NOVARTIS

Global Clinical Development - General Medicine

OMB157/Ofatumumab

Clinical Trial Protocol COMB157G1301 / NCT03249714

A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety and pharmacokinetics of ofatumumab in patients with relapsing multiple sclerosis followed by an extended treatment of at least 24 weeks with open-label ofatumumab

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List of abbreviations

ACR	Albumin/Creatinine Ratio
ADA	Anti-drug-antibody
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
Alb	Albumin
ALT	Alanine Aminotransferase
AP/ALP	Alkaline Phosphatase
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
AV	Atrioventricular
BIL	Bilirubin
BUN	Blood Urea Nitrogen
C-CASA	Columbia Classification Algorithm for Suicide Assessment
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
CQA	Compliance Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSF	Cerebrospinal fluid
(e)CSSRS	(electronic) Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
FAS	Full Analysis Set
FS	Functional Score
FU	Follow-up
GCP	Good Clinical Practice
Gd	Gadolinium
GGT	Gamma-Glutamyl-Transferase
HA, HB, HC, HE	Hepatitis A, B, C, E

[redacted]

HBc	Hepatitis B core
HBV, HCV, HEV	Hepatitis B Virus, Hepatitis C Virus, Hepatitis E Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-To-Treat
iv	Intravenous(ly)
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLQ	Lower Limit of Quantification
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Image
MS	Multiple Sclerosis
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PPS	Per-Protocol Set
q4, q12	Every 4, every 12
QM	Quality Management
QTcF	The Fridericia QT correction formula
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RPR	Rapid Plasma Reagin
RRMS	Relapsing-Remitting MS
SAE	Serious Adverse Event
SAF	Safety Set
sc	Subcutaneous(ly)
sCR	Serum Creatinine
[redacted]	[redacted]
SPMS	Secondary progressive MS
TBIL/TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
US	United States

[redacted]

WBC	White Blood Cell
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)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
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)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with United States (US) Code of Federal Regulations (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
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
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

[redacted]

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 study consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Protocol summary

Protocol number	COMB157G1301
Full Title	A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety and pharmacokinetics of ofatumumab in patients with relapsing multiple sclerosis followed by an extended treatment of at least 24 weeks with open-label ofatumumab
Brief title	Study of efficacy and safety of ofatumumab compared to placebo in patients with relapsing multiple sclerosis followed by extended treatment with open-label ofatumumab
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Biological (human Immunoglobulin G (IgG) 1k lytic monoclonal antibody (mAb) to human CD20 antigen)
Study type	Interventional
Purpose and rationale	This study is designed, in conjunction with the global Phase 3 studies (COMB157G2301 and COMB157G2302), to provide the necessary data to support registration of ofatumumab for the treatment of relapsing multiple sclerosis (MS) in Japan. The study will provide efficacy, safety, tolerability and pharmacokinetics (PKs) data for ofatumumab 20 mg subcutaneous (sc) injections every 4 weeks (q4) compared with placebo for 24 weeks in patients from Japan (neither Caucasian nor African) and the other countries (mainly Caucasian, not East Asian) and also provide the extended efficacy, safety, tolerability and pharmacokinetics data.
Primary Objective(s)	Demonstrate that ofatumumab is superior to placebo in reducing the cumulative number of Gadolinium (Gd)-enhanced T1 lesions across 4 Magnetic Resonance Image (MRI) scans at Week 12, 16, 20 and 24 in patients with relapsing MS
Secondary Objectives	**Core part** Assess the consistency of the efficacy of ofatumumab versus placebo across regions (Japan vs other countries) in the cumulative number of Gd-enhanced T1 lesions on MRI scans at Week 12, 16, 20 and 24. Assess the efficacy of ofatumumab versus placebo in the number of new or enlarging T2 lesions on MRI scans Assess the efficacy of ofatumumab versus placebo in annualized relapse rate (ARR) and time to first relapse Assess the safety and tolerability of ofatumumab versus placebo Assess the similarity of the PK and B-cell count following the treatment with ofatumumab across regions (Japan vs other countries) **Extension part (including Core part)** Assess extended safety and tolerability of ofatumumab Assess extended efficacy of ofatumumab in: • Number of Gd-enhanced T1 lesions • Number of new or enlarging T2 lesions • Annualized relapse rate • Time to first relapse

[redacted]

	Assess the PK and B-cell count following the extended treatment with ofatumumab
Study design	This study has 2 parts: A controlled Core and an open-label Extension. • Core part: A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety and tolerability and PK of ofatumumab in patients with relapsing MS. • Extension part: The Core part is followed by an Extension part in which all patients receive open-label ofatumumab. In the Extension part, patients are treated for at least 24 weeks and no longer than 48 weeks. Patients who complete the Extension part will be transferred into a planned open label ofatumumab umbrella extension study (under separate protocol). All patients who prematurely discontinue study treatment or who do not enter the separate umbrella extension study, will be followed for a total of at least 36 weeks after study drug discontinuation in the Safety Follow-up (FU) period. It is planned that a total of 60 patients will be randomized in a 2:1 ratio to ofatumumab or placebo in the Core part; approximately half of the study patients will be from Japan (neither Caucasian nor African) and the other half from the other countries (mainly Caucasian, not East Asian). Randomization will be stratified by region (Japan or other countries) and baseline number of Gd-enhanced T1 weighted lesions (0 or ≥ 1).
Population	Adult patients with relapsing 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 • At least 1 appearance of a new neurological abnormality or worsening of pre-existing neurological abnormality during the previous 2 years prior to Screening AND an MRI activity (Gd-enhanced T1 lesions or new or enlarging T2 lesions) in brain during the previous 1 year prior to randomization. • Disability status at Screening with an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 (inclusive) • Neurologically stable within 1 month prior to randomization
Key Exclusion criteria	• Patients with primary progressive MS or Secondary progressive MS (SPMS) without disease activity • Patients meeting criteria for neuromyelitis optica • 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 • Patients with an active chronic disease of the immune system other than MS • Patients with neurological findings consistent with progressive multifocal leukoencephalopathy (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) • Patients with active systemic infections or known to have acquired

[redacted]

	immune deficiency syndrome (AIDS) or to test positive for human immunodeficiency virus (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, dimethyl fumarate, fingolimod, natalizumab, ofatumumab, rituximab, ocrelizumab, alemtuzumab, cyclophosphamide, teriflunomide 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	**<Core part>** **Double-blind treatment period:** Ofatumumab 20 mg sc injections or ofatumumab-matching placebo sc injections on Day 1, 7, 14, Week 4 and every 4 weeks thereafter **<Extension part>** **Double-blind loading dose period:** Patients randomized to ofatumumab in Core part: Ofatumumab 20 mg sc injections at Week 24 and ofatumumab-matching placebo sc injections at Week 25 and 26. Patients randomized to placebo in Core part: Ofatumumab 20 mg sc injections at Week 24, 25 and 26. **Open-label treatment period:** In all patients: Ofatumumab 20 mg sc injections at Week 28 and every 4 weeks thereafter
Efficacy assessments	MRI, MS relapse, EDSS, [redacted]
Key safety assessments	Adverse events, Physical examinations (including skin), Vital signs, Laboratory evaluations (including total IgM and IgG levels), Pregnancy testing, Electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (CSSRS)
Other assessments	Pharmacokinetics, B-cell and T-cell counts, Anti-human antibodies (ADAs)
Data analysis	The primary and secondary analyses will be conducted at the end of the Core part. All efficacy data will be analyzed according to the intent-to-treat principle. The primary endpoint (Cumulative number of Gd-enhanced T1 lesions across 4 MRI scans at Week 12, 16, 20 and 24) will be analyzed in a negative binominal regression model. Secondary analyses include MRI-(Number of new/enlarging T2 lesions) and Clinical (Annualized Relapse Rate) endpoints, both will be analyzed in a negative binominal regression model. For the regulatory submission in Japan, a data cut-off at Week 48 will be used to analyze extended safety and efficacy data in the 48 week ofatumumab continuous treatment group.
Key words	Interventional, clinical trial, efficacy and safety, double-blind, placebo-controlled, ofatumumab, relapsing multiple sclerosis, Japanese patients

[redacted]

Amendment 1

Amendment rationale

Amendment 1 was created to clarify the exclusion criteria for patients at potential risk of HBV reactivation, based on inquiry from Japanese health authority. Changes were made to maintain consistency among Section 4.2, Section 6.5.4.4 and Section 15.2.

Additional small changes include revisions to match protocol to the new Novartis RaveX system or eCRFs, the addition of EUDRACT number to the cover page, and other non-substantial changes to correct/clarify minor errors or omissions throughout the protocol.

