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Global Clinical Development - General Medicine

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Protocol COMB157G2102 / NCT03560739

A 12 week randomized open label parallel group multicenter study to evaluate bioequivalence of 20 mg subcutaneous ofatumumab injected by pre-filled syringe or autoinjector in adult RMS patients.

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List of abbreviations

γ-GT	Gamma-glutamyl transferase
ABE	Average bioequivalence
ACR	Albumin/creatinine ration
ADA	Anti-drug antibodies
ADCC	Anitbody dependent cell-mediated cytotoxicity
AE	Adverse event
AI	Autoinjector
AIDS	Acquired immunodeficiency syndrome
Alb	Albumin
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AUC	Area under the curve
BE	Bioequivalence
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulation
CI	Confidence interval
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRP	C-Reactive protein
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Common Toxicity Criteria
CV	Coefficient of variation
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DTPA	Diethylenetriamine pentaacetic acid
DWI	Diffusion-weighted imaging
EC	Ethics committee
ECG	Electrocardiogram
eCSSRS	Electronic Columbia Suicide Severity Rating Scale
EDC	Electronic Data Capture
EDSS	Expanded Disability Status scale
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
FDA	Food and Drug Administration

[redacted]

FLAIR	Fluid-Attenuated Inversion Recovery
FSs	Functional scores
FU	Follow up
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HA	Health Authority
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCP	Health Care provider
HCV	Hepatitis C Virus
HDL	high density lipoprotein
HEV	Hepatitis E Virus
HIV	human immunodeficiency virus
IB	Investigator Brochure
Ig	Immunoglobulins
IN	Investigator Notification
IRT	Interactive Response Technology
iv	Intravenous
ICH	International Council of Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	low density lipoprotein
LFT	Liver Function Test
LLN	lower limit of normal
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NCA	Non- Compartmental Analysis
[redacted]	[redacted]
NYHA	New York Heart Association
PCR	protein-creatinine ratio
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)
PML	Progressive Multifocal Leukoencephalopathy
QM	Quality Managmenet
QTcF	QT correction formula
RBC	Red blood cells
RNA	Ribonucleic Acid
RRMS	Relapsing-remitting Multiple Sclerosis
RSABE	Reference scaled average bioequivalence
SAE	Serious Adverse Event
sc	Subcutaneous
[redacted]	[redacted]

[redacted]

SOP	Standard operating procedure
SPMS	Secondary progressive Multiple Sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TOST	Test one sided test
ULN	upper limit of normal
US	United States
WBC	white blood cell(s)
WHO	World Health Organization

[redacted]

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration (mass x time/volume)
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration (mass x time/volume)
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau (mass x time/volume)
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration (mass/volume)
Tmax	The time to reach the maximum concentration after drug administration (time)

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit (eg 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (ie prior to starting any of the procedures described in the protocol).
Healthy subject	A person with no known significant health problems who volunteers to be a study participant
Induction	Initial treatment regimen to ensure b cell depletion.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
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 with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	The subdivisions of the trial design (eg 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
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened and didn’t pass the screening criteria and is not treated or randomized
Study disposition	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.

Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.
Withdrawal	Withdrawal of study consent: Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol summary

