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Global Clinical Development - General Medicine

OMB157/Ofatumumab

Clinical Trial Protocol COMB157G2302 / NCT02792231

A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis

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List of abbreviations

Ab	Antibody
ACR	Albumin/Creatinine Ratio
ADA	Anti-drug-antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
AEP	Accelerated Elimination Procedure
AIDS	Acquired Immune Deficiency Syndrome
Alb	Albumin
ALT	Alanine Aminotransferase
AP/ALP	Alkaline Phosphatase
ARBA	Annualized Rate of Brain Atrophy
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
BCRP	Breast Cancer Resistant Protein
BIL	Bilirubin
BUN	Blood Urea Nitrogen
BVL	Brain Volume Loss
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CDC	Complement-dependent cytotoxicity
6mCCD	6-month Confirmed Cognitive Decline
CDI	Confirmed Disability Improvement
6mCDI	6-month Confirmed Disability Improvement
CDW	Confirmed Disability Worsening
3mCDW	3-month Confirmed Disability Worsening
6mCDW	6-month Confirmed Disability Worsening
CNS	Central Nervous System
COA	Clinical Outcome Assessments
CQA	Compliance Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
(e)CSSRS	(electronic) Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTRD	Clinical Trial Results Database
DAR	Dose Administration Record
DMC	Data Monitoring Committee
DMT	Disease-Modifying Therapy
DNA	Deoxyribonucleic Acid
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale

[redacted]

EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
[redacted]	[redacted]
EU	European Union
FAS	Full Analysis Set
FS	Functional System
FU	Follow-up
GCP	Good Clinical Practice
Gd	Gadolinium
GGT	Gamma-Glutamyl-Transferase
HA, HB, HC, HE	Hepatitis A, B, C, E
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
9HPT	9-Hole Peg Test
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intention-To-Treat
Ig	Immunoglobulin
IEC	Independent Ethics Committee
INR	International Normalized Ratio
iv	Intravenous(ly)
IRB	Institutional Review Board
IRT	Interactive Response Technology
KM	Kaplan-Meier
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLQ	Lower Limit of Quantification
M	Month
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Image
MS	Multiple Sclerosis
MSIS	Multiple Sclerosis Impact Scale
n.a.	Not applicable
NB	Negative Binomial
NEDA	No Evidence of Disease Activity
NYHA	New York Heart Association
NfL	Neurofilament light chain
OC/RDC	Oracle Clinical/Remote Data Capture
PBVC	Percentage Brain Volume Change

[redacted]

PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PG	Pharmacogenetics
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
po	oral(ly)
PRO	Patient Reported Outcome
PT	Prothrombin Time
q4, q12	Every 4, every 12
qd	Once a Day
QM	Quality Management
RBC	Red Blood Cell
RMS	Relapsing MS
RNA	Ribonucleic Acid
RoW	Rest of the world
RRMS	Relapsing-Remitting MS
SAE	Serious Adverse Event
SAF	Safety Set
sc	Subcutaneous(ly)
sCR	Serum Creatinine
SDMT	Symbol Digit Modalities Test
SPMS	Secondary progressive MS
SUSAR	Suspected Unexpected Serious Adverse Reactions
T25FW	Timed 25-Foot Walk
TBIL/TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analog Scale
WBC	White Blood Cell
[redacted]	[redacted]
WHO	World Health Organization

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: Screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 2

Amendment rationale

Amendment 2 was created to update the secondary objectives of the study and to provide clarification of the rescreening of patients.

Modifications to the secondary objectives include:

- Addition of endpoints related to neurofilament light chain (NfL) as secondary objectives
- Additional endpoint related to cognitive decline as measured on the Symbol Digit Modalities Test (SDMT)
- Addition of composite endpoint related to physical disability and cognition, as measured by disability worsening on Expanded Disability Status Scale (EDSS) and cognitive decline on SDMT

The Withdrawal of consent and study discontinuation language have been modified to fully implement the European Economic Area General Data Protection Regulation.

Other non-substantial changes and updates have been made to correct/clarify minor errors or omissions throughout the protocol.

Changes to the protocol

The main changes and Sections affected are listed as follows:

Protocol summary and Section 2.2: additions to the secondary objectives:

- Neurofilament light chain (NfL) concentration in serum as key secondary objective
- Time to a 6-month confirmed cognitive decline (6mCCD), defined as a 4-point worsening on Symbol Digit Modalities Test (SDMT), and a composite endpoint of time to 6-month confirmed disability worsening (6mCDW) or 6-month confirmed cognitive decline(6mCCD) as other secondary objectives
- Analyses related to NfL in the subgroup of newly diagnosed, treatment-naïve patients

Section 3.1: addition of the allowance of rescreening in patients.

Section 5.5.1: clarification of numbering when patients are rescreened.

Section 5.5.6: clarification on multiple sclerosis (MS) relapse treatment.

Section 5.5.8: clarification on the prohibited medications.

Section 5.6.3: clarification on the withdrawal of consent

Section 5.6.6: text was updated to provide further clarity that T25FW, 9HPT, SDMT may be administered by the Investigator or another qualified healthcare professional, including the EDSS rater

Table 6-1: addition of footnote for liver function test (LFT) testing at Day 14.

Section 6.4: addition of NfL as efficacy assessment.

[redacted]

Section 6.4.3: modification of the contrast that is used as standard.

Section 6.4.4: addition of section regarding NfL.

Section 6.4.7: addition of reference on SDMT.

Section 6.5.2: clarification on number of pulse measurements taken.

Figure 9-1: update to reflect changes in analysis.

Section 9.4.1.1: added NfL as part of secondary analysis.

Section 9.5.1.1.1: clarification on analysis with cognition.

Section 9.5.1.1.2: additional confirmation of analysis for disability-related endpoints.

Section 9.5.1.1.5: additional section added on NfL.

Section 9.5.1.2: clarification on the other secondary endpoints

[redacted]

Section 9.8: addition of NfL to sample size calculation

Section 9.8.7: additional section added on NfL sample size calculations

Section 12: additional references added

[redacted]

Amendment 1 effective 19-JAN-2017

Amendment rationale

Amendment 1 was created at the request of several Health Authorities to provide additional guidance to the Investigators in regards to:

- switching to alternative disease modifying therapy for patients that have discontinued study drug
- re-evaluation of benefit/risk of continuing study treatment in patients, who experience relevant progression of their disease (have met criterion for 6-month confirmed disease worsening) while on study medication.

Further clarification and instructions to Investigators in regards to the use of pre-medication in the home-administration setting have been added. This was part of the Local Amendment 1 for Germany (COMB157G2302 v00.01 DE, clean version electronic document identifier 090095a889dac40e) which was created and released on 18 October 2016 at the request of the Paul-Ehrlich Institut (PEI, German Federal Institute for Vaccines and Biomedicines). Since the study in Germany has not yet started, the decision was taken to incorporate these clarification and instructions in the amendment 1. The amendment 1 will replace the local amendment in Germany.

In addition, procedures and assessments, including administration of T25FW, 9HPT and SDMT no longer required to be administered by Independent personnel, have been clarified based on feedback from Investigators.

Other non-substantial changes and updates have been made to correct/clarify minor errors or omissions throughout the protocol.

Changes to the protocol

The main changes and Sections affected are listed as follows:

Section 3.1: a new sentence has been added to clarify that after study drug discontinuation, patients who continue to stay in the study may initiate an alternative MS therapy if clinically appropriate and corresponding reference to section 5.6.2, where details are provided, has been inserted.

Section 3.5.1: the purpose of the interim analyses for DMC has been clarified.

Section 4.2: the exclusion criteria # 11, 12, 14, 19 and 23 have been updated:

- #11 with a footnote stating that Quantiferon®-TB Gold test may be requested to be done by the Central laboratory to assess patient's eligibility
- #12 with the hepatitis C testing steps
- #14 with daclizumab, which is now an approved MS therapy
- #19 to clarify that this exclusion criterion refers to either one or both serum immunoglobulin (IgG, IgM) level(s) below LLN

[redacted]

- # 23 clarifies that in regards to lactose intolerance only severe conditions are exclusionary

Section 5.5.4: the time window for Day7 and Day14 subcutaneous injection has been added and guidance on missing injections and subsequent injections has been clarified.

Section 5.5.7: this section has been modified to add and clarify specific instructions for the Investigators in regards to the use of premedication in the home-administration setting and to ensure that appropriate information and material on potential injection related reactions and their treatment are provided to the patients.

Table 5-1: daclizumab has been added to prohibited medications while patients are on study medication.

Section 5.6.2: a paragraph has been added to clarify that study drug discontinuation should be considered if patients meet the criterion for 6-month confirmed disability worsening on EDSS and if the Investigator assesses the benefit/risk as negative for study treatment continuation.

Section 5.6.2: a paragraph has been added to clarify that after study drug discontinuation, patients may initiate alternative MS therapy if clinically appropriate and guidance on switching to another MS therapy is provided.

Sections 5.6.6 and 6.4.3: the starting point (randomization) of blinding of efficacy data (EDSS and MRI) has been clarified.

Section 5.6.6: T25FW, 9HPT and SDMT may be administered by the Investigator or another qualified health care professional experienced with the administration of these assessments. Therefore no specific blinding procedures apply to these assessments.

Table 6-1: clarifications have been provided:

- the line for Samples for Total IgG and IgM has been shaded in grey to clarify that this sample should be taken as per schedule after study drug discontinuation
- the following footnotes have been updated:
  - #8 to clarify that it refers to both End of Study (EOS) and End of Treatment (EOT)
  - #18 to clarify the need to test syphilis and tuberculosis as part of the eligibility check (unless completed in the last 6 months prior to screening with documented negative results) and that the Quantiferon®-TB Gold test may be requested to be done by the Central laboratory to assess patient's eligibility
  - #20 has been updated with timing of the pre and post-injection vital signs collection
  - #23 has been added to clarify that routine laboratory must be drawn to allow adequate time for results to be obtained before randomization to ensure patient's eligibility
- the starting points for additional LFT testing (Day 14) and phone interviews (Month 2) have been clarified.

Table 6-2: time points for Routine laboratory and for Total IgG and Ig M assessments have been added.

Sections 6.4.5 and 6.4.6 and 6.4.7: T25FW, 9HPT and SDMT may be administered by the Investigator or another qualified health care professional experienced with the administration of these assessments.

[redacted]

Section 6.5.2: the timing of the pre and post-injection vital signs collection has been added for clarity.

Section 6.5.4.4: the hepatitis C testing steps have been clarified, In addition clarity has been provided on the need to test syphilis and tuberculosis as part of the eligibility check (unless completed in the last 6 months prior to screening with documented negative results) and on the possibility to request the Central laboratory to do the Quantiferon®-TB Gold test to assess patient's eligibility.

Section 7.2.2: the first paragraph has been updated to clarify the SAE reporting time frame.

Section 12: new reference has been added.

Section 15.1: clarification has been added with regards to the MRI sequences recommended for differential diagnosis.

In addition, several updates have been made in the Data analysis section (Section 9) to correct some errors and align with the Statistical Analysis Plan.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	COMB157G2302
Title	A randomized, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of ofatumumab versus teriflunomide in patients with relapsing multiple sclerosis
Brief title	Study of efficacy and safety of ofatumumab compared to teriflunomide in patients with relapsing multiple sclerosis
Sponsor and Clinical Phase	Novartis Phase 3 (confirmatory)
Investigation type	Biological (human IgG1k lytic monoclonal antibody (mAb) to human CD20 antigen)
Study type	Interventional
Purpose and rationale	Study, in conjunction with second study of identical design (COMB157G2301) conducted in parallel, to provide data in support of regulatory approval worldwide as a treatment for patients with relapsing multiple sclerosis
Primary Objective	To demonstrate that ofatumumab is superior to teriflunomide in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR) in patients with relapsing MS
Secondary Objectives	**Key secondary objectives** To evaluate if ofatumumab is superior to teriflunomide on: • Time to disability worsening as measured by 3-month confirmed worsening (3mCDW) on Expanded Disability Status Scale (EDSS) • Time to disability worsening as measured by 6-month confirmed worsening (6mCDW) on EDSS • Time to disability improvement as measured by 6-month confirmed improvement (6mCDI) on EDSS • Number of T1 gadolinium (Gd)-enhancing lesions per Magnetic Resonance Image (MRI) scan • Number of new or enlarging T2 lesions on MRI per year (annualized T2 lesion rate) • Neurofilament light chain (NfL) concentration in serum • Rate of brain volume loss (BVL) based on assessments of percentage brain volume change from baseline **Other secondary objectives** To evaluate if ofatumumab is superior to teriflunomide on: • Time to first relapse • Annualized relapse rates > 8 weeks after the onset of treatment • Risk of a 3mCDW > 8 weeks after the onset of treatment

	• Risk of a 6mCDW > 8 weeks after the onset of treatment • Time to a 6-month confirmed cognitive decline (6mCCD), defined as a 4-point worsening on Symbol Digit Modalities Test (SDMT) • Time to 6mCDW or 6mCCD, whichever is reached first • Change in cognitive performance relative to baseline as measured by the SDMT • Time to 6-month confirmed worsening of at least 20% in the timed 25-foot walk test (T25FW) • Time to 6-month confirmed worsening of at least 20% in the 9-hole peg test (9HPT) • Time to 6mCDI sustained until end of study as measured by EDSS • Number of new or enlarging T2 lesions between Month 12 and End of Study (EOS) • Change in T2 lesion volume relative to baseline • Proportion of patients with no evidence of disease activity (NEDA-4) at year 1 and 2 • Physical and psychological impact of MS disease as measured by the Multiple Sclerosis Impact Scale (MSIS-29) In the subgroup of newly diagnosed, treatment-naïve patients, evaluate if: • High NfL (above median) concentration at baseline is predictive of higher disease activity post baseline • Patients with a high NfL (above median) concentration at baseline benefit from a stronger relative treatment effect of ofatumumab vs teriflunomide • The safety profile of ofatumumab vs terifluomide is comparable in patients with high NfL (above median) concentration at baseline To evaluate the safety and tolerability of ofatumumab compared to teriflunomide To evaluate the pharmacokinetic (PK) of ofatumumab
Study design	Randomized, double-blind, double-dummy, parallel-group, active-comparator controlled, adaptive design, maximal treatment duration of 30 months for an individual patient
Population	Adult patients with relapsing multiple sclerosis (MS)
Key Inclusion criteria	• Male or female patients aged 18 to 55 years (inclusive) at Screening • Diagnosis of MS according to the 2010 Revised McDonald criteria • Relapsing MS: relapsing-remitting course (RRMS), or secondary progressive (SPMS) course with disease activity • Disability status at Screening with an EDSS score of 0 to 5.5 (inclusive) • Documentation of at least: 1 relapse during the previous 1 year OR 2 relapses during the previous 2 years prior to Screening OR a positive Gd-enhancing MRI scan during the year prior to randomization (Note:

[redacted]

	Screening MRI scan may be used if no positive Gd-enhancing scan exist from prior year). • Neurologically stable within 1 month prior to randomization
Key Exclusion criteria	• Patients with primary progressive MS or SPMS without disease activity • Patients meeting criteria for neuromyelitis optica • Disease duration of more than 10 years in patients with an EDSS score of 2 or less • Pregnant or nursing (lactating) women • Women of child-bearing potential unless using highly effective methods of contraception during study drug dosing and for 12 months post-dosing • Sexually active males unless they agree to use condom during intercourse while on study drug • Patients with an active chronic disease of the immune system other than MS • Patients with neurological findings consistent with PML or confirmed PML • Patients at risk of developing or having reactivation of hepatitis: positive results at Screening for serology markers for hepatitis A, B, C and E (HA, HB, HC, and HE) indicating acute or chronic infection • Patients with active systemic infections or known to have AIDS or to test positive for HIV antibody at Screening • Patients at risk of developing or having reactivation of syphilis or tuberculosis • Have received any live or live-attenuated vaccines within 2 months prior to randomization • Have been treated with medications as specified or within timeframes specified (e.g. corticosteroids, ofatumumab, rituximab, ocrelizumab, alemtuzumab, natalizumab, cyclophosphamide, teriflunomide, leflunomide, etc.) • Any other disease or condition that could interfere with participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures.
Study treatment	Ofatumumab (OMB157G) 20 mg sc injections once every 4 (q4) weeks (following initial loading regimen of three 20 mg sc doses/week in first 14 days) + teriflunomide-matching placebo capsules orally once daily Teriflunomide 14 mg capsules orally once daily + ofatumumab-matching sc placebo injections
Efficacy assessments	MS relapse, Expanded Disability Status Scale (EDSS), Magnetic Resonance Imaging (MRI), Timed 25-Foot Walk (T25FW), Nine Hole Peg Test (9HPT), Symbol Digit Modalities Test (SDMT), Multiple Sclerosis Impact Scale (MSIS-29), Neurofilament light chain (NfL)
Key safety assessments	Adverse events, Physical examinations (including skin), Vital signs,

[redacted]

	Laboratory evaluations (blood and urine), Pregnancy testing, electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (CSSRS)
Other assessments	Pharmacokinetics, [redacted]
Data analysis	All efficacy data will be analyzed according to the intent-to-treat principle. The primary analysis (ARR) will use a negative binomial regression model with log-link and time-in-study as offset. Key-secondary analyses include disability endpoints (i.e., time-to-3mCDW, 6mCDW and 6mCDI all analyzed in Cox proportional hazards models), MRI-endpoints (i.e., number of T1 Gd-enhancing lesions, number of new/ enlarging T2 lesions both analyzed in negative binomial regression models and percentage brain volume change analyzed in a random coefficients model) and log(NfL) analyzed in a repeated measures model . The primary hypothesis (ARR) and all MRI- and NfL-related hypotheses will be addressed within the present study (COMB157G2302). All disability endpoints will be addressed in the combined data from 2 studies of identical design (COMB157G2302 and COMB157G2301). To adjust for multiplicity, a testing procedure is implemented in order to control the Type-I error rate.
Key words	Interventional, clinical trial, efficacy and safety, double-blind/double-dummy, ofatumumab, teriflunomide, relapsing multiple sclerosis

[redacted]

1 Introduction

1.1 Background

Multiple Sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability. MS affects ~ 2.5 million individuals worldwide.

Relapsing-remitting MS is the most frequent clinical presentation of the disease. Approximately 85% of patients present with relapsing-remitting MS (RRMS), characterized by recurrent acute exacerbations (relapses) of neurological dysfunction followed by recovery. After 15-20 years, ~50% of patients with RRMS have progressed to secondary progressive MS (SPMS), which is a stage of the disease characterized by continuous worsening of disability that occurs independently of relapses. SPMS can be segregated based on whether patients continue to experience relapses (relapsing SPMS) or not (purely progressive SPMS).

There is accumulating evidence that the immune-mediated damage in MS involves more than just T cells. Specifically, the early role of B-cells in the contribution to the immune-mediated histopathology in MS (Archelos et al. 2000; Frohman et al. 2006; McFarland 2008), has become clearer. B-cells have essential functions in regulating immune response and may contribute to disease pathogenesis by self-antigen presentation, serving as cellular adjuvants for $CD4^+$ T-cell activation (Bouaziz et al. 2007) and by regulating T-cell function and inflammation via cytokine production (Lund 2008), in addition to producing autoantibodies. B-cells are present in the chronic plaques, areas of demyelination, and in the cerebrospinal fluid of MS patients (Klaus et al. 2013).

Clinical evidence from randomized, placebo-controlled Phase 2 studies with the chimeric mouse/human anti-CD20 monoclonal antibody (mAb) rituximab (Hauser et al. 2008) and the humanized anti-CD20 mAb ocrelizumab (Kappos et al. 2011) showed B-cell depletion by these agents lead to marked reductions in MRI-measured inflammatory activity in relapsing MS patients. Recently the efficacy of ocrelizumab was confirmed in 2 Phase 3 trials in patients with RMS (Hauser et al. 2015). These studies showed that ocrelizumab significantly reduced relapse rates, reduced MRI disease activity and, delayed the time to disability worsening vs interferon beta 1a over 2 years. Ocrelizumab was well tolerated with no major safety findings reported in these clinical trials.

Both rituximab and ocrelizumab are delivered in a clinical setting by intravenous (iv) infusion. There is still unmet need for an advanced treatment targeting B-cell pathology with a similar mechanism of action with high efficacy, an acceptable safety profile and the convenience of self-administration.

Ofatumumab

Ofatumumab is a human anti-CD20 monoclonal antibody (mAb) approved for the treatment of patients with chronic lymphocytic leukemia (Arzerra®). The actions of ofatumumab on B-cells are similar to rituximab and ocrelizumab. Ofatumumab recognizes a unique epitope localized close to the cell membrane on the 2 extracellular domains of the $CD20^+$ molecule, N-proximal of the epitope for the anti-CD20 monoclonal antibody (mAb) rituximab. CD20-binding of ofatumumab induces B-cell lysis primarily through complement-dependent cytotoxicity (CDC)

[redacted]

and antibody-dependent cell-mediated cytotoxicity (ADCC). As a fully human antibody (Ab), ofatumumab is predicted to have low potential for immunogenicity, as confirmed by the very low incidence of anti-drug antibodies (ADA) against ofatumumab observed in clinical studies (< 1% of patients in oncology studies, Arzerra® US prescribing information).

Ofatumumab has been evaluated in 2 Phase 2 studies in patients with RRMS (Studies OMS115102 and OMS112831). Study OMS115102 was a 48-week (24-week cross-over), double-blind, placebo-controlled study that evaluated the effects of ofatumumab administered iv in 38 patients with RRMS (Soerensen et al. 2014). The study consisted of 3 dose cohorts (100 mg, 300 mg, 700 mg) with 12 patients randomized in each cohort to ofatumumab or placebo in a 2:1 ratio. After 24 weeks, patients on ofatumumab were switched to placebo and patients on placebo were switched to the ofatumumab dose of their cohort and followed for 24 weeks (Week 24-48). The study showed that iv administration of ofatumumab resulted in a profound reduction in circulating B-cell counts and suppression of MRI lesion activity at each dose level evaluated in both treatment periods (Week 0-24 and Week 24-48).

Study OMS112831 was a randomized, placebo-controlled, dose-ranging, 48-week study (24-week double-blind treatment phase, then 24-week follow-up phase) that examined the efficacy and safety of repeat-dose subcutaneous ofatumumab in RRMS. Patients were randomized (2:1:1:1:2) to placebo, ofatumumab 3mg, 30mg, or 60mg every 12 (q12) weeks, or ofatumumab 60 mg every 4 (q4) weeks. The primary endpoint was the cumulative number of new gadolinium-enhancing lesions during weeks 0–12 on brain magnetic resonance imaging (MRI). MRI and relapse outcomes, safety and tolerability and B-cell counts were also assessed. Of 232 randomized patients, 231 received ≥ 1 study drug dose; 214 (92.6%) completed 24 weeks, 212 (91.8%) completed 48 weeks. Ofatumumab reduced the mean cumulative number of new gadolinium-enhancing lesions by 65% vs placebo during weeks 0–12 ($p < 0.001$), and by ≥ 90% during weeks 4–12 vs placebo in a post hoc analysis of cumulative ofatumumab doses ≥ 30mg ($p < 0.001$). Dose-dependent decreases were maintained up to week 48, with the greatest reduction in the ofatumumab 60 mg q4 weeks treatment group versus other dose groups. Ofatumumab reduced cumulative new/newly enlarged T2 lesions vs placebo during weeks 0–12 (60–72%; $p \leq 0.002$). Between 24–48 weeks, new/newly enlarged T2 lesion counts were stable for all ofatumumab doses apart from the 3 mg dose group. The results also demonstrated a rapid, dose and dose frequency dependent reduction in B-cell counts, the effect being less pronounced with the 3 mg q12 regimen. Monthly dosing showed no signs of B-cell repletion during the inter-dosing interval. Both 30 mg and 60 mg q12 weeks showed approximately 75% suppression of B-cells prior to re-dosing. Once dosing was ceased, all treatments showed similar rate of B-cell repopulation over 60 weeks of follow up.

Overall, ofatumumab was safe and well tolerated in patients with RRMS. The safety profile of ofatumumab was consistent with previous data; no new signals were reported.

In study OMS112831 of sc ofatumumab, the most commonly reported AEs across the ofatumumab dose groups were injection-related reactions (52% for ofatumumab, 15% for placebo). Injection-related reactions occurred primarily post-first dose, diminished on subsequent dosing and were mostly mild/moderate in severity (97% of the events). There were no notable differences across treatment groups in the overall incidence of infection-related AEs, including urinary and respiratory tract infections. Few serious adverse events (SAEs) were reported. These were mainly systemic injection-related reactions (3 patients), all occurring on

[redacted]

Day 1 and in the 60 mg ofatumumab dose groups. There were no cases of opportunistic infections reported during the study.

For further details about ofatumumab, please refer to the Investigator's Brochure.

1.2 Purpose

The study is designed, in conjunction with a second study of identical design conducted in parallel, to provide efficacy, safety and tolerability data for ofatumumab sc compared to oral (po) teriflunomide (Aubagio®) in patients with relapsing MS. The data will support regulatory approval to make ofatumumab sc available for clinical use worldwide as a treatment for this patient population.

2 Study objectives and endpoints

2.1 Primary objective(s)

Demonstrate that ofatumumab 20 mg sc once every 4 (q4) weeks is superior to teriflunomide 14 mg po once daily in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR) in patients with relapsing MS.

2.2 Secondary objective(s)

Key secondary objectives

All disability-related key-secondary objectives will be addressed in the combined data (meta-analysis) from this study and the second study of identical design. All other objectives will be addressed based on the data from this study alone.

The key secondary objectives are to evaluate if ofatumumab 20 mg sc q4 weeks is superior to teriflunomide 14 mg po once daily on the following efficacy measures:

- Time to disability worsening as measured by 3-month confirmed worsening (3mCDW) on The Expanded Disability Status Scale (EDSS)
- Time to disability worsening as measured by 6-month confirmed worsening (6mCDW) on EDSS
- Time to disability improvement as measured by 6-month confirmed improvement (6mCDI) on EDSS
- Number of T1 Gd-enhancing lesions per MRI scan
- Number of new or enlarging T2 lesions on MRI per year (annualized T2 lesion rate)
- Neurofilament light chain (NfL) concentration in serum
- Rate of brain volume loss (BVL) based on assessments of percentage brain volume change from baseline

Other secondary objectives

Evaluate if ofatumumab 20 mg sc q4 weeks is superior to teriflunomide 14 mg po once daily on the following efficacy measures:

[redacted]

- Time to first relapse
- Annualized relapse rates > 8 weeks after the onset of treatment
- Risk of a 3mCDW > 8 weeks after the onset of treatment
- Risk of a 6mCDW > 8 weeks after the onset of treatment
- Time to a 6-month confirmed cognitive decline (6mCCD), defined as a 4-point worsening on Symbol Digit Modalities Test (SDMT)
- Time to 6mCDW or 6mCCD, whichever is reached first
- Change in cognitive performance relative to baseline as measured by the SDMT
- Time to 6-month confirmed worsening of at least 20% in the timed 25-foot walk test (T25FW)
- Time to 6-month confirmed worsening of at least 20% in the 9-hole peg test (9HPT)
- Time to 6mCDI sustained until End of Study (EOS) as measured by EDSS
- Number of new or enlarging T2 lesions between Month 12 and EOS
- Change in T2 lesion volume relative to baseline
- Proportion of patients with no evidence of disease activity (NEDA-4; defined in Section 9.5.1.2) at year 1 and 2
- Physical and psychological impact of MS disease as measured by the Multiple Sclerosis Impact Scale (MSIS-29)

In the subgroup of newly diagnosed, treatment-naïve patients, evaluate if:

- High NfL (above median) concentration at baseline is predictive of higher disease activity post baseline
- Patients with a high NfL (above median) concentration at baseline benefit from a stronger relative treatment effect of ofatumumab vs teriflunomide
- The safety profile of ofatumumab vs terifluomide is comparable in patients with high NfL (above median) concentration at baseline

Evaluate the safety and tolerability of ofatumumab 20 mg sc q4 weeks compared to teriflunomide 14 mg po once daily.