No subject was included in this study as of 03-Oct-2017.

Changes to the protocol

The main changes and Sections affected are listed as follows:

Section 4.2: The exclusion criterion # 10 has been modified to clarify the exclusion of patients at potential risk of HBV reactivation.

Section 5.5.1 and Section 6.1: The sentence regarding the Screening disposition CRF was modified because Novartis revised clinical data collection standard does not have the CRF page.

Section 6.2: "Year of birth" was deleted and "age" was added as patient demographic data, based on the Novartis revised clinical data collection standard.

Section 6.5.4.4: This section was modified to clarify exclusion of patients who are at potential risk of HBV reactivation.

Section 7.1: The description of actions taken with study drug in response to AE in CRF was modified based on the Novartis revised clinical data collection standard. "No action taken" was changed to "study treatment dose not changed", and "recovering/resolving" was deleted from "its outcome".

Section 7.3: The sentence regarding the liver events CRF was modified because the Novartis revised clinical data collection standard does not have a specific page for liver events.

Section 7.4: The sentence regarding the renal events CRF was modified because the Novartis revised clinical data collection standard does not have a specific page for renal events.

Table 13-2: "Complete liver CRF" was changed to "Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs" in the actions required column, in accordance with the Novartis revised clinical data collection standard for liver events.

Table 14-1: "Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed" was changed to "Record AE/SAE and any contributing factors (concomitant medications, other co-morbid

conditions/procedures) in the appropriate CRFs" in accordance with Novartis revised clinical data collection standard.

Section 15.2: This section was modified to clarify exclusion of patients at potential risk of HBV reactivation to keep consistency among Section 4.2 and Section 6.5.4.4.

[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 (RRMS) is the most frequent clinical presentation of the disease. Approximately 85% of patients present with RRMS, characterized by recurrent acute exacerbations (relapses) of neurological dysfunction followed by recovery. After 15 to 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. The term of relapsing MS applies to those affected patients either with a RRMS or SPMS with superimposed relapses. Patients with relapsing MS constitute a common target for current treatment options. There are no clear criteria that mark the transition from RRMS to SPMS (EMA/CHMP/771815/2011, Rev. 2. 2015).

For the patients with relapsing MS, interferon-β and glatiramer acetate have long been used as first-line drugs. However, these drugs require frequent self-injections and increase the burden on patients. In the recent years, oral drugs such as fingolimod, dimethyl fumarate and teriflunomide (not approved in Japan) have become available and enhanced the convenience of treatment for the patients. In addition, treatment with more potent drugs including natalizumab, alemtuzumab (not approved in Japan) and ocrelizumab (not approved in Japan) have been put into practice. Despite the increased options available, patients whose disease activity cannot be fully controlled exist due to the heterogeneity of MS or patients who are intolerable to the current available drugs exist. The need therefore remains to develop drugs with alternative mechanisms of action, convenient dosing, and a favorable safety profile.

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 (Lehmann-Horn 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 relapsing MS (Hauser et al 2017). These studies showed that ocrelizumab significantly reduced relapse rates, reduced MRI disease activity and, delayed the time to

[redacted]

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 (CLL) (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 mAb rituximab. CD20-binding of ofatumumab induces B-cell lysis primarily through complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). As a fully human antibody, 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 two 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 3 mg, 30 mg, or 60 mg 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). 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 ≥ 30 mg ($p < 0.001$). Dose-dependent decreases were maintained up to Week 48. 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 adverse events (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 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 Brochure (IB).

Two multinational Phase 3 studies of ofatumumab (COMB157G2301 and COMB157G2302) are ongoing to provide efficacy, safety and tolerability data for sc injection of ofatumumab 20 mg every 4 weeks compared to oral teriflunomide in patients with relapsing MS, targeting 900 patients to be randomized in each study. Japan has not joined the Phase 3 studies because teriflunomide is not approved for use in patients with MS in Japan. Therefore, this placebo-controlled COMB157G1301 study, using the same dosing regimen in the Phase 3 studies, was planned to support registration of ofatumumab for treatment of relapsing MS in Japan.

1.2 Purpose

This study is designed, in conjunction with the global Phase 3 studies (COMB157G2301 and COMB157G2302), to provide the necessary data to support registration of ofatumumab for the treatment of relapsing MS in Japan.

The study will provide efficacy, safety, tolerability and pharmacokinetics data for ofatumumab 20 mg subcutaneous injections every 4 weeks compared with placebo for 24 weeks in patients from Japan (neither Caucasian nor African) and the other countries (mainly Caucasian, not East Asian) and also provide the extended efficacy, safety, tolerability and pharmacokinetics data.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

2.1.1 Primary objective(s)

Demonstrate that ofatumumab is superior to placebo in reducing the cumulative number of Gd-enhanced T1 lesions across 4 MRI scans at Week 12, 16, 20 and 24 in patients with relapsing MS.

[redacted]

2.1.2 Secondary objective(s)

Core part

Assess the consistency of the efficacy of ofatumumab versus placebo across regions (Japan vs other countries) in the cumulative number of Gd-enhanced T1 lesions on MRI scans at Week 12, 16, 20 and 24.

Assess the efficacy of ofatumumab versus placebo in the number of new or enlarging T2 lesions on MRI scans.

Assess the efficacy of ofatumumab versus placebo in annualized relapse rate (ARR) and time to first relapse.

Assess the safety and tolerability of ofatumumab versus placebo.

Assess the similarity of the pharmacokinetics (PK) and B-cell count following the treatment with ofatumumab across regions (Japan vs other countries).

Extension part (including Core part)

Assess extended safety and tolerability of ofatumumab.

Assess extended efficacy of ofatumumab in:

- Number of Gd-enhanced T1 lesions
- Number of new or enlarging T2 lesions
- Annualized relapse rate
- Time to first relapse

Assess the PK and B-cell count following the extended treatment with ofatumumab.

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This study has 2 parts: A randomized, double-blind, placebo controlled Core part, and an Extension part in which all patients receive open-label ofatumumab.

- Core part: A 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety and tolerability and PK of ofatumumab in patients with relapsing MS.
- Extension part: The Core part is followed by an Extension part in which all patients receive open-label ofatumumab. In the Extension part, patients are treated for at least 24 weeks and no longer than 48 weeks. Patients who complete the Extension part will be transferred into a planned open label ofatumumab umbrella extension study (under separate protocol).

All patients who prematurely discontinue study treatment or who do not enter the separate umbrella extension study, will be followed for a total of at least 36 weeks after study drug discontinuation in the Safety Follow-up (FU) period.

It is planned that a total of 60 patients will be randomized in a 2:1 ratio to ofatumumab or placebo in the Core part; approximately half of the study patients will be from Japan (neither Caucasian nor African) and the other half from the other countries (mainly Caucasian, not East Asian). Randomization will be stratified by region (Japan or other countries) and baseline number of Gd-enhanced T1 weighted lesions (0 or $\geq$ 1).

3.1.1 Core part

The Core part consists of 2 periods; **Screening period** and **Double-blind treatment period** (Figure 3-1).

The **Screening period** can last up to 45 days and consists of 2 sections; Screening section and Baseline section. The Baseline section 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 Baseline assessments.

The **Double-blind treatment period** will start on Day 1 with randomization of the patient. Patients will be randomly assigned in a 2:1 ratio to receive either ofatumumab 20 mg sc or matching placebo sc in a double-blind fashion. Injectable study treatments (ofatumumab or placebo) will be administered on Day 1, Day 7, Day 14, Week 4 and every 4 weeks thereafter. The Double-blind treatment period will continue until the completion of all assessments required for the Core part at Week 24 (refer to Section 5.5.4 for further details).

Patients who prematurely discontinue double-blind study medication will have their end of Study (EOS) visit as soon as possible (Table 6-1) and will be followed up for safety in the Safety FU period (Section 3.1.3) for a minimum of 36 weeks (Table 6-2).

[redacted]

3.1.2 Extension part

The Extension part consists of 2 periods; **Double-blind loading dose period** and **Open-label treatment period**.

The **Double-blind loading dose period** will be applicable for patients who complete the Double-blind treatment period. All patients will receive ofatumumab 20 mg sc at Week 24; the Extension part starts with the injection of the Week 24. Patients randomized to ofatumumab in the Double-blind treatment period will receive the matching placebo sc at Week 25 and 26. Patients randomized to placebo in the Double-blind treatment period will receive ofatumumab 20 mg sc at Week 25 and 26. All patients will receive the study drug in a double-blind manner at Week 25 and 26.

The **Open-label treatment period** will begin at Week 28 and all patients will receive open-label ofatumumab 20 mg sc every 4 weeks in this period. This period will continue until the last patient is transferred to a planned umbrella extension study (under separate protocol requiring another informed consent).