Protocol number	COMB157G2102
Full Title	A 12 week randomized open label parallel group multicenter study to evaluate bioequivalence of 20 mg subcutaneous ofatumumab injected by pre-filled syringe or autoinjector in adult RMS patients.
Brief title	An open label study evaluating bioequivalence of ofatumumab using a prefilled syringe or autoinjector.
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The primary objective of this study is to demonstrate pharmacokinetic bioequivalence of ofatumumab injected by PFS versus AI devices and thereby establish a bridge between the ongoing Phase 3 program and the [redacted].
Primary Objective(s)	To demonstrate pharmacokinetic bioequivalence of 20 mg ofatumumab injected by the PFS or AI devices
Secondary Objectives	To characterize the pharmacokinetics following subcutaneous administration of ofatumumab to either the abdominal region or the thigh Assessment of immunogenicity Assess the safety and tolerability of ofatumumab
Study design	This is a randomized, open-label, multi-center, parallel group 12-week study to evaluate the pharmacokinetic bioequivalence of ofatumumab injected by PFS or AI devices. The study design includes four parallel groups of RMS patients. Assessment of the primary and secondary endpoints are performed based on data collected through the dosing interval between Week 8 and Week 12 where approximate steady-state pharmacokinetics are anticipated.
Population	Adult patients with RMS
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Male or female patients aged 18 to 55 years (inclusive) at screening. • Diagnosis of MS • Relapsing MS: relapsing-remitting course (RRMS), or Secondary progressive (SPMS) course with disease activity • Disability status at Screening with an EDSS score of 0 to 5.5 (inclusive) • Documentation of at least: 1 relapse during the previous year OR 2 relapses during the previous 2 years prior to Screening OR a positive Gd-enhancing MRI scan during the year prior to randomization. • Neurologically stable within 1 month prior to randomization
Key Exclusion criteria	• Patients with primary progressive MS or SPMS without disease activity • Patients meeting criteria for neuromyelitis optica • Disease duration of more than 10 years in patients with EDSS score of 2 or less • Pregnant or nursing (lactating) women

[redacted]

	• Women of child-bearing potential unless they are using highly effective methods of contraception. • Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (eg rheumatoid arthritis, scleroderma, Sjögren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with immunodeficiency syndrome (hereditary immune deficiency, drug-induced immune deficiency) • Patients with active systemic bacterial, viral or fungal infections, or known to have AIDS or to test positive for HIV antibody at Screening • Patients with neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML), or confirmed PML • Patients at risk of developing or having reactivation of syphilis or tuberculosis • Patients at risk of developing or having reactivation of hepatitis
Study treatment	Investigational drug will be provided in pre-filled syringes containing 20 mg ofatumumab (50 mg/ml, 0.4 ml content) or autoinjector containing 20 mg ofatumumab (50 mg/ml, 0.4 ml content) for subcutaneous administration. Ofatumumab is a clear to opalescent, colorless to pale yellow, essentially particle-free liquid.
Efficacy assessments	[redacted]
Key safety assessments	• Adverse events • Physical examination (including skin) • Vital signs • Laboratory Evaluations • Pregnancy testing (females of childbearing potential) • ECG • Electronic Columbia Suicide Severity Rating Scale (eCSSRS)
Other assessments	[redacted] PK, B-cells, ADA [redacted]
Data analysis	The analysis will be conducted per statistical analysis plan. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.
Key words	Open label, Bioequivalence, autoinjector, pre-filled syringe, [redacted]

[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.

For the patients with relapsing MS (RMS), interferon-β and glatiramer acetate have long been used as first-line drugs. These drugs require frequent self-injections which may become an increasing burden for patients over time. In the recent years, oral drugs such as fingolimod, dimethyl fumarate and teriflunomide have become available and enhanced the convenience of treatment for the patients. In addition, treatment with more potent drugs including natalizumab, alemtuzumab and ocrelizumab have been put into practice. Despite the increased options available, there are patients whose disease activity cannot be fully controlled by the existing drugs, or are experiencing intolerable side effects from current available drugs. 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 in MS by self-antigen presentation, serving as cellular adjuvants for $CD4^+$ T-cell activation (Bouaziz et al 200712 References) 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). Recently, it has been recognized that CD20 expression is not restricted to B-cells, but it also present in a subset of T-cells. Anti-CD20 therapy eliminates these T-cells.

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 disability worsening vs interferon beta 1a over 2 years.

Both rituximab and ocrelizumab are delivered in an outpatient setting by intravenous (iv) infusion. However, self-administrated treatment at home with a B-cell targeting therapy with high efficacy, and safety profile, as approached with sc ofatumumab, is highly desirable.