Evaluate the pharmacokinetics (PK) of ofatumumab.

[redacted]

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This is a randomized, double-blind, double-dummy, active comparator-controlled, parallel-group, multi-center study with variable treatment duration in approximately 900 patients with relapsing MS. The treatment duration for individual patients will be variable based on when the End of Study (EOS) criteria are met. The maximal duration for an individual patient will be 30 months (2.5 years).

Eligible patients will be randomized to receive either ofatumumab 20 mg sc injections q4 weeks (after initial loading regimen of three weekly 20 mg doses in the first 14 days) or teriflunomide 14 mg orally once daily. In order to blind for the different formulations, a double-dummy design will be used: patients in the active ofatumumab treatment arm will additionally take placebo capsules orally once daily; patients in the active teriflunomide treatment arm will additionally take q4 weeks placebo-containing sc injections (after initial regimen of three weekly injections in the first 14 days) (Section 5.5). Other measures to protect study blind include:

- Use of an *independent EDSS rater* for clinical efficacy assessments (Section 5.6.6), who is not the same person as the *Investigator* (Section 5.6.6)
- MRI scans are read by a blinded central MRI reading center (Section 6.4.3)
- And laboratory assessments that may lead to potential unblinding (Section 6.5.4) will not be revealed to the site staff or Sponsor study team.

A second study of identical design (COMB157G2301) will be conducted simultaneously. Both studies have the same primary (reduction in ARR) and key-secondary objectives. Both studies will be conducted globally, but individual sites can only participate in one study to ensure independence between the 2 studies. Key-secondary hypotheses with high sample size requirements, i.e. those related to disability worsening or disability improvement, will be tested on the basis of the combined data from the 2 studies (meta-analysis). Multiplicity adjustments are defined in Section 9.4.1.1. Poolability of the 2 studies will be assumed on the basis of the identical design, the simultaneous and global conduct of the 2 studies. For information only, the heterogeneity of the treatment effect between the 2 studies will be tested for disability-related outcomes in the meta-analysis.

[redacted]

Prior to the completion of enrolment, a blinded data review (i.e. the treatment code will not be broken) will be performed for the 2 studies to re-assess sample size assumptions for ARR (for each study separately) and for 3mCDW (for pooled studies). Based on this blinded review, the number of patients to be enrolled may be increased to a maximum number of 1250 randomized patients in each study (Section 9.7.2.1).

End of Study (EOS) will be reached for both studies when **all** of the following conditions are met simultaneously:

1. Each study has collected sufficient data to provide 90% power for the primary ARR endpoint.
2. Across the 2 studies, sufficient 3mCDW events have been observed to provide 90% power for the key-secondary 3mCDW endpoint.
3. Across the 2 studies sufficient 6mCDW events have been observed to provide 80% power for the key-secondary 6mCDW endpoint.

An analysis of blinded data will be conducted to determine the time point at which EOS is reached. Blinded data reviews are described in Section 9.7.2 and a formal definition of the EOS criteria can be found in the statistical Section 9.7.2.2.

The EOS analysis will be based on the completed core study i.e. based on all patients who have completed the Treatment epoch including partial data from the Safety Follow-up epoch available at the time of EOS cut-off (Section 9.5.2.6).

The core study consists of 3 epochs; **Screening epoch** (including Baseline), **Treatment epoch** (double-blind) and **Safety Follow-up (FU) epoch** (Figure 3-1). Patients who complete the double-blind Treatment epoch may be eligible to enter an open-label ofatumumab Extension study that is planned (under separate protocol). Patients who complete the Treatment epoch (on study drug), but do not enter the Extension study will be followed up for safety in the Safety Follow-up (Safety FU) for a minimum of 9 months.

The **Screening epoch** can last up to 45 days and consists of 2 periods, Screening and Baseline: The Baseline period can last up to the point of first study drug administration (Day -7 to Day 1). Patient eligibility will be determined based on the Screening and/or Baseline assessments. If a patient is declared a screen failure, he/she may be rescreened and all assessments must be repeated.

The double-blind **Treatment epoch** will start on Day 1 with randomization of the patient. Patients will be randomly assigned to receive either sc ofatumumab or oral teriflunomide in a double-blind, double-dummy fashion. In the first 4 weeks, injectable study treatment (ofatumumab or placebo) will be administered on Day 1, Day 7 and Day 14 and Day 28 (Week 4, study Month 1). Thereafter, injections will be administered every 4 weeks. All patients will also take one capsule orally once daily (teriflunomide or placebo) starting on Day 1. The Treatment epoch for an individual patient will continue until the End of Study (EOS) has been declared, or for a maximal duration of 30 months, if the EOS has not been declared earlier.

All patients will receive their first sc injection at the site administered by the study staff (Investigator or Study Nurse/Study Coordinator), and will return to the site on Day 7, Day 14 and Day 28 (Month 1) for sc injections under supervision of the study staff (refer to Section

[redacted]

5.5.4 for further details). Patients will thereafter return to the site for assessments at Month 3 and every 3 months thereafter for the duration of the Treatment epoch. All patients will have an EOS Visit at the end of the Treatment epoch (either when EOS is declared for all patients, or when the patient has reached the maximum of 30 months, or if the patient discontinues from study drug and is not willing to follow the Treatment epoch visits and assessments further).

Patients who prematurely discontinue double-blind study medication and agree to continue to follow the assessment schedule of the Treatment epoch (recommended) will have their end of treatment (EOT) visit and assessments at the time of study medication discontinuation. These patients will then be asked to continue to follow the schedule of assessments (Table 6-1) and have their EOS Visit at the end of the Treatment epoch. After study drug discontinuation, patients may initiate alternative MS therapy according to local standard of care if clinically indicated (see Section 5.6.2).

The **Safety FU epoch** (Table 6-2) will be applicable for the following patients:

- Patients who complete the Treatment epoch on study drug and do not enter the planned Extension study
- Patients who prematurely discontinue study treatment and do not agree to continue to be followed in the Treatment epoch
- Patients who have prematurely discontinued study treatment, are being followed in the Treatment epoch but have had less than 9 months of off-treatment follow up at the time of EOS/Month 30 (whichever is earlier)

All Safety FU visits must be scheduled relative to the EOS Visit.

All patients will be followed for a total of at least 9 months after study drug discontinuation in the Treatment epoch and/or the Safety FU epoch (by 9 months the vast majority of patients are expected to have repleted their circulating B-cells, see Section 3.3). The duration of the Safety FU epoch for an individual patient will depend on how long the patient has been off study drug at the time he/she enters the Safety FU epoch. For example, a patient who completes the Treatment epoch on study drug and has EOS (and does not enter the extension study), will be followed for at least 9 months in the Safety FU epoch. However, a patient who discontinues study drug at an earlier time point and had 4 months of follow up after study drug discontinuation in the Treatment epoch, may only need to be followed for an additional 5 months in the Safety FU epoch (for a total of 9 months).

A longer than 9 months of post-treatment follow up in the Safety FU epoch will be required for the following patients:

- Patients who have not repleted their B-cells (i.e. B-cells not back to baseline value or to lower limit of normal (LLN) whichever comes first as determined by central lab) at 9 months
- Patients in whom teriflunomide plasma levels are above 0.02 mg/L (analyzed centrally) at 9 months

These patients will continue to be followed with 3-monthly assessments until their B-cell counts have repleted or teriflunomide plasma levels are below 0.02 mg/L. To protect the study blind, the assessment of B-cell counts and teriflunomide plasma levels will be performed centrally and the Investigators and Sponsor study team will only be informed of whether or not continued follow up is necessary.

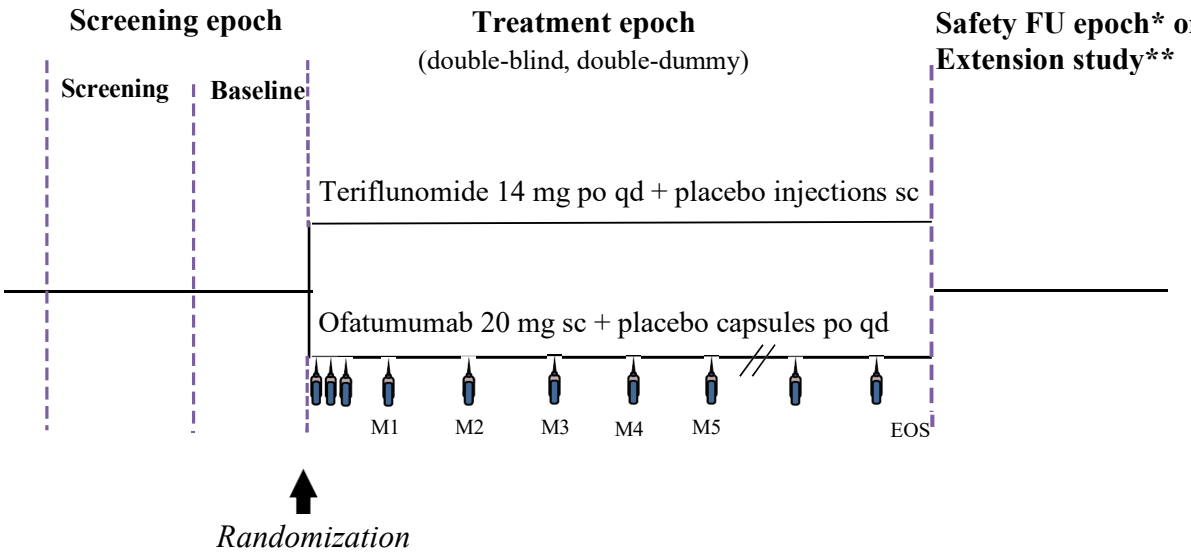
[redacted]

Patients who have initiated therapy with another disease modifying/immunosuppressive therapy before the end of the 9-month follow up will not be monitored beyond 9 months.

Due to the long elimination of teriflunomide (8 months up to 2 years), all patients who have discontinued study drug and have completed at least 9 months of follow up (in the Treatment epoch or the Safety FU epoch) and who plan to become pregnant/father a child or do not agree to continue to use highly effective contraception, should undergo the teriflunomide-accelerated elimination procedure (AEP) described in Section 7.8. To protect study blind, the decision to do the accelerated elimination procedure must be made without knowledge of the core study treatment assignment. Patients may not re-start study drug after accelerated elimination.

Patients who complete the Treatment epoch (while on study drug) may be eligible to participate in the long-term, open-label ofatumumab **Extension study**. The details of the design and assessments of the Extension study will be described in a separate protocol. This extension will last for up to 5 years for individual patients or until the development of ofatumumab in relapsing MS has been decided to be discontinued, if earlier.

Figure 3-1 Study design



*Patients who complete the Treatment Epoch and do not enter the planned Extension study or who prematurely discontinue study drug and do not agree to complete the study Treatment epoch or have less than 9 months of follow up after study drug discontinuation, will enter the Safety FU epoch. **Extension study will be conducted under separate protocol. M=month, EOS=End of Study, FU=Follow-Up, po qd= orally once a day

3.2 Rationale for study design

Double-blind, parallel group, active comparator design is an established scientific method to assess safety and efficacy of a new therapy in conditions where approved medications are available. Double-dummy blinding is necessary to blind treatment group assignment when the investigational and comparator drugs utilize different formulations/routes of administration.

The study has a flexible duration where the end of the study is determined by an analysis of blinded data. The End of Study is declared when sufficient data has been collected to provide the required power for the statistical tests (explained in Section 9.7.2.2).

The sample size of the study can be adjusted if the disease activity of the recruited patient population is lower than initially assumed as indicated by an analysis of the blinded data (explained in Section 9.7.2.1). Adaptive design features aim to maximize the efficiency of the trial by limiting the exposure of patients to double-dummy treatment to the minimum that is required to address the scientific objectives of the study. All design adaptations in this study are based on an analysis of blinded data and do not jeopardize the scientific integrity of the study.

Two studies (COMB157G2302 and COMB157G2301) of identical design will be conducted in parallel as part of the ofatumumab Phase 3 program in order to allow an assessment of the reproducibility of the primary results. Both studies will be independently powered to address the primary objective (ARR) and key secondary MRI objectives, and results from the 2 studies will be independent as centers/sites/Investigators can only participate in one or the other trial (but not in both). The design makes efficient use of the patients' data. If the ARR is significantly lower in ofatumumab treated patients compared with those treated with teriflunomide in both studies, all disability-related key-secondary endpoints will be analyzed in a meta-analysis of the combined data from the 2 studies. Poolability of the studies is justified based on the identical design and the simultaneous global conduct. A testing procedure and multiplicity adjustments are specified to control the false positive rate (one-sided) to $\leq$ 2.5% within study (Section 9.4.1.1).

Patients with relapsing MS (RRMS or SPMS with disease activity as defined by Lublin et al. 2014) with EDSS scores of 0 to 5.5 will be enrolled. Specific disease activity criteria define a population with active inflammatory disease based on recent relapse in the one or 2 years before enrollment or one or more Gd-enhancing lesions on MRI in the year prior to randomization. The defined trial population is typical for relapsing MS.

Given the long-lasting effect of ofatumumab on B-cells and the long half-life of teriflunomide, all patients who discontinue study drug (prematurely or at study completion) and do not enter the planned long-term Extension study, will continue to be followed up for safety for at least 9 months until B-cell repletion or teriflunomide plasma levels are below 0.02 mg/L (Section 3.1).

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The dose regimen for ofatumumab for this study is a *loading dose regimen* of 20 mg at Day 1, Day 7 and Day 14, followed by a monthly *maintenance dose regimen* of 20 mg administered every 4 weeks starting at week 4. The dose selection relies on the clinical hypothesis that the depletion of B-cells in lymphatic tissues is key for efficacy (as measured by MRI and relapses), and that the depletion of brain parenchymal and meningeal B-cells may be an additional factor for the mode of action; blood B-cell count is an imperfect, epiphenomenal measure of tissue status. This hypothesis suggests that in order to attain the desired efficacy, 2 conditions should be met:

- A loading regimen with high enough initial PK for lymphatic depletion, and

[redacted]

- A continued maintenance dose that would keep B-cell depletion levels below desired threshold.

The Phase 2 study of ofatumumab sc in relapsing MS patients (Study OMS112831) provided important information regarding the relationship between peripheral B-cell depletion and efficacy as measured by MRI Gd-enhancing brain lesions. Clear dose-response relationship was detected using a quasi-Poisson regression model that related new Gd-enhancing lesion volumes, baseline lesion number and treatment group. The dose-response was fully explained by the extent of the $CD19^+$ cell count drop. The model indicates that lower $CD19^+$ cells levels lead to better control of lesion volumes and, subsequently, high level of depletion of $CD19^+$ cells (e.g. $\leq$ 8 cells/µL) should be maintained throughout the treatment course in order to ensure desired efficacy.

Pharmacokinetic/pharmacodynamic (PK/PD) modeling on the Phase 2 data of study OMS112831 suggested that a single dose of ofatumumab 20 mg sc is insufficient to reduce B-cell levels to $\leq$ 8 cells/µL. A loading regimen of 3 separate 20 mg (at weeks 0, 1 and 2) was required to attain target depletion ($\leq$ 8 cells/µL) in > 95% of patients based on modeling, and is extrapolated to be more effective than a single 60 mg load. In study OMS112831, patients dosed with 60 mg q4 weeks showed no signs of B-cell repletion during the inter-dosing interval. Based on PK/PD modeling, 20 mg ofatumumab appears to be sufficient to either maintain or to further deplete B-cells in > 95% of patients who have previously depleted, even in patients with high repletion rates.

High number of PK values below the lower limit of quantification (LLQ) did not allow for use of a full PK/PD modeling. For this reason, a second modeling approach (K-PD) was used to relate the individual time-course of B-cells to the dosing history and patient specific covariates, taking the inter-patient variability into account. This approach also confirmed that the desired levels of B-cell depletion in nearly all patients can be attained through the described loading/maintenance dose regimen.

With regards to safety and tolerability, the dose regimens of 60 mg q12 and q4 weeks were associated with more adverse events (AEs) than the lower dose regimens of 3 or 30 mg q12 weeks. In particular, post injection systemic reactions reported as SAEs on Day 1 were seen only with the 60 mg dose regimens. In the presence of B-cells at first dosing, and when B-cells have started repleting, systemic reactions are an expected AE and their severity is likely to be dose and B-cell count related.

With regards to repletion of B-cells after discontinuation of ofatumumab, simulations based on a model developed using the data from the Phase 2 study (OMS112831) predict that the vast majority of patients will replete their B-cells within 9 months of follow-up. Based on these simulations it is estimated that around 5 months are needed to achieve 80% of repletion after treatment discontinuation.

Since relapsing MS is a chronic disease with anticipated long-term treatment, dose selection should therefore aim to balance efficacy and safety aspects. The ofatumumab subcutaneous loading dose regimen of 20 mg at Day 1, Day 7 and Day 14, followed by a monthly maintenance dose regimen of 20 mg administered every 4 weeks (starting at week 4) is selected because it will deplete and subsequently maintain B-cells at the levels below 8 cells/µL for nearly all patients and it is expected to have maximal clinical benefit and better tolerability than higher

doses. Taken together, the strong relationship between MRI lesions and relapses (Sormani et al. 2009; Sormani et al. 2013) and the observed inhibition of lesions at the cumulative doses tested, combined with maintaining B-cells below threshold support selection of the proposed dose regimen.

Duration of treatment

The treatment duration is variable for individual patients. Double-blind treatment will end for all patients when End of Study is declared based on reaching a sufficient amount of data for the primary endpoint (ARR) and disability worsening-related key secondary endpoint analyses (see Section 3.1). For an individual patient the maximum treatment duration will be 30 months, if the End of Study has not been reached earlier.

3.4 Rationale for choice of comparator

The comparator used in this study is teriflunomide (Aubagio®). Teriflunomide is an oral, once daily tablet approved as a first line disease modifying treatment for patients with relapsing MS. It is approved at once daily doses of 14 mg in countries and regions worldwide including the United States (US) and the European Union (EU). In the US, teriflunomide is additionally approved at a lower 7 mg dose. Since this study will be conducted globally, the dose of 14 mg will be used in this study. The efficacy and safety of teriflunomide 14 mg once daily in reducing clinical and MRI disease activity and brain volume loss in patients with relapsing MS has been demonstrated in Phase 3 clinical studies (O'Connor et al. 2011; Confavreux et al. 2014; Freedman 2013; Radue et al. 2015).

Oral administration increases compliance compared to treatments requiring frequent injections such as interferon-beta and glatiramer acetate. As an oral, once daily treatment, teriflunomide is becoming increasingly used as an alternative to these current injectable first line therapies. Furthermore, an once daily oral agent is preferred in a double-blind/double-dummy design as frequently injected comparators (e.g. interferon-beta) increases the difficulty of successful blinding, a critical element for the design of a successful trial.

For these reasons, teriflunomide was selected as an appropriate agent to be used as active comparator in this study of ofatumumab in patients with relapsing MS.

3.5 Purpose and timing of interim analyses/design adaptations

No unblinding interim analysis for efficacy is planned for this study.

3.5.1 Interim analysis for Data Monitoring Committee (DMC)

Regular interim analyses for safety and for benefit/risk assessment will be performed for the DMC by an independent team of statisticians and programmers who are not otherwise involved in the conduct of the study. The review will be done by the DMC.

3.5.2 Reviews of blinded study data

The purpose of blinded data reviews by the Sponsor team is to adapt design features (e.g. sample size, follow-up time) in order to maximize the efficiency of the study by limiting patient exposure to study drug to what is needed for addressing the scientific objectives of the study.

[redacted]

Reviews of aggregate data (i.e. analysis that consider all patients as one group without revealing treatment allocation) do not pose a scientific risk in terms of bias or type-I-error control and can be used to modify the sample size or follow up time if this is indicated by the results.

Blinded data in this study will be reviewed for:

1. Sample size re-assessment: The initial sample size for this trial is planned as 900 randomized patients. The sample size can be increased to a maximum of 1250 randomized patients following an analysis-based review of blinded relapse and disability data if the activity of the recruited patient is lower than initially anticipated. The blinded sample size re-assessment will be done prior to completion of enrollment and is described in Section 9.7.2.1.
2. Declaration of End of Study: Patients are followed up for a flexible period of time (but for a maximum of 30 months) in this study. The amount of information (defined in Section 9.7.2.3) for the primary ARR analysis, and the number of confirmed disability worsening will be monitored in the accumulating blinded data. End of study (as defined in Section 9.7.2.2) will be declared when sufficient information has been captured to provide sufficient power for the primary and the key-secondary objectives of this study. End of study will be declared only once as described in Section 9.7.2.

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with eligibility criteria, close clinical monitoring, avoidance of prohibited treatments and adherence to protocol contraception requirements and Investigator guidance regarding specific safety areas.

Ofatumumab is approved for patients with chronic lymphocytic leukemia and is administered via iv infusion at doses up to 2000 mg. Risks in this population include: infusion reactions, tumor lysis syndrome, cytopenia, progressive multifocal leukoencephalopathy (PML), hepatitis B virus infection and reactivation, and bowel obstruction (please refer to Arzerra® Prescribing Information).

The experience with ofatumumab in MS patients to date is limited (approximately 267 RRMS patients in total exposed to ofatumumab iv (N=38) and sc (N=229) in 2 Phase 2 studies). No unexpected safety findings were observed to date. In the 48-week, placebo-controlled, cross-over study (cross-over at 24 weeks) of intravenous doses of ofatumumab up to 700 mg, adverse events reported more frequently on ofatumumab vs placebo included: rash, throat irritation, erythema, fatigue, viral infection and flushing. In the placebo-controlled, dose-ranging study of ofatumumab administered at sc doses up to 60 mg every 4 weeks for up to 24 weeks, injection-related reactions were observed more frequently in the overall ofatumumab group. There may be yet unknown risks to MS patients taking ofatumumab, which may be serious and unforeseen.

Ofatumumab sc has demonstrated profound suppression of MRI lesion activity (≥ 90% versus placebo over weeks 4-12) in relapsing RRMS patients in the Phase 2 studies. Confirmation of clinical efficacy will be evaluated in the present study. The efficacy of ocrelizumab, another B-cell depleting compound on clinical and MRI disease activity has been reported in 2 Phase 3 trials in relapsing MS patients (Hauser et al. 2015). Taken together, available information provides support for the potential of ofatumumab to demonstrate efficacy on relevant clinical and MRI outcomes in patients with relapsing MS.

[redacted]

The comparator, teriflunomide is approved for the treatment of relapsing MS. The risks of teriflunomide in patients with relapsing MS include: elevated liver enzymes (especially alanine aminotransferase (ALT)), infections, elevated blood pressure, respiratory reactions, hematological reactions, skin reactions, peripheral neuropathy and teratogenicity (please refer to the local product information for details). The efficacy of teriflunomide in reducing clinical (ARR and disability progression) and MRI disease activity as well as brain volume loss, has been demonstrated in Phase 3 clinical trials (Confavreux et al. 2014; O'Connor et al. 2011; Freedman 2013; Radue et al. 2015).

The inclusion of an active comparator arm ensures all patients in the study will receive active therapy (i.e. no placebo arm).

Overall, the balance of benefit and risk supports the proposed clinical study to evaluate the potential of ofatumumab sc as an effective and safe therapy to address the medical need in the target population of patients with relapsing MS.

4 Population

The study population will consist of adult patients with relapsing MS fulfilling all the eligibility criteria listed below*.

The study is planned to be conducted in approximately 300 centers worldwide. It is aimed to randomize a total of 900 patients. To reach this number it is anticipated that the total number of patients to be screened is approximately 1250. Patients, who have been randomized and prematurely discontinue study, will not be replaced.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Male or female patients aged 18 to 55 years (inclusive) at Screening
3. Diagnosis of MS according to the 2010 Revised McDonald criteria (Polman et al. 2011)
4. Relapsing MS: relapsing-remitting course (RRMS), or secondary progressive (SPMS) course with disease activity, as defined by Lublin et al 2014
5. Disability status at Screening with an EDSS score of 0 to 5.5 (inclusive)
6. Documentation of at least: 1 relapse during the previous 1 year OR 2 relapses during the previous 2 years prior to Screening OR a positive Gd-enhancing MRI scan during the year prior to randomization. Note: Screening MRI scan may be used if no positive Gd-enhancing scan exist from prior year.
7. Neurologically stable within 1 month prior to randomization

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible patients.

[redacted]

1. Patients suspected of not being able or willing to cooperate or comply with study protocol requirements in the opinion of the Investigator
2. Patients with primary progressive MS (Polman et al. 2011) or SPMS without disease activity (Lublin et al. 2014)
3. Patients meeting criteria for neuromyelitis optica (Wingerchuk et al. 2006)
4. Disease duration of more than 10 years in patients with EDSS score of 2 or less
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 12 months after stopping study medication. Given the long elimination time of teriflunomide of up to 2 years, women planning to become pregnant may undergo the accelerated elimination process (as per teriflunomide label) after the 12-month period. Highly effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject, if accepted by the local regulation). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male partner sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner.
   - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study drug.

     Note: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
7. Sexually active males, unless they agree to use a condom during active treatment. Male patients should not father a child in this period. Given the long elimination time of teriflunomide of up to 2 years, the male patient wishing to father a child during the study should discontinue study drug and undergo the accelerated elimination process (refer to

[redacted]

Section 7.8). A condom is required to be used also by vasectomized males in order to prevent accidental exposure of their female partner to study drug via seminal fluid

8. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g. rheumatoid arthritis, scleroderma, Sjögren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with immunodeficiency syndrome (hereditary immune deficiency, drug-induced immune deficiency)
9. Patients with active systemic bacterial, viral or fungal infections, or known to have AIDS or to test positive for HIV antibody at Screening
10. Patients with neurological findings consistent with PML or confirmed PML
11. Patients at risk of developing or having reactivation of syphilis or tuberculosis (e.g. patients with known exposure to or history of syphilis or tuberculosis). Testing for syphilis and tuberculosis will be done at Screening unless such testing has been performed in the past 6 months prior to Screening with documented negative result. Testing should be done per local clinical practice (for syphilis e.g. by positive rapid plasma reagin (RPR); for tuberculosis** e.g. skin test or blood test as per local practice).