Patients who prematurely discontinue study treatment will have their EOS visits as soon as possible and will be followed up for safety in the Safety FU period (Section 3.1.3) for a minimum of 36 weeks (Table 6-2). After study drug discontinuation, during Core or Extension parts, patients may initiate alternative MS therapy according to local standard of care if clinically indicated (see Section 5.6.2).

3.1.3 Safety FU period

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

- Patients who complete this study and do not enter the planned umbrella long-term extension study
- Patients who prematurely discontinue study treatment in Core or Extension part

All Safety FU visits must be scheduled relative to the date of EOS visit.

These patients will be followed for a total of at least 36 weeks after study drug discontinuation (by 36 weeks the vast majority of patients are expected to have repleted their circulating B-cells, see Section 3.3).

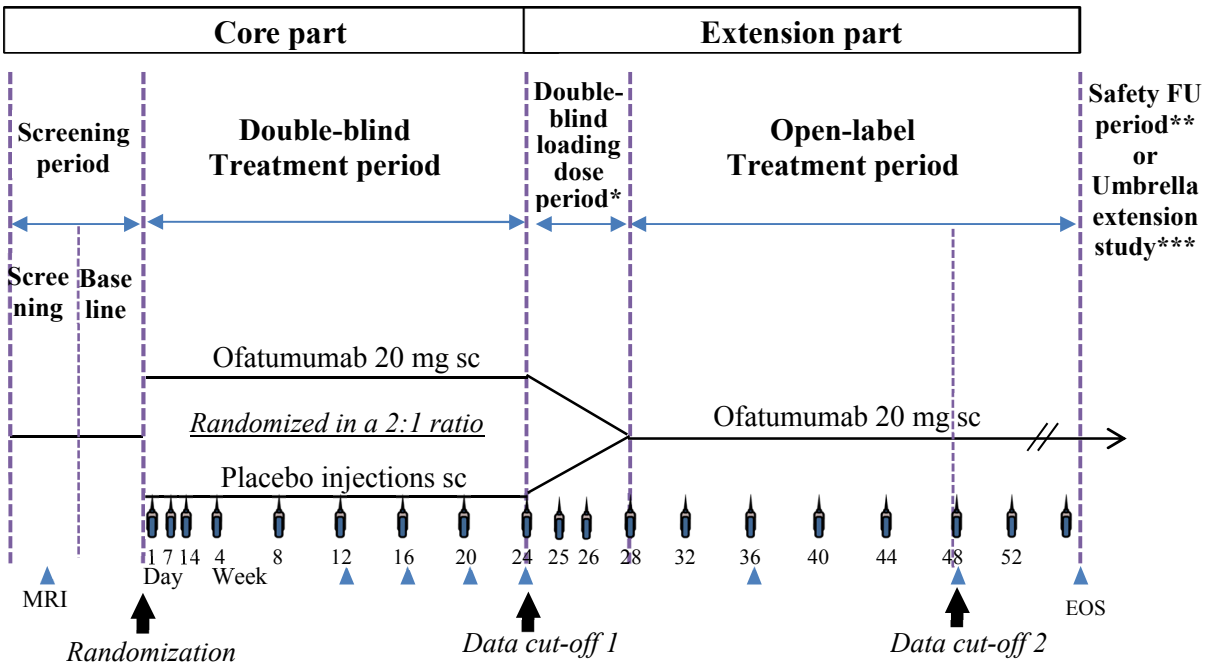
A longer than 36 weeks of post-treatment Safety FU period will be required for patients who have not repleted their B-cells (i.e. B-cells not back to baseline value or to lower limit of normal (LLN) whichever comes first as determined by central lab) at 36 weeks.

These patients will continue to be followed with 12-weekly assessments until their B-cell counts have repleted. To protect the study blind, the assessment of B-cell counts will be performed centrally and the Investigators and Sponsor study team will only be informed of whether or not continued follow-up is necessary.

Patients who have initiated therapy with another disease modifying/immunosuppressive therapy before the end of the 36-week follow-up will not be monitored beyond 36 weeks.

[redacted]

Figure 3-1 Study design



* Patients randomized to placebo in the Double-blind treatment period will receive ofatumumab 20 mg sc at Week 24, 25 and 26 as loading dose regimen. Patients randomized to ofatumumab in the Double-blind treatment period will receive ofatumumab 20 mg sc at Week 24 and the matching placebo sc at Week 25 and 26. In all patients, the extension part starts with the Week 24 injection.

** Patients who prematurely discontinue study drug or patients who do not enter the umbrella extension study will enter the Safety FU period following their EOS visits.

*** Umbrella extension study (planned) will be conducted under separate protocol.

Data cut-off 1 is defined as the date the last patient completes all the assessments for Week 24.

Data cut-off 2 is defined as the date the last patient completes all the assessments for Week 48.

3.2 Rationale for study design

The Core part is a randomized, double-blind, placebo-controlled, parallel-group design that is an established scientific method to assess safety and efficacy of a new therapy.

Placebo control and a parallel arm design are statistically efficient and minimize the number of patients required to demonstrate efficacy. A 2:1 randomization to ofatumumab or placebo minimizes the chance of placebo exposure.

Stratification by region (Japan vs other countries) allows to assess the consistency of the effect of ofatumumab 20 mg sc every 4 weeks on MRI endpoint and pharmacokinetic/pharmacodynamic (PK/PD) across regions (Japan vs other countries). This information is required to support the registration of ofatumumab in Japan.

The Extension part of this study allows patients to start (original placebo patients) or continue treatment with open-label ofatumumab with the aim to provide data on extended safety, tolerability and efficacy measures.

Double-blind loading dose period in the Extension part allows the patients originally randomized to placebo in the Core part to undergo the loading regimen when starting ofatumumab treatment in the Extension part, without unnecessary reloading the patients

randomized to ofatumumab in the Core part. Patients randomized to ofatumumab in the Core part will receive placebo at Week 25 and 26 in the double-blinded manner. This procedure will protect the blind of the Core assessments.

Patients, aged 18 to 55 years (inclusive), with relapsing MS with an Expanded Disability Status Scale (EDSS) score 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 2 years prior to Screening AND an MRI activity in brain during the year prior to Randomization. The defined trial population is typical for relapsing MS. Stratification by baseline number of Gd-enhanced T1 weighted lesions (0 or ≥ 1) allows to evaluate the effect of ofatumumab 20 mg sc on MRI endpoint appropriately.

Given the long-lasting effect of ofatumumab on B-cells, all patients who prematurely discontinue study drug or who complete both the Core and Extension parts while on study drug but do not enter the planned umbrella extension study will continue to be followed up for at least 36 weeks until B-cell repletion from the safety point of view (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 *maintenance dose regimen* of 20 mg administered every 4 weeks starting at Week 4. Patients randomized to placebo in the Core will receive the ofatumumab 20 mg *loading dose regimen* during the extension at Week 24, 25 and 26, followed by a *maintenance dose regimen* of 20 mg administered every 4 weeks starting at Week 28.

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

The Phase 2 study of ofatumumab sc (3 mg, 30 mg, 60 mg every 12 (q12) weeks, 60 mg every 4 (q4) weeks) 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. ≤ 8 cells/µL) should be maintained throughout the treatment course in order to ensure desired efficacy.

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 ≤ 8 cells/µL. A loading

[redacted]

regimen of 3 separate 20 mg (at Day 1, 7 and 14) was required to attain target depletion (≤ 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, ofatumumab 20 mg sc 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 (PK-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 AEs than the lower dose regimens of 3 mg 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, 7 and 14, followed by a monthly maintenance dose regimen of 20 mg administered every 4 weeks (starting at Week 4) is selected to deplete and subsequently maintain B-cells at the levels below 8 cells/µL in nearly all patients. 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 and Bruzzi 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.

The results of the Study OMB112758 in East Asian (Japanese and Korean) patients with refractory chronic lymphocytic leukemia (CLL) and the Study OMB111773 in mainly Caucasian patients with refractory CLL demonstrated no evident PK difference between Japanese and non-Japanese subjects. Therefore, the same dosing regimen will be used in the patients from Japan and the other countries in this study (COMB157G1301).

Duration of treatment

The 24-week duration of the double-blind treatment period is sufficient to observe a relevant effect on reducing MRI disease activity and has been an accepted standard duration for

[redacted]

Phase 2 trials in relapsing MS. The available MRI data of ofatumumab in Phase 2 study (Study OMS112831) demonstrated that meaningful differences versus placebo could be detected in this time frame.

