Elimination

Exhalation of CO_2 is the primary route of dimethyl fumarate elimination accounting for 60% of the dose. Renal and faecal elimination are secondary routes of elimination, accounting for 15.5% and 0.9% of the dose respectively.

The terminal half-life of monomethyl fumarate is short (approximately 1 hour) and no circulating monomethyl fumarate is present at 24 hours in the majority of individuals. Accumulation of parent drug or monomethyl fumarate does not occur with multiple doses of dimethyl fumarate at the therapeutic regimen.

Linearity

Dimethyl fumarate exposure increases in an approximately dose proportional manner with single and multiple doses in the 120 mg to 360 mg dose range studied.

Pharmacokinetics in special patient groups

Based on the results of Analysis of Variance (ANOVA), body weight is the main covariate of exposure (by C_{max} and AUC) in relapsing remitting multiple sclerosis (RRMS) subjects, but did not affect safety and efficacy measures evaluated in the clinical studies.

Gender and age did not have a clinically significant impact on the pharmacokinetics of dimethyl fumarate. The pharmacokinetics in patients aged 65 and over has not been studied.

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191/Protocol MA30005, Version 5

Paediatric population

The pharmacokinetics in patients below the age of 18 has not been studied.

Renal impairment

Since the renal pathway is a secondary route of elimination for dimethyl fumarate accounting for less than 16% of the dose administered, evaluation of pharmacokinetics in individuals with renal impairment was not conducted.

Hepatic impairment

As dimethyl fumarate and monomethyl fumarate are metabolised by esterases, without the involvement of the CYP450 system, evaluation of phamacokinetics in individuals with hepatic impairment was not conducted.

5.3 Preclinical safety data

The adverse reactions described in the Toxicology and Reproduction toxicity sections below were not observed in clinical studies, but were seen in animals at exposure levels similar to clinical exposure levels.

Mutagenesis

Dimethyl fumarate and mono-methylfumarate were negative in a battery of *in vitro* assays (Ames, chromosomal aberration in mammalian cells). Dimethyl fumarate was negative in the *in vivo* micronucleus assay in the rat.

Carcinogenesis

Carcinogenicity studies of dimethyl fumarate were conducted for up to 2 years in mice and rats. Dimethyl fumarate was administered orally at doses of 25, 75, 200 and 400 mg/kg/day in mice, and at doses of 25, 50, 100, and 150 mg/kg/day in rats. In mice, the incidence of renal tubular carcinoma was increased at 75 mg/kg/day, at equivalent exposure (AUC) to the recommended human dose. In rats, the incidence of renal tubular carcinoma was increased at 100 mg/kg/day, approximately 3 times higher exposure than the recommended human dose. The relevance of these findings to human risk is unknown.

The incidence of squamous cell papilloma and carcinoma in the nonglandular stomach (forestomach) was increased at equivalent exposure to the recommended human dose in mice and below exposure to the recommended human dose in rats (based on AUC). The forestomach in rodents does not have a human counterpart.

Toxicology

Nonclinical studies in rodent, rabbits, and monkeys were conducted with a dimethyl fumarate suspension (dimethyl fumarate in 0.8% hydroxypropyl methylcellulose) administered by oral gavage. The chronic dog study was conducted with oral administration of the dimethyl fumarate capsule.

Kidney changes were observed after repeated oral administration of dimethyl fumarate in mice, rats, dogs, and monkeys. Renal tubule epithelial regeneration, suggestive of injury, was observed in all species. Renal tubular hyperplasia was observed in rats with life time dosing (2-year study). Cortical atrophy was observed in dogs and monkeys, and single cell necrosis and interstitial fibrosis were observed in monkeys that received daily oral doses of dimethyl fumarate for 12 months, at 6 times the recommended dose based on AUC. The relevance of these findings to humans is not known.

In the testes, degeneration of the seminiferous epithelium was seen in rats and dogs. The findings were observed at approximately the recommended dose in rats and 6 times the recommended dose in dogs (AUC basis). The relevance of these findings to humans is not known.

Findings in the forestomach of mice and rats consisted of squamous epithelial hyperplasia and hyperkeratosis; inflammation; and squamous cell papilloma and carcinoma in studies of 3 months or longer in duration. The forestomach of mice and rats does not have a human counterpart.

Reproduction toxicity

Oral administration of dimethyl fumarate to male rats at 75, 250, and 375 mg/kg/day prior to and during mating had no effects on male fertility up to the highest dose tested (at least 2 times the recommended dose on an AUC basis). Oral administration of dimethyl fumarate to female rats at 25, 100, and 250 mg/kg/day prior to and during mating, and continuing to Day 7 of gestation, induced reduction in the number of estrous stages per 14 days and increased the number of animals with prolonged diestrus at the highest dose tested (11 times the recommended dose on an AUC basis). However, these changes did not affect fertility or the number of viable fetuses produced.