    NOTE: The Investigator may consult with an infectious disease expert if e.g. test results are unclear or there is suspicion of false positive test results. If the infectious disease expert considers the test results false positive and not clinically relevant, the Investigator must document (in source data and as a comment in the electronic case report form (eCRF)) that the test results are considered false positive and may then randomize the patient.
12. Patients at risk of developing or having reactivation of hepatitis: Positive results at Screening for serological markers for hepatitis (H) A, B, C, and E indicating acute or chronic infection:

    - anti-HA Immunoglobulin (Ig) M (IgM)
    - HBs Ag and/or anti-HBc IgM and/or HB virus deoxyribonucleic acid (DNA)
    - anti-HBs negative and Anti-HBc positive
    - anti-HC IgG (if positive IgG, HCV-RNA PCR will be performed and if negative, patient can be randomized)
    - anti-HE IgM (if positive IgG and/or IgM, perform HE-RNA PCR and if negative, patient can be randomized)

      NOTE: If the Investigator suspects false positive hepatitis serology results, such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, an infectious disease expert may be consulted. If the infectious disease expert finds no evidence of acute or chronic hepatitis infection and considers the serology results false positive and not clinically relevant, the Investigator must document (in source data and as a comment in the eCRF) that the serology results are considered false positive and may then randomize the patient.
13. Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months prior to randomization

[redacted]

14. Have been treated with any of the medications listed below (Note: no wash-out period is required in the case of prior treatment with interferon-β or glatiramer acetate):

Medication	Exclusionary if used/used within required wash-out period
Systemic corticosteroids, adrenocorticotropic hormone	30 days prior to Screening MRI scan
Dimethyl fumarate	1 month prior to randomization
Intravenous immunoglobulin, fingolimod, natalizumab (patients who have discontinued natalizumab in the 6 months prior to randomization should be evaluated to rule out PML)	2 months prior to randomization
Daclizumab	4 months prior to randomization
Teriflunomide	3.5 months prior to randomization or 1 month prior to randomization if patient undergoes AEP and has documented teriflunomide plasma level below 0.02 mg/L before randomization (if discontinued for reason related to safety or lack of efficacy, patient is not eligible, see below)
Mildly to moderately immunosuppressive/chemotherapeutic medications (e.g. azathioprine, methotrexate)	6 months prior to randomization
Highly immunosuppressive/chemotherapeutic medications (mitoxantrone, cyclophosphamide, cladribine) B-cell targeted therapies such as rituximab, ocrelizumab Laquinimod	2 years prior to randomization
Mitoxantrone (with evidence of cardiotoxicity following treatment or cumulative life-time dose > 60 mg/m^2) Alemtuzumab Lymphoid irradiation; bone marrow transplantation Other strongly immunosuppressive treatments (with effects potentially lasting over 6 months) Ofatumumab Teriflunomide (if discontinued for reasons related to safety or lack of efficacy)	Any time

15. Patients currently treated with or needing treatment with cholestyramine (unless for accelerated teriflunomide elimination, Section 7.8) or leflunomide during the study

16. Use of other investigational drugs at the time of enrolment (Screening) or within the prior 30 days, or five elimination half-lives, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer

17. History of malignancy of any organ system (other than basal cell carcinoma, in *situ* squamous cell carcinoma of skin, or *in situ* carcinoma of cervix of the uterus that have been

[redacted]

radically treated e.g. completely excised with clear margins), within the past 5 years, regardless of whether or not there is evidence of local recurrence or metastases

18. Any of the following conditions or treatments that may impact the safety of the patient:
    - History of, or current, significant cardiac disease including cardiac failure (NYHA functional class II-IV), myocardial infarction (within 6 months), unstable angina (within 6 months), transient ischemic attack (within 6 months), stroke, cardiac arrhythmias requiring treatment or uncontrolled arterial hypertension
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker on Screening electrocardiogram (ECG)
    - History of familial long QT syndrome or known family history of Torsades de Pointe
    - History of or active severe respiratory disease, including Chronic Obstructive Pulmonary Disease, interstitial lung disease or pulmonary fibrosis
    - Patients with asthma requiring regular treatment with oral steroids
    - Severe hepatic impairment (Child-Pugh class C) or any chronic liver or biliary disease
    - Patients with severe renal impairment (Glomerular Filtration Rate < 30 ml/min/1.73 m2)
    - Any medically unstable condition as determined by the Investigator
19. Any of the following abnormal laboratory values prior to randomization:
    - Total or conjugated bilirubin (BIL) greater than 1.5 times upper limit of normal (ULN) range, unless in the context of Gilbert's syndrome
    - Alkaline phosphatase (ALP) greater than 1.5 times the ULN range
    - AST or ALT greater than 1.5 times ULN or gamma-glutamyl-transferase (GGT) greater than 2 times ULN range
    - White blood cell (WBC) count < 3,500/mm3 (< 3.5 x 10^9/L)
    - Lymphocyte count < 800/mm3 (< 0.8 x 10^9/L)
    - Serum IgG and/or serum IgM < lower limit of normal (according to central laboratory range)
    - Any other clinically significant laboratory assessment as determined by the Investigator (e.g. significant anemia, neutropenia, thrombocytopenia, signs of impaired bone marrow function)
20. Patients with severe hypoproteinaemia e.g. in nephrotic syndrome
21. Patients with any of the following neurologic/psychiatric disorders prior to randomization:
    - Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the Columbia -Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-

[redacted]

Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years

- Ongoing substance abuse (drug or alcohol) or any other factor (i.e. serious psychiatric condition, recurrent substance abuse) that may interfere with the subject's ability to cooperate and comply with the study procedures
- History of clinically significant CNS disease (e.g. stroke, traumatic brain or spinal injury, history or presence of myelopathy) or neurological disorders which may mimic MS

22. Patients unable or unwilling to undergo MRI scans
23. History of hypersensitivity to any of the study drugs or excipients (including rare hereditary problems of galactose intolerance, Lapp lactase deficiency and glucose-galactose malabsorption) or to drugs of similar chemical classes

Note: If a patient fails on one or more laboratory (or other) assessment criteria, as part of the Screening process, the assessment(s) may be repeated at the discretion of the Investigator, and the patient may be included if criteria are then met, provided the assessments are completed within the Screening or Baseline time window.

*If additional restrictions and/or assessments are required in order to comply with the local legal (e.g. in regards to a higher legal age for study participation) or regulatory (e.g. in regards to compliance with local prescribing informations) requirements, the local requirements must be followed.

** For sites that don't have the possibility to test tuberculosis locally, Quantiferon®-TB Gold test may be requested to be done by the Central laboratory to assess patient's eligibility.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Investigational drug will be provided in pre-filled syringes for subcutaneous administration containing 20 mg ofatumumab (50 mg/ml, 0.4 ml content). Ofatumumab (OMB157) is clear to opalescent, colorless to pale yellow, essentially particle-free liquid in a pre-filled syringe. The matching placebo to ofatumumab pre-filled syringe will have the same appearance as the investigational drug.

Control treatment, teriflunomide (Aubagio®) 14 mg, will be provided as over-encapsulated tablets (either a hard gelatin capsule or a hydroxy propyl methyl cellulose (vegetarian-based) capsule will be used, referred to as capsule hereafter) for oral administration. Teriflunomide-matching placebo capsule (capsule containing placebo-tablet) will have the same appearance as the active comparator. Teriflunomide and teriflunomide-matching placebo capsules will be provided in blisters. It is possible that a switch from blisters to bottles will be performed during the course of the study.

Study drug will be supplied by Novartis.

[redacted]

5.1.2 Additional treatment

No additional treatment beyond investigational drug and comparator drug are provided as part of study drug supplies for this study.

5.2 Treatment arms

The study includes 2 treatment arms:

- Ofatumumab arm: ofatumumab 20 mg sc injections on Day 1, 7, 14, Week 4 (Study Month 1) and every 4 weeks thereafter + teriflunomide-matching placebo capsule orally once daily.
- Teriflunomide arm: teriflunomide 14 mg capsule orally once daily + ofatumumab-matching placebo injections on Day 1, 7, 14, Week 4 (Study Month 1) and every 4 weeks thereafter.

5.3 Treatment assignment and randomization

Eligible patients will be randomized in a 1:1 ratio to either the active ofatumumab 20 mg group or to the active teriflunomide 14 mg group. The randomization will be stratified by geographical region and by MS subtype (RRMS, SPMS). Study sites can only participate in one of the 2 studies to ensure independence of each study.

On Day 1 (randomization visit), all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The Investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and Investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

5.4 Treatment blinding

This study will be conducted using a double-blind, double-dummy design. Patients will be assigned to receive either active ofatumumab (plus teriflunomide-matching placebo) or active teriflunomide (plus ofatumumab-matching placebo) as described in Section 5.2.

A double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products utilize different formulations.

[redacted]

Patients, Investigator staff, persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study with the following exceptions: Data Monitoring Committee (DMC) members, Independent Statisticians and Independent Programmers. (2) The identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

The randomization codes associated with PK samples will be disclosed to the Bioanalysts who will keep PK and ADA results confidential until data base lock.

The following measures will be taken to protect the blinding of the Independent EDSS Rater (Rater):

- Prohibited access to patients' study data
- Separate binders of worksheets and CRF materials for Investigator and the Rater
- Prohibited cross-over of Investigator and Rater
- Use of appropriate clothing by patients to cover potential injection sites during neurological examinations
- Limited interactions between Rater and patient: permitting only a minimum required to perform the EDSS rating.

Additionally, potentially unblinding laboratory parameters (e.g. B-cell counts, teriflunomide plasma level results) will not be communicated to the Investigator or other study staff as described in Section 3.1 and Section 6.5.4.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and at the conclusion of the core study.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise the Investigator on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient Number which is composed by the site number assigned by Novartis and a sequential number assigned by the Investigator (as described below). Once assigned to a patient, the Subject Number will not be reused.

If an enrolled patient fails to be randomized or treated for any reason, the reason will be entered on the Screening Study Disposition CRF. If the patient is re-screened later on, a new Patient Number will be assigned; site will capture the re-screening information in the CRF book. Upon signing the informed consent form, the patient is assigned the next sequential number by the Investigator. The Investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. At each site, the first patient is assigned patient number 1, and subsequent patients/subjects are assigned consecutive numbers (e.g. the second patient is assigned patient number 2; the third patient is assigned patient number 3). The Investigator or his/her staff will contact the IRT and provide the

requested identifying information for the patient to register them into the IRT. Once assigned to a patient, the patient number will not be reused. The site must select the CRF book with a matching Subject Number from the electronic data capture (EDC) system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening epoch Study Disposition CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms and a specific visit. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, Investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Sponsor local Quality Assurance contact.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The Investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients/subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Sponsor monitor or to the Sponsor address provided in the Investigator folder at each site.

5.5.4 Instructions for prescribing and taking study treatment

The study medication (ofatumumab injections + teriflunomide-matching placebo containing capsules or teriflunomide containing capsules + ofatumumab-matching placebo injections) will be dispensed starting at the Randomization Visit (Day 1). Drug will then be dispensed at scheduled visits throughout the treatment period according to Table 6-1.

[redacted]

In the first 4 weeks after randomization, patients will receive 4 sc injections of ofatumumab or matching placebo (on Day 1, Day 7, Day 14 (loading dose regimen) and week 4 (study Month 1)), followed by once monthly (every 4 weeks) sc injections (maintenance dose regimen). Injection volume is 0.4 ml. Patients will receive their first sc injection on site administered by the study staff (e.g. Investigator, Study Nurse/Study Coordinator) and will return to the site on Day 7, Day 14 and week 4 (study Month 1) for sc self-injections under supervision of the study staff . Site personnel will provide training to the patients on the correct procedure for self-administration of the sc injections. Ability to self-administer must be demonstrated and documented before home-administration is permitted after Month 1. If a patient is unable/unwilling to self-administer injections, home-administration may be performed by another individual (e.g. partner, relative or a healthcare professional) who has accompanied the patient to the site and has been trained on and demonstrated ability to correctly administer the sc injections. The patient may also continue to have injections administered at the site if this is the patient's preference. Patients with severe neurological deficits should not self-administer injections.

A patient injection instructions leaflet will be provided which includes detailed information, precautions and instructions for administering sc injections. This information should be reviewed with the patient (and his/her partner/relative as applicable) to ensure that they understand the correct procedure for self/home administration.

Capsules (teriflunomide or matching placebo) must be taken orally once a day, preferably at the same time every day, with or without food and should be swallowed whole. The first capsule on Day 1 will be taken on site under the supervision of the study staff (e.g. Study Nurse/Study Coordinator).

In order to assess tolerability of the initial dose of study medication (injectable + oral), patients will be closely monitored following administration for any reactions including injection related. Patients must remain at the site under observation for a minimum of approximately **5 hours** following dosing on Day 1.

On Day 7 and Day 14, the same time-window (+/- 1 day) as for study visit applies. Starting at week 4, the subcutaneous injections should be administered at 4-week (28 days) intervals (+/- 3 days). Injections may not be advanced by more than 3 days. The patient should be instructed to record any missed doses in the patient diary provided for the study and to inform the study staff of any missed sc injection(s). This can be done at the visits and/or during the monthly structured telephone interviews (according to the script provided to the sites for the study) during which the study site staff will inquire about the patient's status and compliance with study drug administration or issues related to the home administration.

Patients, who miss sc injections or temporarily interrupt study drug without discontinuing from the study or withdrawing consent, will be permitted to resume study drug if determine to be safe and appropriate in the opinion of the Investigator. When resuming study drug, the timing of the next sc injection will be determined based on the original study schedule as followed:

- If one monthly injection is missed by 1 week or less, the patient should take the injection as soon as possible. The next injection should then be administered according to the original schedule.

[redacted]

- If one monthly injection in missed by more than 1 week, the patient should skip the dose and take the next dose at the time when the next injection would be due according to the original schedule.
- If 2 or more consecutive monthly injections are missed, the Investigator should inform the local Sponsor Medical Advisor before re-starting dosing. Missed injection syringes should not be used and returned to the site at the next visit.

If a patient misses any daily capsules, daily dosing should be resumed as soon as possible (i.e. patients should not compensate for a missed dose by increasing the frequency on subsequent doses). The patient should be instructed to record any missed doses in the patient diary provided for the study and to inform the study staff at the next visit or during the monthly telephone interview of any missed doses. The patient should be instructed to return any missed doses. If more than 3 consecutive months are missed, resumption of oral dosing should only be initiated if it is determined to be safe and appropriate in opinion of the Investigator.

All kits of study medication assigned by the IRT will be databased in the IRT system.

All dosages prescribed to the patient and all dose interruptions/changes during the study must be recorded on the Dosage Administration Record eCRF.

The Investigator must promote compliance by instructing the patient to take the study medication exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

The patients will record information concerning their home study drug administrations in a diary provided for the study. The information to be recorded includes date and time of each sc injection and any symptoms related to the administration as well as any missed doses of study drug. The Investigator will review the diary with the patient at each visit and record the information on the relevant eCRFs.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted during the study. Interruptions are permitted if clinically indicated.

Conditions/events that may lead to the study drug interruptions based on Investigator judgment and overall clinical assessment include:

- reported serious adverse event;
- emergency medical condition, unplanned hospitalization, involving use of excluded concomitant medications;
- abnormal laboratory value(s) or abnormal test or examination result(s)

Should the patient interrupt the study drug for whatever reason, both sc and oral study medication must be interrupted. Re-start decision should be made on a case-by-case basis (refer also to Section 5.5.4). Should the Investigator decide, after informing the Sponsor, to re-initiate treatment with study drug, depending on the duration of the interruption, the first sc and oral dose at re-start may need to take place at the study site to ensure observation in a similar manner as on Day 1.

[redacted]

The reason for the interruption of treatment and date of interruption should be appropriately documented in the source documents as well as in the Dosage Administration Record eCRF.

5.5.6 Recommendations for the treatment of MS relapses

The decision to treat MS relapses should be based on the Investigator's judgement and or local clinical practices. If MS relapses require treatment, the standard treatment should consist of a short course of corticosteroids of 3-5 days and up to 1,000 mg methylprednisolone/day or equivalent on an impatient or outpatient basis. Standard of care will be followed during treatment.

Taper with oral steroids is not permitted. Plasmaspheresis may be used if subject does not respond to standard treatment with corticosteroids.

Investigators should consider the added immunosuppressive effects of corticosteroid therapy and increase vigilance regarding infections during such treatment and in the weeks following administration.

Use of steroids for treatment of relapse must be recorded on the Prior or Concomitant medications eCRF.

5.5.7 Concomitant medication

The Investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications (including dose changes), procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / surgical and medical procedures CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the Investigator should contact the Sponsor Medical Advisor before randomizing a patient or allowing a new medication to be started.

If a patient is receiving dalfampridine (Ampyra®) concomitantly with study drug, the patient should remain as far as possible on stable dose throughout the Treatment epoch.

Based on the double-blinded design, the Investigator will need to consider the drug interaction potential of teriflunomide when study drug is co-administered with certain classes of drugs (refer to list of drugs and potential interactions in Appendix 4).

Premedication prior to sc injection

Premedication with acetaminophen and/or antihistamines (or equivalent) is recommended and may be administered at the discretion of the Investigator. For the first injection only, the addition of premedication with steroids (methylprednisolone 100 mg iv or equivalent) is recommended. Premedication should be administered 30 to 60 minutes prior to study drug injection.

Any administration of premedication must be recorded in the Prior and Concomitant medications CRF.

Additional information in regards to premedication for home-administration use:

[redacted]

From Month 2 (5th injection) onwards, patients may inject study medication at home (refer to Section 5.5.4). Use of premedication is at the discretion of the Investigator. Based on the experience with the initial 4 injections administered at the site and with the use of any premedication, the Investigator will evaluate whether or not premedication (such as acetaminophen and/or antihistamines) should be used before injections administered at home. If premedication is prescribed, the study staff must ensure that the patient will receive a sufficient supply of premedication for home-use (i.e. to last at least until the next visit) and clear instructions (oral and written) about type and dose of premedication, and when to take it (i.e. 30-60 minutes before the injection). The Investigator will evaluate the need for premedication, or a change in the prescription, at each visit (scheduled and unscheduled) including at the monthly telephone interview appointments (interview script includes specific questions about any injection-related symptoms and the use of premedication). If, based on the telephone interview, a change in premedication may be needed, the patient should be asked to return to the site for an unscheduled visit.

The patients must be comprehensively informed (through the patient information and consent process) about the possibility that injection-related reactions may occur despite use of pre-medications and about the possible symptoms of a systemic injection reaction and their management. The patients will additionally receive an injection instructions leaflet (Instructions for Home administration and Use) which also includes information about such reactions, their management as well as Investigator/site contact numbers. Furthermore, patients must be reminded to always carry their Patient Card which includes the Investigator and site telephone contact numbers in case of an emergency.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-1 is NOT allowed in combination with study treatment, due to increased risk of immunosuppression and confounding of efficacy evaluations.

Exclusionary medications for study eligibility are listed in the exclusion criteria (Section 4.2). Use of excluded medications is not allowed after randomization while the patient is on study medication.

Table 5-1 Prohibited medication

Medication	Additional action to be taken
Immunosuppressive/chemotherapeutic medications (including herbal) or procedures, including but not limited to cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and hematopoietic stem cell transplantation	Discontinue study treatment, increase vigilance regarding infections. NOTE: Restarting study treatment in patients exposed to these medications is not permitted.
Monoclonal antibodies targeting the immune system, including but not limited to natalizumab, alemtuzumab, daclizumab and B-cell depleting agents such as but not limited to rituximab, ocrelizumab and obinutuzumab	Discontinue study treatment, increase vigilance regarding infections. NOTE: Restarting study treatment after exposure to B-cell depleting agents is not permitted. For others only after consultation with the Sponsor Medical Advisor.

[redacted]

Medication	Additional action to be taken
Any other immunomodulatory or disease-modifying MS treatment, including but not limited to fingolimod, interferon beta, glatiramer acetate, dimethyl fumarate	Discontinue study treatment, increase vigilance regarding infections.
Systemic corticosteroids (except for when given for MS relapse treatment as defined in Section 5.5.6).	Interrupt study treatment, increase vigilance regarding infections.
Leflunomide	Discontinue study treatment
Administration of any live or live-attenuated vaccine (including for measles) is prohibited while patients are exposed to study drug (long-lasting effects of the study drugs should be taken into consideration)	They may be administered when patients are no longer exposed to study drug. Consider risk/benefit and follow local labels

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The Investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Sponsor monitor for the site and the Study Team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The Investigator will provide:

- protocol number
- study drug name
- patient number

In addition, oral and written information to the patient must be provided on how to contact the Investigator's backup in cases of emergency, or when the Investigator is unavailable, to ensure that un-blinding can be performed at any time.

After an emergency treatment code break, the patient should discontinue study drug and continue to be followed in the study Treatment epoch (Table 6-1) or in the Safety Follow-up (Table 6-2) (if the patient does not agree to be followed under Table 6-1). If the patient does not agree to stay in the study, the EOS Visit should be competed.

5.6 Study Completion and Discontinuation

5.6.1 Study completion and post-study treatment

A patient has completed the core study when the patient has completed the End of Study (EOS) visit of the double-blind core study Treatment epoch.

[redacted]

The core study is completed for all patients when EOS is declared for the study as described in Section 3.1.

Patients, who complete the core study (Table 6-1) on study drug, may be eligible for inclusion in the planned Extension study (under separate protocol).

Patients who complete the core study on study drug and do not enter the Extension study will enter the Safety Follow-up period (Table 6-2) for continued follow up.

Patients who prematurely discontinue study drug and either a) complete the core study Treatment epoch off study drug but have less than 9 months of follow up after study drug discontinuation, or b) do not agree to complete the Treatment epoch, will enter the Safety Follow-up period (Table 6-2) for continued follow up.

The Safety Follow-up is complete when all patients who entered have been followed for the stipulated period of time or have withdrawn participation prematurely.

The Investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.6.2 Discontinuation of Study Treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the Investigator.

The Investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Discontinuation of study treatment does not mean discontinuation from study. After stopping the treatment, the patient is encouraged to return for all regular visits as detailed in the schedule of assessments (Table 6-1). The patient should return to the clinic as soon as possible, after discontinuation of study drug, for an end of treatment visit (EOT). EOT visit assessments should be completed and results recorded in the CRF. The Investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the appropriate CRF.

Study treatment must be permanently discontinued under the following circumstances:

- Patient wish (withdrawal of consent Section 5.6.3)
- Pregnancy (see Section 6.5.6 and Section 7.6)
- Use of prohibited treatment (Table 5-1)
- Diagnosis of PML
- Patient with active serious infections or reactivation (e.g. tuberculosis, hepatitis B or C)
- Skin and /or mucosal reactions which raise the suspicion of severe generalized major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome)
- Hypersensitivity to the study medication
- Any situation in which study participation might result in a safety risk to the patient

[redacted]

- Protocol violation that results in a significant risk to the patient's safety
- Emergence of certain adverse events, such as malignancy (except successfully treated basal cell carcinoma, *in situ* squamous cell carcinoma and *in situ* carcinoma of cervix of uterus), liver failure or, serious chronic infection (such as HIV)
- Laboratory abnormalities (e.g. liver function tests (LFT)) and abnormal test procedure as defined in Appendix 1
- Severe hypoproteinemia
- Interstitial lung disease or new onset or worsening of pulmonary symptoms, such as persistent cough and dyspnea, with or without associated fever, suspicious of interstitial lung disease
- Non-compliance with study treatment

Study treatment discontinuation should be considered under the following circumstance:

- For patients who meet the criterion for 6-month confirmed disability worsening on EDSS (see definition in Section 9.5.1.1.1) during the study, the benefits and risks of continuing study treatment must be reassessed by the Investigator. The Investigator will also discuss the further treatment with the patient, including any other MS treatment options that may be available to the patient. The outcome of the discussion with the patient must be documented in the patient's file.
- In case the Investigator deems the benefit-risk of continuing study treatment to be unfavorable or if the patient does not wish to continue the study treatment, the patient will be discontinued from study treatment and continues to follow the schedule of assessments (Table 6-1 and/or Table 6-2 as applicable). The Investigator will be notified by the Sponsor when a patient meets the criterion for 6-month confirmed disability worsening.

If the patient cannot attend any further study visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient, unless the patient has withdrawn informed consent (see Section 5.6.3). This telephone contact should preferably be done according to the study visit schedule.

The Investigator must also contact the IRT to register the patient's discontinuation from study treatment.

After discontinuation of study drug, the patient may undergo the teriflunomide accelerated elimination procedure (Section 7.8) if the Investigator deems this to be indicated.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

Note: Patients who discontinue from study drug, but agree to follow in the assessment schedule should have an EOT evaluation at the time of discontinuation from study drug. Every patient will have an EOS assessment when discontinuing from the study. Follow-up in the Safety follow-up epoch (Table 6-2) may be required after EOS if patients have not had at least 9 months of follow up after last dose of study drug.

[redacted]

The Investigator should consider the benefit/risk of initiation of alternative MS therapy in terms of the patient's clinical status, local regulations, treatment guidelines and local prescribing information. In some cases, as described below, information on the patient's circulating B-cell status may be requested if in the Investigator's opinion this is needed to ensure safe switch to another MS therapy.

The duration of the washout period after last dose of study drug will depend on the type of therapy to be initiated and the patient's clinical status:

- A washout period of at least 5 months is recommended before initiation of lymphocyte depleting/suppressing/trafficking blocking agents (e.g. alemtuzumab, fingolimod, natalizumab, etc.). This is in line with the teriflunomide product information (at least 3.5 months washout in absence of accelerated elimination) and the expected circulating B-cell repletion course after ofatumumab discontinuation (estimated around 5 months needed for 80% repletion; see protocol Section 3.3)
- If, in the opinion of the Investigator, the safe initiation of another therapy cannot be considered without the patient's B-cell status, the Investigator must submit a request to Novartis in writing. The request of B-cell status must be justified based on clinical grounds.

  The Investigator must ensure data entry is complete for any such patients. The Investigator will be notified of whether or not the patient has B-cell counts at or above lower limit of normal or baseline values, whichever is lower.

  The detailed procedure for requesting and receiving the information on a patient's B-cell status will be provided separately.

  The patients should be encouraged to stay in the study and continue to follow the procedures and assessment schedule as specified in the protocol.

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation (EOS) at the time of the subject's study withdrawal should be made as detailed in the schedule of assessments (Table 6-1).

[redacted]

Novartis/Sponsor will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled End of Study visit has passed.