The 24-week double-blind treatment period is followed by the Extension part of at least 24 weeks and no longer than 48 weeks, using open-label ofatumumab. The Extension part will continue until the last patient completes 24 weeks in this part and is transferred into the umbrella extension study (planned under a separate protocol).

3.4 Rationale for choice of comparator

The primary goal of this study is to demonstrate the efficacy of ofatumumab 20 mg sc every 4 weeks on the inflammatory MRI lesions, by distinguishing ofatumumab from an appropriate control agent. The choice of placebo as a control agent is important to obtain information concerning the specific versus non-specific effects of the active treatment and provides the best way of evaluating the efficacy and of assessing the true safety and tolerability profile of ofatumumab.

The placebo-controlled study design allows the scientific and regulatory objectives of the study to be met with a smaller sample size than if an active comparator would be used, thus reducing the necessary number of patients especially from Japan and maintaining feasibility.

Currently, despite the availability of treatment for relapsing MS, the selection of placebo as a control agent in this study can be accepted by the following:

- Patients who randomized to placebo in a 24-week Double-blind treatment period (Core part) and complete its period will have the opportunity to receive ofatumumab 20 mg sc every 4 weeks in the Extension part.
- Patients should be informed by the investigators about locally available approved MS therapies for treating their MS and about the probability to receive the placebo based on randomization in a 2:1 ratio to either ofatumumab or placebo in this study. Patients need to consent in writing.
- A standard short course of corticosteroids may be used to treat MS relapses based on investigator's judgment. Patients who have MS relapses during this study will be informed again about the current available treatments for patients with relapsing MS. If the patients agree to stay in this study, they will be asked to sign the informed consent form to document their decision.
- Patients can select to discontinue study treatment and consider to start treatment with an approved 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 condition (see Section 5.6.2).

3.5 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned for this study.

Regular analyses for safety and for benefit/risk assessment will be performed for the global program Data Monitoring Committee (DMC) of OMB157G by an independent team of statisticians and programmers who are not otherwise involved in the conduct of the studies of OMB157G. The data review including other OMB157G studies will be done by the DMC.

[redacted]

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.

The risk for patients exposed to placebo to worsen will be minimized by limiting the placebo exposure to a maximum of 24 weeks, allowing patients to receive standard of care treatment in the case that they present with clinical relapses (i.e., high dose methyl-prednisolone), and requesting for patients presenting with clinical relapses that the investigator considers benefit/risk of continuing study drug or to switch to an approved disease-modifying therapy.

Ofatumumab is approved for treatment of CLL 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 (HBV) infection and reactivation, and bowel obstruction (please refer to locally available Arzerra® Prescribing Information). The dose of ofatumumab in CLL are 100 times higher than the dose to be used in this study in MS.

The experience with ofatumumab in MS patients is limited. 267 of RRMS patients have been exposed to ofatumumab iv (N=38) and sc (N=229) in 2 Phase 2 studies (Study OMS115102 and OMS112831). However, in parallel to this study (COMB157G1301), two global Phase 3 studies (COMB157G2301 and G2302) are being conducted with a planned total sample size of 1800 randomized patients. A DMC will monitor the safety and risk/benefit for the entire OMB157G program including COMB157G2301, G2302 and G1301. No unexpected safety findings were observed in MS patients who received ofatumumab in the completed studies. 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 MS patients in the Phase 2 studies. Confirmation of clinical efficacy will be evaluated in the Phase 3 studies (Study COMB157G2301 and G2302). 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 2017). Taken together, available information of relevant clinical and MRI outcome supports the potential efficacy of ofatumumab in patients with relapsing MS.

Overall, the balance of benefit and risk supports the rationale of COMB157G1301 study to evaluate the efficacy and safety of ofatumumab sc to address the unmet medical need of patients with relapsing MS.

[redacted]

4 Population

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

A total of 60 patients, including 30 patients from Japan (neither Caucasian nor African) and 30 patients from the other countries (mainly Caucasian, not East Asian), are planned to be randomized.

The study is planned to be conducted in approximately 15 centers in Japan and approximately 5 to 10 centers in Europe and/or North America. 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
5. At least 1 appearance of a new neurological abnormality or worsening of pre-existing neurological abnormality during the previous 2 years prior to Screening AND an MRI activity (Gd-enhanced T1 lesions or new or enlarging T2 lesions) in brain during the previous 1 year prior to randomization. Note: Screening MRI scan may be used.
6. Disability status at Screening with an EDSS score of 0 to 5.5 (inclusive)
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.

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. 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 human chorionic gonadotropin (hCG) laboratory test.
5. 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. 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,

[redacted]

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.

6. 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)
7. Patients with active systemic bacterial, viral or fungal infections, or known to have AIDS or to test positive for HIV antibody at Screening
8. Patients with neurological findings consistent with PML or confirmed PML
9. Patients at risk of developing or having reactivation of syphilis or tuberculosis (e.g. patients with known exposure to or history of syphilis or active or latent tuberculosis, even if previously treated). 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. For syphilis testing, it should be done per local clinical practice (e.g. by positive rapid plasma reagin (RPR)). For tuberculosis testing, QuantiFERON®-TB Gold test will be done by the central laboratory to assess patient's eligibility at Screening.
   NOTE:
   - For syphilis and tuberculosis skin test: patients can be enrolled if results are negative. If the test results are unclear or there is suspicion of false positive test results of a tuberculin skin test, the Investigator may consult with an infectious disease expert. If the infectious disease expert considers the test results false positive and not clinically relevant, the Investigator must document (in source data) that the test results are considered false positive and may then randomize the patient.

[redacted]

- Patients with an indeterminate QuantiFERON®-TB Gold test may be enrolled if the repeat QuantiFERON®-TB Gold test is negative prior to randomization.
- Patients with positive QuantiFERON®-TB Gold test are not eligible.

10. 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 as below:
    - anti-HA Immunoglobulin (Ig) M (IgM)
    - HBs antigen positive or HBc IgM/IgG antibody positive, regardless of HBV DNA testing result
    - HBs antibody positive and other HBV parameters negative (HBs antigen negative and HBc IgM/IgG antibody negative) without known history of anti-HBV immunization
    - anti-HC IgG (if positive IgG, Hepatitis C Virus (HCV)-ribonucleic acid (RNA) polymerase chain reaction (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) that the serology results are considered false positive and may then randomize the patient.
11. Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months prior to randomization
12. Have been treated with any of the medications listed below:

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, plasmapheresis, fingolimod	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 accelerated elimination procedure and has documented teriflunomide plasma level below 0.02 mg/L before randomization
Natalizumab Mildly to moderately immunosuppressive/chemotherapeutic medications (e.g. azathioprine, methotrexate)	6 months prior to randomization

[redacted]

Medication	Exclusionary if used/used within required wash-out period
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	Any time

13. 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
14. 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 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
15. Any of the following conditions or treatments that may impact the safety of the patient:
    - Cardiac or cardiac repolarization abnormality, including any of the following:
        - History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
        - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third degree AV block)
    - Resting the Fridericia QT correction formula (QTcF) $\geq$ 450 msec (male) or $\geq$ 460 msec (female) at pretreatment (screening or baseline) or inability to determine the QTcF interval
    - Risk factors for Torsades de Point including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia or any of the following:
        - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
        - Concomitant medication(s) with a "Known Risk of Torsades de Point" that cannot be discontinued or replaced by safe alternative medication.
    - 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

[redacted]

- Patients with severe renal impairment (Glomerular Filtration Rate < 30 ml/min/1.73 m^2)
- Any medically unstable condition as determined by the Investigator

16. Any of the following abnormal laboratory values prior to randomization:
    - Total or conjugated bilirubin (BIL) > 1.5 times upper limit of normal (ULN) range, unless in the context of Gilbert's syndrome
    - Alkaline phosphatase (AP) > 1.5 times the ULN range
    - Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) > 1.5 times ULN or gamma-glutamyl-transferase (GGT) > 2 times ULN range
    - White blood cell (WBC) count < 3,500/mm^3 (< 3.5 x 10^9/L)
    - Lymphocyte count < 800/mm^3 (< 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)
17. 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 (CSSRS), 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-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
18. Patients unable or unwilling to undergo MRI scans (e.g. contraindications for MRI include like weight ≥ 140 kg, pacemaker, cochlear implants, presence of foreign substances in the eye, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, claustrophobia or inability to receive gadolinium contrast agent (e.g. hypersensitivity, renal dysfunction))
19. History of hypersensitivity to any of the study drugs 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 requirements, the local requirements must be followed.

[redacted]

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 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.

Study drug will be supplied by Novartis.