Dimethyl fumarate has been shown to cross the placental membrane into fetal blood in rats and rabbits, with ratios of fetal to maternal plasma concentrations of 0.48 to 0.64 and 0.1 respectively. No malformations were observed at any dose of dimethyl fumarate in rats or rabbits. Administration of dimethyl fumarate at oral doses of 25, 100, and 250 mg/kg/day to pregnant rats during the period of organogenesis resulted in maternal adverse effects at 4 times the recommended dose on an AUC basis, and low fetal weight and delayed ossification (metatarsals and hindlimb phalanges) at 11 times the recommended dose on an AUC basis. The lower fetal weight and delayed ossification were considered secondary to maternal toxicity (reduced body weight and food consumption).

Oral administration of dimethyl fumarate at 25, 75, and 150 mg/kg/day to pregnant rabbits during organogenesis had no effect on embryo-fetal development and resulted in reduced maternal body weight at 7 times the recommended dose and increased abortion at 16 times the recommended dose, on an AUC basis.

Oral administration of dimethyl fumarate at 25, 100, and 250 mg/kg/day to rats during pregnancy and lactation resulted in lower body weights in the F1 offspring, and delays in sexual maturation in F1 males at 11 times the recommended dose on an AUC basis. There were no effects on fertility in the F1 offspring. The lower offspring body weight was considered secondary to maternal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Enteric-coated microtablets

Microcrystalline cellulose
Croscarmellose sodium
Talc
Silica, colloidal anhydrous
Magnesium stearate
Triethyl citrate
Methacrylic acid – methyl methacrylate copolymer (1:1)
Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%
Simeticone
Sodium laurilsulfate
Polysorbate 80

Capsule shell

Gelatin
Titanium dioxide (E171)
Brilliant Blue FCF
(E133)
Yellow iron oxide (E172)

Capsule print (black ink)
Shellac
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

120 mg gastro-resistant hard capsules: 4 years 240 mg gastro-resistant hard capsules: 3 years

6.4 Special precautions for storage

Do not store above 30ºC.
Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

120 mg capsules: 14 capsules in PVC/PE/PVDC-PVC aluminium blister packs.
240 mg capsules: 56 or 168 capsules in PVC/PE/PVDC-PVC aluminium blister packs. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biogen Idec Ltd
Innovation House
70 Norden Road
Maidenhead
Berkshire
SL6 4AY
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/837/001
EU/1/13/837/002
EU/1/13/837/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 January 2014

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

SmPC for Tysabri

1. NAME OF THE MEDICINAL PRODUCT

TYSABRI 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 20 mg of natalizumab.

When diluted (see section 6.6), the solution for infusion contains approximately 2.6 mg/ml of natalizumab.

Natalizumab is a recombinant humanised anti-α4-integrin antibody produced in a murine cell line by recombinant DNA technology.

Excipient with known effect

Each vial contains 2.3 mmol (or 52 mg) sodium. When diluted in 100 ml sodium chloride 9 mg/ml (0.9%) the medicinal product contains 17.7 mmol (or 406 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Colourless, clear to slightly opalescent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TYSABRI is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups:

- Adult patients aged 18 years and over with high disease activity despite treatment with a beta-interferon or glatiramer acetate.

  These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon or glatiramer acetate. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1 Gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

- Adult patients aged 18 years and over with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.2 Posology and method of administration

TYSABRI therapy is to be initiated and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI.

Patients treated with TYSABRI must be given the patient alert card and be informed about the risks of the medicinal product (see also package leaflet). After 2 years of treatment, patients should be re- informed about the risks of TYSABRI, especially the increased risk of Progressive Multifocal Leukoencephalopathy (PML), and should be instructed together with their caregivers on early signs and symptoms of PML.

Resources for the management of hypersensitivity reactions and access to MRI should be available.

Patients can switch directly from beta interferon or glatiramer acetate to natalizumab providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia. If there are signs of treatment-related abnormalities these must return to normal before treatment with natalizumab is started.

Some patients may have been exposed to immunosuppressive medicinal products (e.g. mitoxantrone, cyclophosphamide, azathioprine). These medicinal products have the potential to cause prolonged immunosuppression, even after dosing is discontinued. Therefore the physician must confirm that such patients are not immunocompromised before starting treatment with TYSABRI (see also section 4.4).

Posology

TYSABRI 300 mg is administered by intravenous infusion once every 4 weeks.

Continued therapy must be carefully reconsidered in patients who show no evidence of therapeutic benefit beyond 6 months

Data on the safety and efficacy of natalizumab at 2 years were generated from controlled, double– blind studies. After 2 years continued therapy should be considered only following a reassessment of the potential for benefit and risk. Patients should be re-informed about the risk factors for PML, like duration of treatment, immunosuppressant use prior to receiving TYSABRI and the presence of anti- John Cunningham virus (JCV) antibodies (see section 4.4.).