5.6.5 Early study termination by the Sponsor

The study can be terminated by the Sponsor at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

5.6.6 Role of Key site personnel

Key site personnel include (but are not limited to) the following individuals:

Investigator

The Investigator will be responsible for:

- Overall conduct of the study at the study site including assigning per protocol required study staff
- Management of the routine clinical care of the study patients
- Administration and supervision of initial sc injections and training/supervision of ability to self/home-administer. The Investigator may delegate this responsibility to the Study Nurse/Study Coordinator as appropriate and permissible by local regulation
- Confirmation of patient's eligibility for randomization

[redacted]

- Administration of T25FW, 9HPT and SDMT (may be delegated to the Independent EDSS rater, a back-up physician, a Study Nurse/Study Coordinator or other accordingly experienced medical professionals)
- Referral of patients with neurological symptoms consistent with MS relapse to the Independent EDSS Rater
- Management of adverse events and MS relapses
- Review of patient diaries
- Ensuring that all site personnel are informed of concomitant medications excluded per protocol (e.g. the use of systemic steroids other than for the treatment of MS relapses or as pre-medication before injection)

It is strongly recommended that the Investigator remain unchanged throughout the entire course of the study. Occasionally, the Investigator may designate other medical personnel/health care professionals (other than the Independent EDSS Rater, e.g., a back-up physician or Study Nurse/Study Coordinator) at the study site to perform some of the tests and evaluations listed above. The Investigator is also responsible for ensuring access to appropriate expertise for consultation (e.g. infectious disease, ECG interpretation, mental health care) during the study as needed.

Independent EDSS Rater

The Independent EDSS Rater will be responsible for:

- Obtaining an EDSS score based on detailed neurological examination of patients with neurological symptoms consistent with MS relapse as referred by the Investigator at scheduled or unscheduled visits
- Obtaining an EDSS score based on detailed neurological examination at scheduled visits
- Administration of T25FW, 9HPT and SDMT if delegated by the Investigator and if experienced with the administration of these assessments

The Independent EDSS Rater is a physician, or other trained healthcare professional who is qualified to perform the neurological examination and has been trained and certified as an EDSS rater.

The Independent EDSS Rater must not be involved in any other aspect of the patient's care and/or management of his/her MS treatment and have no access to patient study data.

To ensure consistency in the EDSS scoring across Raters, the Independent EDSS Rater must participate in the standardized training and certification session on EDSS scoring (unless already certified at required level (highest level) in past 12 months) prior to enrollment of patients at their site and will need to obtain recertification on a yearly basis. The Independent EDSS Rater should remain the same throughout the study, whenever possible.

The communication of new neurological findings on the neurological examination, including the EDSS score, from the Independent EDSS Rater to the Investigator is not permitted after Randomization. The roles of the Investigator and the Independent EDSS Rater, including their back-ups, are not interchangeable. The Independent EDSS Rater must remain blinded to

[redacted]

adverse events, concomitant medications, laboratory data and any other data that have the potential of revealing the treatment assignment.

The patient and his/her caregiver should be instructed to take care not to discuss aspects of the patient's treatment or potential AEs, including injection site reactions, with the Independent EDSS Rater. During the examination, the patient should wear appropriate clothing that covers injection sites.

Study Nurse/Study Coordinator

The Study Nurse/Study Coordinator's responsibilities may include:

- Assisting the Investigator in patient management, including the assessment and treatment of adverse events, MS relapses and the recording of adverse events, concomitant medications and monitoring of compliance (returned capsule and syringe counts)
- Administration and supervision of initial injections and training/supervision of ability to self/home-administer as delegated by the Investigator
- Administration of T25FW, 9HPT and SDMT as delegated by the Investigator and if experienced with the administration of these assessments
- Scheduling visits and assessments as outlined in the protocol, maintaining proper source documentation and transcription of the data to the CRFs
- Coordination with and between the study selected central labs, drawing and processing lab samples
- Ensuring patient understanding of injection handling and home administration instructions, questionnaires, diaries and the completion of these
- Providing patient with a Patient Information Card (identifying patients as study participant in a clinical trial with pertinent information and site contact information (see also Section 15.2)
- Conducting monthly phone calls with the study patients, as delegated by the Investigator

MRI technician

The MRI technician will be responsible for:

- Familiarization with the MRI manual procedures and the study specific MRI protocol
- Performance of a "dry" or "dummy" run using the MRI parameters outlined by the MRI protocol
- Performance of high-quality MRI scans using the study specific parameters stored in the designated MRI scanner for the duration of the study
- Submission of the MRIs in the appropriate format to the central MRI reader immediately upon completion

Neuroradiologist/Radiologist

The local neuroradiologist/radiologist will be responsible for:

[redacted]

- Reviewing each MRI scan performed for the study patients and contacting the Investigator in case of unexpected safety-related findings detected on the MRI scan

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients should be seen for all visits on the designated day per the schedule of assessments, or as close to it as possible within the visit windows. Missed or rescheduled visits should not lead to automatic discontinuation.

In case a visit is performed outside the schedule, subsequent visits shall be performed in keeping with the original visit schedule (one month is defined as 28 calendar days). In addition to the scheduled visits, patients may have unscheduled visits due to a MS relapse, an acute illness of undetermined cause, for other reasons, or at the discretion of the Investigator. Data collected during unscheduled visits will be recorded in the unscheduled visit CRFs.

Patients who stop taking study medication should be scheduled for the end of treatment (EOT) visit as soon as possible. The patients will be asked to remain in the study and continue completing the study visits and assessments (shaded in Table 6-1) until the end of the study (EOS).

End of treatment (EOT) visit is not mandatory for all patients. It is only applicable to patients who prematurely discontinue double-blind study treatment and will continue to follow the assessment schedule of the Treatment epoch (Table 6-1).

End of study (EOS) visit is mandatory for all patients. The EOS Visit is conducted at the end of the Treatment epoch (i.e. when the patient has completed up to 30 months, or when EOS is declared for all patients, or at time of premature withdrawal from study). At the time EOS is declared for all patients, all patients ongoing in the Treatment epoch should be contacted and their EOS Visit should be scheduled to occur as soon as possible.

Patients who prematurely discontinued study drug but do not agree to continue to be followed in the study Treatment epoch per Table 6-1, but agree to continued safety follow up, will have their EOS Visit and then enter the Safety Follow-up (FU) according to schedule in Table 6-2 .

Patients who complete the Treatment epoch on study drug but do not enter the Extension study, will have their EOS Visit and then enter the Safety Follow-up (FU) schedule in Table 6-2.

During the study, patients will be asked to complete a diary from Month 1 onwards to record information pertinent to study drug administration (including date and time of sc injections) and home pregnancy testing (date and results) for females of childbearing potential. The patient is requested to bring the completed diaries with them to each visit and the Investigator/Study Nurse/Study Coordinator must review these for completeness and for potential AEs, injection related reactions, study drug interruptions etc. and record information obtained from the diaries on the relevant CRFs.

A structured telephone interview script provided for the study will be conducted by site personnel every month starting at Month 2 (Table 6-1). The interview should take place around time of the monthly sc self/home-injection to query about any new or worsening symptoms

[redacted]

warranting an unscheduled visit, injection reactions, and, as applicable, results of home pregnancy testing, compliance with contraception requirements and with any scheduled local LFT lab testing.

Some protocol procedures may be done via an outpatient setting (e.g. at patient's home) with the support of study staff or a healthcare professional registered with the study site for the study, if this is permissible per the local regulatory authority.

[redacted]

Table 6-1 Assessment schedule

Epoch	Screening		Treatment											
Visit	**SCR (D-45 to D-8)**	**BL (D -7 to D1 (pre-treatment)**	**D1[1]**	**D7**	**D14**	**M1**	**M3**	**M6**	**M9**	**M12/24**	**M15/21/27[9]**	**M18**	**EOT[9]**	**EOS[9]**
Visit No.	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108/112**	**109/111/113**	**110**	**198**	**199**
Visit Window (days)	**n.a.**	**n.a.**	**n.a.**	**±1**	**±1**	**±3**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**n.a.**	**n.a.**
Informed consent	**X**													
Demography, Height	**X**													
Medical history	**X**													
MS History/Treatments	**X**													
Incl/Excl	**X[18]**	**X**												
IRT contact	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Dispense study drug			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Phone interview						monthly between scheduled visits[11]								
Physical Exam[21]	**X[2a]**	**X[2a]**						**X**		**X**		**X**	**X**	**X**
Patient diary review							**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Contraception status[16]	**X**	**X**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital signs, Weight	**X**	**X**	**X[20]**	**X[20]**	**X[20]**	**X[20]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Routine lab samples[19], including urine	**X[3]**	**X[23]**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Sample for B-cells	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Teriflunomide plasma levels														**X[15]**
Additional LFT testing					**X[10]**	**X[10]**								
Sample for Total IgG, IgM	**X[2a]**	**X[2a]**				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

[redacted]

Epoch	Screening		Treatment											
Visit	SCR (D-45 to D-8)	BL (D -7 to D1 (pre-treatment)	D1[1]	D7	D14	M1	M3	M6	M9	M12/24	M15/21/27[9]	M18	EOT[9]	EOS[9]
Visit No.	1	2	101	102	103	104	105	106	107	108/112	109/111/113	110	198	199
Pregnancy Test[4]	X		X			X	X	X	X	X	X	X	X	X
ECG	X[2a]	X[2a]											X	X
MRI	X									X			X[8]	X[8]
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Con Meds[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sample for population PK[13]		X				X	X	X		X			X	X
Sample for ADA[13]		X				X		X		X			X	X
Samples for biomarkers[22]	X[2a]	X[2a]					X			X			X	X
[redacted]														
eCSSRS	X[6]	X[6]	X	X	X	X	X	X	X	X	X	X	X	X
MS Relapse			X	X	X	X	X	X	X	X	X	X	X	X
EDSS	X	X[2b]	X[2b]				X	X	X	X	X	X	X	X
T25FW	X[2a]	X[2a]					X	X	X	X	X	X	X	X
9HPT	X[2a]	X[2a]						X		X		X	X	X
SDMT (oral)	X[2a]	X[2a]						X		X		X	X	X
MSIS-29[7]	X[2a]	X[2a]						X		X		X	X	X
[redacted]														
PRO completion form	X[2a]	X[2a]						X		X		X	X	X
AEP			X[12]											
End of Treatment													X	X[17]

[redacted]

Epoch	Screening		Treatment										
Visit	**SCR (D-45 to D-8)**	**BL (D -7 to D1 (pre-treatment)**	**D1[1]**	**D7**	**D14**	**M1**	**M3**	**M6**	**M9**	**M12/24**	**M15/21/27[9]**	**M18**	**EOT[9]**	**EOS[9]**
Visit No.	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108/112**	**109/111/113**	**110**	**198**	**199**
Study Phase Completion														**X**

ADA= Anti-drug-antibody ; AEs= Averse events; AEP= Accelerated elimination procedure; BL=baseline; D= day; [redacted] eCSSRS=electronic Columbia-Suicide Severity Rating Scale; EDSS=Expanded Disability Status scale; [redacted]; EOS=End of Study: EOT=End of Treatment; Excl.=exclusion; HPT=9-Hole Peg Test; Ig= immunoglobulin; Incl.=inclusion; IRT= Interactive response technology; LFT=liver function test; M=month; MRI=magnetic resonance imaging ;MS=multiple sclerosis; MSIS= Multiple Sclerosis Impact Scale; n.a=not applicable; PK=pharmacokinetic; PRO= Patient Reported Outcome; SDMT= Symbol Digit Modalities Test; T25FW=Timed 25-foot Walk; [redacted]

1. Randomization and first dose (usually expected on the same day). If first dose occurs on a different day after randomization, the day of first dose should be considered to be Day 1
2. a) Assessment can be conducted either at Screening OR Baseline visit b) Assessment can be conducted at either the Baseline OR the Day 1 visit (they must be conducted before the first dose of investigational treatment).
3. Serology testing to check patient eligibility conducted at Screening only
4. Female patients only: Serum pregnancy tests will be conducted at Screening, EOT and EOS Visits. Urine pregnancy test on Day 1 should be conducted prior to dosing on Day 1. Urine pregnancy tests will be conducted at all other scheduled visits as indicated in Table 6-1. In addition monthly urine pregnancy tests will be conducted between clinic visits. The patient must contact the Investigator immediately in the case of a positive test for confirmatory testing at the Investigator's discretion

[redacted]

6. The eCSSRS must be assessed once before randomization, either at the Screening (recommended) or the Baseline visit.

[redacted]

8. MRI scan at the End of Treatment (EOT) and/or End of Study (EOS) is needed if there was no MRI scan in the last 3 months
9. For patients who reach Month 27 visit, the next (and last) 3-monthy scheduled visit is the EOS Visit; EOS assessments will be done for all patients; End of treatment (EOT) assessments are done only for patients who prematurely discontinue study drug (at the time of study drug discontinuation) and who continue to stay in the Treatment epoch

[redacted]

10. Additional monthly LFT testing will be required at Month 2, 4 and 5 i.e. between scheduled lab visits in first 6 months in all patients. More frequent LFT testing may be required in patients in countries/regions where the local teriflunomide prescribing information stipulates more frequent LFT testing. E.g. in the EU LFT testing should be performed every 2 weeks in the first 6 months and every 8 weeks thereafter (i.e., once between 3-monthly scheduled visits). A local lab for the additional LFT testing may be used (Section 6.5.4.2)
11. Telephone interview by site staff every month starting at Month 2. The interview should take place around time of the monthly sc self/home injection to query about any new or worsening symptoms warranting an unscheduled visit, injection reactions, results of home pregnancy testing, compliance with contraception requirements and compliance with local LFT lab testing as applicable
12. AEP: applicable only for patients who have permanently discontinued study drug. Patients may undergo an accelerated elimination process at Investigator's discretion (Section 7.8)
13. PK and ADA visits: at the Month 1 visit, the PK and ADA samples should be drawn before the patient takes their Month 1 injection. For later PK and ADA visits, if the monthly injection is scheduled for the same day as the visit, the patient should take the injection after the PK/ADA sample has been drawn (patient should be instructed not to take the injection before coming to the site for the visit)
14. Including corticosteroids used to treat MS relapse; any newly started MS treatment as applicable (for patients who have discontinued study medications)
15. Only for patients who had EOT ≥ 9 months earlier
16. Patients contraception status must be reviewed and documented to ensure method of contraception continues to be appropriate per protocol requirement for highly effective contraception
17. Only for patients for whom the EOT page has not already been completed (i.e. have not had an EOT visit)
18. Syphilis and Tuberculosis testing must be done as part of eligibility check (Exclusion criterion #11) unless completed in the last 6 months prior to screening with documented negative results. If sites don't have the possibility to test tuberculosis locally, Quantiferon®-TB Gold test may be requested to be done by the Central laboratory to assess patient's eligibility.
19. More frequent hematology testing (excluding B-cells and IgG and IgM for blinding purpose) may be performed by local laboratory if this is required by the local regulatory authority
20. Vital signs should be obtained 30-60 min before sc injection (if premedication is administered, pre-injection vital signs should be obtained before premedication is administered), and again approximately 60 min post-injection on Day 1, Day 7, Day 14 and Month 1
21. A complete physical examination will be performed at the visits indicated in Table 6-1 and will include an assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, neurological function and comments on general appearance. A complete neurological examination will be part of the initial physical examination at Screening
22. Samples for biomarkers will be collected as described in Section 6.6.5
23. Labs must be drawn to allow adequate time for results to be obtained before randomization to ensure patient's eligibility

Note: Patients who have prematurely discontinued study drug (EOT) and continue to be followed under the Table 6-1 schedule after study drug discontinuation, will only do the assessment shaded in grey

[redacted]

Table 6-2 Assessment schedule for Safety Follow-up epoch

Visit Month[1] (relative to EOS)	**+M3**	**+M6**	**+M9**	**Every 3 months**[5]	**End of Safety-FU**[2]
Visit Number	**201**	**202**	**203**	**204/20X**	**299**
Visit window (days)	**±14**	**±14**	**±14**	**±14**	
AEs	X	X	X	X	X
Concomitant Meds*	X	X	X	X	X
Vital Signs	X	X	X	X	X
eCSSRS	X	X	X	X	X
Urine pregnancy test[3]	X	X	X	X	X
Contraception status	X	X	X	X	X
Routine lab samples	X	X	X	X	X
Sample for Total IgG, IgM	X	X	X	X	X
Sample for B-cells	X	X	X	X	X
Sample for teriflunomide plasma level[6]	X	X	X	X	X
MS Relapse	X	X	X	X	X
EDSS	X	X	X	X	X
AEP	X[4]				

AEs= Averse events; AEP=Accelerated elimination procedure; DMT=disease modifying therapy; eCSSRS=electronic Columbia-Suicide Severity Rating Scale; EOS=End of Study: FU=Follow-up

1. Time measured from the EOS Visit. M=month.
2. If scheduled visit and End of Safety-FU occur at the same time only End of Safety-FU visit should be done. If patient is prematurely withdrawn from the Safety-FU epoch, the End of Safety-FU assessments should be done at time of withdrawal.
3. Female patients only: monthly urine home pregnancy testing will be conducted between clinic visits. The patient must contact the Investigator immediately in the case of a positive test for confirmatory testing at the Investigator's discretion.
4. AEP. Patients may undergo an accelerated elimination process at Investigator's discretion as described in Section 7.8
5. As needed for patients requiring prolonged B-cell/teriflunomide plasma level monitoring (Section 3.1)
6. As needed (teriflunomide level assessed only when patient has had a total of at least 9 months of follow up and then 3-monthly as needed after study drug discontinuation as described in Section 3.1)

*including steroids for MS relapse and newly started DMT as applicable

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the Screening disposition CRF for the Screening epoch completed. Demographics, inclusion/exclusion, and serious adverse event (SAE) data will be collected for these patients. Adverse events that are not SAEs will be followed by the Investigator and recorded only in the source data.

[redacted]

6.2 Patient demographics/other baseline characteristics

Patient demographic data and baseline characteristics to be collected on the Demography CRF will include date of birth, sex, race and ethnicity. Alcohol and smoking history and relevant medical history/current medical condition present before signing informed consent and any medications taken to treat these conditions will also be captured on the corresponding CRFs. Where possible, diagnoses, and not symptoms should be recorded. Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

MS disease history (including date of onset and diagnosis, number of previous MS relapses), previous MS treatment and employment status will also be collected on the corresponding CRFs.

6.3 Treatment exposure and compliance

In order to collect accurate information about the study drug exposure, the following records should be maintained for each randomized patient: records of study medication dosages administered and intervals between visits. These data should be transcribed on the Dosage Administration Record CRFs.

Compliance will be assessed by the Investigator and/or study personnel at each visit using syringe and capsule counts and information provided by the patient (patient diary is provided for recording of missed doses). This information should be captured in the source document at each visit. A monitor will perform and document drug accountability during site visits and at the end of the study. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.4 Efficacy

This study includes the following efficacy assessments conducted at visits as shown in Table 6-1:

- MS relapse
- EDSS
- Magnetic resonance imaging (MRI)
- Neurofilament light chain (NfL)
- Timed 25-foot walk (T25FW)
- Nine Hole Peg Test (9HPT)
- Symbol Digit Modalities Test (SDMT)
- Multiple Sclerosis Impact Scale 29 items (MSIS-29)

An overview of each of these assessments is provided in the sections below. Details of the administration of each of these assessments will be provided in the site manuals.

[redacted]

6.4.1 MS Relapse

Patients must be instructed to immediately report new neurological symptoms, re-occurring or worsening of previous symptoms to the Investigator. If a patient reports symptoms that may be consistent with relapse, an unscheduled visit to the Investigator and the Independent EDSS Rater must be scheduled as soon as possible (whenever possible within 7 days of onset of the symptoms).

The assessment, management and reporting of MS relapse is made by the Investigator. Confirmation of MS relapse and severity grading, based on the EDSS score (provided by the Independent EDSS Rater), will be done centrally.

MS relapse definition: appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event (McDonald et al. 2001). The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or known infection.

Diagnosing MS relapses during the study: a patient may report symptoms indicative of a relapse at a scheduled visit or at any other time. Patients will be instructed to immediately contact the Investigator if he/she develops new or re-occurring or worsening neurological symptoms. At each Telephone interview (Table 6-1), the patient will also be asked whether any such symptoms have occurred. If a patient reports new neurological symptoms or worsening of previous symptoms, an unscheduled visit is to be scheduled as soon as possible, preferably within 7 days. During this visit, the Investigator will first assess whether the new/worsening neurological abnormality is consistent with the definition of MS relapse above. If so, the standard neurological examination (for the EDSS score) will be performed by the Independent EDSS Rater. If there is any doubt in the opinion of the Investigator, the default must always be to refer the case to the Independent EDSS Rater to perform an EDSS rating. The independent EDSS rater should perform the EDSS rating the same day as the patient's visit to the Investigator whenever possible. Later EDSS assessments can still be utilized for confirmation of MS relapses, but should be avoided to reduce the risk of changes in patient status in between the initial assessment by the Investigator and the EDSS rating by the Independent EDSS rater.

Confirmation of MS relapse: the definition of a confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS performed by the Independent EDSS Rater, i.e. an increase of at least 0.5 points on the EDSS score, or an increase of 1 point on two functional scores (FSs) or 2 points on one FS, excluding changes involving bowel/bladder or cerebral FS compared to the previous available rating (the last EDSS rating that did not occur during a relapse). Confirmation of MS relapse based on these definitions will be done centrally.

All MS relapses, regardless if they meet definition for confirmation based on EDSS or not, are reported on the MS relapse CRF. Severity of MS relapse will be calculated centrally per criteria in Table 6-3 below. MS relapse should not be reported as an AE/SAE unless, in the judgment of the Investigator it is unusually severe or medically unexpected and warrants specific notification as an SAE (as described in Section 7.2.2.1).

Table 6-3 Severity of MS relapse

Mild relapse	Moderate relapse	Severe relapse

EDSS increase of 0.5 point	EDSS increase of 1 or 2 points	Exceeding Moderate criteria
Or	Or	Or
1 point FS change in one to three systems	2-point FS change in one or two systems	Exceeding Moderate criteria
	Or	Or
	1-point change in four or more systems	Exceeding Moderate criteria
EDSS=Expanded Disability Status Scale; FS=Functional Score (Panitch et al. 2002)		

6.4.2 Expanded Disability Status Scale (EDSS)

EDSS will be determined, based on neurological examination, by the Independent EDSS Rater at scheduled visits according to Table 6-1 and in case of a suspected MS relapse.

The EDSS is an ordinal scale used for assessing neurologic impairment in MS based on a neurological examination. It consists of scores in each of seven functional systems (FSs) and an ambulation score that are then combined to determine the EDSS steps (ranging from 0 (normal) to 10 (death due to MS)). The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral functions (Fatigue contributes). The FSs and EDSS steps will be assessed in a standardized manner. EDSS is a widely used and accepted instrument to evaluate disability status at a given time and, longitudinally, to assess accumulation of disability in clinical studies in MS.

Definitions for disability worsening and disability improvement based on the EDSS and confirmation of worsening (3 and 6-month confirmed worsening) and improvement (6-month confirmed improvement) are provided in Section 9.5.1.1.

Disability worsening should not be reported as an AE/SAE unless, in the judgment of the Investigator it is unusually severe or medically unexpected and warrants specific notification as an SAE (as described in Section 7.2.2.2).

6.4.3 Magnetic Resonance Imaging (MRI)

All patients will undergo MRI scanning of the brain according to the schedules in Table 6-1.

MRI scans will be read by the central MRI reading center. The central reading center will be blinded with no access to information on treatment assignments. Prior to the start of the study, MRI technician from each center will receive an MRI Manual, outlining technical implementation, image quality requirements and MRI administrative procedures. Each site will be asked to program the MRI scanner that is designated for evaluation of the study patients and perform and submit a dummy scan (so called “dummy or dry run”) to the MRI reading center to assess the image quality and to evaluate the compatibility of the electronic data carrier. Once the dummy run has been accepted, all the parameter settings for the study specific MRI sequences must remain unchanged for the duration of the study.

Each MRI scan performed for the study needs to be previewed by a local neuroradiologist/radiologist. The Investigator will review the MRI performed during the screening epoch to assess patient's eligibility. After Randomization, the Investigator will be

[redacted]

contacted in case of unexpected findings (e.g. not consistent with MS) detected on the MRI scan.

During the study, the quality of each scan performed will be assessed by the central blinded MRI reading center. The MRI scan should be sent to the central MRI reading center upon completion. As soon as the scan is received by the central MRI reading center, it will be evaluated for quality, completeness and adherence to the protocol. Confirmation of MRI quality or a description of the quality problems, if detected, will be communicated to the site. If scan is incomplete or incorrectly performed, the study center will be asked to repeat it as soon as possible. After completion of the quality check, all scans will be analyzed according to the MRI protocol.

Restrictions for MRI schedule

To avoid interferences caused by steroids (in regards to Gd-enhancing lesions) for the treatment of MS relapse, the following restrictions apply for this study:

- In case of relapse, if an MRI has been scheduled within 30 days of the initiation of steroid treatment, MRI (with Gd-enhancement) should be performed **before** steroid treatment is initiated.
- No MRI (with Gd-enhancement) should be performed while a patient is on steroid therapy for relapse and within the following 30 days upon termination of steroid therapy.

As a result of these restrictions, MRI scheduling can be adjusted accordingly. In case a visit is performed outside the visit window, any subsequent visits should be performed according to the original visit schedule.

Scanning

All sequences/scans will be performed according to the MRI manual.

Sequences include T1 hypointense images (with and without *gadolinium-based contrast agent*), T2-weighted images, and brain volume will be performed.

The gadolinium based contrast medium may occasionally cause nausea and vomiting. Allergic reactions may also occur very rarely and, in extremely rare instances, can be potentially serious and require immediate anti-anaphylactic treatment.

6.4.4 Neurofilament light chain (NfL)

Blood samples for analysis of NfL levels will be drawn according to the schedule in Table 6-1 (refer to Samples for Biomarkers). NfL is a component of the neuronal cytoskeleton and is released into the cerebrospinal fluid and into subsequently blood following neuro-axonal damage. It has been identified as biomarker to indicate treatment response and to predict disability worsening in patients with MS (Kuhle et al. 2016; Disanto et al. 2017; Piehl et al. 2017; Barro et al. 2018; Siller et al. 2018).

The details describing the collection, handling, storage, and shipment requirements of samples will be provided in the laboratory manuals.

[redacted]

6.4.5 Timed 25-Foot Walk (T25FW)

The Timed 25-Foot Walk (T25FW) will be assessed according to the schedule in Table 6-1. The T25FW is an objective quantitative test of neurological function. It is widely used in clinical MS trials. It is an ambulation measurement assessing speed of walking: a timed (in seconds) walk of 25 feet (7.62 meters). The T25FW will be administered (2 trials) according to standardized instructions by the Investigator or by another qualified health care professional experienced with the administration of the T25FW (refer to Section 5.6.6).

6.4.6 Nine Hole Peg Test (9HPT)

The Nine Hole Peg Test (9HPT) will be assessed according to the schedule in Table 6-1. The 9HPT is an objective quantitative test of neurological function. It is widely used in clinical MS trials to assess upper extremity function. It is measured to assess both right and left arm scores, the metric is the time, in seconds, required to insert and remove 9 pegs. The 9HPT will be administered (2 trials per hand) according to standardized instructions by the Investigator or by another qualified health care professional experienced with the administration of the 9-HPT (refer to Section 5.6.6).