5.1.2 Additional treatment

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

5.2 Treatment arms

The study includes 2 treatment arms:

- Ofatumumab arm
  <Core part>
  Double-blind treatment period: Ofatumumab 20 mg sc injections on Day 1, 7, 14, Week 4 and every 4 weeks thereafter.
  <Extension part>
  Double-blind loading dose period: Ofatumumab 20 mg sc injections at Week 24 and ofatumumab-matching placebo sc injections at Week 25 and 26.
  Open-label treatment period: Ofatumumab 20 mg sc injections at Week 28 and every 4 weeks thereafter.
- Placebo arm
  <Core part>
  Double-blind treatment period: Ofatumumab- matching placebo injections on Day 1, 7, 14, Week 4 and every 4 weeks thereafter.
  <Extension part>
  Double-blind loading dose period: Ofatumumab 20 mg sc injections at Week 24, 25 and 26.
  Open-label treatment period: Ofatumumab 20 mg sc injections at Week 28 and every 4 weeks thereafter.

5.3 Treatment assignment and randomization

Eligible patients will be randomized in a 2:1 ratio to either the active ofatumumab 20 mg group or to the placebo group. Randomization will be stratified by region (Japan or other countries) and baseline number of Gd-enhanced T1 weighted lesions (0 or ≥ 1).

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

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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 study drug 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 design. Patients will be assigned to receive either active ofatumumab or ofatumumab-matching placebo as described in Section 5.2.

Patients, Investigator staff, persons performing the assessments, and data analysts will remain blinded to the identity of the treatment assignment 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: DMC members, Independent Statisticians and Independent Programmers. (2) The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

The randomization codes associated with PK samples will be disclosed to the Bioanalysts who will keep PK and Anti-human antibodies (ADA) results confidential until database 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) 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 part.

[redacted]

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 Subject Number assigned by Novartis. The Subject Number is composed of a site number and a sequential number. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number available in electronic data capture (EDC) system. 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. The site must select the CRF book with a matching Subject Number in the 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 appropriate 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

[redacted]

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 or ofatumumab-matching placebo injections) will be dispensed starting at the Randomization Visit (Day 1). Drug will then be dispensed at planned visits throughout the treatment period according to Table 6-1. 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).

In order to assess tolerability of the initial dose of study medication (injectable), 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 and Week 24, the first dose of Double-blind treatment period in the Core part and Double-blind loading dose period of the Extension part.

From Day 1 until Week 20, patients will receive the sc injection at site. The site staff (e.g. Investigator, Study Nurse/Study Coordinator) will administer the first sc injection on Day 1. From the second sc injection (on Day 7), patients or a caregiver may inject the study medication 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.

Following all assessments required for the visit of Week 24, the injection of study medication begins the Double-blind loading dose period (see Section 5.2). Patients must remain at the site under observation for a minimum of **5 hours** following dosing on Week 24.

From Week 25 onwards, patients may inject the study medication at home by themselves or have a caregiver who have been trained by the study staff on the proper technique and safety precautions, inject the study medication. Ability to self-administer injections must be demonstrated and documented before home-administration is permitted. 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.

From Week 28, patients will receive the open-label ofatumumab sc injection every 4 weeks.

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:

[redacted]

- 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.
- If one monthly injection is 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 Sponsor before re-starting dosing. Missed injection syringes should not be used and returned to the site at the next visit.

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

All dosages prescribed and dispensed to the patient and all dose interruptions during the study must be recorded on the appropriate Electronic Case Report Forms (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.

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.

The patients will record information concerning their home study drug administrations in a diary provided for the Extension part in 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 patient should be instructed to record any missed doses in the patient diary 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. 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, re-start decision should be made on a case-by-case basis (refer also to Section 5.5.4). Should the Investigator decide,

[redacted]

after informing the Sponsor, to re-initiate treatment with study drug, depending on the duration of the interruption, the first sc at re-start may need to take place at the study site to ensure observation in a similar manner as on Day 1 and Week 24.

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

5.5.6 Recommendations for the treatment of MS relapses

MS relapses may be treated with a standard short course of corticosteroids (e.g. methylprednisolone) on an inpatient or outpatient basis. Steroid treatment should consist of 3-5 days and up to 1,000 mg methylprednisolone/day or equivalent. The decision to treat should be based on Investigator's judgment and/or local clinical practice. Standard of care will be followed during treatment.

Taper with oral steroids is not permitted.

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 appropriate 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 appropriate CRF.

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

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. Only for the first injection of Double-blind treatment period (Day 1) and Double-blind loading dose period (Week 24), the addition of premedication with steroids (methylprednisolone 100 mg iv or equivalent) is recommended. Premedication should be administered 30 to 60 min prior to study drug injection.

Any administration of premedication must be recorded in the appropriate CRF.

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

From Week 25 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 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

[redacted]

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 min before the injection). The Investigator will evaluate the need for premedication, or a change in the prescription, at each visit (planned and unplanned) 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 unplanned 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.
Any other immunomodulatory or disease-modifying MS treatment, including but not limited to fingolimod, interferon beta, glatiramer acetate, dimethyl fumarate, intravenous immunoglobulin, plasmapheresis or systemic corticosteroids (except for when given for MS relapse treatment as defined in Section 5.5.6).	Interrupt or discontinue study treatment, increase vigilance regarding infections.

[redacted]

Medication	Additional action to be taken
Leflunomide, teriflumonide	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 will have their EOS visit as soon as possible (Table 6-1). Patients will be followed up for safety in the Safety FU period (Table 6-2).

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will complete this study when the patient has completed the End of Study (EOS) visit.

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

Either patients who complete their EOS visits on study drug and do not enter the umbrella extension study (planned) or patients who prematurely discontinue study drug and complete their EOS visits will enter the Safety FU period (Table 6-2) for continued follow-up.

[redacted]

The Safety FU will complete when all patients who entered have been followed for the stipulated period of time (for at least 36 weeks after study drug discontinuation) (see Section 3.1.3) 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. The patient should return to the site as soon as possible, after discontinuation of study drug, for EOS visit. EOS visit assessments (Table 6-1) 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
- 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

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.

[redacted]

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

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

Note: Patients who prematurely discontinue study drug and complete their EOS visits will enter the Safety FU period (Table 6-2) for continued follow-up (See Section 3.1, Section 5.6.1). The patients should be encouraged to stay in the study and continue to follow the procedures and assessment schedule as specified in the protocol.

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, teriflunomide, etc.). This is in line with the expected circulating B-cell repletion course after ofatumumab discontinuation (estimated around 5 months needed for 80% repletion; see 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.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

[redacted]

In this situation, the Investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient'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 patient 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 patient's study withdrawal should be made as detailed in the schedule of assessments (Table 6-1).

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 planned EOS 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 discontinued 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 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]

[redacted]

- 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 planned or unplanned visits
- Obtaining an EDSS score based on detailed neurological examination at planned visits

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 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 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.

[redacted]

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 syringe counts)
- Administration and supervision of injections and training/supervision of ability to self/home-administer as delegated by the Investigator
- [redacted]
- 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)
- Review of patient diaries, as delegated by the Investigator
- 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

Radiologist/Neurologist

The local radiologist/Neurologist will be responsible for:

- Reviewing each MRI scan performed for the study patients and contacting the Investigator in case of unexpected or 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.

[redacted]

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 planned visits, patients may have unplanned 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 unplanned visits will be recorded in the unplanned visit CRFs.

At Week 24, all assessments required for the Core part MUST be completed prior to the first study drug administration for the Extension part.

In the Extension part, patients will be asked to complete a diary 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 only for patients who administer the monthly sc injection at home (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 warranting an unplanned visit, injection reactions, and, as applicable, results of home pregnancy testing and compliance with contraception requirements. Conduct and results of home pregnancy testing is to be recorded in the source documentation.

Patients who stop taking study medication should be scheduled for the EOS visit as soon as possible and then enter the Safety FU according to schedule in Table 6-2. Patients who complete this study on study drug but do not enter the umbrella extension study (planned) will also have their EOS visit and then enter the Safety FU according to schedule in Table 6-2.