Readministration

The efficacy of re-administration has not been established, for safety see section 4.4.

Special populations

Elderly

TYSABRI is not recommended for use in patients aged over 65 due to a lack of data in this population.

Renal and hepatic impairment

Studies have not been conducted to examine the effects of renal or hepatic impairment.

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.

Paediatric population

TYSABRI is contraindicated in children and adolescents below the age of 18 years (see section 4.3).

Method of administration
TYSABRI is for intravenous use.

For instructions on dilution of the medicinal product before administration, see section 6.6.

After dilution (see section 6.6), the infusion is to be administered over approximately 1 hour and patients are to be observed during the infusion and for 1 hour after the completion of the infusion for signs and symptoms of hypersensitivity reactions.

TYSABRI must not be administered as a bolus injection.

4.3 Contraindications

Hypersensitivity to natalizumab or to any of the excipients listed in section 6.1.

Progressive multifocal leukoencephalopathy (PML).

Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies, e.g. mitoxantrone or cyclophosphamide, see also sections 4.4 and 4.8).

Combination with beta-interferons or glatiramer acetate.

Known active malignancies, except for patients with cutaneous basal cell carcinoma.
Children and adolescents below the age of 18 years.

4.4 Special warnings and precautions for use

Progressive Multifocal Leukoencephalopathy (PML)

Use of TYSABRI has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of TYSABRI treatment should be individually reconsidered by the specialist physician and the patient; patients must be monitored at regular intervals throughout and should be instructed together with their caregivers on early signs and symptoms of PML. JC virus also causes JCV granule cell neuronopathy (GCN) which has been reported in patients treated with TYSABRI. Symptoms of JCV GCN are similar to symptoms of PML (i.e. cerebellar syndrome).

The following risk factors are associated with an increased risk of PML.

- The presence of anti-JCV antibodies.
- Treatment duration, especially beyond 2 years. After 2 years all patients should be re-informed about the risk of PML with TYSABRI.
- Immunosuppressant use prior to receiving TYSABRI.

Patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of TYSABRI therapy, **and** have received prior immunosuppressant therapy) have a significantly higher risk of PML.

In anti-JCV antibody positive TYSABRI treated patients who have not used prior immunosuppressants the level of anti-JCV antibody response (index) is associated with the level of risk for PML.

In patients considered at high risk treatment with TYSABRI should only be continued if the benefits outweigh the risks. For the estimation of PML risk in the different patient subgroups, please refer to the Physician Information and Management Guidelines.

Anti-JCV antibody testing

Anti-JCV antibody testing provides supportive information for risk stratification of TYSABRI treatment. Testing for serum anti-JCV antibody prior to initiating TYSABRI therapy or in patients receiving the medicinal product with an unknown antibody status is recommended. Anti-JCV antibody negative patients may still be at risk of PML for reasons such as a new JCV infection, fluctuating antibody status or a false negative test result. Re-testing of anti-JCV antibody negative patients every 6 months is recommended. Retesting low index patients who have no history of prior immunosuppressant use every 6 months once they reach the 2 year treatment point is recommended.

The anti-JCV antibody assay (ELISA) should not be used to diagnose PML. Anti-JCV antibody testing should not be performed during, or for at least two weeks following, plasma exchange due to the removal of antibodies from the serum.

For further information on anti-JCV antibody testing please see Physician Information and Management Guidelines.

MRI screening for PML

Before initiation of treatment with TYSABRI, a recent (usually within 3 months) MRI should be available as a reference, and be repeated at least on a yearly basis. More frequent MRIs (e.g. on a 3 to 6 monthly basis) using an abbreviated protocol should be considered for patients at higher risk of PML. This includes:

- Patients who have all three risk factors for PML (i.e., are anti-JCV antibody positive **and** have received more than 2 years of TYSABRI therapy, **and** have received prior immunosuppressant therapy),

or

- Patients with a high anti-JCV antibody index who have received more than 2 years of TYSABRI therapy and without prior history of immunosuppressant therapy.

Current evidence suggests that the risk of PML is low at an index equal to or below 0.9 and increases substantially above 1.5 for patients who have been on treatment with TYSABRI for longer than 2 years (see the Physician Information and Management Guidelines for further information).

PML should be considered as a differential diagnosis in any MS patient taking TYSABRI presenting with neurological symptoms and/or new brain lesions in MRI. Cases of asymptomatic PML based on MRI and positive JCV DNA in the cerebrospinal fluid have been reported.

Physicians should refer to the Physician Information and Management Guidelines for further information on managing the risk of PML in TYSABRI-treated patients.

If PML or JCV GCN is suspected, further dosing must be suspended until PML has been excluded.