Ofatumumab

Ofatumumab is a fully human anti-CD20 monoclonal antibody (mAb), depleting B-cells similar to rituximab and ocrelizumab. Ofatumumab recognizes a unique epitope localized close to the cell membrane on the two extracellular domains of the CD20 molecule, N-proximal to the

[redacted]

epitopes for the anti-CD20 mAbs rituximab and ocrelizumab. CD20 binding of ofatumumab induces B-cell lysis primarily through complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) (Klein et al 2013, Teeling et al 2004).

Ofatumumab iv, Phase II data: OMS115102 was a double-blind, randomized, placebo-controlled, multicenter, dose-escalation study of intravenous ofatumumab in RRMS patients. This trial showed a dose-dependent B-cell depletion and a reduction of MRI lesion activity of 99% compared to placebo, and an acceptable safety profile of ofatumumab in MS (Sorensen et al 2014).

Ofatumumab sc, Phase II data: OMS112831 (MIRROR study) was a double-blind, placebo-controlled, parallel-group, dose-ranging study evaluating the safety and MRI efficacy of sc ofatumumab in subjects with RRMS. The objective of OMS112831 was to evaluate efficacy as assessed by MRI, and the tolerability and safety of a range of doses of ofatumumab (3, 30, or 60 mg) to enable selection of a dosing regimen for further study in Phase III. Cumulative doses > 30 mg showed a reduction of MRI lesion activity of > 90% compared with placebo during weeks 4-12 and reduction was maintained up to the last observation at Week 48. In addition, analysis of peripheral B-cell counts demonstrated a rapid, dose and dose frequency dependent B-cell depletion.

Overall, ofatumumab was safe and well tolerated in patients with RRMS. The safety profile of ofatumumab was consistent with previous data; no new safety signals were reported. For detailed safety information, please refer to the current version of the investigator's Brochure.

PK/PD modelling of the ofatumumab sc Phase 2 clinical trial data in RRMS patients indicate that an induction regimen (3 weekly doses of 20 mg) followed by a maintenance dose regimen of ofatumumab 20 mg every 4 weeks, will achieve and maintain effective tissue depletion of circulating CD20+ B-cells. This dosing scheme was chosen for the Phase 3 studies in relapsing MS.

Novartis initiated a Phase 3 clinical program in relapsing MS (RMS) which completed recruitment in March 2018, enrolling a total of 1884 patients. Two worldwide, double-blind, double-dummy, active-controlled trials of identical design, are being conducted in parallel in RMS patients (OMG157G2301, aka ASCLEPIOS I and OMB157G2302, aka ASCLEPIOS II). These trials evaluate the efficacy and safety of ofatumumab 20 mg subcutaneously (sc) vs teriflunomide 14 mg orally. Ofatumumab is administered starting with a loading dose regimen of three doses of 20 mg every week for the first three doses (Day 1, Day 7 and Day 14) followed by a maintenance dose of 20 mg every 4 weeks starting at Day 28.

Ofatumumab administration

This study will use the same treatment regimen as the Phase 3 program that is described above. The induction regimen was chosen to ensure a fast and effective depletion of CD20-positive B-cells without the need for administration of high doses. Thereafter, the maintenance regimen starting at week 4 is subcutaneous administration of 20 mg every 4 weeks. Subcutaneous administration in the Phase 3 studies is provided via a pre-filled syringe (PFS) whereas the

[redacted]

[redacted]

In order to demonstrate that administration of ofatumumab via the AI leads to equivalent drug concentration profiles compared to administration via the PFS, bioequivalence endpoints (Cmax and AUCtau) will be determined in the study and compared statistically according to health authority requirements.

1.2 Purpose

The primary objective of this study is to demonstrate pharmacokinetic bioequivalence of ofatumumab injected by PFS versus AI devices and thereby establish a bridge between the ongoing Phase 3 program [redacted].