[redacted]

Table 6-1 Assessment schedule

Part	Core part													Extension part							
Period	Screening		Double-blind treatment											Double-blind loading dose		Open-label treatment					
Visit	SCR (D-45 to D-8)	BL (D-7 to D1 (pre-treatment)	D1[1]	D2	D5	D7	D14	W4 (D28)	W8	W12	W16	W20	W24	W25[19]	W26[19]	W28	W36	W48	W60[20]	W72[20]	EOS[2]
Visit No.	1	20	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	1999
Visit Window (days)	n.a.	n.a.	n.a.	0	−1	±1	±1	±3	±7	±7	±7	±7	±7	±1	±1	±3	±7	±7	±14	±14	n.a.
Informed consent	X																				
Demography, Height	X																				
Medical history	X																				
MS History/ Treatments	X																				
Incl/Excl	X[3]	X																			
IRT contact	X		X			X	X	X	X	X	X	X	X			X	X	X	X	X	X
Dispense study drug[17]			X			X	X	X	X	X	X	X	X[4]	X	X	X	X[5]	X[5]	X[5]	X[5]	
Pretreatment[6]			S/A/A			A/A	A/A	A/A	A/A	A/A	A/A	A/A	S/A/A	A/A	A/A	A/A	A/A	A/A	A/A	A/A	
Vital signs	X	X	X[7]			X[7]	X[7]	X[7]	X	X	X	X	X[7]			X	X	X	X	X	X
Weight		X											X					X			X
Physical Exam[8]	X[9a]	X[9a]											X					X		X	X
ECG	X[9a]	X[9a]											X					X			X
Lab samples including urine	X	X[18]						X		X			X			X	X	X	X	X	X
Sample for $CD19^+$ B-cells and $CD3^+CD20^+$ T-cells		X		X	X	X	X	X		X			X			X	X	X	X	X	X
Pregnancy test[10]	X	X[18]						X	X	X	X	X	X			X	X	X	X	X	X

[redacted]

Part	Core part													Extension part							
Period	Screening		Double-blind treatment											Double-blind loading dose		Open-label treatment					
Visit	SCR (D-45 to D-8)	BL (D-7 to D1 (pre-treatment)	D1[1]	D2	D5	D7	D14	W4 (D28)	W8	W12	W16	W20	W24	W25[19]	W26[19]	W28	W36	W48	W60[20]	W72[20]	EOS[2]
Visit No.	1	20	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	1999
Visit Window (days)	n.a.	n.a.	n.a.	0	−1	±1	±1	±3	±7	±7	±7	±7	±7	±1	±1	±3	±7	±7	±14	±14	n.a.
Contraception status[11]	X	X						X	X	X	X	X	X			X	X	X	X	X	X
PK sampling[12]		X		X	X	X	X	X		X			X			X	X	X	X	X	X
ADA sampling[12]		X						X		X			X			X	X	X	X	X	X
[redacted]																					
Total IgM, IgG levels	X[9a]	X[9a]						X		X			X			X	X	X	X	X	X
Serological markers for hepatitis A, B, C, and E	X												X								
HIV test	X																				
MRI[13]	X									X	X	X	X				X	X			X[14]
EDSS	X	X[9b]	X[9b]							X			X				X	X	X	X	X
[redacted]																					
eCSSRS	X[9a]	X[9a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X
Prior/Con Meds[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone interview[16]														X	X	monthly between planned visits					
Patient diary review														X	X	X	X	X	X	X	
Disposition													X								X

A/A=Acetaminophen/Antihistamine; ADA=Anti-drug-antibody; AEs=Averse events; BL=baseline; Con meds=Concomitant medications; D=day; Excl.=exclusion; Incl.=inclusion; n.a.=not applicable; S= Steroid; SCR=screening; W=week.

[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. Patients must remain at the site under observation for a minimum of 5 hours following dosing on Day 1.
2. EOS visit will be required for all patients (Patients who permanently discontinue study drug and patients who complete the study).
3. Syphilis and Tuberculosis testing must be done as part of eligibility check (Exclusion criterion #9) unless completed in the last 6 months prior to screening with documented negative results. For syphilis testing, it should be done per local clinical practice (e.g. by positive RPR). For tuberculosis testing, QuantiFERON®-TB Gold test will be done by the central laboratory to assess patient's eligibility at Screening.
4. All assessments required for the Core part MUST be completed before the patient receives the first dose for the Extension part at Week 24. Patients must remain at the site under observation for a minimum of 5 hours following dosing at Week 24.
5. After Week 36 visit, patients may visit every 12 weeks. In this case, patients will need to continue study treatment every 4 weeks at home. For PK and ADA visits the patient should not take injection before coming to the site (see footnote 12).
6. S/A/A means Steroid/Acetaminophen/Antihistamine. Premedication with acetaminophen and/or antihistamines (or equivalent) is recommended and may be administered at the discretion of the Investigator. For the first injection of Double-blind treatment period (Day 1) and Double-blind loading dose period (Week 24) only, the addition of premedication with steroids (methylprednisolone 100 mg iv or equivalent) is recommended. Premedication should be administered 30 to 60 min prior to study drug injection.
7. 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, 7, 14 and Week 4 in the Core part and on the first injection in the Extension part (at Week 24).
8. 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.
9. 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).
10. Pregnancy test is conducted on female patients only: Serum pregnancy tests will be conducted at Screening and EOS visit. Urine pregnancy tests will be conducted at all other planned visits as indicated in Table 6-1. After Week 28, 4-weekly urine pregnancy tests will be conducted at home between site visits. The patient must contact the Investigator immediately in the case of a positive test for confirmatory testing at the Investigator's discretion.
11. Patient's contraception status must be reviewed and documented to ensure method of contraception continues to be appropriate per protocol requirement for highly effective contraception.
12. PK and ADA visits: The PK (Plasma) and ADA (Serum) samples should be drawn before the patient takes their injection.
13. In case of relapse, if an MRI for efficacy has been scheduled within 14 days of the initiation of steroid treatment, the MRI should be performed before steroid treatment is initiated. No MRI for efficacy should be performed while a patient is on steroid therapy for relapse and within 14 days upon termination of steroid therapy.
14. MRI scan at the EOS is needed if there was no MRI scan in the last 3 months.
15. Including corticosteroids used to treat MS relapse; any newly started MS treatment as applicable (for patients who have discontinued study medications).

[redacted]

16. Applicable for patients who take study treatment by home-administration. Telephone interview by site staff should take place around time of the sc self/home injection to query about any new or worsening symptoms warranting an unplanned visit, injection reactions, results of home pregnancy testing, compliance with contraception requirements as applicable.
17. Patients will receive sc injections of Double-blind treatment period on Day 1, Day 7 (± 1 day), Day 14 (± 1 day), Week 4 (± 3 days), Week 8 (± 3 days), Week 12 (± 3 days), Week 16 (± 3 days) and Week 20 (± 3 days), the sc injection of the Double-blind loading dose period at Week 24 (± 3 days), Week 25 (± 1 day) and Week 26 (± 1 day), and the Open-label ofatumumab sc injection from Week 28 (± 3 days), followed by every 4 weeks (± 3 days).
18. Labs must be drawn to allow adequate time for results to be obtained before randomization to ensure patient's eligibility
19. Patients do not have to visit the site at Week 25 and 26 if they are permitted to administer the sc injection at home at investigator’s discretion.
20. If the trial is extended beyond Week 72, every 12 weeks visit (Week 84, 96 and so forth) will be performed with same measurements as at Week 60, 72 and so forth.

[redacted]

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

Visit Week[1] (relative to EOS)	**+W12**	**+W24**	**+W36**	**Every 12 weeks[2]**	**End of Safety-FU[3]**
Visit Number	**410**	**420**	**430**	**440/4XX**	**2999**
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[4]	X	X	X	X	X
Contraception status	X	X	X	X	X
Laboratory sample including sample for B-cells and T-cells	X	X	X	X	X
Sample for Total IgG, IgM	X	X	X	X	X
MS Relapse	X	X	X	X	X
EDSS	X	X	X	X	X

W=week.

1. Time measured from the EOS visit.
2. As needed for patients requiring prolonged B-cell plasma level monitoring (Section 3.1)
3. If planned 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 period, the End of Safety-FU assessments should be done at time of withdrawal.
4. 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.

* including steroids for MS relapse and newly started disease modifying therapy as applicable

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have their disposition recorded on the appropriate CRF. 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.

6.2 Patient demographics/other baseline characteristics

Patient demographic data and baseline characteristics to be collected on the appropriate CRF will include age, 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 CRF capturing medical history 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 appropriate CRFs.

Compliance will be assessed by the Investigator and/or study personnel at each visit using syringe 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)
- [redacted]

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.

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 unplanned 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 planned 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 unplanned visit is to be scheduled as soon as possible,

[redacted]

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 appropriate 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

(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 planned 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.

[redacted]

Definitions for disability worsening and disability improvement based on the EDSS [redacted]

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 radiologist/neurologist. The Investigator will review the MRI performed during the Screening period to assess patient's eligibility. After Randomization, the Investigator will be contacted in case of unexpected or safety-related findings detected on the MRI scan. The investigator may review the MRI scans from Week 36 onwards, regardless of safety concerns.

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 14 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 14 days upon termination of steroid therapy.

[redacted]

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 institute MRI manual.

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

The 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.

[redacted]

6.4.5 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.