The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are typical of MS or possibly suggestive of PML or JCV GCN. If any doubt exists, further evaluation, including MRI scan preferably with contrast (compared with pre-treatment baseline MRI), CSF testing for JC Viral DNA and repeat neurological assessments, should be considered as described in the Physician Information and Management Guidelines (see educational guidance). Once the clinician has excluded PML and/or JCV GCN (if necessary, by repeating clinical, imaging and/or laboratory investigations if clinical suspicion remains), dosing of TYSABRI may resume.

The physician should be particularly alert to symptoms suggestive of PML or JCV GCN that the patient may not notice (e.g. cognitive, psychiatric symptoms or cerebellar syndrome). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

PML has been reported following discontinuation of TYSABRI in patients who did not have findings suggestive of PML at the time of discontinuation. Patients and physicians should continue to follow the same monitoring protocol and be alert for any new signs or symptoms that may be suggestive of PML for approximately 6 months following discontinuation of TYSABRI.

If a patient develops PML the dosing of TYSABRI must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML improved outcome has been seen.

PML and IRIS (Immune Reconstitution Inflammatory Syndrome)

IRIS occurs in almost all TYSABRI PML patients after withdrawal or removal of the medicinal product, e.g. by plasma exchange (see section 5.2). IRIS is thought to result from the restoration of immune function in patients with PML, which can lead to serious neurological complications and may be fatal. Monitoring for development of IRIS, which has occurred within days to several weeks after plasma exchange in TYSABRI treated patients with PML, and appropriate treatment of the associated inflammation during recovery from PML should be undertaken (see the Physician Information and Management Guidelines for further information).

Infections including other opportunistic infections

Other opportunistic infections have been reported with use of TYSABRI, primarily in patients with Crohn's disease who were immunocompromised or where significant co-morbidity existed, however increased risk of other opportunistic infections with use of the medicinal product in patients without these co-morbidities cannot currently be excluded. Opportunistic infections were also detected in MS patients treated with TYSABRI as a monotherapy (see section 4.8).

TYSABRI increases the risk of developing encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the postmarketing setting in multiple sclerosis patients receiving TYSABRI (see section 4.8). If herpes encephalitis or meningitis occurs, the medicinal product should be discontinued, and appropriate treatment for herpes encephalitis or meningitis should be administered.

Prescribers should be aware of the possibility that other opportunistic infections may occur during TYSABRI therapy and should include them in the differential diagnosis of infections that occur in TYSABRI-treated patients. If an opportunistic infection is suspected, dosing with TYSABRI is to be suspended until such infections can be excluded through further evaluations.

If a patient receiving TYSABRI develops an opportunistic infection, dosing of the medicinal product must be permanently discontinued.

Educational guidance

All physicians who intend to prescribe TYSABRI must ensure they are familiar with the Physician Information and Management Guidelines.

Physicians must discuss the benefits and risks of TYSABRI therapy with the patient and provide them with a Patient Alert Card. Patients should be instructed that if they develop any infection then they should inform their physician that they are being treated with TYSABRI.

Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment (see hypersensitivity).

Hypersensitivity

Hypersensitivity reactions have been associated with TYSABRI, including serious systemic reactions (see section 4.8). These reactions usually occurred during the infusion or up to 1 hour after completion of the infusion. The risk for hypersensitivity was greatest with early infusions and in patients re-exposed to TYSABRI following an initial short exposure (one or two infusions) and extended period (three months or more) without treatment. However, the risk of hypersensitivity reactions should be considered for every infusion administered.

Patients are to be observed during the infusion and for 1 hour after the completion of the infusion (see section 4.8). Resources for the management of hypersensitivity reactions should be available.

Discontinue administration of TYSABRI and initiate appropriate therapy at the first symptoms or signs of hypersensitivity.

Patients who have experienced a hypersensitivity reaction must be permanently discontinued from treatment with TYSABRI.

Concurrent or prior treatment with immunosuppressants

The safety and efficacy of TYSABRI in combination with other immunosuppressive and antineoplastic therapies have not been fully established. Concurrent use of these agents with TYSABRI may increase the risk of infections, including opportunistic infections, and is contraindicated (see section 4.3).

Patients with a treatment history of immunosuppressant medicinal products are at increased risk for PML. Care should be taken with patients who have previously received immunosuppressants to allow sufficient time for immune function recovery to occur. Physicians must evaluate each individual case to determine whether there is evidence of an immunocompromised state prior to commencing treatment with TYSABRI (see section 4.3).

In Phase 3 MS clinical trials, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection. Short courses of corticosteroids can be used in combination with TYSABRI.

Immunogenicity

Disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In these cases the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in efficacy of TYSABRI and an increased incidence of hypersensitivity reactions (see section 4.8).