Characterization of the pharmacokinetics of ofatumumab administered via the PFS used in clinical trials [redacted] at the clinical dose of 20 mg will be conducted after an initial depletion of CD20 positive B-cells. Comparing the ofatumumab pharmacokinetics between the two drug-device combinations only after the induction period is expected to reduce initial high variability due to target-mediated clearance. This ensures a more stable baseline for PK comparison in a parallel group study design and reflects the clinical situation where systemic concentrations are at steady-state. In order to justify the resulting long-term B-cell depletion, a PK comparability study between the PFS and the AI can only be conducted in MS patients rather than in healthy subjects to balance the risk/benefit and to obtain PK data from the relevant patient population. In order for patients to obtain a clinical benefit from participation in the study, continued treatment with ofatumumab will be offered to all eligible patients through enrollment into the open-label Phase 3 extension study (separate protocol, COMB157G2399).

A secondary objective of the study is to characterize the pharmacokinetics following subcutaneous administration of ofatumumab to either the abdominal region or the thigh which are two injections sites allowed in the Phase 3 study and planned for inclusion in the label. Another secondary objective is assessment of immunogenicity during the 12 weeks duration of the study addressing potential differences in ofatumumab anti-drug antibody formation between the PFS and AI devices as well as between abdomen and thigh injection sites.

[redacted]

2 Study objectives and endpoints

[redacted]

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To demonstrate pharmacokinetic bioequivalence of 20 mg ofatumumab injected by the PFS or AI devices	AUCtau Cmax
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To characterize the pharmacokinetics following subcutaneous administration of ofatumumab to either the abdominal region or the thigh	AUCtau Cmax
Assessment of immunogenicity	Proportion of patients with anti-ofatumumab antibodies
Assess the safety and tolerability of ofatumumab	Adverse events including injection related reaction, lab, vital signs, ECG, and eCSSRS

[redacted]

3 Investigational plan

3.1 Study design

This is a randomized, open-label, multi-center, parallel group 12-week study to evaluate the pharmacokinetic bioequivalence of ofatumumab injected by PFS or AI devices. The study design includes four parallel groups of RMS patients. Assessment of the primary and secondary endpoints are performed based on data collected through the dosing interval between Week 8 and Week 12 where approximate steady-state pharmacokinetics are anticipated.

Randomization: A total of approximately 150 eligible patients will receive open-label ofatumumab 20 mg sc every 4 weeks (after an initial loading regimen of three weekly 20 mg doses in the first 14 days). Patients will be randomized in a 5:5:1:1 ratio into the following 4 groups dependent on what type of injection device they will use and the location of their injection (62 subjects for groups 1 and 2, and 13 subjects for groups 3 and 4). Randomization will be stratified by body weight (< 60 kg, 60-90 kg, > 90 kg) to ensure a balance between covariates with potential impact on the primary endpoint. Randomization will not be blinded as

[redacted]

the endpoints of the study are primarily related to pharmacokinetics and all patients will be receiving active treatment at identical dosing regimens.

- Group 1: PFS, abdomen
- Group 2: AI, abdomen
- Group 3: PFS, thigh
- Group 4: AI, thigh

Interim analyses: The study will feature one interim analysis that will be conducted when approximately 36 patients have completed Week 12 (Section 3.5).

The study has 3 Parts:

- Part 1 – Screening
- Part 2 - Treatment
- Part 3 - Safety follow-up

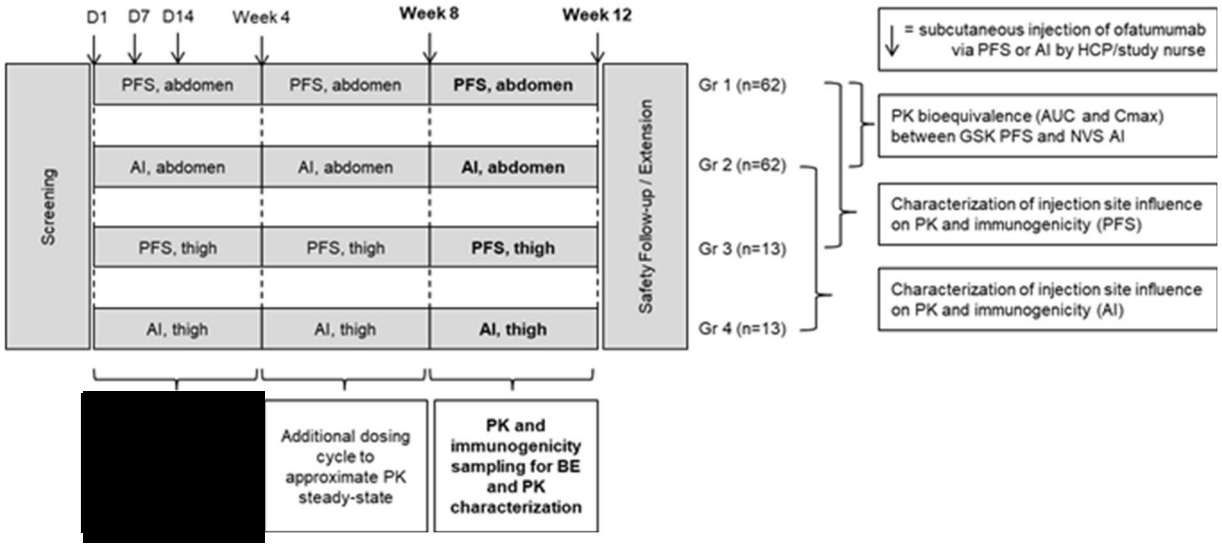
Part 1 – Screening

- The Screening period can last up to 30 days and consists of Screening and Baseline assessments. Patient eligibility will be determined based on the Screening and/or Baseline assessments.
- Patients may be rescreened if they do not initially meet eligibility criteria. All assessments must be repeated, [redacted]

Part 2 – Treatment

Graphical outline of Part 2, Treatment period study design with four parallel groups. Evaluation of primary and secondary end-points are performed between Week 8 and Week 12.

Figure 3-1 Study design – Part 2



The study Part 2 Treatment period will consist of an initial induction phase (Week 0 to Week 4) and a pharmacokinetics phase (Week 8 to Week 12) at approximate steady-state conditions.

[redacted]

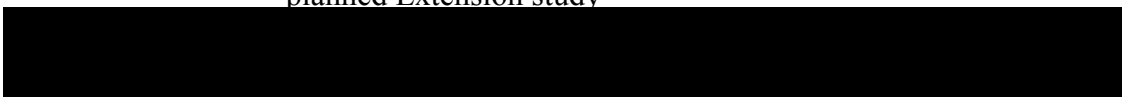
Week 4 to Week 8 ensures that approximate steady-state conditions are reached prior to the pharmacokinetics phase. A schematic presentation of the study design is provided in Figure 3-1.

The pharmacokinetics will be assessed for primary objectives during Week 8 to Week 12 at approximate steady-state conditions. The rationale for this is to avoid the expected larger inter-individual variation in exposure at treatment initiation due to the potentially different levels of target expression between patients. This would result in high variability in the pharmacokinetics parameter leading to an increased sample size of the study. Further, the approximate steady-state condition is a clinically relevant situation as full target depletion would be expected in contrast to the situation after administration of a single dose typically used for bioequivalence assessment. During the study, ofatumumab will be administered to the respective groups of patients by a health care provider and according to specified instructions.