6.4.7 Symbol Digit Modalities Test (SDMT)

The SDMT will be assessed according to the schedule in Table 6-1. The SDMT is a sensitive and specific test to assess processing speed which is typically affected in cognitive impaired MS patients (Benedict et al. 2017). During the administration of the SDMT only the examiner and the patient should be in the testing room. The SDMT will be administered according to standardized instructions by the Investigator or another qualified health care professional experienced with the administration of the SDMT (refer to Section 5.6.6). Patients are presented with a test instrument at the top of which is a row of nine numbers paired with unique symbols. Below this part of the test instrument is an array of symbols paired with empty spaces, the patient's task is to verbally match the number for each symbol as rapidly as possible. The SDMT incorporates a number of practice items at the start of each test to familiarize the patient (these results are not included in the final score). The test takes approximately 5 minutes to administer.

Alternate versions of the SDMT will be used in an alternating pattern to minimize learning effects. The test scoring is calculated based on the number of correct answers in 90 seconds.

6.4.8 Multiple Sclerosis Impact Scale (MSIS-29)

The Multiple Sclerosis Impact Scale (MSIS-29) version 2 (Hobart and Cano, 2009) will be used to assess health-related quality of life and will be evaluated according to the schedule in Table 6-1. MSIS-29 is a 29-item, self-administered questionnaire that includes 2 domains, physical and psychological. Responses are captured on a 4-point scale ranging from “not at all” (1) to “extremely” (4), where higher scores reflect greater impact on day to day life.

It is a clinically useful and scientifically sound measure of the impact of MS from the patient's perspective suitable for clinical trials and epidemiological studies (Hobart et al. 2001). It is considered a reliable, valid and responsive PRO measure that complements other indicators of disease severity used to improve our understanding of the impact of MS.

[redacted]

The questions in the scale ask the patient for their views about the impact of MS on their day-to-day life during the past 2 weeks. The MSIS-29 takes approximately 5 minutes to complete, and has been translated into many languages.

6.4.9 Appropriateness of efficacy assessments

The relapse, disability (EDSS) and MRI assessments to be performed in this study are standard and widely accepted efficacy assessments used in clinical MS studies to monitor disease activity and to evaluate treatment effects. They also serve to characterize the patient population in terms of their MS disease status.

The T25FW, 9HPT, SDMT and MSIS-29 assess ambulation (walking speed), upper extremity function, cognitive function (processing speed) and physical and psychological impact of disease, respectively. They are widely used in MS clinical trials and assess relevant additional aspects of the MS pathology.

6.5 Safety

Safety assessments will include:

- Adverse events
- Physical examination (including skin)
- Vital signs
- Laboratory evaluations
- Pregnancy testing (females of childbearing potential)
- ECG
- Columbia Suicide Severity Rating Scale (CSSRS) (Section 7.7)

Additional safety assessments may be conducted should these be requested by the local regulatory authority. Any new or worsening clinically relevant findings from such additional assessments meeting definition of an adverse event (AE) or serious AE should be recorded as AE/SAE (refer to Section 7).

Medical history, including MS history and prior MS treatments will be assessed during the Screening. Concomitant medications will be assessed at every visit following informed consent.

Periodic safety reviews (generally twice a year) will be performed by a Data Monitoring Committee (DMC).

6.5.1 Physical examination

A complete physical examination will be performed at the visits indicated in the Study Assessments (Table 6-1) and will include an assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, neurological function and comments on general appearance. A complete neurological examination will be part of the initial physical examination at Screening.

Information for all physical examinations (including skin exams) must be included in the source documentation at the study site. All significant findings that are present prior to signing informed consent must be reported on the relevant medical history/current medical conditions

[redacted]

CRF. Significant findings seen after signing the informed consent and being randomized meet the definition of an AE and must be recorded on the adverse events CRF.

6.5.2 Vital signs

Vital signs will include sitting pulse rate (measured as radial pulse for 60 seconds), sitting systolic and diastolic blood pressure and body temperature (oral, or per local practice) which will be assessed at the visits indicated in Table 6-1 and Table 6-2.

For the first 4 injections (Days 1, 7, 14 and Month 1), vital signs should be obtained 30-60 minutes before sc injection and again approximately 60 minutes post-injection. If pre-medication is administered, the vital signs should be taken prior to pre-medication administration.

After the patient has been sitting for five minutes, with their back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured 3 times using an automated validated device (manual sphygmomanometer may be used if automated device is not available at the study site). The pulse will also be measured 3 times. The repeat sitting measurements of blood pressure and pulse will be made at 1-2 minute intervals. If an automated blood pressure device is used, it will need to have been calibrated according to the manufacturer's guidelines. In case the cuff sizes available are not large enough for the patient's arm circumference, a manual sphygmomanometer with an appropriately sized cuff may be used.

6.5.3 Height and weight

Height will be assessed at the Screening visit only.

Weight will be assessed at the visits indicated in Table 6-1. Body weight (to the nearest 0.1 kg) in indoor clothing, but without shoes, will be measured.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected (exception: additional frequent LFT panels as described in Section 6.5.4.2 below). Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the laboratory manual. Abnormal laboratory parameters, inconsistent with clinical presentation of MS or which cause suspicion of an underlying medical condition, should be repeated for confirmation.

Parameters that may lead to unblinding to treatment assignment such as B-cell counts will be blinded to the Investigator and Sponsor study team (e.g. will not be included on the routine safety lab reports sent to the Investigators by the central laboratory). This information will remain blinded during the double-blind Treatment epoch and Safety FU epoch until the treatment code for the study has been broken.

6.5.4.1 Hematology

Blood samples will be collected at the scheduled visits indicated in Table 6-1 and Table 6-2. The parameters assessed will include: red blood cell (RBC) count, hemoglobin, hematocrit, platelets, total WBC count, WBC differential counts (neutrophils, lymphocytes, basophils, eosinophils, monocytes) and $CD19^{+}$ B-cell counts.

[redacted]

For study blinding purposes, the B-cell counts will not be provided to the Investigators and Sponsor study team. B-cell counts will be assessed by personnel not otherwise involved in the study for the purpose of determining if continued follow up is required (Section 3.1)

6.5.4.2 Clinical chemistry

Blood samples will be collected at the scheduled visits indicated in Table 6-1 and Table 6-2. The parameters assessed will include: electrolytes (Na, K, Cl, bicarbonate, Ca, Mg, P), random glucose, total protein, blood urea nitrogen (BUN), albumin (Alb), alkaline phosphatase, ALT, AST, GGT, total bilirubin (TBIL), conjugated bilirubin, creatinine, amylase, total cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL), C-Reactive protein (CRP).

To assist for patients with travel restrictions, blood samples for liver panel assessments as described in Table 6-1 (LFT-only Visits) may be drawn by a local lab and the results report sent to the Investigator within 48 hours of obtaining the results. The LFT battery will include ALT, AST, AP, GGT, BIL (total and conjugated). If any significant findings are observed on these reports, a confirmatory blood sample should be drawn by the site and sent to the central laboratory. If no significant findings are observed then the results of any local laboratory values (including reference ranges) should be included in the local liver function test results CRF to document the values. Blood samples for these visits may also be obtained by other methods as appropriate in a particular country or region and processed through the central laboratory (e.g., flying nurse, local phlebotomist etc.).

All patients with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse events is identified, even after study medication has been discontinued. See Appendix 1 and Appendix 2 for definition and follow up requirements of liver and renal events.

6.5.4.3 Urinalysis

Urine will be collected at the scheduled visits indicated in Table 6-1 and the dipstick parameters assessed will include: blood, glucose, specific gravity and protein. In case of an abnormal dipstick test, a urine sample will be sent to the central laboratory for testing including additional parameters such as microscopy and white blood cell and red blood cell sediments.

6.5.4.4 Other

Testing of lab samples will be conducted at Screening to determine the patient's eligibility for inclusion in the study with respect to hepatitis and HIV viruses, total IgG and IgM serology status. Testing for syphilis and tuberculosis at Screening is needed unless such testing has been done in the past 6 months with documented negative results (see Exclusion criterion 11, Section 4.2). If sites don’t have the possibility to test tuberculosis locally, Quantiferon®-TB Gold test may be requested to be done by the Central laboratory to assess patient's eligibility.

A positive result for any of the following serological markers for hepatitis A, B, C, and E indicating acute or chronic infection is an exclusion criterion:

- anti-hepatitis A virus IgM

[redacted]

- hepatitis B surface antigen and anti-hepatitis B core antigen IgM/IgG, HBV-DNA PCR: if negative, patient can be included
- anti-hepatitis C virus IgG (if positive IgG, HCV-RNA PCR will be performed: if negative, patient can be included)
- anti-hepatitis E virus IgM (positive IgG and/or IgM: do HEV-RNA PCR: if negative, patient can be included).

  NOTE: If the Investigator suspects false positive hepatitis serology results, such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms, an infectious disease expert may be consulted. If the infectious disease expert finds no evidence of acute or chronic hepatitis infection and considers the serology results false positive and not clinically relevant, the Investigator may document (in source data and in a CRF comment) that the serology results are considered false positive and randomize the patient.

Samples will additionally be collected during the study according to Table 6-1 and Table 6-2 for:

- total IgM and IgG levels
- teriflunomide plasma levels

For study blinding purpose, the results of these tests will not be included as part of the laboratory reports provided to the Investigators or Sponsor study team during the study. Teriflunomide levels will be assessed by personnel not otherwise involved in the study for the purpose of determining if continued follow up is required (Section 3.1). IgM and IgG levels will be assessed by personnel, not otherwise involved in the study, for the purpose of safety and guidance provided in Appendix 3 should be followed.

Additional samples for PK, ADA, [redacted] will be taken (Sections 6.6.2 to 6.6.5)

6.5.5 Electrocardiogram (ECG)

An ECG will be performed in this study as part of the eligibility assessment and at end of treatment/end of study. Additional unscheduled ECGs may be performed at Investigator's discretion if clinically indicated.

Single 12 lead ECGs are collected. The ECG should be recorded (after 10 minutes rest in the supine position to ensure a stable reading) according to the local site practice. Clinically significant ECG findings at Baseline must be discussed with the Sponsor before administration of study treatment.

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

The original ECGs on non-heat-sensitive paper / and a certified copy on non-heat sensitive paper), appropriately signed, must be collected and archived at the study site. Each ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents.

[redacted]

Findings and clinically significant abnormalities must be recorded on the relevant section of the Medical history/Current medical conditions and AE CRF page as appropriate.

6.5.6 Pregnancy and assessments of fertility

Serum pregnancy tests will be conducted for all women who are of child bearing potential at the Screening, EOT and EOS Visits. Urinary pregnancy tests will be conducted for all women who are of child bearing potential at all other scheduled clinic visits as indicated in Table 6-1 and Table 6-2. In addition, the women will be provided with urinary pregnancy test kits for monthly home pregnancy testing required between the scheduled 3-monthly clinic visits. The patients will document the date and result of each home pregnancy test in a diary provided for the study. A monthly structured telephone interview (Table 6-1) will also be conducted with the patients which includes questions to confirm that the home urine pregnancy testing was done and the result. In the case of a positive test result the patient must contact the Investigator immediately for confirmatory testing at the Investigator's discretion.

In addition, the Investigator will review the contraception status with the patient at each visit per Table 6-1 and Table 6-2 to ascertain that the patient continues to comply with protocol requirements for highly effective contraception as applicable.

6.5.7 Appropriateness of safety measurements

The safety assessments included in this study (Table 6-1) are standard for the MS indication and study patient population and appropriate based on the current safety profile of ofatumumab iv and sc (Investigator's Brochure) and the teriflunomide (Aubagio®) prescribing information.

The use of an instrument such as the C-SSRS to detect suicidal ideation or behavior is currently mandated in studies of CNS active drugs.

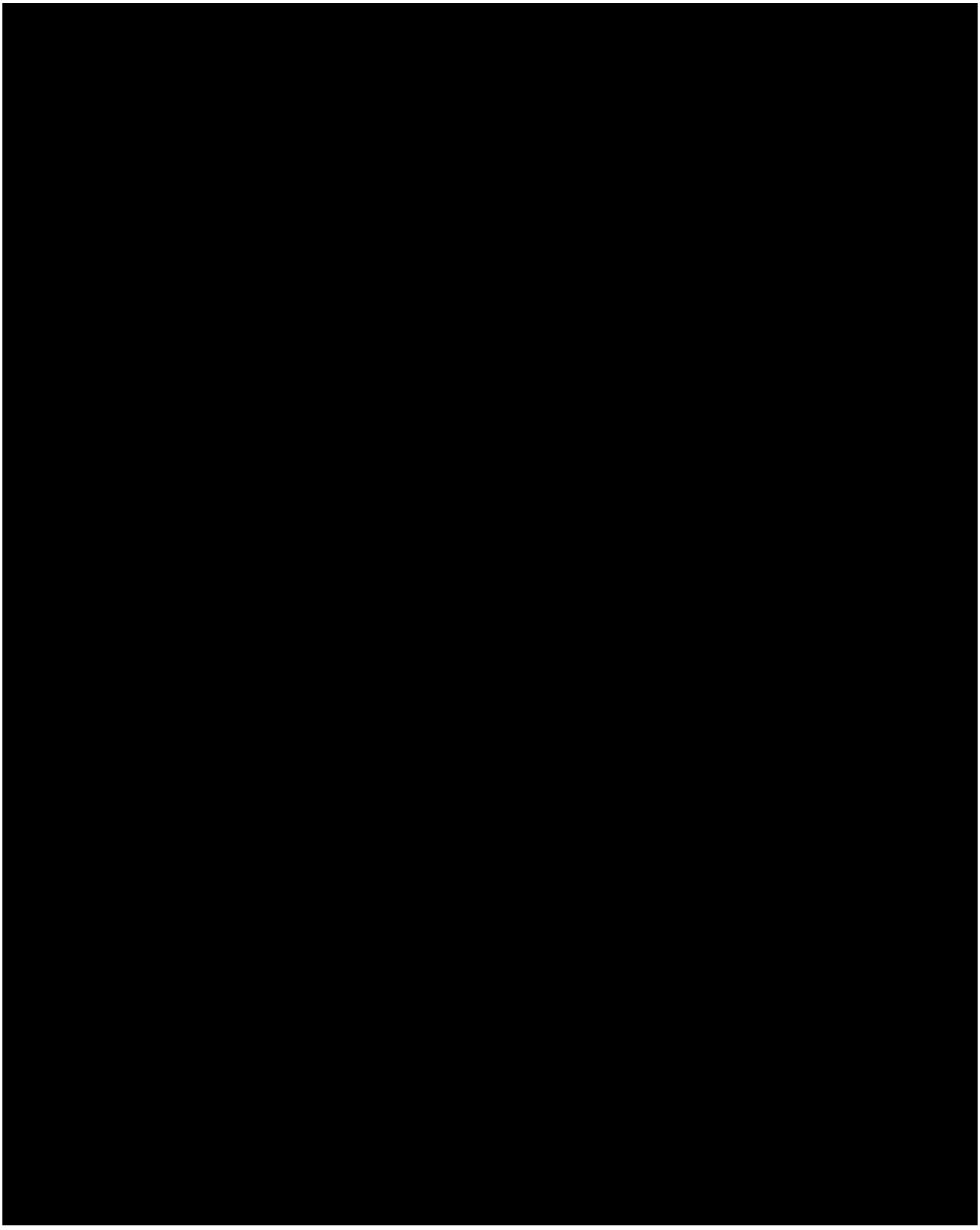
6.6 Other assessments

MS is associated with a variable combination of symptoms, including sensory loss, imbalance, mobility loss, bladder and bowel dysfunction, cognitive dysfunction, spasticity, pain, and sexual dysfunction. Measurement of these wide-ranging effects of MS on the lives of patients is beyond the scope of the clinician assessed endpoints commonly used to evaluate therapeutic effectiveness in MS studies. Patient-reported outcome measures [redacted] are included in this study to provide an empirical assessment from the patient's perspective of the benefits of treatment that cannot be gained from MRI, EDSS, or relapse measurement.

Samples for PK, immunogenicity potential (ADA), [redacted] will also be assessed and evaluated as applicable in relation to efficacy, safety data and population under study.

[redacted]

[redacted]



[redacted]

6.6.2 Pharmacokinetics

PK trough values at steady state for ofatumumab will be used to conduct a population pharmacokinetics analysis. Sampling time points are provided in Table 6-1. Samples for PK assessment should be taken prior to dosing at the Month 1 visit. For any later PK visits, if the visit coincides with the day the monthly injection is scheduled, the patient should not take the injection in the morning before coming to the site so that the PK sample can be drawn before the injection. The PK sample collection date and time must be entered on the appropriate CRF.

Further details on sample collection, numbering, processing and shipment will be provided in the Laboratory Manual provided to the sites.

6.6.3 Immunogenicity

ADA will be assessed to evaluate the immunogenicity potential of ofatumumab. Sampling time points are provided in Table 6-1. Samples for ADA assessment should be taken prior to dosing at the Month 1 visit. For any later ADA visits, if the visit coincides with the day the monthly injection is scheduled, the patient should not take the injection in the morning before coming to the site so that the ADA sample can be drawn before the injection. The ADA sample collection date and time must be entered on the appropriate CRF.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study participation. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Clinically notable laboratory findings are defined according to the Common Terminology Criteria for Adverse Events (CTCAE).

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the Common Terminology Criteria AE (CTCAE) grade (1-4)

  If CTCAE grading does not exist for an adverse event, use:

  1=mild

  2=moderate

  3=severe

  4=life-threatening (see Section 7.2 for definition of SAE)

  CTCAE Grade 5 (death) is not used, but is collected as a seriousness criteria and also collected in other CRFs (Study Completion, Death/Survival).

  There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria)
- its relationship to the study treatment
  - Yes
  - No
- its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding (investigational) treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- study treatment dosage increased/reduced
- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions if any required to treat it, and the outcome. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Information about common side effects already known about the investigational drug (ofatumumab) can be found in the Investigator Brochure (IB). For information about risks and

[redacted]

common side effects related to the comparator (teriflunomide), please refer to the local product label. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of ofatumumab that is identified between Investigators Brochure updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The Investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the Investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g. hospitalization for MS relapse treatment)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe.

[redacted]

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until the patient last visit (defined as End of Study (EOS) visit or End of Safety FU visit) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this period should only be reported to Novartis if the Investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The Investigator must assess the relationship of each SAE to *each specific component of study treatment (if study treatment consists of several components)* complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the Investigator folder provided to each site.

Follow-up information is submitted as instructed in the Investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology (DS&E) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

[redacted]

7.2.2.1 Reporting of MS Relapse as SAE

MS relapses are one of the efficacy endpoints in this study; hence they are exempt from SAE reporting although they may meet the SAE definition on the basis that they are considered medically significant and are frequently associated with hospitalization. These events will therefore be reported on the MS relapse CRF instead of the SAE form. However, if, in the judgment of the Investigator, a MS relapse is unusually severe or medically unexpected and warrants specific notification, then an SAE form must be completed and submitted according to SAE reporting procedures outlined above.

7.2.2.2 Reporting of Disability Worsening as SAE

Disability worsening is one of the efficacy endpoints in this study; hence it is exempt from SAE reporting although it may meet the SAE definition "results in persistent or significant disability/incapacity" (Section 7.2). However, if, in the judgment of the Investigator the disability worsening is unusually severe or medically unexpected and warrants specific notification, then an SAE form must be completed and submitted according to SAE reporting procedures outlined above.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 13-1 in Appendix 1 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-1 in Appendix 1 should be followed up by the Investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 13-2 in Appendix 1.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

[redacted]

Repeat laboratory tests must be entered on the appropriate unscheduled local laboratory CRF page.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on Investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values should be considered during the course of the study:

- Serum event:
  - confirmed (after ≥ 24h) increase in serum creatinine (sCR) of ≥ 25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥ 1+) proteinuria; confirmed by doubling in the urinary albumin/creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥ 1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 14-1 in Appendix 2 should be followed up by the Investigator or designated personnel at the trial site as summarized in Appendix 2. Renal-related events should be recorded on the Renal event CRF pages.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

[redacted]

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Treatment error type	Document in Dose Administration (DAR) CRF (Yes/No)	Document in AE CRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the Investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

7.7 Prospective suicidality assessment

The Columbia Suicide Severity Rating Scale (CSSRS) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior. The CSSRS must be administered at each visit, including unscheduled visits.

A validated version of the CSSRS will be used to capture self-reported C-SSRS data via an interactive voice response telephone system (eCSSRS). The eCSSRS uses a detailed branched logic algorithm to perform the C-SSRS patient interview, evaluating each patient's suicidality ideation and behavior in a consistent manner. At the conclusion of each assessment, the Investigator will receive a detailed eCSSRS Findings Report via e-mail or fax. If the system assesses the patient as having positive suicidal signs, the Investigator will be immediately notified by either fax, email and/or via telephone.

If, at any time after Screening and/or Baseline, the score is “yes” on item 4 or item 5 of the Suicidal Ideation section of the CSSRS or “yes” on any item of the Suicidal Behavior section, the patient must be referred to a mental health care professional for further assessment and/or

treatment. The decision on whether the study treatment should be discontinued is to be taken by the Investigator in consultation with the mental health professional to whom the patient is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a patient answers "yes" to one of the questions in the Suicidal Behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the Suicidal Behavior section) should be reported as AEs and assigned the appropriate severity grade.

All SAEs relating to suicidal behavior must be reviewed by the DMC.

7.8 Accelerated elimination procedure related to active comparator teriflunomide

Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes on average 8 months to reach plasma concentrations less than 0.02 mg/L, although, because of individual variations in drug clearance, it may take as long as 2 years. The teriflunomide label includes guidance on accelerated elimination of teriflunomide in patients in whom a rapid elimination is desirable.

In order to protect the blind and integrity of the present study (double-blind/double-dummy study of ofatumumab vs teriflunomide), a decision to initiate the teriflunomide-specific accelerated elimination procedure must be taken without knowledge of the patient's treatment assignment.

It is recommended that patients who permanently discontinue study drug undergo the accelerated elimination procedure (during study Treatment epoch or during Safety Follow-up) if this is in the patient's best interest as determined by the Investigator or in order to facilitate further treatment or management decisions. This procedure (described below) must be carried out under the supervision of the Investigator.

For patients who develop an SAE (e.g. serious infection, liver event) leading to study drug discontinuation per protocol criteria or per the Investigators clinical judgment, an accelerated elimination may similarly be considered.

As described in the EU and US labels for teriflunomide (Aubagio®), elimination of teriflunomide can be accelerated by either of the following procedures:

- Administration of cholestyramine 8 g every 8 hours for 11 days. If cholestyramine 8 g 3 times a day is not well tolerated, cholestyramine 4 g 3 times a day can be used.
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days.
- If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly.

The procedure should be documented on the Accelerated Elimination Procedure CRF. Any AEs reported during the procedure must be recorded on the AE CRF.

[redacted]

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative will review the protocol and CRFs with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Designated Investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (OC/RDC) system. Designated Investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated Investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the Investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Sponsor staff (or Contract Research Organization (CRO) working on behalf of Sponsor) review the data entered into the CRFs by investigational staff for completeness and accuracy and

[redacted]

instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated Investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Sponsor staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the Investigator site.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Sponsor (or a designated CRO).

MRI scans will be analyzed centrally and derived results will be sent electronically to Sponsor (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Sponsor (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Sponsor.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Sponsor Development management.

[redacted]

8.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be in place to oversee the study. Details are provided in the DMC charter.

The DMC will be responsible for on-going review of enrollment, safety and, if requested by the DMC, efficacy data and will provide regular assessments on the safety and overall risk to benefit ratio of the study conduct, advise the Sponsor of a need for protocol modification/amendment

[redacted]

in order to minimize potential risk for patients, request additional information or make recommendation including stopping of enrollment and/or treatment, if needed.

A Sponsor designee will be responsible for the timely coordination and delivery of the data to the DMC on a regular basis. The chair of the DMC will be responsible for providing summaries/executive reports of each DMC meeting to Sponsor, arranging on-going communication between members of the DMC, arranging meetings and maintaining files with all correspondence pertaining to the study.

9 Data analysis

The analysis will be conducted on all subject data at the time of EOS (i.e. including partial data from the Safety Follow-up epoch). Any data analysis carried out independently by the Investigator should be submitted to Sponsor before publication or presentation.

9.1 Analysis sets

Full analysis set (FAS): The FAS comprises all randomized subjects with assigned treatments. Subjects will be analyzed according to the randomized treatment assignment following the intention-to-treat (ITT) principle, even if they actually received a different treatment.

The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

Per-protocol set (PPS): The PPS is a subset of FAS, consists of all randomized subjects who take at least one dose of study medication and have no major protocol deviations that could confound the interpretation of analyses conducted on the FAS. Major protocol deviations will be determined according to the pre-defined protocol deviation criteria before treatment unblinding (e.g. non-compliance for a large proportion of the time in study). For analyses performed on the PPS, only on-treatment assessments will be used.

The PPS will primarily be used for the supportive analyses of the primary efficacy variable and selected key secondary variables.

Safety set (SAF): The SAF set includes all subjects who received at least one dose of study medication. Subjects will be analyzed according to the actual treatment received. The Safety Set will be used for all safety analyses.

9.2 Patient demographics and other baseline characteristics

Demographics, MS disease history, MRI baseline characteristics, MS medication history and employment status, will be summarized by treatment group for the FAS.

9.3 Treatments

Exposure to investigational study medication is defined as the number of days spent on study drug divided by 365.25 days. In this double-dummy design all patient will receive capsules (active or placebo) and injections (active or placebo) to maintain the blind. For the calculation of exposure to study medication only the active drug will be considered. Intermediate treatment interruptions will be subtracted from drug exposure.

[redacted]

Exposure to investigational study medication will be summarized by treatment with number and percentage of patients by time category, and with summary statistics of the number of patient years of exposure. Number of patient years will be summarized by age and gender, by gender and weight, as well as by race.

Time-at-risk is defined as the number of days spent in the study, from first dose to the last dose of study medication, plus the safety data cut-off of 100 days. Intermediate treatment interruptions will be included in time-at-risk calculations. Time-at-risk corresponds to the time window used for adverse event reporting and can serve as a denominator to safety (e.g. in exposure-adjusted incidence rates). Time-at-risk will be summarized in a similar way to exposure to investigational study medication.

9.4 Analysis of the primary variable

The primary endpoint is the annualized relapse rate (ARR), which is defined as the number confirmed MS relapses in a year. In the primary analysis, the ARR is estimated based on the FAS which follows the intent-to-treat principle in a negative binomial model by using individual relapse count as the response variable with time in study as an offset variable.