Since patients who have received an initial short exposure to TYSABRI and then had an extended period without treatment are at a higher risk of developing anti-natalizumab antibodies and/or hypersensitivity upon redosing, the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after at least 6 weeks, the patient should not receive further treatment with TYSABRI.

Hepatic events

Spontaneous serious adverse reactions of liver injury have been reported during the post marketing phase. These liver injuries may occur at any time during treatment, even after the first dose. In some instances, the reaction reoccurred when TYSABRI was reintroduced. Some patients with a past medical history of an abnormal liver test have experienced an exacerbation of abnormal liver test while on TYSABRI. Patients should be monitored as appropriate for impaired liver function, and be instructed to contact their physician in case signs and symptoms suggestive of liver injury occur, such as jaundice and vomiting. In cases of significant liver injury TYSABRI should be discontinued.

Stopping TYSABRI therapy

If a decision is made to stop treatment with natalizumab, the physician needs to be aware that natalizumab remains in the blood, and has pharmacodynamic effects (e.g increased lymphocyte counts) for approximately 12 weeks following the last dose. Starting other therapies during this interval will result in a concomitant exposure to natalizumab. For medicinal products such as interferon and glatiramer acetate, concomitant exposure of this duration was not associated with safety risks in clinical trials. No data are available in MS patients regarding concomitant exposure with immunosuppressant medication. Use of these medicinal products soon after the discontinuation of natalizumab may lead to an additive immunosuppressive effect. This should be carefully considered on a case-by-case basis, and a wash-out period of natalizumab might be appropriate. Short courses of steroids used to treat relapses were not associated with increased infections in clinical trials.

Sodium content in TYSABRI

TYSABRI contains 2.3 mmol (or 52 mg) sodium per vial of medicinal product. When diluted in 100 ml sodium chloride 9 mg/ml (0.9%) this medicinal product contains 17.7 mmol (or 406 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

TYSABRI is contraindicated in combination with beta-interferons or glatiramer acetate (see section 4.3).

Immunisations

In a randomised, open label study of 60 patients with relapsing MS there was no significant difference in the humoral immune response to a recall antigen (tetanus toxoid) and only slightly slower and reduced humoral immune response to a neoantigen (keyhole limpet haemocyanin) was observed in patients who were treated with TYSABRI for 6 months compared to an untreated control group. Live vaccines have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

Data from clinical trials, a prospective pregnancy registry, post-marketing cases and available literature do not suggest an effect of TYSABRI exposure on pregnancy outcomes.

The completed prospective TYSABRI pregnancy registry contained 355 pregnancies with available outcomes. There were 316 live births, 29 of which were reported to have birth defects. Sixteen of the 29 were classified as major defects. The rate of defects corresponds to the defect rates reported in other pregnancy registries involving MS patients. There is no evidence of a specific pattern of birth defects with TYSABRI.

Cases from published literature reported transient mild to moderate thrombocytopenia and anaemia observed in infants born to women exposed to TYSABRI in their third trimester of pregnancy. Therefore, it is recommended that newborns of women exposed to the medicinal product during the third trimester of pregnancy are monitored for potential haematological abnormalities.

If a woman becomes pregnant while taking TYSABRI, discontinuation of the medicinal product should be considered. A benefit-risk evaluation of the use of TYSABRI during pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping the medicinal product.

Breast-feeding

Natalizumab is excreted in human milk. The effect of natalizumab on newborn/infants is unknown. Breast-feeding should be discontinued during treatment with TYSABRI.

Fertility

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility.
It is considered unlikely that natalizumab will affect fertility performance in humans following the maximum recommended dose.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with TYSABRI. However, given that dizziness has been commonly reported, patients who experience this adverse reaction should be advised not to drive or use machines until it has resolved.

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled trials in 1,617 MS patients treated with natalizumab for up to 2 years (placebo: 1,135), adverse events leading to discontinuation of therapy occurred in 5.8% of patients treated with natalizumab (placebo: 4.8%). Over the 2-year duration of the studies, 43.5% of patients treated with natalizumab reported adverse reactions (placebo: 39.6%).

The highest incidence of adverse reactions identified from placebo-controlled trials in multiple sclerosis patients with natalizumab given at the recommended dose, are reported as dizziness, nausea, urticaria and rigors associated with infusions.

Tabulated list of adverse reactions

Adverse reactions reported with natalizumab with an incidence of 0.5% greater than reported with placebo are shown below.