No clinically significant difference in ofatumumab exposure is expected between the two administration sites (abdomen vs thigh) (Xu et al 2010). Groups 3 and 4 will enable an assessment of the pharmacokinetics of ofatumumab injected to the thigh which can then be compared to abdominal administration using the PFS and AI, respectively. The aim of assessment of the injection site influence on ofatumumab pharmacokinetics is not to demonstrate bioequivalence but to enable an evaluation of the potential clinical significance of differences in pharmacokinetic parameters. Potentially, the absorption rate may vary between different injection sites for subcutaneous single dose administration of ofatumumab possibly resulting in different Tmax and Cmax values. However, under steady-state conditions and with the primary target being depletion of CD20-positive B-cells, the comparison of AUCs over the dosing period would be the most relevant parameter to evaluate. In order for patients to obtain a clinical benefit from participation in the study, continued treatment with ofatumumab will be offered to the eligible patients through enrollment into the umbrella open-label Phase 3 extension study (COMB157G2399). Patients waiting for open label extension study to open can continue to receive study drug. Patients should return every 12 weeks and complete assessments per Table 6.1.

Part 3 – Safety follow-up/Extension study

- The Safety FU period Table 6-2 will be applicable for the following patients:
  a. Patients who complete the Treatment period on study drug and do not enter the planned Extension study



b. Patients who prematurely discontinue study treatment

- All Safety FU visits must be scheduled relative to the EOS Visit.
- All patients will be followed for a total of at least 9 months after study drug discontinuation (by 9 months the vast majority of patients are expected to have repleted their circulating B-cells, see IB).
- A longer than 9 months of post-treatment follow up in the Safety FU period will be required for patients who have not repleted their B-cells (ie B-cells not back to baseline value or to lower limit of normal (LLN) whichever comes first as determined by central lab) at 9 months. These patients will continue to be followed with 3-monthly assessments until their B-cell counts have repleted. Patients who have initiated therapy with another disease modifying/immunosuppressive therapy before the end of the 9-month follow up will not be monitored beyond 9 months.

3.2 Rationale for study design

The study is a parallel-group design with four groups (PFS (abdomen), AI (abdomen), PFS (thigh), and AI (thigh)). The two main groups are designed to address the primary objective of demonstrating bioequivalence. The two additional groups are designed to address the secondary objective of evaluating potential difference in the pharmacokinetic parameters with different administration sites. The parallel-groups design is chosen to avoid potential carryover treatment effect which is difficult to control with a cross-over study design. The primary and secondary objective will be evaluated during approximate pharmacokinetic steady-state conditions anticipated during Week 8 and Week 12. This will contribute to a reduction of variability between subjects compared to an assessment after a single dose. Further, an evaluation at steady-state will be more clinically relevant.

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

The dosing regimen for ofatumumab in this study comprises an initial induction phase with 20 mg subcutaneous administration on treatment initiation (Day 1) and on Day 7, and Day 14. Thereafter, the maintenance regimen will be subcutaneous administration of 20 mg every 4 weeks starting at week 4. Subcutaneous injection is the route of administration used in the Phase 3 program, [redacted]. The duration of the study is planned to be 12 weeks.

[redacted]

[redacted]

3.4 Rationale for choice of comparator

There is no comparator in this study.

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis of the variability of Cmax and AUCtau is planned to enable a re-estimation and potential increase of the final sample size in case the observed variability is higher than initially predicted. This interim analysis is to be conducted when approximately 36 patients total completed Week 12 in the PFS (abdomen) and AI (abdomen) treatment groups.

3.6 Risks and benefits

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

Ofatumumab is approved for 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 this study in MS patients is 20 mg; ie, 100 times lower than the dose used in CLL. 267 RRMS patients have been exposed to

[redacted]

ofatumumab (i.v. N=38 and sc N=229 in 2 Phase 2 studies (Study OMS115102 and OMS112831). 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 iv. doses of ofatumumab up to 700 mg (OMS115102), 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 (OMS112831) 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. Safety and tolerability of ofatumumab is currently being further investigated in two large global Phase 3 studies (COMB157G2301 and G2302), with a planned total sample size of 1800 randomized patients. A DMC is monitoring the safety and risk/benefit for the Ofatumumab controlled, blinded studies

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 intravenously administered 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.