Two variables are required for the calculation of the ARR (excluding covariates):

- The cumulative number of confirmed MS relapses by patient is the response variable in the negative binomial model. The confirmation based on EDSS will be derived as defined in section 6.4.1.
- The time-in-study by patient will be used as an offset variable to adjust for the various length patients have been observed and at-risk of a confirmed MS relapse in the study.

9.4.1 Statistical model, hypothesis, and method of analysis

The null hypothesis is that there is no difference in the ARR between ofatumumab 20 mg sc once monthly and teriflunomide 14 mg po once daily in reducing the frequency of confirmed MS relapses as measured by ARR. The alternative hypothesis is that there is a difference between the 2 treatment groups.

- Superiority of ofatumumab 20 mg sc over teriflunomide 14 mg po will be concluded if the observed ARR on ofatumumab 20 mg sc is lower than on teriflunomide 14 mg po and if the null hypothesis can be rejected at the two-sided significance level of 0.05.

The null hypothesis will be tested based on the FAS, using a negative binomial regression model with log-link, treatment and region as factors, number of relapses in previous year, baseline EDSS, baseline number of Gd-enhancing lesions and the patient's age at baseline as covariates. In the analysis, the response variable is the number of confirmed relapses observed from each patient and the patient's time in study (natural log of time in years) is used as an offset variable to adjust for the varying lengths of patient's time in the study. The adjusted ARR (i.e., model-based estimate adjusted for covariates) for each treatment and the corresponding 95% confidence interval, and ARR ratio (also expressed as percentage reduction relative to control group) along with the 95% confidence interval for the ARR ratio and the corresponding p-value will be obtained.

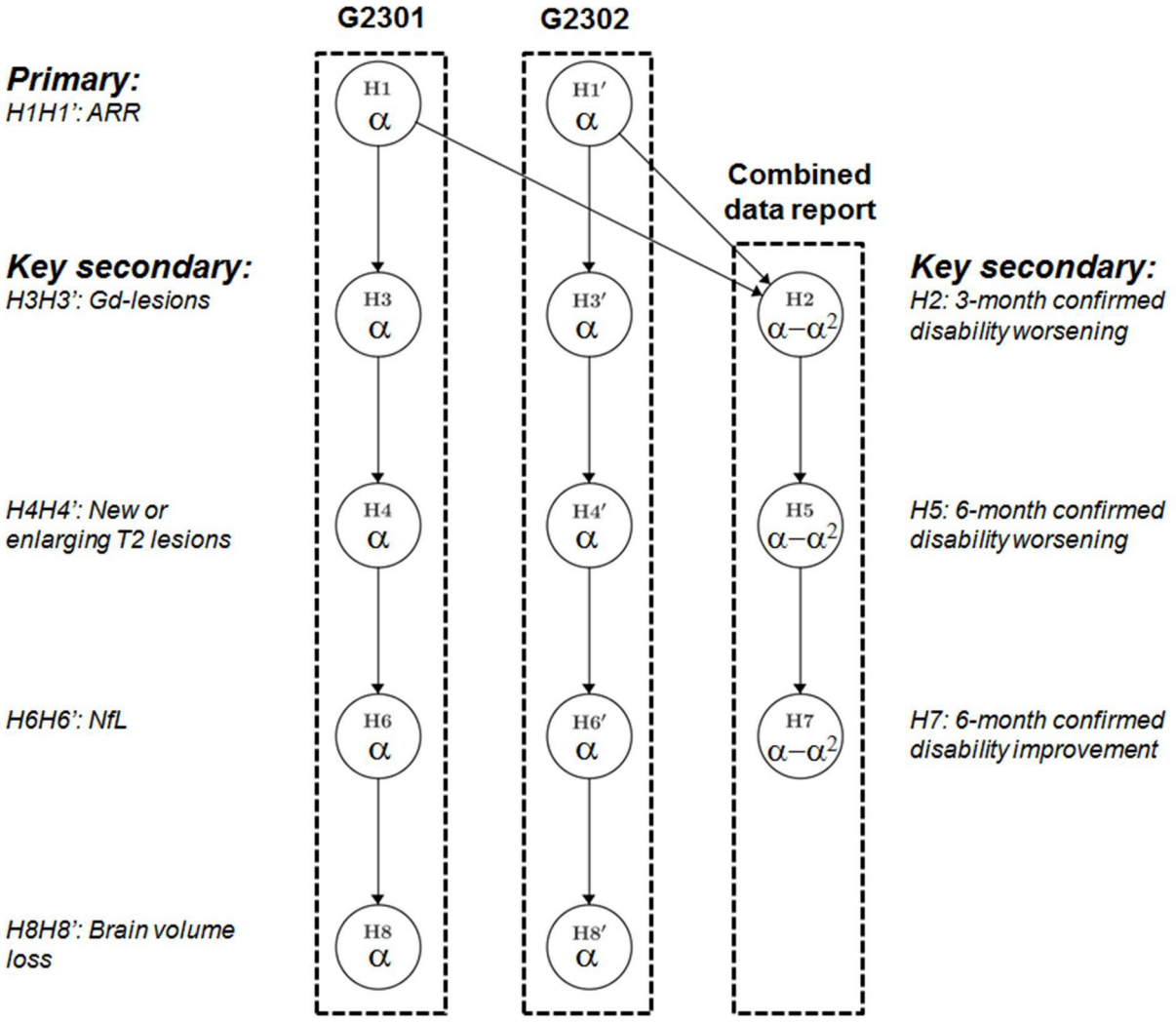
[redacted]

The definition of Region is intended to correspond to that used for the stratification of the randomization. However, the definition of Region may be modified and defined in the statistical analysis plan if that is indicated based on statistical criteria (e.g. non-convergence of models). In addition, the statistical analysis plan may define a process how the primary model can be simplified (e.g. by excluding covariates) in case of non-convergence.

9.4.1.1 Multiplicity adjustment

The planned submission consists of 2 studies of identical design (COMB157G2302 and COMB157G2301), each with multiple endpoints. In order to control the type-I error rate ("false positive rate") at the level of the individual studies, and at the level of the submission as a whole, the testing strategy illustrated in Figure 9-1 below will be implemented.

Figure 9-1 Testing procedure and type-I-error control



Testing procedure and type-I-error control in the planned ofatumumab submission which consists of studies COMB157G2302 and COMB157G2301 (both with identical design). Hypotheses can only be tested in sequential order as indicated by the arrows. The number

associated with each hypothesis (α, or α-α^2) indicates the significance level at which that hypothesis can be tested. If the null-hypothesis for the primary objective (ARR) can be rejected within a study, MRI- and NfL-related hypotheses will be tested in sequential order within that study as long as all proceeding hypotheses can successfully be rejected. Disability-related hypotheses will only be tested in the combined data of the 2 studies, if the primary null-hypotheses can be rejected in both studies first. At the study-level, the type-I error rate (one-sided) is controlled at ≤ 0.025. In the submission, the type-I error rate is controlled at ≤ 0.000625 (=0.025^2) for the primary hypothesis and at ≤ 0.025 when considering all endpoints.

The primary hypothesis (ARR) and all MRI- and NfL-related key-secondary hypotheses will be tested in hierarchical order within study (Figure 9-1). The testing procedure starts with the statistical test of the primary null-hypothesis (ARR) and continues to lower ranking hypotheses as long as the proceeding null hypotheses can all be rejected in favor of ofatumumab in a two-sided statistical test with a p-value ≤ 0.05. This testing procedure controls the type-I error rate to ≤ 0.05 within study.

If both studies independently reject the primary null-hypothesis (ARR) in favor of ofatumumab in a two-sided statistical test with p-value ≤ 0.05, disability-endpoints will be addressed in the combined data of COMB157G2302 and COMB157G2301, at the submission level. Disability endpoints will be tested in hierarchical order as indicated by arrows in Figure 9-1. The testing procedure continues to the next lower ranking disability-hypothesis as long as the previous null-hypothesis can be rejected in favor of ofatumumab in a two-sided statistical test with a p-value ≤ 0.04875 (=2*[0.025-0.025^2]).

Provided the primary hypothesis can be rejected in both studies, disability-related endpoints can be tested regardless of the outcome of MRI- and NfL-related endpoints, and vice-versa.

Under the global null-hypothesis (i.e. no difference between ofatumumab and teriflunomide), the testing procedure controls the type-I error rate (one-sided) at the study-level to ≤ 0.025, and at the submission level to ≤ 0.000625 (=0.025^2). Considering all possible configurations of true and false positive null hypotheses, the type-I error control at the level of the submission is ≤ 0.000625 for the primary objective, and ≤ 0.025 for all hypotheses.

The type-I error is controlled by the testing procedure. All confidence intervals and p-values in the study report will be presented without adjustments.

9.4.2 Handling of missing values/censoring/discontinuations

The primary NB (negative binomial) model with an offset for the time in study adjusts for missing information (drop-out) under the assumption of non-informative drop-out, information is missing at random, and constant relapse rate over time. According to the protocol, subjects who discontinue study treatment should remain in the study and follow the assessment schedule. The primary analysis will use all available data collected in the double-blind treatment epoch, irrespective if collected after the permanent discontinuation of study treatment. In addition, a sensitivity analysis will be conducted to allow for the possibility that relapse rates may be non-constant over time (i.e. higher during the onset-of action of both drugs for a period of 8 weeks).

[redacted]

9.4.3 Sensitivity analyses

The primary analysis will be repeated based on all reported MS relapses (rather than on only the confirmed ones).

The primary analysis will be repeated using the per-protocol set to provide an analysis of on-treatment data from subjects who have no major protocol violations. Relapses which occurred after permanent discontinuation of study medication will be excluded and natural log (time on study drug in years) rather than natural log (time on study in years) will be used as the offset variable in the negative binomial model.

To estimate relapse rates and the treatment effect between ofatumumab 20 mg sc once monthly and teriflunomide 14 mg po once daily during the initial "onset of action" period of 8 weeks (≤ 56 days=8*7 days), and relapse rates and the treatment effect thereafter (> 56 days; long-term efficacy) a sensitivity analysis will be conducted. This analysis will be implemented as a piecewise negative binomial model assuming different event rates and ARR-ratios before and after week 8, but constant dispersion. Per patient, 2 cumulative count-records (confirmed relapses ≤ 56 days, and > 56), and 2 corresponding time records (time-in-study ≤ 56 days, and > 56) will be calculated. The negative binomial model will be defined with the number of confirmed relapses as the response variable, with log-link and time-in-study as the offset variable. The model will use the same factors and covariates as the primary model.

For each time period (≤ 56 days, and > 56 days), the adjusted ARR (i.e., model-based estimate adjusted for covariates) and the corresponding 95% confidence intervals will be provided by treatment, together an ARR ratio between ofatumumab 20 mg sc once monthly and teriflunomide 14 mg po once daily (also expressed as percentage reduction relative to control group) with corresponding 95% confidence intervals and p-values.

Additionally, the time-to-first relapse will be analyzed in a Cox proportional hazards model. In comparison with the primary analysis in a negative binomial model, the Cox proportional hazards model does not assume constant relapse rates (but rather it assumes proportional hazards). The Cox proportional hazards model will be specified with treatment, region, number of relapses in previous year, baseline EDSS, baseline number of T1 Gd-enhancing lesions and the patient's age at baseline as covariates.

Additional sensitivity analyses may be defined in the analysis plan prior to database lock.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

All efficacy analysis will be done based on the FAS, unless explicitly stated otherwise

9.5.1.1 Key-secondary efficacy endpoints

9.5.1.1.1 Disability worsening (3-month or 6-month confirmed)

A 3-month confirmed disability worsening (3mCDW) is defined as an increase from baseline in EDSS sustained for at least 3 months (Table 9-1). Analogously, a 6-month confirmed disability worsening (6mCDW) is defined as an increase from baseline in EDSS sustained for

[redacted]

at least 6 months. This means that after a scheduled or unscheduled visit at which the patient fulfills the disability worsening criterion, all EDSS assessments (scheduled or unscheduled) need to also fulfill the worsening criteria until the worsening ("the event") can be confirmed at the first scheduled visit that occurs 3-months (or 6 months) after the onset of the worsening, or later.

Censoring occurs in all patients who did not experience a 3mCDW (or 6mCDW) event in the study (censoring also occurs in patients who had a "tentative" disability worsening that could not be confirmed due to an early discontinuation or any another reason). The censoring time is defined as the time from the first dose to the last available EDSS assessment.

Table 9-1 Criterion for disability worsening based on change in EDSS score

Total EDSS at baseline*	"Disability worsening" criterion
0	≥ +1.5
1 to 5	≥ +1
≥5.5	≥ +0.5

EDSS=Expanded Disability Status Scale

A 3-month confirmed disability worsening (3mCDW) can have an onset at any scheduled or unscheduled visit if the disability worsening criterion is met. A disability worsening can only be confirmed at a scheduled visit if, over a period of 3 months (≥ 90 days=3*30) time interval, all assessments meet the worsening criterion.

A 6-month confirmed disability worsening (6-mCDW) can have an onset at any scheduled or unscheduled visit if the disability worsening criterion is met. A disability worsening event can only be confirmed at a scheduled visit if, over a period of 6 months (≥ 166 days=6*30-14) time interval, all assessments meet the worsening criterion.

If a patients dies due to MS (EDSS=10 at any time), it will be considered a confirmed disability worsening regardless of the baseline EDSS or the change in EDSS.

* Baseline EDSS is defined as the last EDSS assessment prior to the first dose of study medication (protocol inclusion criterion is EDSS 0-5.5)

Hypothesis and Analysis of disability worsening (3mCDW, 6mCDW)

The hypothesis and the analysis methods will be identical for 3mCDW and 6mCDW. For brevity the hypothesis and analysis methods are only specified in full for 3mCDW.

The null hypothesis is that there is no difference in the time to 3mCDW between ofatumumab 20 mg sc and teriflunomide 14 mg po

- Superiority of ofatumumab 20 mg sc over teriflunomide 14 mg po will be concluded if there is a reduction in risk (estimated hazard ratio from Cox-model< 1) in patients treated with ofatumumab compared with teriflunomide and the observed p-value for the between-treatment comparison is less than the two-sided significance level of ≤ 0.04875 (=2*[0.025-0.025^2]). The multiplicity adjustment explained in Section 9.4.1.1 applies.

Confirmatory analysis for disability-related endpoints: The confirmatory analysis of time-to-3mCDW will be done in a meta-analysis based on the combined FAS populations from COMB157G2302 and COMB157G2301.

[redacted]

The null hypothesis will be tested using a stratified Cox proportional hazards model with study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate. The model will contain a treatment-by-study interaction. For confirmatory purposes the hazard ratio between ofatumumab and teriflunomide will be estimated with 95% confidence interval and p-value from the combined data from both studies in this meta-analysis. In addition, between-study heterogeneity will be tested as the type-3 test of the treatment-by-study interaction; the corresponding p-value will be provided. For information only, the hazard ratio for each study will be estimated by study from the same model with corresponding 95% confidence intervals and p-values.

Supportive analysis: Kaplan-Meier curves (and/or cumulative incidence plots) will be provided by treatment for the combined study populations as well as by-study to present the time-dependent cumulative probability of subjects reaching 3mCDW.

By-treatment Kaplan-Meier (KM) estimates (and/or 1-KM estimates) will be calculated for the combined study data at Month 6, and in 6 monthly intervals from there until less than 100 patients per arm are at-risk, with 95% confidence intervals. Similar estimates will be provided by study.

To estimate the hazard ratio between ofatumumab 20 mg sc once monthly and teriflunomide 14 mg po once daily during the initial "onset of action" period of 8 weeks (≤ 56 days=8*7 days), and thereafter (> 56 days; long-term efficacy) a sensitivity analysis will be conducted. The Cox-proportional hazards model will be specified as above, but in addition a time-dependent indicator variable (0 if record corresponds to the first 8 weeks, 1 otherwise) and an indicator-by-treatment interaction will be included in the model. From this model separate hazard ratios with 95% confidence intervals and p-values will be estimated for the first 8 weeks of treatment and the time period thereafter.

A sensitivity analysis to the confirmatory Cox proportional hazard ratio will consider all patients who discontinue from the study due to "lack of efficacy" as patients with a confirmed event. The event time for these patients will be calculated based on the date of the discontinuation from study relative to the first dose date. Additional analyses or imputation schemes may be described in the statistical analysis plan prior to database lock.

9.5.1.1.2 Disability improvement (6-month confirmed)

A 6-month confirmed disability improvement (6mCDI) is defined as a decrease from baseline EDSS sustained for at least 6 months (Table 9-2). Censoring occurs in patients who did not experience a 6mCDI event in the study. The censoring time is defined as the time from the first dose to the last EDSS assessment.

Table 9-2 Criterion for disability improvement based on change in EDSS score

Total EDSS at baseline*	**"Disability improvement" criterion**
0 to 1.5	No improvement possible
≥2 to 6	≤ -1
≥6.5 to 9.5	≤ -0.5
EDSS=Expanded Disability Status Scale; 6mCDI=6-month Confirmed Disability Improvement.	

[redacted]

6mCDI: A disability improvement can have an onset at any scheduled or unscheduled visit if the disability improvement criterion is met. A disability improvement can only be "confirmed" at a scheduled visit if, over a period of 6 months (≥166 days=6*30-14) time interval, all assessments meet the improvement criterion. A 6mCDI sustained until the End of Study is defined as a 6mCDI after which all EDSS assessments meet the disability improvement criterion through End of Study.
*protocol inclusion criterion is EDSS 0-5.5

Hypothesis and Analysis of disability improvement

The null hypothesis is that there is no difference in the time to 6mCDI between ofatumumab 20 mg sc and teriflunomide 14 mg po

- Superiority of ofatumumab 20 mg sc over teriflunomide 14 mg po will be concluded if there is an improved chance of a 6mCDI (estimated hazard ratio from Cox-model > 1) in patients treated with ofatumumab compared with teriflunomide and the observed p-value for the between-treatment comparison is less than the two-sided significance level of ≤ 0.04875 (=2*[0.025-0.025^2]). The multiplicity adjustment explained in Section 9.4.1.1 applies.

Confirmatory analysis for disability-related endpoints: The confirmatory analysis of time-to-6mCDI will be done in a meta-analysis based on the combined FAS populations from COMB157G2302 and COMB157G2301.

The null hypothesis will be tested using a stratified Cox proportional hazards model with study as stratum, treatment, and region as factors and baseline EDSS as a continuous covariate. The model will contain a treatment-by-study interaction. For confirmatory purposes the hazard ratio between ofatumumab and teriflunomide will be estimated with 95% confidence interval and p-value from the combined data from both studies in this meta-analysis. In addition, between-study heterogeneity will be tested as the type-3 test of the treatment-by-study interaction; the corresponding p-value will be provided. For information only, the hazard ratio for each study will be estimated by study from the same model with corresponding 95% confidence intervals and p-values.

Kaplan-Meier curves (and/or cumulative incidence plots) and by-treatment Kaplan-Meier (KM) estimates (and/or 1-KM estimates) will be calculated for the combined study data at Month 6, and in 6 monthly intervals from there until less than 100 patients per arm are at-risk, with 95% confidence intervals. Similar estimates will be provided by study.

A similar analysis (Cox proportional hazards model, Kaplan-Meier curves) will be performed for 6mCDI sustained until the End of Study.

9.5.1.1.3 Number of Gd-enhancing lesions per scan

The null hypothesis is that there is no difference in the number of Gd-enhancing lesions per scan between ofatumumab 20 mg sc and teriflunomide 14 mg po

- Superiority of ofatumumab 20 mg sc over teriflunomide 14 mg po will be concluded if there are fewer Gd-enhancing lesions per scan (estimated rate ratio from a negative binomial model< 1) in patients treated with ofatumumab compared with teriflunomide and the observed p-value for the between-treatment comparison is less than the two-

[redacted]

sided significance level of 0.05. The multiplicity adjustment explained in Section 9.4.1.1 applies.

Confirmatory analysis of the number of Gd-enhancing lesions per scan: The confirmatory analysis of the number of Gd-enhancing lesions per MRI-scan will be done based on the FAS using a negative binomial regression model with log-link. The total number of Gd-enhancing lesions (cumulative count of Gd-enhancing lesions across all the MRI-scans per patient) will be used as the response variable, and the natural log of the number of MRI-scans will serve as the offset variable to adjust for the different number of MRI-scans between patients related to the flexible follow-up time in this study. The model will include treatment and region (factors), and age, and number of Gd-enhancing lesions at baseline as continuous covariates.

The number of Gd-enhancing lesions per scan will be estimated by treatment with 95% confidence interval. The between treatment effect will be calculated as rate ratio with 95% confidence interval and p-value. In addition the relative reduction in the number of Gd-enhancing lesion per scan will be computed as the rate ratio minus one (1) and expressed as a percentage.

9.5.1.1.4 Annualized rate of new or enlarging T2 lesions

The null hypothesis is that there is no difference in the number of new or enlarging T2 lesions between ofatumumab 20 mg sc and teriflunomide 14 mg po

- Superiority of ofatumumab 20 mg sc over teriflunomide 14 mg po will be concluded if there are fewer new or enlarging T2 lesions (estimated rate ratio from a negative binomial model< 1) in patients treated with ofatumumab compared with teriflunomide and the observed p-value for the between-treatment comparison is less than the two-sided significance level of 0.05. The multiplicity adjustment explained in Section 9.4.1.1 applies.

Confirmatory analysis of the Annualized rate of new or enlarging T2 lesions: The confirmatory analysis of the annualized rate of new or enlarging T2 lesions will be done based on the FAS using a negative binomial regression model with log-link. The number of new or enlarging T2 lesions on the last available MRI scan relative to baseline will be used as the response variable, and the natural log of the time (in years) of the MRI-assessment from the baseline/Screening scan will serve as the offset variable to adjust for the various lengths of follow-up times between patients in this study. The model will include treatment and region (factors), and age, and baseline volume of T2 lesions as continuous covariates.

The number of new or enlarging T2 lesions per year will be estimated by treatment with 95% confidence interval. The between treatment effect will be calculated as rate ratio with 95% confidence interval and p-value. In addition the relative reduction in the number new or enlarging T2 lesions per year will be computed as the rate ratio minus one (1) and expressed as a percentage.

The number of new or enlarging T2 lesions are a cumulative measure of disease activity. Since the number of new or enlarging T2 lesion is assessed relative to the MRI scan collected at Screening (i.e. well before the start of study medication intake), it is expected that this analysis underestimates the true treatment effect. Therefore, a supportive analysis will be performed

[redacted]

based on the new or enlarging T2 lesions between the Month 12 scan and the End of Study scan (this analysis is described in Section 9.5.1.2).

9.5.1.1.5 Neurofilament light chain

The null hypothesis is that there is no difference in NfL between ofatumumab and 20 mg sc teriflunomide 14 mg po by month 3.

- Superiority of ofatumumab 20 mg sc over teriflunomide 14 mg po will be concluded if NfL levels are already lower at month 3 in patients treated with ofatumumab compared with teriflunomide and the observed p-value for the between-treatment comparison is less than the two-sided significance level of 0.05. The multiplicity adjustment explained in Section 9.4.1.1 applies.

Confirmatory analysis of NfL: The NfL concentration (geometric mean concentration) will be estimated by treatment and time point with 95% confidence intervals using a repeated measures model on the basis of all evaluable log-transformed NfL values. The treatment effect will be estimated in terms of a geometric mean ratio with 95% confidence interval per time point. The statistical hypothesis test will be based on the treatment contrast and p-value obtained at month 3. An unstructured covariance matrix will be used. The model will include treatment, region and the time point as factors, and age, number of Gd-enhancing lesions at baseline, baseline T2 lesion volume and the log-transformed NfL baseline concentration as continuous adjustments. The treatment effect of ofatumumab versus teriflunomide will be visualized in a line plot with confidence intervals.

9.5.1.1.6 Brain volume loss

The null hypothesis is that there is no difference in brain volume change between ofatumumab 20 mg sc and teriflunomide 14 mg po

- Superiority of ofatumumab 20 mg sc over teriflunomide 14 mg po will be concluded if there is less brain volume loss (positive difference in slope from the random coefficient model) in patients treated with ofatumumab compared with teriflunomide and the observed p-value for the between-treatment comparison is less than the two-sided significance level of 0.05. The multiplicity adjustment explained in Section 9.4.1.1 applies.

Confirmatory analysis of brain volume loss: The percentage change from baseline in brain volume will be estimated on the basis of all scans up to the last available MRI scan that evaluated percentage brain volume change relative to baseline. A random coefficients model will be used as main analysis for this endpoint in order to adjust for the various length of follow-up time in this study (brain volume change was approximately linear over time and approximately normally distributed in 3 independent studies of the fingolimod Phase 3 program). The random coefficients model will include treatment, region as fixed effects (factors), and time, number of Gd-enhancing lesions at baseline, baseline T2 volume, and normalized brain volume at baseline as continuous covariates. Time is defined as the time from

[redacted]

first dose date to the date of MRI scan in year and will be calculated by ((MRI scan date – date of last scan prior to the first dose of study medication) +1)/365.25. Time as a continuous covariate allows for estimation of different slopes and intercepts among treatment groups. The model will also contain random terms to account for deviations about the population slope and intercept. The statistical test will address the question whether there is a difference in the slope of brain volume change by treatment group. The annual rate of percent change from baseline in brain volume is approximated as the population slope within the treatment group. Since the random coefficients model allows for the estimation of different slopes and intercepts among the treatment groups, differences between treatments at any time can be summarized using this model. Model estimates of percentage brain volume change at Month 12 and 24 will be provided by treatment with corresponding 95% confidence interval. Treatment differences will be estimated at the same time points with confidence interval and a p-value for the test of a difference in slope.

Additionally, percentage brain volume change (PBVC) and the annualized rate of brain atrophy (ARBA) will be summarized by visit. ARBA describes the "averaged annual percentage change" in brain volume. It is designed to adjust for differences in the time spent between 2 scans that are compared by standardizing the percentage change in brain volume to 1 year. The logic of interest rates applies. ARBA = $[(PBVC/100+1)^{(365.25/days)}-1]*100$, where "PBVC" represents the percentage brain volume change obtained between 2 scans and "days" stands for the number of days between the 2 scans that are being compared. Cross-sectional comparisons at each visit will be made using ANCOVA models with ARBA as the response variable, treatment and region as factors, number of Gd-enhancing lesions at baseline, baseline T2 volume, and normalized brain volume at baseline as continuous covariate. Line plots of percentage brain volume change over time by treatment will be provided.

In addition, the percentage change from baseline in brain volume will be estimated on the basis of all available MRI scans that evaluated percentage brain volume change relative to baseline in a repeated measures model. A repeated measure model with the percent change in brain volume from baseline up to end of study as the dependent variables with unstructured covariance matrix will be used. The model will include treatment and scanning time point as factors, region, number of Gd-enhancing lesions at baseline, baseline T2 volume and normalized brain volume at baseline as covariates. For the purpose of this model, visit windows will be used to map all available MRI assessments to Month 12 or 24. The comparison of treatment differences in mean at Month 12, 24 will be made using this model.