The reactions are reported as MedDRA preferred terms under the MedDRA primary system organ class. Frequencies were defined as follows:

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Adverse reaction	Frequency category
Infections and infestations	Urinary tract infection	Common
	Nasopharyngitis	Common
Immune system disorders	Urticaria	Common
	Hypersensitivity	Uncommon
Nervous system disorders	Headache	Common
	Dizziness	Common
	Progressive Multifocal Leukoencephalopathy (PML)	Uncommon
Gastrointestinal disorders	Vomiting	Common
	Nausea	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Rigors	Common
	Pyrexia	Common
	Fatigue	Common

Description of selected adverse reactions

Infusion reactions

In 2-year controlled clinical trials in MS patients, an infusion-related event was defined as an adverse event occurring during the infusion or within 1 hour of the completion of the infusion. These occurred in 23.1% of MS patients treated with natalizumab (placebo: 18.7%). Events reported more commonly with natalizumab than with placebo included dizziness, nausea, urticaria and rigors.

Hypersensitivity reactions

In 2-year controlled clinical trials in MS patients, hypersensitivity reactions occurred in up to 4% of patients. Anaphylactic/anaphylactoid reactions occurred in less than 1% of patients receiving TYSABRI. Hypersensitivity reactions usually occurred during the infusion or within the 1-hour period after the completion of the infusion (See section 4.4). In post-marketing experience, there have been reports of hypersensitivity reactions which have occurred with one or more of the following associated symptoms: hypotension, hypertension, chest pain, chest discomfort, dyspnoea, angioedema, in addition to more usual symptoms such as rash and urticaria.

Immunogenicity

In 10% of patients antibodies against natalizumab were detected in 2-year controlled clinical trials in MS patients. Persistent anti-natalizumab antibodies (one positive test reproducible on retesting at least 6 weeks later) developed in approximately 6% of patients. Antibodies were detected on only one occasion in an additional 4% of patients. Persistent antibodies were associated with a substantial decrease in the effectiveness of TYSABRI and an increased incidence of hypersensitivity reactions.
Additional infusion-related reactions associated with persistent antibodies included rigors, nausea, vomiting and flushing (see section 4.4).

If, after approximately 6 months of therapy, persistent antibodies are suspected, either due to reduced efficacy or due to occurrence of infusion-related events, they may be detected and confirmed with a subsequent test 6 weeks after the first positive test. Given that efficacy may be reduced or the incidence of hypersensitivity or infusion-related reactions may be increased in a patient with persistent antibodies, treatment should be discontinued in patients who develop persistent antibodies.

Infections, including PML and opportunistic infections

In 2-year controlled clinical trials in MS patients, the rate of infection was approximately 1.5 per patient-year in both natalizumab- and placebo-treated patients. The nature of the infections was generally similar in natalizumab- and placebo-treated patients. A case of *cryptosporidium* diarrhoea was reported in MS clinical trials. In other clinical trials, cases of additional opportunistic infections have been reported, some of which were fatal. The majority of patients did not interrupt natalizumab therapy during infections and recovery occurred with appropriate treatment.

In clinical trials, herpes infections (Varicella-Zoster virus, Herpes-simplex virus) occurred slightly more frequently in natalizumab-treated patients than in placebo-treated patients. In post marketing experience,serious, life-threatening, and sometimes fatal cases of encephalitis and meningitis caused by herpes simplex or varicella zoster have been reported in multiple sclerosis patients receiving TYSABRI. The duration of treatment with TYSABRI prior to onset ranged from a few months to several years (see section 4.4).

Cases of PML have been reported from clinical trials, post-marketing observational studies and post-marketing passive surveillance. PML usually leads to severe disability or death (see section 4.4). Cases of JCV GCN have also been reported during postmarketing use of TYSABRI. Symptoms of JCV GCN are similar to PML.

Hepatic events

Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post marketing phase (see section 4.4).

Anaemia and haemolytic anaemia

Rare, serious cases of anaemia and haemolytic anaemia have been reported in patients treated with TYSABRI in post-marketing observational studies.

Malignancies

No differences in incidence rates or the nature of malignancies between natalizumab- and placebo-treated patients were observed over 2 years of treatment. However, observation over longer treatment periods is required before any effect of natalizumab on malignancies can be excluded. See section 4.3.

Effects on laboratory tests

In 2-year controlled clinical trials in MS patients TYSABRI treatment was associated with increases in circulating lymphocytes, monocytes, eosinophils, basophils and nucleated red blood cells. Elevations in neutrophils were not seen. Increases from baseline for lymphocytes, monocytes, eosinophils and basophils ranged from 35% to 140% for individual cell types but mean cell counts remained within normal ranges. During treatment with TYSABRI, small reductions in haemoglobin (mean decrease 0.6 g/dl), haematocrit (mean decrease 2%) and red blood cell counts (mean decrease 0.1×10^6/l) were seen. All changes in haematological variables returned to pre-treatment values, usually within 16 weeks of last dose of the medicinal product and the changes were not associated with clinical symptoms. In post-marketing experience, there have also been reports of eosinophilia (eosinophil count >1,500/mm^3) without clinical symptoms. In such cases where TYSABRI therapy was discontinued the elevated eosinophil levels resolved.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressive agents, ATC code: L04AA23

Pharmacodynamic effects

Natalizumab is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.