[redacted]

6.5 Safety

Safety assessments will include:

- Adverse events
- Physical examination (including skin)
- Vital signs
- Laboratory evaluations
- Pregnancy testing (females of childbearing potential)

[redacted]

- 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 the global program 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 section of the CRFs capturing medical history/current medical conditions. Significant findings seen after signing the informed consent and being randomized meet the definition of an AE and must be recorded on the appropriate CRF capturing AEs.

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 injections on Days 1, 7, 14 and Week 4 in the Core part and on the first injection in the Extension part (at Week 24), vital signs should be obtained 30-60 min before sc injection and again approximately 60 min 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 min, 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 repeat sitting measurements of blood pressure and pulse will be made at 1-2 min 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.

[redacted]

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. 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 and T-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 Core part of this study until the treatment code for the study has been broken.

6.5.4.1 Hematology

Blood samples will be collected at the planned 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), $CD19^+$ B-cell counts and $CD3^+CD20^+$ T-cell counts.

For study blinding purposes, the B-cell and T-cell counts will not be provided to the Investigators and Sponsor study team. B-cell and T-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 planned 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).

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 planned visits indicated in Table 6-1 and the dipstick parameters assessed will include: blood, glucose, specific gravity and protein. In case of an abnormal

[redacted]

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 9, Section 4.2). For syphilis testing, it should be done per local clinical practice (e.g. by positive RPR). For tuberculosis testing, QuantiFERON®-TB Gold test will be done by the central laboratory to assess patient's eligibility at Screening.

A positive result for any of the following serological markers for hepatitis A, B, C, and E as below is an exclusion criterion:

- anti-hepatitis A virus IgM
- HBs antigen positive or HBc IgM/IgG antibody positive, regardless of HBV DNA testing result
- HBs antibody positive and other HBV parameters negative (HBs antigen negative and HBc IgM/IgG antibody negative) without known history of anti-HBV immunization
- 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 Hepatitis E virus (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) 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.

For study blinding purpose, the results of immunoglobulin levels will not be included as part of the laboratory reports provided to the Investigators or Sponsor study team during the study. 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 (Section 6.6.1, Section 6.6.2, [redacted]

6.5.5 Electrocardiogram (ECG)

An ECG will be performed at Screening, Week 24, Week 48, EOS visits. Additional unplanned ECGs may be performed at Investigator's discretion if clinically indicated.

[redacted]

Single 12 lead ECGs are collected. The ECG should be recorded (after 10 min 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. 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 number, date and time, and filed in the study site source documents.

Findings and clinically significant abnormalities must be recorded on the relevant section of the CRFs capturing medical history/current medical conditions and AEs.

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 and EOS Visits. Urinary pregnancy tests will be conducted for all women who are of child bearing potential at all other planned 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 planned clinic visits after Week 28. 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 (IB).

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

6.6 Other assessments

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.

6.6.1 Pharmacokinetics

Following a single sc injection of ofatumumab 20 mg, PK during the absorption and distribution phase will be assessed. PK trough values at steady state for ofatumumab will be

[redacted]

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 visit. For PK visits after Week 36, 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 recorded as instructed in the lab manual 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.

6.6.2 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 visit. For ADA visits after Week 36, 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]

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

[redacted]

- 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, version 4.03 will be used and can be found on the following web-site: http://ctep.cancer.gov).

Adverse events must be recorded in the appropriate CRF capturing AEs 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)

- its relationship to the study treatment
- 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:

- study treatment dose not changed (e.g. further observation only)
- study treatment dose increased/reduced
- study treatment interrupted/withdrawn
- concomitant medication or another therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; 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 CRF capturing AEs.

[redacted]

Information about common side effects already known about the investigational drug (ofatumumab) can be found in the IB. 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 (IN) 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.

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

[redacted]

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 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 IB or Package Insert (new occurrence) and is thought to be related to the study treatment a Patient Safety 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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

[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 appropriate CRF capturing MS relapse 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 (AE/SAE) and any contributing factors (concomitant medications, other co-morbid conditions/procedures), which will require close observation, follow-up monitoring should be entered into the appropriate CRFs

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 appropriate CRFs.

Repeat laboratory tests must be entered on the appropriate unplanned assessment CRFs.

[redacted]

- 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 CRFs, including the liver event overview.

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 ≥ 24 hours) 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. The renal AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) should be recorded in the appropriate CRFs.

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.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported

[redacted]

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.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in study treatment eCRF (Yes/No)	Document in AE eCRF	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 Patient Safety 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.

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 unplanned visits.

A validated version of the CSSRS will be used to capture self-reported CSSRS data via an interactive voice response telephone system (eCSSRS). The eCSSRS uses a detailed branched logic algorithm to perform the CSSRS 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.

[redacted]

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.

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 Clinical Research Associate (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 Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to United States (US) Code of Federal Regulations (CFR) 21 Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the

[redacted]

data to the Contract Research Organisation (CRO) working on behalf of Novartis. 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.

The Principal Investigator is responsible for assuring that the data entered by the site personnel into CRF is complete, accurate, and that entry and updates are performed in a timely manner

8.3 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

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 data 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.

8.4 Data Monitoring Committee

A global program DMC of OMB157G will be in place to oversee the studies of OMB157G. 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, advice the Sponsor of a need for protocol

[redacted]

modification/amendment 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 data analysis will occur in three steps:

1. The first analysis will be conducted for the Core part. Data up to the Week 24 cut-off will be used. The analysis will be performed when the last patient has completed the double-blind loading dose period until Week 28. This analysis will be used in support of the registration of ofatumumab in Japan.
2. A second data analysis will be conducted at the Week 48 cut-off (cut-off 2). The analysis will include assessments of maintenance of efficacy and extended safety and partial data from the Safety FU period.
3. The final analysis will be conducted at EOS (i.e. including all data from the Safety FU period).

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.

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.

[redacted]

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-blind design all patient will receive injections (active or placebo) to maintain the blind. For the calculation of exposure to study medication the intended dosing frequency will be taken into account and intermediate treatment interruptions will be subtracted when deriving drug exposure.

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.

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(s)

9.4.1 Primary Variable(s)

The primary variable is the number of Gd enhanced T1 weighted MRI lesions per scan.

9.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis is that there is no difference in the number of Gd-enhanced T1 weighted MRI lesions per scan between ofatumumab and placebo during the Core part. The alternative hypothesis is that there is a difference between the 2 treatment groups.

- Superiority of ofatumumab over placebo will be concluded if the mean number of Gd-enhanced T1 weighted MRI lesions per scan in patients treated with ofatumumab is lower compared with placebo and the observed p-value for the between-treatment comparison is less than the two-sided significance level of 0.05.

The null hypothesis will be tested on the FAS using a negative binomial regression model with log-link. Each patient's total number of Gd-enhanced T1 weighted MRI lesions during the Core part will be used as the response variable, and 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. The model will include treatment, region (Japan or other countries), and baseline number of Gd-enhanced T1 weighted lesions (0 or ≥ 1) as factors.

[redacted]

9.4.3 Handling of missing values/censoring/discontinuations

The primary negative binomial model with an offset for the number of MRI scans adjusts for missing information (drop-out) under the assumption of non-informative drop-out, information is missing at random, and constant number of Gd-enhancing T1 weighted MRI lesions per scan within patient. Missing values will not be imputed. However, deviations from assumptions will be tested in sensitivity analyses.

9.4.4 Sensitivity analyses

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.

The time-to-first relapse analysis (Section 9.5.1.3) does not assume a constant number of Gd-enhancing T1 weighted MRI lesions per scan and can be regarded as a sensitivity analysis to the primary analysis.

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

9.4.5 Consistency across regions

Consistency in efficacy across regions on the primary variable will be evaluated using a statistical model similar to the primary model, but with a treatment-by-region (Japan or other countries) interaction term added. The mean number of Gd-enhancing T1 weighted MRI lesions per scan will be provided by treatment and region. The rate-ratio (ofatumumab/placebo) will be presented for individual regions separately, together with 95% confidence intervals. The p-value of the treatment-by-region interaction will be displayed.

The estimates for individual regions will be displayed via a forest plot to visualize consistency.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables (Core part)

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

9.5.1.1 Number of new or newly T2 lesions on MRI scans

Analysis of the number 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, region (Japan or other countries), baseline number of Gd-enhancing T1 weighted lesions (0 or ≥ 1) as factors, 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.

[redacted]

9.5.1.2 Annualized relapse rate (ARR)

Analysis of ARR will be done based on the FAS, using a negative binomial regression model with log-link, treatment, region (Japan or other countries), baseline number of Gd-enhancing T1 weighted lesions (0 or ≥ 1) as factors, and number of relapses in previous year and baseline EDSS 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.