Percentage brain volume change is cumulative measure of disease activity. Since the percentage brain volume change is assessed relative to the MRI scan collected at Screening (i.e. well before the start of study medication intake), it is expected that these analyses tend to underestimate the true treatment difference between study drugs.

9.5.1.2 Other secondary efficacy variables

- The analysis of "Time of first relapse" and "Annualized relapse rates > 8 weeks after the onset of treatment" is described in (Section 9.4.3) as sensitivity analysis to the primary analysis.

[redacted]

- The analysis of the "Risk of a 3mCDW > 8 weeks after the onset of treatment" and "Risk of a 6mCDW > 8 weeks after the onset of treatment" is described in (Section 9.5.1.1.1) as a supportive analysis to the key-secondary 3mCDW and the 6mCDW, respectively.
- Time to 6mCCD will be analyzed in the combined FAS from studies COMB157G2301 and COMB157G2302, in a Cox proportional hazards model with study as stratum, treatment and region as factors, and baseline SDMT as continuous covariates.
- Time to 6mCDW or a 6mCCD, whichever is reached first, will be analyzed in the combined FAS from studies COMB157G2301 and COMB157G2302, in a Cox proportional hazards model with study as stratum, treatment and region as factors, and baseline EDSS and baseline SDMT as continuous covariates.
- SDMT scores and change from baseline will be summarized by visit and by treatment. The change from baseline will be analyzed and compared between treatments in a repeated measures mixed effects model.
- Time to 6-month confirmed worsening of at least 20% in the timed 25-foot walk test (T25FW) will be analyzed in the combined FAS from studies COMB157G2302 and COMB157G2301, in a Cox proportional hazards model with study as stratum, treatment, and region as factors and the baseline T25FW-result as a continuous covariate. The baseline 25TWT-result is defined as the last assessment prior to the first dose of study medication; the 20% worsening is defined relative to this reference value.
- Time to 6-month confirmed worsening of at least 20% in the 9-hole peg test (9HPT) will be analyzed in the combined FAS from studies COMB157G2302 and COMB157G2301, in a Cox proportional hazards model with study as stratum, treatment, and region as factors and baseline 9HPT-result as a continuous covariate. The baseline 9HPT-result is defined as the last assessment prior to the first dose of study medication; the 20% worsening is defined relative to this reference value.
- Change in T2 lesion volume on MRI will be summarized by visit. Cross-sectional analyzes will be done by using a rank ANCOVA with treatment and region (factors), and baseline T2 volume as a continuous covariate.
- Number of new or enlarging T2 lesions on MRI between Month 12 and EOS will be analyzed in a negative binomial regression model, and presented similarly to that used for the annualized rate of new or enlarging T2 lesions. The number of new T2 lesions on the EOS scan relative to the Month 12 scan will be used as the response variable, the natural log of the time (in years) of the EOS MRI-assessment from the Month 12 scan will serve as the offset variable to adjust for the various lengths of follow-up times between patients in this study.
- Proportion of patients free of clinical and MRI disease activity (No evidence of disease activity; NEDA-4) will be analyzed cross-sectionally at year 1 and year 2 in a logistic regression model with treatment and region as factor, and age, baseline EDSS, and number of Gd-lesions at baseline as covariates. NEDA-4 is defined as no 3mCDW, no confirmed MS relapse, no new or enlarging T2 lesions on any MRI scan compared to baseline, and brain volume change > -0.4%/year on all MRI scans (brain volume as measured by ARBA, see Section 9.5.1.1.5). The main analysis will consider only those patients who were

[redacted]

followed-up to the assessment time point in the analysis (e.g. only patients with ≥ 12 months of follow-up in the 12-month assessment of disease freedom, etc.). Intermediate missing values (e.g. due to missing MRI assessments) will be considered not free of disease activity. A sensitivity analysis will be conducted considering all patients who discontinued from the study prior to the assessment timepoint, or have missing MRI assessments prior to the assessment timepoint, as not free of disease activity.

- MSIS-29 physical impact score (items 1-20), psychological impact score (items 21-29) and the corresponding changes from baseline will be summarized by visit. The change from baseline at specific post-baseline visits will be compared between treatment groups using a repeated measures mixed effects analysis.

If ofatumumab significantly reduces NfL as compared with teriflunomide, the following additional analyses will be performed: In the subgroup of newly diagnosed (within 3 years prior to the screening visit), treatment-naïve (no prior MS DMT) patients, the hypotheses will be tested that patients with a high (>median) NfL concentration at baseline will experience more new or enlarging T2 lesions, a higher ARR and tend to have a worse disease course on EDSS during the study compared with patients with low (≤median) NfL concentration at baseline:

- The T2 lesion rate will be estimated using a negative binomial model similar to the one specified in section 9.5.1.1.4. In addition, the model will include a treatment-by-NfL baseline category interaction. The T2 lesion rate will be estimated by treatment within baseline NfL category. The treatment effect will be expressed as a lesion rate ratio with 95% confidence interval, for low and high baseline NfL category, respectively. The statistical hypothesis test with regards to the prognostic value of NfL for new lesion formation will be based on the high vs low baseline NfL category contrast in the teriflunomide group.
- The ARR will be estimated using a negative binomial model similar to the primary model specified in section 9.4. In addition, the model will include a treatment-by-NfL baseline category interaction. The ARR will be estimated by treatment within baseline NfL category. The treatment effect will be expressed as an ARR-ratio with 95% confidence interval, for low and high baseline NfL category, respectively. The statistical hypothesis test with regards to the prognostic value of NfL for on-study relapses will be based on the high vs low baseline NfL category contrast in the teriflunomide group.
- The disease course based on EDSS will be analyzed as time to 3mCDW, 6mCDW or 6mCDI using Kaplan-Meier curves and a Cox proportional hazard model based on the combined data from COMB157G2301 and COMB157G2302. The model will include study as stratum, treatment, region and baseline NfL category as factors and baseline EDSS as a continuous covariate. The treatment effect will be expressed as hazard ratio with 95% confidence interval, for low and high baseline NfL category, respectively. The statistical hypothesis test of the prognostic value of NfL for disability changes will be based on the main effect of NfL category (due to the expected low number of events in this subgroup). It is acknowledged that the study will not be powered to show an effect on disability outcomes in subgroups.
- The benefit/risk profile of ofatumumab in the subgroup of newly diagnosed, treatment-naïve patients with high NfL will be compared to the overall trial results based on the above described efficacy analyses. The safety profile in the subgroup of newly diagnosed,

[redacted]

treatment-naïve patients with high NfL will be compared to the overall trial population by summarizing adverse events by treatment side-by-side for the subgroup and the overall trial.

9.5.2 Safety variables

Safety analyses will be conducted using the safety (SAF) dataset. Patients will be grouped by the actual treatment received. Unless explicitly otherwise stated, only data up to and including the safety cutoff of 100 days after permanent study drug discontinuation will be included in the analysis and data beyond this time point for a given patient will be excluded from the safety analysis. The safety cutoff of 100 days (5 x 20 days) takes the long half-life of the comparator-drug into account.

The assessment of safety will be primarily based on the frequency of adverse events (including death and non-fatal serious adverse events). Additional safety assessments include laboratory tests, physical examination (including examination of skin), vital sign measures, ECG evaluations and assessment of suicidality. Clinically significant findings in these additional safety assessments will be reported as adverse events and analyzed as such. In addition all safety assessments will be summarized or listed as appropriate. The analyses of additional safety assessments will be defined on the level of the statistical analysis plan.

9.5.2.1 Adverse events

Treatment emergent adverse events (TEAE) will be reported up to and including safety cut off of 100 days after permanent study drug discontinuation. All serious TEAEs and death will be included, regardless of safety cut-off.

TEAEs will be summarized (number of cases as a percentage of number at risk) by treatment group. Number and percentage of patients with TEAE will be summarized by primary system organ class and preferred term. Serious TEAEs, drug related TEAEs and TEAEs leading to premature discontinuation from study drug will be presented in a similar format as adverse events. In addition, TEAEs will be reported by CTCAE grade.

Given the flexible follow-up of the study, TEAEs will also be summarized by reporting exposure-adjusted incidence rates (assuming a Poisson-process for adverse events). This will be done for all TEAEs, and for only serious TEAEs, per primary system organ class and preferred term. The analysis will be performed in a time-at-risk as defined in Section 9.3. Similar tables can be produced for selected risks (e.g. SMQs) on an as-needed basis.

9.5.2.2 Laboratory data

The summary of laboratory evaluations will be presented for 3 groups of laboratory tests: Hematology, Chemistry and Urinalysis.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values, and by presenting shift tables using clinically notable ranges (baseline to most extreme post-baseline value). Laboratory data, and specifically liver enzymes, will also be summarized by maximum change from baseline.

[redacted]

For liver enzymes, the number of subjects with newly occurring liver enzymes abnormalities will be summarized by treatment group. Newly occurring liver enzymes abnormalities are defined relative to the upper limit of normal (ULN). Example of a newly occurring liver enzyme event are ALT or AST > 3xULN & TBL > 2xULN & ALP ≤ 2xULN or a reported Hy's Law case (refer also to Appendix 1).

SMQ and preferred terms searches for drug-related hepatic disorders will be conducted. Results of these searches will be analyzed and presented in a similar format as other adverse events. In case of liver events detailed listings will be provided.

In case of renal events, the overall frequency of events and percentage of patients with renal events during the treatment period will be summarized and detailed listings provided. Additional analyses of renal events can be defined in the statistical analysis plan.

9.5.2.3 Vital signs

Vital sign measurements and their change from baseline will be summarized with descriptive (mean, median, standard deviation, min, max) by visit. The number and percentage of subjects with clinically notable vital signs will be presented.

9.5.2.4 Suicidality evaluations

The Columbia Suicide Severity Rating Scale (C-SSRS) data will be mapped to Columbia Classification Algorithm for Suicide assessment (C-CASA) as per FDA guidance on suicidality.

The proportion of subjects who have completed suicide, suicide attempt, preparatory actions toward imminent suicidal behavior, suicidal ideation, and self-injurious behavior without suicidal intent as per the C-CASA scale during the study will be summarized by treatment group.

9.5.2.5 Other safety evaluations

All clinically significant safety findings based on additional safety evaluations (e.g. ECG or physical examination including assessments of skin, lymph nodes, lung, etc.) must be reported as adverse events on the AE CRF. The statistical analysis of these findings will be done in the analysis of adverse events.

Other safety data will be summarized or listed as appropriate.

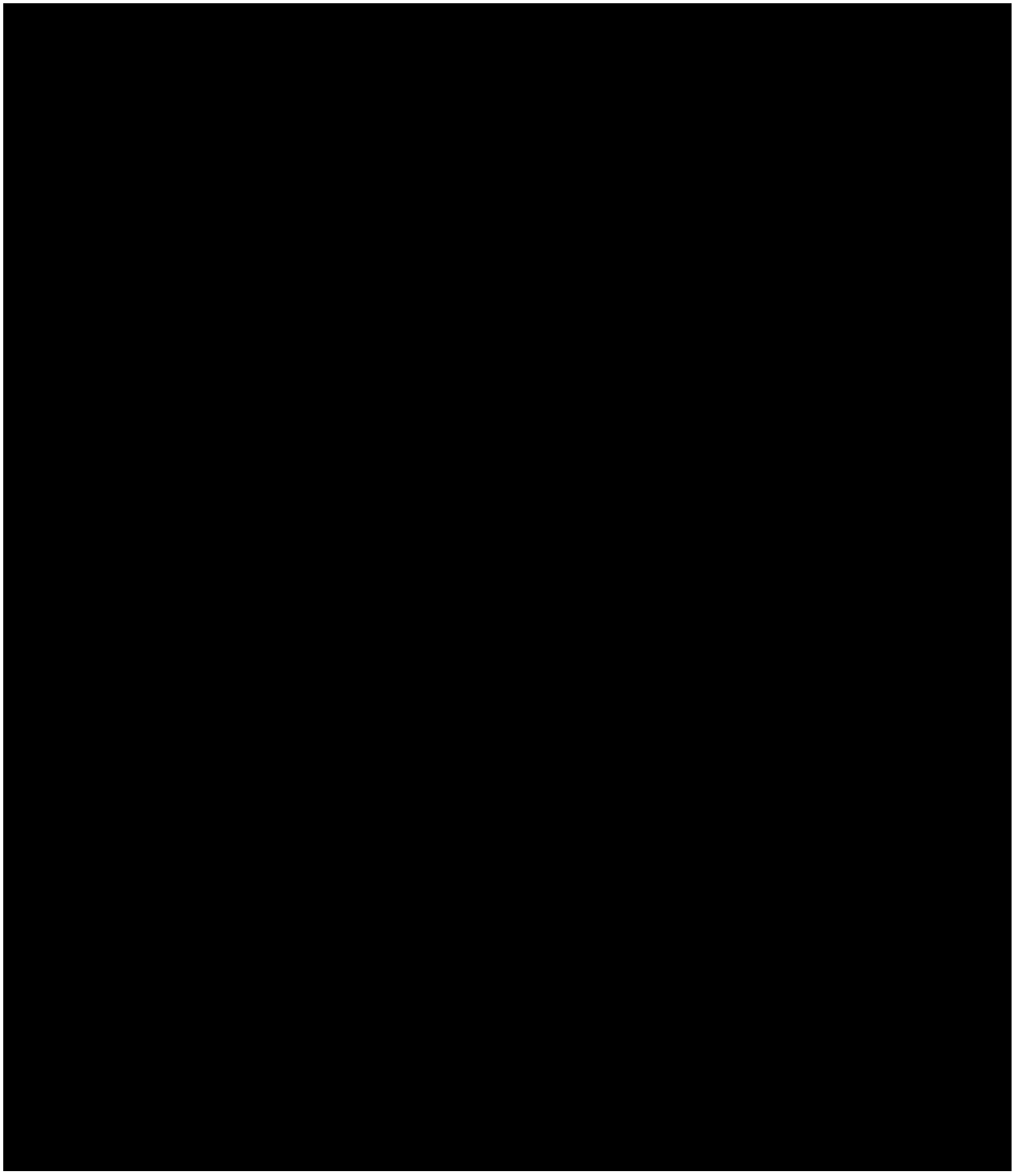
9.5.2.6 Safety evaluation during the Safety Follow-up epoch

Safety data collected during the Safety Follow-up epoch includes adverse events, laboratory assessments to measure B-cell repletion. All safety assessments after study drug discontinuation will be analyzed, summarized or listed.

Safety data collected during the Safety Follow-up epoch will be reported separately. These analyses will include laboratory assessments including B-cell repletion, adverse events, vital signs, MS relapses and change in EDSS. For patients who discontinued from study drug but followed the assessment schedule of the Treatment epoch, change variables will be defined relative to the end of treatment visit (EOT), for all other patients change is defined relative to the End of Study visit (EOS). Since post-treatment safety follow-up in the Safety Follow-up epoch may continue for up to 9 months (or longer if criteria for loner follow up are met) after

[redacted]

completion of the Treatment epoch study, the study report for the core study (Screening and Treatment epoch) will be completed based on the completed core study i.e. based on all patients who have completed the Treatment epoch, and the partial data from the Safety Follow-up epoch available at that time. A complete analysis of the post-treatment safety follow-up will be provided in an addendum to the study report when all patients who entered the Safety Follow-up epoch have completed this epoch.



[redacted]

9.5.5 PK/PD modelling

PK concentration data summarized by visit together with by-patient listings will be provided in the study report.

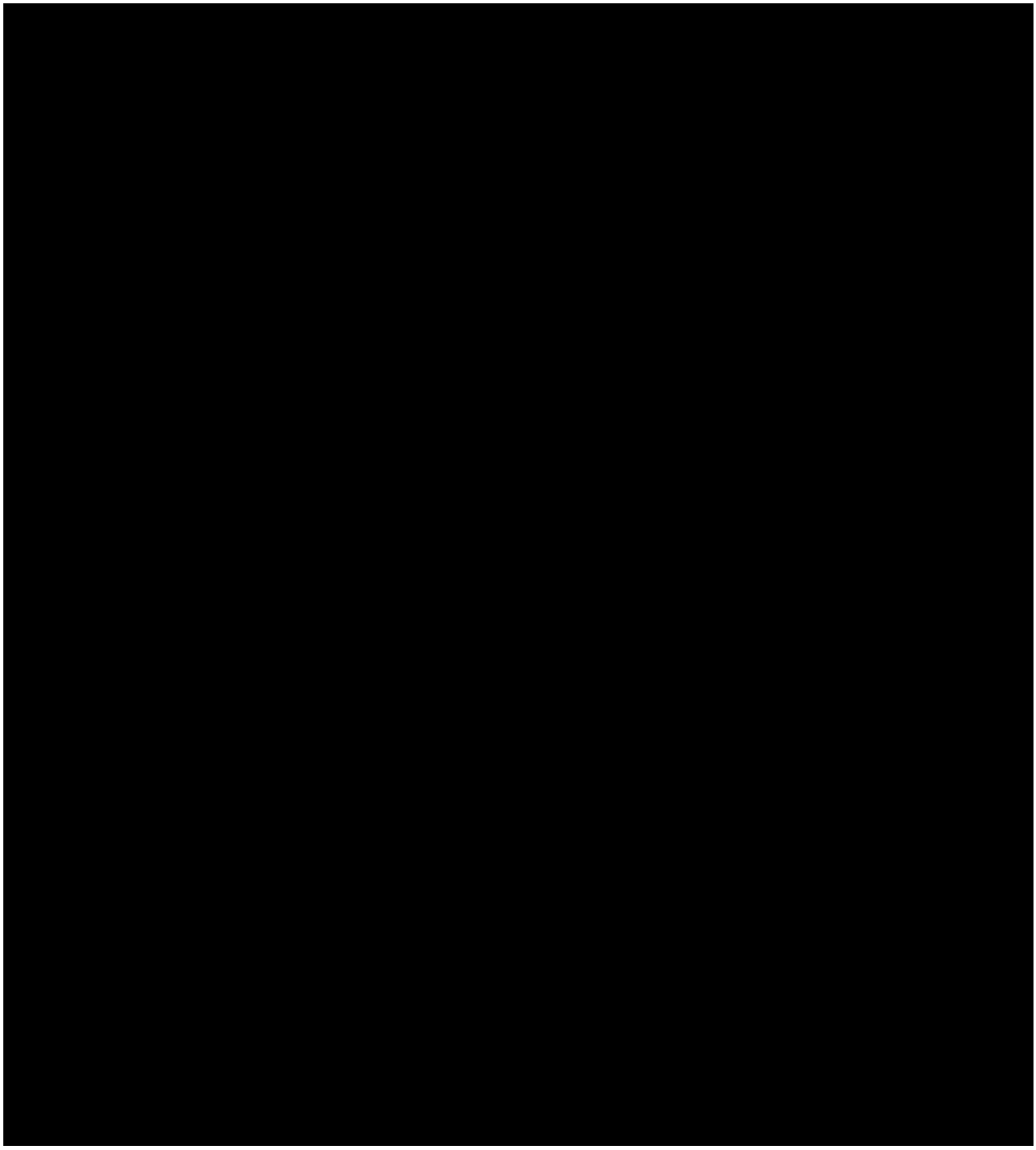
[redacted]

9.5.6 Immunogenicity assessment

Samples will be analyzed for of the presence of human anti-drug antibodies (ADA). The data will be summarized by visit and overall (i.e. proportion of patients with ADA) as an assessment of the immunogenicity potential of ofatumumab. A listing by patient will also beprovided.

[redacted]

[redacted]



9.7 Interim analyses

9.7.1 Unblinding interim analysis

No unblinding interim efficacy analysis is planned for this study.

Regular safety interim analyses will be performed for the independent DMC by an independent team of statisticians and programmers who are not otherwise involved in the conduct of the

study. The data review will be done by the DMC. The DMC will be independent of Novartis and the team involved in the study conduct.

9.7.2 Blinded data reviews

The purpose of the blinded data reviews is to ensure an adequate sample size and follow-up time to address the scientific objectives of the study without un-necessarily exposing patients by adapting design features such as sample size and follow-up duration as indicated by the accumulating data.

Blinded data reviews will be conducted in this study for:

(1) Blinded sample size re-assessment: relapse- (and disability) -related assumptions will be re-assessed based on a review of blinded data to adjust sample size if indicated by the accumulating data. This review will occur prior to the completion of enrolment.

(2) Declaration of End of Study: the 'Information' (Section 9.7.2.3) collected by the study on relapse rates and disability worsening events will be monitored. End of Study will be declared only once when sufficient information has been collected to address the study's primary and key-secondary objectives.

9.7.2.1 Blinded sample size re-estimation

A blinded data review will be done prior to the completion of recruitment based on the initially assumed sample size.

The purpose of the blinded sample size re-estimation is to re-adjust the sample size depending on the activity of the population. If indicated by the data, the sample size of the study can be increased from initially 900 randomized patients to a maximum of 1250 randomized patients.

- The ARR (λ) and the between-patients variability (κ, dispersion parameter) in the overall patient population (i.e., without revealing the treatment code) will be estimated from the blinded data by fitting a negative binomial regression model with log-link to the data, with intercept and age at baseline as the only continuous covariate. Given the 1:1 randomization ratio and the assumed relapse rates by treatment (Section 9.8), the blinded ARR is expected at $\lambda_{blinded}$=0.224 and the dispersion parameter at 0.82. Sample size can be increased if the study acquires 'Information' for ARR at a lower rate than initially anticipated.
- A secondary objective of the blinded review is to review the rate of accumulation of disability. The time to the first 3mCDW and the time to the first 6mCDW will be reviewed based on Kaplan-Meier curves for the overall patient population without revealing the treatment code. These curves will be compared to those expected under the assumption of an exponential distribution of event times and the hazard ratios provided in Section 9.8. Sample size can be increased if rates are substantially lower than anticipated (Table 9-3).

Table 9-3 Anticipated cumulative event probabilities on teriflunomide

Time-at-risk	3mCDW	6mCDW
6 months	4.0%	3.1%

[redacted]

1 year	7.8%	6.2%
2 years	15%	12%
3mCDW=3-month Confirmed Disability Worsening; 6mCDW=6-month Confirmed Disability Worsening The blinded hazard rates, due to the 1:1 randomization ratio, are assumed as the mean of those assumed for ofatumumab and teriflunomide (Section 9.8).		

9.7.2.2 Review of blinded data to declare End of Study

The accumulating blinded data will be analyzed and End of Study (EOS) will be declared for both studies simultaneously when **all** of the following conditions are met.

- Each study (COMB157G2302 and COMB157G2301) have individually collected ≥ 40.3 units of Information for the primary ARR endpoint ("Information" is defined and explained in Section 9.7.2.3). At this time-point both studies will provide 90% power for the detection of a 40% relative treatment effect on ARR in the primary statistical test at a one-sided alpha level of 0.025.
- In the combined data of the 2 studies (COMB157G2302 and COMB157G2301) ≥ 178 3mCDW events have been observed. At this time-point the combined studies have collected sufficient information to provide 90% power for the detection of 38.6% (hazard ratio=0.614) relative reduction in risk of a 3mCDW in a log-rank test at a one-sided alpha-level of 0.025-0.025[2].
- In the combined data of COMB157G2302 and COMB157G2301 studies ≥ 133 6mCDW events have been observed. At this time-point the combined studies have collected sufficient information to provide 80% power for the detection of 38.6% (hazard ratio=0.614) relative reduction in risk of a 6mCDW in a log-rank test at a one-sided alpha-level of 0.025-0.025[2].

9.7.2.3 Statistical 'Information' for annualized relapse rates

The primary endpoint of the study is the annualized relapse rate (ARR). We assume that the number of MS relapses follows a negative binomial distribution, which is a common assumption in MS. The primary hypothesis will be tested in a negative binomial regression model based on the estimation of the ARR-ratio between treatments (the 'estimate'). The power of the statistical test of the primary hypothesis (ARR) does not depend on the sample size or the treatment duration per se; instead, it depends on the Information collected.

- Information is defined as the reciprocal of the estimate's variance, as in a group sequential design.

In the blinded review we will estimate the amount of information (I) generated by the study based on a blinded analysis-based review of the relapse activity (λ) of the recruited patient population and the observed dispersion parameter (κ) in the accumulated study data. A mathematical derivation of the 'information' for a negative binomial distribution is provided in Appendix 5.

Equation 1: Information $I = [1/n \{1/(\lambda_1 T) + 1/(\lambda_2 T) + 2\kappa\}]^{-1}$

where n = number of patients per arm, T the common follow-up time (i.e., the study duration), λ_1 = ARR for ofatumumab and λ_2 = ARR for teriflunomide, and κ = the dispersion parameter ($\kappa > 0$) which describes the between-patient variability.

[redacted]

For this study, ≥ 90% power is required for the primary endpoint. The sample size assumptions for this study are initially T=1.5 years, λ_1=0.168, λ_2=0.28, and κ=0.82 which would provide I=40.3 units of statistical information which corresponds to 90% power for the statistical test of the ARR-ratio between ofatumumab and teriflunomide at the one-sided 2.5% alpha level.

Trial designs with another sample size, or follow-up time, but the same amount of statistical Information, also provide an equivalent power for the detection of 40% reduction in ARR at the one sided 2.5% alpha level. Therefore the first EOS-criterion is met when I ≥ 40.3 units of Information have been collected.

Estimating 'Information' for ARR in a blinded review

As in a blinded sample size review (Friede and Schmidli 2010), fitting a negative binomial model to the aggregate data (i.e., the relapse data of all patients combined) provides an estimate of the overall ARR λ and the dispersion parameter κ. For an assumed rate ratio (clinically meaningful difference) of $\theta = \lambda_1/\lambda_2$, estimates can be obtained of the ARRs in the two groups, $\lambda_1 = 2^* \lambda^* \theta/(1+\theta)$ for ofatumumab, and $\lambda_2 = 2^* \lambda/(1+\theta)$ for teriflunomide.

Since the treatment allocation of the patients ($i = 1,\ldots n_i$) is unknown in this blinded review but randomization was done in a 1:1 ratio, we make the assumption that the follow-up times in the two groups (j = 1,2 with 1 = ofatumumab and 2 = teriflunomide) are the same, i.e., that $T._1 = T._2 = T_{total}/2$, where T_{total} is the total of the follow-up times at the review time. It is further assumed that the sum of the squared follow-up times is the same in both groups, i.e., that $\Sigma_i T_{i1}^2 = \Sigma_i T_{i2}^2 = \Sigma_j \Sigma_i T_i^{\ 2}/2 = T^2_{tota}/2$. The evaluation of the information in Appendix 5 based on blinded information is then:

Equation 2: Information $I = [2/(\lambda_1 T_{total}) + 2/(\lambda_2 T_{total}) + 4\kappa T2_{total}/T_{total}^2]^{-1}$

where λ_1, λ_2, and κ are the re-estimated values at the blinded review.

The information will then be estimated based on Equation 2. The first EoS-criterion is met when ≥40.3 units of information have been collected. The study is then powered at ≥90% for the detection of a 40% reduction in ARR at the one-sided alpha level of 0.025.