In MS, lesions are believed to occur when activated T-lymphocytes cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and endothelial cells of the vessel wall. The interaction between α4β1 and its targets is an important component of pathological inflammation in the brain and disruption of these interactions leads to reduced inflammation. Under normal conditions, VCAM-1 is not expressed in the brain parenchyma. However, in the presence of pro-inflammatory cytokines, VCAM-1 is upregulated on endothelial cells and possibly on glial cells near the sites of inflammation. In the setting of central nervous system (CNS) inflammation in MS, it is the interaction of α4β1 with VCAM-1, CS-1 and osteopontin that mediates the firm adhesion and transmigration of leukocytes into the brain parenchyma and may perpetuate the inflammatory cascade in CNS tissue. Blockade of the molecular interactions of α4β1 with its targets reduces inflammatory activity present in the brain in MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation or enlargement of MS lesions.

Clinical efficacy

Efficacy as monotherapy has been evaluated in one randomised, double-blind, placebo-controlled study lasting 2 years (AFFIRM study) in relapsing-remitting MS patients who had experienced at least 1 clinical relapse during the year prior to entry and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5. Median age was 37 years, with a median disease duration of 5 years.
The patients were randomised with a 2:1 ratio to receive TYSABRI 300 mg (n = 627) or placebo (n = 315) every 4 weeks for up to 30 infusions. Neurological evaluations were performed every 12 weeks and at times of suspected relapse. MRI evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually. Study features and results are presented in the table below.

AFFIRM study: Main features and results		
Design	Monotherapy; randomised double-blind placebo-controlled parallel-group trial for 120 weeks	
Subjects	RRMS (McDonald criteria)	
Treatment	Placebo / Natalizumab 300 mg i.v. every 4 weeks	
One year endpoint	Relapse rate	
Two year endpoint	Progression on EDSS	
Secondary endpoints	Relapse rate derived variables / MRI-derived variables	
Subjects	Placebo	Natalizumab
Randomised	315	627
Completing 1 years	296	609
Completing 2 years	285	589
Age yrs, median (range)	37 (19-50)	36 (18-50)
MS-history yrs, median (range)	6.0 (0-33)	5.0 (0-34)
Time since diagnosis, yrs median (range)	2.0 (0-23)	2.0 (0-24)
Relapses in previous 12 months, median (range)	1.0 (0-5)	1.0 (0-12)
EDSS-baseline, median (range)	2 (0-6.0)	2 (0-6.0)
RESULTS		
Annual relapse rate		
After one year (primary endpoint)	0.805	0.261
After two years	0.733	0.235
One year	Rate ratio 0.33 $CI_{95\%}$ 0.26 ; 0.41	
Two years	Rate ratio 0.32 $CI_{95\%}$ 0.26 ; 0.40	
Relapse free		
After one year	53%	76%
After two years	41%	67%
Disability		
Proportion progressed[1] (12-week confirmation; primary outcome)	29%	17%
	Hazard ratio 0.58, $CI_{95\%}$ 0.43; 0.73, p<0.001	
Proportion progressed[1] (24-week confirmation)	23%	11%
	Hazard ratio 0.46, $CI_{95\%}$ 0.33; 0.64, p<0.001	
MRI (0-2 years)		
Median % change in T2-hyperintense lesion volume	+8.8%	-9.4% (p<0.001)
Mean number of new or newly-enlarging T2-hyperintense lesions	11.0	1.9 (p<0.001)
Mean number of T1-hypointense lesions	4.6	1.1 (p<0.001)
Mean number of Gd-enhancing lesions	1.2	0.1 (p<0.001)

[1] Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 or 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS =0 sustained for 12 or 24 weeks.

In the sub-group of patients indicated for treatment of rapidly evolving relapsing remitting MS (patients with 2 or more relapses and 1 or more Gd+ lesion), the annualised relapse rate was 0.282 in the TYSABRI treated group (n = 148) and 1.455 in the placebo group (n = 61) (p <0.001). Hazard ratio for disability progression was 0.36 (95% CI: 0.17, 0.76) p = 0.008. These results were obtained from a *post hoc* analysis and should be interpreted cautiously. No information on the severity of the relapses before inclusion of patients in the study is available.

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The European Medicines Agency has deferred the obligation to submit the results of studies with TYSABRI in one or more subsets of the paediatric population in multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following the repeat intravenous administration of a 300 mg dose of natalizumab to MS patients, the mean maximum observed serum concentration was 110 ± 52 µg/ml. Mean average steady-state trough natalizumab concentrations over the dosing period ranged from 23 µg/ml to 29 µg/ml. The predicted time to steady-state was approximately 36 weeks.