9.5.1.3 Time to first relapse

Analysis of time to first relapse will be done based on the FAS, using a Cox proportional hazard model with treatment, region (Japan or other countries), and baseline number of Gd-enhancing T1 weighted lesions (0 or ≥ 1) as factors, and number of relapses in previous year and baseline EDSS as covariates. The hazard ratio (also expressed as percentage reduction relative to control group) along with the 95% confidence interval for the hazard ratio and the corresponding p-value will be obtained.

In addition, Kaplan-Meier curves by treatment will be used to present the time-dependent cumulative frequency and percentage of subjects reaching the first relapse; by-treatment Kaplan-Meier estimates (with 95% confidence interval) at end of study will be obtained.

9.5.2 Safety variables (Core part)

Safety analyses will be conducted using the safety (SAF) dataset. Patients will be grouped by the actual treatment received. Safety data for the core part will be reported for the first time when the double-blind loading dose period has been completed by the last patient (data cut-off 1).

Unless explicitly otherwise stated, safety data will be reported up to and including the safety cut off of 30 days after permanent study drug discontinuation in patients who discontinued 30 days or more prior to cut-off 1, and up to cut-off 1 in all other patients.

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 30 days after permanent study drug discontinuation in patients who discontinued 30 days or

[redacted]

more prior to cut-off 1, for all other patients TEAE will be reported up to cut-off 1. 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.

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.

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 > 3 x ULN & TBL > 2 x ULN & ALP ≤ 2 x ULN or a reported Hy's Law case (refer also to Appendix 1).

Standardised MedDRA Queries (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 (CSSRS) data will be mapped to Columbia Classification Algorithm for Suicide assessment (C-CASA) as per Food & Drug Administration (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.

[redacted]

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 CRFs capturing AEs. 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 period

Safety data collected during the Safety Follow-up period 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 period 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 all patients change is defined relative to the End of Study visit (EOS). Since post-treatment safety follow-up in the Safety Follow-up period may continue for up to 36 weeks (or longer if criteria for loner follow-up are met) after completion of the Treatment period study, the study report for the Core part (Screening and Double-blind treatment period) will be completed based on the completed core part i.e. based on all patients who have completed the Double-blind treatment period, and the partial data from the Safety Follow-up period 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 period have completed this period.

9.5.3 DNA

Not Applicable.

9.5.4 PK/PD

PK concentration and B-cell count data will be summarized by visit for the overall population, and separately by region (Japan or other countries) and provided together with by-patient listings in the study report.

[redacted]

9.5.5 Immunogenicity assessment

Samples will be analyzed for of the presence of human anti-drug antibodies (ADA). The proportion of patients with ADA 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 be provided.

[redacted]

[redacted]

9.7 Analysis of the Extension part

Analyses will include the combined data of the Core and Extension parts.

The extension FAS will include all available assessments of the Core and Extension parts. The main between-group comparisons of the efficacy variables will be based on the original randomization at the start of the Core part. The comparison will be between patients who were randomized to ofatumumab, and those who were initially randomized to placebo and received ofatumumab delayed, i.e. at the start of the Extension. Efficacy analyses will use similar models as described for the Core part of the study.

[redacted]

Extended safety and tolerability will be described by safety parameter summaries covering the whole period of continuous treatment with ofatumumab, i.e. by combining double-blind and open-label ofatumumab treatment. Placebo data will be excluded in this analysis. Details will be provided in the statistical analysis plan.

Details of analysis for the Extension part will be defined in a SAP document.

9.8 Interim analyses

No interim analysis will be conducted.

9.9 Sample size calculation

A total sample size of 60 patients, randomized 2:1 to ofatumumab and placebo, will provide more than **90% power** for a statistical test of superiority of ofatumumab compared with placebo at a one-sided alpha level 0.025. The power was calculated based on a negative binomial model under the assumption of 1.0 Gd-enhancing lesions per scan for placebo and a 92% relative reduction with ofatumumab (i.e. 0.08 Gd-enhancing T1 lesions per scan for ofatumumab), and a dispersion parameter $\kappa = 4.5$ (as observed in the combined Phase 3 placebo-controlled studies of fingolimod, namely FREEDOMS and FREEDOMS II studies for the same parameter, data on file). The sample size allows for a dropout rate of 10%.

Sample size calculation was done in EAST 6, version 6.3, Cytel Inc.

[redacted]

9.9.1 Evaluation of consistency in the treatment effect on the primary variable across regions

As a secondary objective the effect of ofatumuab on Gd-enhancing T1 lesion compared with placebo will be estimated for individual regions (Japan and other countries). It is planned to include 30 patients from Japan out of 60 in total.

The randomization will be stratified by region (Japan or other countries), and by Gd-lesion status on the screening scan (0 Gd-enhancing lesions or ≥ 1 Gd-enhancing lesions). Under the protocol assumptions for placebo, it is expected that approximately 2/3 of the patients will be free of Gd-enhancing lesions at baseline.

A simulation was performed to evaluate the consistency in efficacy on the primary variable across regions. Consistency is defined as a rate ratio < 1 in both Japan and other countries. For the simulation the following assumptions apply:

- The assumptions for the primary variable are the same for Japan and other countries and identical to those for the primary endpoint (i.e. 1 Gd-enhancing lesion per scan, a rate-ratio of 0.08 between ofatumumab and placebo, dispersion 4.5)
- In addition, it was assumed that the study would include 30 patients from Japan and 30 from other countries, and that patients would be randomized 2:1 to ofatumumab or placebo group in each region.

The probability to observe a consistent treatment effect between Japan and other countries was estimated to be higher than 99% under these settings.

Furthermore, we estimated the probability to observe a difference in treatment effect (percentage lesion reduction between ofatumumb and placebo) between Japan and other countries under the same assumptions. The probability to observe a difference of 20% or more (one-sided) in treatment effect between Japan and other countries was estimated to be < 3% (Table 9-1).

Table 9-1 Probability to observe a difference in Gd-lesion reduction across regions of more than delta

Delta*	Probability of a difference in percentage lesion reduction > Delta
5%	13.7%
10%	6.1%
20%	2.3%
30%	1.3%

*Delta=Percentage lesion reduction for other countries - percentage lesion reduction for Japan

9.9.2 Numerical comparison of annualized relapse rate (ARR)

As a secondary objective the ARR will be compared between patients treated with ofatumumab or placebo. We evaluated the probability to observe a treatment effect in favor of ofatumumab, as defined by an ARR-ratio (ofatumumab/placebo) less than 1 in the overall population. The following assumptions were made for this evaluation:

- 60 subjects in total are randomized 2:1 to ofatumumab or placebo.
- The true ARRs are 0.4 in the placebo arm, and 0.16 in the ofatumumab arm.

[redacted]

- The dispersion parameter, k, is 0.1.
- The follow-up period is 6 months.

Under these settings, the probability to observe a lower ARR in patients treated with ofatumumab compared with placebo is > 80%.

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 Council 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.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. 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. 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, 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 Standard Operating Procedures (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 including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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.

12 References

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[redacted]

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 × ULN < ALT/AST ≤ 5 × ULN 1.5 × ULN < TBL ≤ 2 × 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

INR= International normalized ratio

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 Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs	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 Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs	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 and INR > 1.5	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs.	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 Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs	ALT, AST, TBL, Alb, PT/INR, AP and GGT until resolution[c] (frequency at Investigator discretion)
> 3 × ULN accompanied by symptoms[b]	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs	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 Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs	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 Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs	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)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 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 Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs	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 Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs	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.
PT=prothrombin time

[redacted]

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 24-48 hours 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 24-48 hours 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:	
Record AE/SAE and any contributing factors (concomitant medications, other co-morbid conditions/procedures) in the appropriate CRFs. 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 radiologist/neurologist. The Investigator will contact the Medical Advisor at Novartis to discuss findings and diagnostic possibilities as soon as possible. A copy of the unplanned 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, 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 Cerebrospinal fluid (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 appropriate eCRF capturing AEs. 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.

[redacted]

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 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). This study excludes the patients who are at potential risk of HBV reactivation (See Section 4.2 Exclusion criterion 10). In patients with suspicion of HBV infection during the study, laboratory testing for HBV should be done. For patients who show new evidence of HBV infection [HBs antigen positive (regardless of antibody status) or HBs antigen negative but HBc IgM/IgG antibody positive], the Investigator is advised to consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy.

Patients with new active HBV infection should 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 due to B-cells depletion.

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 Week 4, 12, 24, 28, 36, 48, subsequent visit for every 12 weeks, and EOS by the central laboratory and will be blinded to the Sponsor and the Investigator. They will only be communicated to the site after

[redacted]

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 repeated 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.

[redacted]