9.8 Summary of sample size calculation

Sample size requirements for this study are primarily driven by the disability-related key endpoints. **A total of approximately 900 patients will be randomized to study drug in a 1:1 ratio (450 per treatment arm)**. A second study of identical design with the same sample size will be conducted in parallel. Both studies are independently powered to address the primary endpoint (ARR) and all key-secondary MRI endpoints.

Key-secondary outcomes related to disability will be analyzed in the combined populations of both trials, provided the primary null-hypothesis can be rejected in both studies. Other secondary efficacy endpoints, as well as safety will be analyzed by study.

The total sample size of this study can be increased from 900 patients per study to a maximum of 1250 patients per study based on a blinded sample size re-estimation if either the blinded relapse rate or the event rate of 3mCDW is substantially lower than expected.

All sample size calculations were done in EAST 6, version 6.3, Cytel Inc.

[redacted]

Primary endpoint:

- **ARR:** The total sample size of 900 randomized patients for this trial is sufficient to achieve 90% power for the demonstration of superiority of ofatumumab over teriflunomide based on the primary endpoint (ARR).

Key-secondary endpoints:

The power mentioned for the key-secondary endpoints is conditional on the successful rejection of the null hypothesis for the primary endpoint (ARR), and the successful rejection of all key-secondary endpoints that are to be tested at a higher hierarchical level. Multiplicity adjustments and the testing procedure are defined in Section 9.4.1.1.

- **3mCDW:** A total sample size of 1800 patients across 2 studies of identical design is required and sufficient to provide ≥ 90% power and for the demonstration of superiority based on the 3mCDW.
- **6mCDW** and **6mCDI:** A total sample size of 1800 patients across 2 studies of identical design is sufficient to provide ≥ 80% power for an analysis of 6mCDW and 6mCDI.
- **MRI endpoints:** A total sample size of 900 randomized patients for this trial is sufficient to provide ≥ 80% power for all MRI endpoints which are part of the testing procedure (Number of Gd-T1 lesions per scan, annualized rate of new or newly enlarging T2 lesions, annualized rate of BVL).
- **NfL:** A total sample size of 900 randomized patients for this trial is sufficient to provide a ≥ 90% power for an analysis of the NfL concentration in serum.

9.8.1 Sample size for the primary endpoint (ARR)

A negative binomial distribution of relapses is assumed for the primary analysis; this is a common assumption in MS. The demonstration of a relative reduction of the ARR in patients treated with ofatumumab (λ_{ofa}=0.168) compared with those treated with teriflunomide (λ_{ter}=0.28) by 40% (λ_{ofa} / λ_{ter} =0.6) with a **power of 90%** at a one-sided alpha-level of 0.025 in a study with 1.5 years follow-up and under the assumption of a dispersion parameter κ=0.82 requires a sample size of 322 completers per treatment arm (644 completers for the study). Allowing for 20% uninformative dropouts equally distributed across treatment arms, a total sample size of **805 randomized patients** is required for the study to demonstrate superiority of ofatumumab based on ARR. A sample size of 900 patients per trial (driven by the 3mCDW endpoint), under otherwise the same assumptions as before, would provide approximately 95% power for the demonstration of superiority of ofatumumab over teriflunomide at a one-sided alpha level of 0.000625 (=0.025^2) using the pooled data from 2 studies of identical design. The formula proposed by Keene et al. 2007 was used for the sample size calculation for the primary endpoint.

9.8.1.1 Justification of assumptions for primary endpoint

In the pivotal studies, patients treated with teriflunomide 14 mg (the control treatment for this study) had an ARR=0.32 (Confavreux et al. 2014) and ARR=0.37 (O'Conner et al. 2011). In an additional Phase 3 study of teriflunomide versus Interferon beta-1a, patients treated with

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teriflunomide 14 mg had an ARR=0.26 which was not significantly different from that observed in patients treated with Interferon beta-1a (ARR=0.22). For the purpose of this study an ARR= 0.28 is assumed for patients treated with teriflunomide 14 mg.

Ocrelizumab is an anti-CD20 monoclonal antibody with a similar mode of action as ofatumumab but is administered as infusion. In the ocrelizumab Phase 3 trials an ARR of 0.156 (OPERA I) and 0.155 (OPERA II) (Hauser et al. 2015) were observed for patients treated with Ocrelizumab 600 mg, the corresponding interferon beta-1a controls had an ARR of 0.292 (OPERA I) and 0.290 (OPERA II); the corresponding relative reductions in ARR were 46% (OPERA I) and 47% (OPERA II). In the ocrelizumab Phase 2 trial, patients treated with ocrelizumab 600 mg had an ARR=0.13, those treated with 1000 mg an ARR=0.17 (Kappos et al. 2011). Compared with the Interferon beta-1a control in the same trial (ARR=0.36), ocrelizumab 600 mg and 2000 mg reduced the ARR by 64% or 53%, respectively. Compared to placebo controls from the same trial (ARR=0.64), ocrelizumab 600 mg and 2000 mg reduced the ARR by 80% or 73%, respectively.

Ofatumumab 60 mg every 12 weeks administered subcutaneously showed in the Phase 2 trial (unpublished data) approximately 34% relative reduction in relapse rate versus placebo over the first 24 weeks, but 60% in the second 12 weeks (Week 12 to 24). The relative reduction of Gd-enhancing lesions of approximately 90% observed in patients treated with ofatumumab relative to those treated with placebo was similar to that observed with ocrelizumab and placebo, suggesting similarly strong anti-inflammatory potency of ofatumumab and ocrelizumab. Based on the combined findings, a relative reduction in the ARR of 40% is assumed between patients treated with ofatumumab compared to those treated with teriflunomide, which corresponds to an absolute ARR=0.168 for patients treated with ofatumumab, similar to that observed with ocrelizumab in Phase 2 and 3.

The dispersion parameter of k=0.82 is assumed based on the values observed for relapse data in the fingolimod Phase 3 program. In the pivotal teriflunomide Phase 3 program 290/1086=27% of the patients discontinued over 104 weeks (O'Connor et al. 2011) in one trial, and 348/1196=30% over 130 weeks in another one (Confavreux et al. 2014). In OPERA I and OPERA II discontinuation rates were lower. For the purpose of the primary analysis we conservatively assume that 20% of the randomized patients will not contribute to the primary analysis at all. This is a conservative assumption because patients who discontinue prematurely from the study can contribute with partial data (relapse counts, exposure) to the primary analysis. In this information-based design patients will be followed until the end of the trial (see EoS criteria), rather than to be observed for a fixed time period. Based on the 3mCDW endpoint it is anticipated that the majority of patients will be exposed for 1 to 2 years. For ease of calculation a fixed follow-up time of 1.5 years is assumed for the primary endpoint. Of note, the power for the primary endpoint will depend on the actual follow-up.

9.8.2 Sample size for 3-month confirmed disability worsening (3mCDW)

For planning purposes only an exponential distribution of event times and proportional hazard is assumed. The cumulative event probability over 2 years is assumed as 15% vs 9.5% in patients treated with teriflunomide vs ofatumumab, respectively. The assumed cumulative event rates translate to a relative risk reduction of 38.6% (hazard ratio=0.614) in patients treated with ofatumumab compared with teriflunomide. The detection of a hazard ratio of 0.614 in a log-

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rank test with **90% power** at a one-sided alpha-level of 0.025-0.025[2] requires 178 qualifying events. Allowing for 20% dropouts over 2 years in both arms, a total sample size of **1774 randomized patients** is required. Assuming an accrual with 500 patients in the first 6 months, and 1500 patients per year thereafter, it is expected that accrual can be completed within approximately 18 months, and that the study duration is projected to last between 2.5 to 3 years.

For comparison to these assumptions, in the pivotal trials of teriflunomide, the cumulative probability of a 3-month confirmed disability worsening over 2 years in patients treated with teriflunomide 14 mg was 15.8% (Confavreux et al. 2014) and 20% (O'Connor et al. 2011), respectively. Furthermore, in combined ocrelizumab Phase 3 studies (Hauser et al. 2015) the Kaplan-Meier estimates were 15.2 and 9.8 at year 2 for interferon beta-1a and ocrelizumab 600 mg, respectively; this corresponds to a hazard ratio 0.6 (40% relative risk reduction between ocrelizumab and interferon beta-1a).

9.8.3 Sample size for 6-month confirmed disability worsening (6mCDW)

The cumulative event probability over 2 years is assumed as 12% vs 7.548% in patients treated with teriflunomide vs ofatumumab, respectively. The assumed cumulative event rates translate to a relative risk reduction of 38.6% (hazard ratio=0.614) in patients treated with ofatumumab compared with teriflunomide. The detection of a hazard ratio of 0.614 in a log-rank test with **80% power** at a one-sided alpha-level of 0.025-0.025[2] requires 133 qualifying events. Allowing for 20% dropouts over 2 years in both arms, a total sample size of **1662 randomized patients** is required (831 per arm).

For comparison: In combined ocrelizumab Phase 3 studies (OPERA 1 and OPERA 2, Hauser et al. 2015) the Kaplan-Meier estimates were 12.0 and 7.4 at year 2 for interferon beta-1a and ocrelizumab 600 mg, respectively; this corresponds to a hazard ratio 0.6 (40% relative risk reduction between ocrelizumab and interferon beta-1a).

9.8.4 Sample size for 6-month confirmed disability improvement (6mCDI)

The cumulative event probability over 2 years is assumed as 12% vs 18.8% in patients treated with teriflunomide vs ofatumumab, respectively. The assumed cumulative event rates translate to a relative increase in chance by 63% (hazard ratio=1/0.614=0.163) in patients treated with ofatumumab compared with teriflunomide. The detection of a hazard ratio of 1/0.614 in a log-rank test with 80% power at a one-sided alpha-level of 0.025- 0.025[2] requires 133 qualifying events. Allowing for 20% dropouts over 2 years 1052 patients who contribute to the analysis are required; due to the definition of 6mCDI, patients with a baseline EDSS < 2 cannot contribute to this analysis. Based on the combined fingolimod Phase 3 trials (FREEDOMS, FREEDOMS II and TRANSFORMS, data on file) it is assumed that approximately 35% of all randomized patients will have baseline EDSS < 2. Hence, **1620** (1052/0.65) **randomized patients** are required to provide **80% power.**

9.8.5 Sample size for number of Gd-enhancing lesions per scan

We assume a negative binomial distribution of the number of Gd-enhancing lesions per scan. Assuming 0.26 Gd-enhancing lesions per scan for teriflunomide and a 90% relative reduction with ofatumumab (i.e. 0.026 Gd-enhancing lesions per scan for ofatumumab), and a dispersion parameter κ_{Gd}=5.3 (as observed in the combined FREEDOMS and FREEDOMS II studies for

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the same parameter, data on file), a total sample size of 210 patients with available MRI scans would be sufficient to provide **90% power** for the statistical test at a one-sided alpha 0.025. Allowing for 20% dropouts, a total sample size of **264 randomized patients** (132 per arm) is required for this endpoint.

9.8.6 Sample size for annualized rate of new/newly enlarging T2 lesions

We assume a negative binomial distribution of the number of T2 lesions. Assuming 2.1 new or newly enlarging T2 lesions over 1.5 years for teriflunomide (1.4 new or enlarging T2 lesions per year with a mean follow-up of 1.5 years) and an 80% relative reduction with ofatumumab (i.e. 0.42 T2 lesions over 1.5 years; 0.28 lesions per year for ofatumumab) and a dispersion parameter κ_{Gd}=3.1 (as observed in the combined fingolimod Phase 3 placebo-controlled trials, data on file) for the same parameter), a total sample size of 74 patients with available MRI scans would be sufficient to provide **90% power** for the statistical test at a one-sided alpha 0.025. Allowing for 20% dropouts, a total sample size of **94 randomized patients** (47 per arm) is required for this endpoint.

9.8.7 Sample size for NfL

We assume a log-normal distribution for NfL concentrations. At month 3, geometric mean NfL concentrations of μ_1=25 pg/ml in teriflunomide and μ_2=17pg/ml in ofatumumab treated patients are assumed, leading to an assumed treatment difference on the log-scale of 0.386 pg/ml. We further assume a common standard deviation of 0.700 pg/ml. A total sample size of 139 randomized patients with available NfL assessments would be sufficient to provide 90% power for the statistical test at a one-sided alpha 0.025. Allowing for 20% dropouts, a total sample size of 174 patients (87 per arm) is required for this endpoint.

9.8.8 Sample size for annualized rate of brain volume loss (BVL)

We assume a normal distribution for the percentage brain volume change. Assuming a mean annualized rate of BVL of 0.45% on teriflunomide and 0.338% on ofatumumab (25% relative reduction) and a common standard deviation of 0.5%, a sample size of 621 patients with available MRI assessments would provide **80% power** at a one-sided alpha level of 0.025. Allowing from 20% dropouts, a total sample size of **778 randomized patients** are required for this endpoint (ca. 390 per arm).

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

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10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study and period after discontinuation of study drug. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of Investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • AP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in AP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

Table 13-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at Investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at Investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at Investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at Investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at Investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at Investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in AP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

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14 Appendix 2: Specific Renal Alert Criteria and Actions

Table 14-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥ 1+ Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; Protein-creatinine ratio (PCR)≥ 150 mg/g or > 15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥ 1+ not due to trauma or menstruation	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at Investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

15 Appendix 3: Safety monitoring Guidance

15.1 Guidance on monitoring of patients with symptoms of neurological deterioration suggestive of PML

Should a patient develop any unexpected neurological or psychiatric symptom/signs in the opinion of Investigator (e.g. cognitive deficit, behavioral changes, cortical visual disturbances or any other neurological cortical symptoms/signs any symptom/sign suggestive of an increase of intracranial pressure) or accelerated neurological deterioration, the Investigator should schedule a complete physical and neurological examination and an MRI as soon as possible before beginning any steroid treatment. Conventional MRI as defined in the protocol as well as additional scanning such as Fluid-Attenuated Inversion Recovery (FLAIR) and Diffusion-weighted imaging (DWI) sequences are recommended to aid in differential diagnosis. The MRI must be evaluated by the local neuroradiologist. The Investigator will contact the Medical Advisor at Novartis to discuss findings and diagnostic possibilities as soon as possible. A copy of the unscheduled MRI should be sent to the MRI Evaluation Center designated by the Sponsor as soon as possible. AE/SAEs need to be filed as appropriate.

If the MRI shows new MS lesions consistent with an MS relapse, assessment and treatment of the relapse will be performed as described in the protocol (Section 6.4.1 and Section 5.5.6,

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respectively). In case of new findings in the MRI images in comparison with the previous available MRI which are not compatible with MS lesions, the study drug will be discontinued and other diagnostic evaluations need to be performed at the discretion of the Investigator. If new lesions are detected on the MRI which may be infectious in origin it is recommended to collect a cerebrospinal fluid sample if indicated. Analysis of the CSF sample including cellular, biochemical, PCR, and microbiological analysis (e.g. herpes virus, JC virus) to confirm/exclude an infection should be performed. In the event of suspected CNS infection (PML), a CSF aliquot should be sent to a central laboratory (designated by the Sponsor) for confirmatory testing.

Only after the evaluations have excluded diagnoses other than MS and after discussion with the Medical Advisor at Novartis, the study drug may be restarted.

15.2 Guidance on monitoring of patients with infections

All infections that develop during the study will be reported as AEs on the respective AE eCRF pages. Treatment and additional evaluations will be performed at discretion of the Investigator.

The Investigator should remind the patient of the risk of infections and instruct them to promptly report any symptoms of infections to the Investigator. The patients must also be reminded to always carry their Patient Information Card (with site contact information and which identifies them as participants in a clinical study with investigational and control agents with potential immunosuppressive effects) and to show this to any local healthcare provider they may consult and ask that the Investigator be contacted.

In the case of suspected or confirmed serious (CTCAE, Grade 3-4) or atypical infection, study drug interruption should be considered. The Investigator should inform the Sponsor Medical Advisor of any such cases.

When evaluating a patient with a suspected infection, the most sensitive tests available should be used (i.e. that directly detect the pathogen, as with PCR).

The Investigator should consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof in consultation with infectious disease experts, as appropriate. The Investigator should inform the Sponsor Medical Advisor of any such cases.

Investigators should consider the added immunosuppressive effects of corticosteroid therapy for treatment of MS attack/relapse and increase vigilance regarding infections during such therapy and in the weeks following administration.

In oncology patients treated with ofatumumab, cases of fatal hepatitis B virus (HBV) reactivation and fatal infection due to hepatitis B in patients who have not been previously infected have occurred (refer to local ARZERRA® prescribing information). The MS patients enrolled in the study who are at potential risk of HBV reactivation (e.g. patients with evidence of prior HBV infection (anti-HBc positive and HBsAg negative) and whose HBV DNA test is negative at Screening, should be closely monitored for signs of active HBV infection or reactivation during the study. In patients with suspicion of HBV infection (active/reactivation), laboratory testing for HBV should be done. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), the Investigator is advised to consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy.

[redacted]

In patients who develop reactivation of HBV while receiving study drug, immediately discontinue study drug and institute appropriate treatment and follow up.

15.3 Guidance on immunization

The safety of and ability to generate a primary or anamnestic response to immunization with live, live-attenuated or inactivated vaccines during ofatumumab treatment has not been investigated. The response to vaccination could be impaired when B-cells are depleted.

It is recommended that the Investigator review the patient's immunization history as part of the initial Screening procedure for a patient being considered for treatment with ofatumumab. Vaccination of the patient, in compliance with local area vaccination guidelines for the patient population being treated, is recommended prior to administration of ofatumumab. In particular, prior to administration of ofatumumab, hepatitis B vaccination, in patients with risk factors for hepatitis B infection or in areas with a high prevalence of hepatitis B, as per local area treatment guidelines should be considered.

Administration of live or live-attenuated vaccines must be avoided during and after treatment with ofatumumab and until B-cell counts are normalized.

15.4 Guidance on monitoring of patients with low immunoglobulin levels

After baseline, the immunoglobulin levels (IgM and IgG) will be measured at each visit from Month 1 to EOS by the central laboratory and will be blinded to the Sponsor and the Investigator. They will only be communicated to the site after baseline in case of notably low levels. A notably low IgG level is defined as a level that is 20% below the LLN and a notably low IgM level is defined as a level 10% below the LLN. Following notification, the immunoglobulin level should be repeated within 2 weeks by the central lab to confirm the reading. If the repeat test confirms the immunoglobulin level to be below the threshold, the study drug must be discontinued and the immunoglobulin levels needs to be monitored at the Investigator's discretion until levels return back to normal limits. The patient should be evaluated and monitored for infections on a regular basis. Immunoglobulin substitution therapy as pert local medical practice is allowed. Re-initiation of the study drug can only be considered once the immunoglobulin levels are back within normal limits.

16 Appendix 4: List of drugs/drug classes with teriflunomide interaction potential

Based on the double-blinded design, the Investigator will need to consider the drug interaction potential of teriflunomide when the blinded study drug is co-administered with certain classes of drugs. The below information has been obtained from the US teriflunomide (Aubagio®) prescribing information (Revised 10/2014):

Effect of teriflunomide on CYP2C8 substrates

Teriflunomide is an inhibitor of CYP2C8 *in vivo*. In patients taking teriflunomide, exposure of drugs metabolized by CYP2C8 (e.g., paclitaxel, pioglitazone, repaglinide, rosiglitazone) may

[redacted]

be increased. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP2C8 as required.

Effect of teriflunomide on warfarin

Coadministration of teriflunomide with warfarin requires close monitoring of the international normalized ratio (INR) because teriflunomide may decrease peak INR by approximately 25%.

Effect of teriflunomide on oral contraceptives

Teriflunomide may increase the systemic exposures of ethinylestradiol and levonorgestrel. Consideration should be given to the type or dose of contraceptives used in combination with teriflunomide.

Effect of teriflunomide on CYP1A2 substrates

Teriflunomide may be a weak inducer of CYP1A2 *in vivo*. In patients taking teriflunomide, exposure of drugs metabolized by CYP1A2 (e.g., alosetron, duloxetine, theophylline, tizanidine) may be reduced. Monitor these patients and adjust the dose of the concomitant drug(s) metabolized by CYP1A2 as required.

Effect of teriflunomide on organic anion transporter 3 (OAT3) substrates

Teriflunomide inhibits the activity of OAT3 *in vivo*. In patients taking teriflunomide, exposure of drugs which are OAT3 substrates (e.g., cefaclor, cimetidine, ciprofloxacin, penicillin G, ketoprofen, furosemide, methotrexate, zidovudine) may be increased. Monitor these patients and adjust the dose of the concomitant drug(s) which are OAT3 substrates as required.

Effect of teriflunomide on BCRP and organic anion transporting polypeptide B1 and B3 (OATP1B1/1B3) substrates

Teriflunomide inhibits the activity of BCRP and OATP1B1/1B3 *in vivo*. For a patient taking teriflunomide, the dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of BCRP (e.g., mitoxantrone) and drugs in the OATP family (e.g., methotrexate, rifampin), especially HMG-Co reductase inhibitors (e.g., atorvastatin, nateglinide, pravastatin, repaglinide, and simvastatin), consider reducing the dose of these drugs and monitor patients closely for signs and symptoms of increased exposures to the drugs while patients are taking teriflunomide.

Additional drugs belonging to the classes above include but are not limited to:

- rifampicin (a medicine used to treat tuberculosis and other infections)
- carbamazepine, phenobarbital, phenytoin (for epilepsy)
- St. John's wort (a herbal medicine for depression)
- indometacin, ketoprofen (for pain or inflammation)
- rosuvastatin for hypercholesterolemia (for treatment of high cholesterol)
- sulfasalazine (for inflammatory bowel disease or rheumatoid arthritis)
- cholestyramine (for high cholesterol or relief from itching in liver disease); may accelerate elimination of teriflunomide (refer also to Section 7.8)

[redacted]

17 Appendix 5: Statistical appendix (information from a controlled clinical trial with count data)

Background

The ARR is the primary clinical endpoint in this Study. The trial compares ofatumumab with teriflunomide.

Objective

To mathematically derive the information obtained from a clinical trial in MS on the ARR ratio of test versus control, on the log-scale based on a negative binomial distribution. The treatment effect is based on the estimation of the ARR-ratio (the 'estimate') between ofatumumab and teriflunomide. The information is defined as the reciprocal of the estimate's variance, as in group sequential designs.

Model

We assume that the number of relapses follows a negative binomial distribution, which is a common assumption in MS trials. More specifically, the available data for patient i in treatment arm j is:

Y_{ij} = number of relapses in follow-up time T_{ij},

for $i = 1,\ldots n_j$ and $j = 1,2$ (1 = test, 2 = control).

The negative binomial model is then written as:

$Y_{ij} \sim \text{NegBin}(\lambda_j T_{ij}, \kappa)$,

with annual relapse rate λ_j (> 0) and over-dispersion parameter κ (> 0).

With this parametrization,

$E(Y_{ij}) = \mu_{ij}$ and $\text{Var}(Y_{ij}) = \mu_{ij}(1 + \kappa \mu_{ij})$, where $\mu_{ij} = \lambda_j T_{ij}$.

An estimate of λ_j is given by $r_j = Y_{.j} / T_{.j}$, where $Y_{.j} = \Sigma_i Y_{ij}$ and $T_{.j} = \Sigma_i T_{ij}$.

Using the delta-method (see details in a next section), a normal approximation for the logarithm of the estimated relapse rate ratio is obtained:

$$\log(r_1/r_2) \sim N(\log(\lambda_1/\lambda_2), 1/(\lambda_1 T_{.1}) + 1/(\lambda_2 T_{.2}) + \kappa\{\Sigma_i T_{i1}^2 / T_{.1}^2 + \Sigma_i T_{i2}^2 / T_{.2}^2\})$$

The information is the reciprocal of the variance, ie, information:

$$I = [1/(\lambda_1 T_{.1}) + 1/(\lambda_2 T_{.2}) + \kappa\{\Sigma_i T_{i1}^2/T_{.1}^2 + \Sigma_i T_{i2}^2/T_{.2}^2\}]^{-1} \quad (1)$$

For the case where $T_{ij} = T$, $n_j = n$,

$$\text{Information } I = [1/n \{1/(\lambda_1 T) + 1/(\lambda_2 T) + 2\kappa\}]^{-1} \quad (2)$$

Of note: Study designs with different parameterizations, but an equivalent amount of information also have an equivalent power for the detection of the specified treatment effect at a fixed alpha-level.

[redacted]

Blinded evaluation of the information

As in a blinded sample size review (Friede and Schmidli 2010), fitting a negative binomial model to the aggregate data (i.e. the relapse data of all patients combined) provides an estimate of the overall annual relapse rate λ and of the dispersion κ. For an assumed rate ratio of $\theta = \lambda_1/\lambda_2$, we obtain estimates of the annual relapse rates in the 2 groups, λ_1 and λ_2.

We also make the assumption that the follow-up times in the 2 groups are the same, i.e., that $T_{.1} = T_{.2} = T_{total}/2$, where T_{total} is the total of the follow-up times at the review time. We further assume that the sum of the squared follow-up times is the same in both groups, i.e., that $\Sigma_i T_{i1}^2 = \Sigma_i T_{i2}^2 = \Sigma_j \Sigma_i T_{ij}^2 / 2 = T2_{total}/2$.

The evaluation of the Information (1) based on blinded information is then

$$\text{Information } I = [2/(\lambda_1 \, T_{total}) + 2/(\lambda_2 \, T_{total}) + 4\,\kappa\, T2_{total}/T_{total}^2]^{-1} \qquad (3)$$

where λ_1, λ_2, and κ are the re-estimated values at the blinded review.

Note: if $T_{ij} = T$, $n_j = n$, then $T_{total} = 2\,n\,T$, and $T2_{total} = 2\,n\,T^2$, and one obtains again (2).

Additional details (delta-method)

For a random variable X with expectation μ and variance σ^2 , the transformed random variable g(X) has approximately expectation $g(\mu)$ and variance $\sigma^2\, g'(\mu)^2$ (delta-method).

For the estimate of λ_j given by $r_j = Y_j/T_j$, we have:

$E(r_j) = \lambda_j$ and $Var(r_j) = \lambda_j/T_j + \kappa\, \lambda_j^2\, \Sigma_i\, T_{ij}^2/T_{.j}^2$

Using the delta-method, the log-transformed annual relapse rate estimate has expectation and variance:

$E(\log(r_j)) = \log(\lambda_j)$

$Var(\log(r_j)) = 1/(\lambda_j\, T_{.j}) + \kappa\, \Sigma_i\, T_{ij}^2/T_{.j}^2$

Hence, approximately:

$\log(r_j) \sim N(\log(\lambda_j)),\ 1/(\lambda_j\, T_{.j}) + \kappa\, \Sigma_i\, T_{ij}^2/T_{.j}^2)$

Note that for the special case of $T_{ij} = T$, we obtain:

$\log(r_j) \sim N(\log(\lambda_j),\ 1/(\lambda_j\, n\, T) + \kappa/n)$

This approximation is used for sample size calculation and re-calculation with negative binomial count data (Keene et al. 2007, Friede and Schmidli 2010).

[redacted]