A population pharmacokinetics analysis was conducted on samples from over 1,100 MS patients receiving doses ranging from 3 to 6 mg/kg natalizumab. Of these, 581 patients received a fixed 300 mg dose as monotherapy. The mean ± SD steady-state clearance was 13.1 ± 5.0 ml/h, with a mean ± SD half-life of 16 ± 4 days. The analysis explored the effects of selected covariates including body weight, age, gender, hepatic and renal function, and presence of anti-natalizumab antibodies upon pharmacokinetics. Only body weight and the presence of anti-natalizumab antibodies were found to influence natalizumab disposition. Body weight was found to influence clearance in a less-than-proportional manner, such that a 43% change in body weight resulted in a 31% to 34% change in clearance. The change in clearance was not clinically significant. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 3-fold, consistent with reduced serum natalizumab concentrations observed in persistently antibody-positive patients**,** (see section 4.8).

The pharmacokinetics of natalizumab in paediatric MS patients or in patients with renal or hepatic insufficiency has not been studied.

The effect of plasma exchange on natalizumab clearance and pharmacodynamics was evaluated in a study of 12 MS patients. Estimates of the total natalizumab removal after 3 plasma exchanges (over a 5-8 day interval) was approximately 70-80%. This compares to approximately 40% seen in earlier studies in which measurements occurred after natalizumab discontinuation over a similar period of observation. The impact of plasma exchange on the restitution of lymphocyte migration and ultimately its clinical usefulness is unknown.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Consistent with the pharmacological activity of natalizumab, altered trafficking of lymphocytes was seen as white blood cell increases as well as increased spleen weights in most *in vivo* studies. These changes were reversible and did not appear to have any adverse toxicological consequences.

In studies conducted in mice, growth and metastasis of melanoma and lymphoblastic leukaemia tumour cells was not increased by the administration of natalizumab.

No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab showed no effects on *in vitro* assays of α4-integrin-positive tumour line proliferation or cytotoxicity.

Reductions in female guinea pig fertility were observed in one study at doses in excess of the human dose; natalizumab did not affect male fertility.

The effect of natalizumab on reproduction was evaluated in 5 studies, 3 in guinea pigs and 2 in *cynomolgus* monkeys. These studies showed no evidence of teratogenic effects or effects on growth of offspring. In one study in guinea pigs, a small reduction in pup survival was noted. In a study in monkeys, the number of abortions was doubled in the natalizumab 30 mg/kg treatment groups versus matching control groups. This was the result of a high incidence of abortions in treated groups in the first cohort that was not observed in the second cohort. No effects on abortion rates were noted in any other study. A study in pregnant *cynomolgus* monkeys demonstrated natalizumab-related changes in the foetus that included mild anaemia, reduced platelet counts, increased spleen weights and reduced liver and thymus weights. These changes were associated with increased splenic extramedullary haematopoiesis, thymic atrophy and decreased hepatic haematopoiesis. Platelet counts were also reduced in offspring born to mothers treated with natalizumab until parturition, however there was no evidence of anaemia in these

offspring. All changes were observed at doses in excess of the human dose and were reversed upon clearance of natalizumab.

In *cynomolgus* monkeys treated with natalizumab until parturition, low levels of natalizumab were detected in the breast milk of some animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate, monobasic, monohydrate
Sodium phosphate, dibasic, heptahydrate
Sodium chloride
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

TYSABRI must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial 4 years

Diluted solution

After dilution with sodium chloride 9 mg/ml (0.9%) solution for injection, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2˚C - 8˚C and infused within 8 hours of dilution. In-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2˚C - 8˚C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product see section 6.3.

6.5 Nature and contents of container

15 ml concentrate in a vial (type I glass) with a stopper (bromobutyl rubber) and a seal (aluminium) with a flip-off cap.
Pack size of one vial per carton.

6.6 Special precautions for disposal and other handling

Instructions for use:

- Inspect the TYSABRI vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.
- Use aseptic technique when preparing TYSABRI solution for intravenous (IV) infusion. Remove flip-off cap from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 ml concentrate for solution for infusion.
- Add the 15 ml concentrate for solution for infusion to 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection. Gently invert the TYSABRI solution to mix completely. Do not shake.
- TYSABRI must not be mixed with other medicinal products or diluents.
- Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

- The diluted medicinal product is to be used as soon as possible and within 8 hours of dilution. If the diluted medicinal product is stored at 2˚C - 8˚C (do not freeze), allow the solution to warm to room temperature prior to infusion.
- The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 ml/minute.
- After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/ml (0.9%) solution for injection.
- Each vial is for single–use only.
- Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Biogen Idec Limited,
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70 Norden Road,
Maidenhead,
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SL6 4AY
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/346/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th June 2006
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.