The OMB157G2102 study involves dosing for 12 weeks which is a short treatment period for MS patients. Therefore, in order to provide a clinical benefit and balance the potential risks associated with B cell depletion, all patients eligible will be offered enrollment in the umbrella open-label extension trial (OMB157G2399) in direct continuation of the G2102 study.

Overall, the balance of benefit and risk supports the rationale of COMB157G2102 study to evaluate the bioequivalence, pharmacokinetics, and immunogenicity in combination with additional safety and efficacy data obtained from the open-label extension study (G2399) of ofatumumab sc to address the unmet medical need of patients with RMS.

4 Population

The study population will consist of adult patients with RMS fulfilling all the eligibility criteria listed below. The study is planned to be conducted in approximately 30 centers worldwide. It is aimed to randomize a total of 150 patients. To reach this number it is anticipated that the total number of patients to be screened is approximately 200 depending on the screen failure rate. Patients, who have been randomized and prematurely discontinue study, will not be replaced. In the event that sample size is to be increased after the planned interim analysis, the number of sites and patients to be screened may be increased to accommodate the increase of up to 284 total randomized patients.

4.1 Inclusion criteria

MS Patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.

[redacted]

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

4.2 Exclusion criteria

MS Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

1. Patients suspected of not being able or willing to cooperate or comply with study protocol requirements in the opinion of the Investigator
2. Patients with primary progressive MS (Polman et al 2011) or SPMS without disease activity (Lublin et al 2014)
3. Patients meeting criteria for neuromyelitis optica (Wingerchuk et al 2006)
4. Disease duration of more than 10 years in patients with EDSS score of 2 or less
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 12 months after stopping study medication.

   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 (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male partner sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner.
   - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study drug.

[redacted]

- 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 (eg age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

7. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (eg rheumatoid arthritis, scleroderma, Sjögren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with immunodeficiency syndrome (hereditary immune deficiency, drug-induced immune deficiency)
8. Patients with active systemic bacterial, viral or fungal infections, or known to have AIDS or to test positive for HIV antibody at Screening
9. Patients with neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML), or confirmed PML
10. Patients at risk of developing or having reactivation of syphilis or tuberculosis (eg 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 tuberculosis testing, QuantiFERON®-TB Gold test can be done locally or by the central lab to assess patient's eligibility at Screening.

    NOTE:

    - 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.
11. Patients at risk of developing or having reactivation of hepatitis: Positive results at Screening for serological markers for hepatitis (H) A, B, C, and E indicating acute or chronic infection:
    - anti-HA Immunoglobulin (Ig) M (IgM)
    - HBs Ag and/or anti-HBc IgM and/or HB virus deoxyribonucleic acid (DNA)
    - anti-HBs negative and Anti-HBc positive
    - anti-HC IgG (if positive IgG, HCV-RNA PCR will be performed and if negative, patient can be randomized)
    - anti-HE IgM (if positive IgG and/or IgM, perform HE-RNA PCR and if negative, patient can be randomized)

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

[redacted]

12. Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 2 months prior to randomization
13. Have been treated with any of the medications listed below (Note: no wash-out period is required in the case of prior treatment with interferon-β or glatiramer acetate):

Medication	Exclusionary if used/used within required wash-out period
Systemic corticosteroids, adrenocorticotropic hormone	30 days prior to Screening MRI scan
Dimethylfumarate	1 month prior to randomization
Intravenous immunoglobulin, plasmapheresis, fingolimod, siponimod, ozanimod	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 Laquinimod Mildly to moderately immunosuppressive/chemotherapeutic medications (eg azathioprine, methotrexate)	6 months prior to randomization
Highly immunosuppressive/chemotherapeutic medications (mitoxantrone, cyclophosphamide, cladribine) B-cell targeted therapies such as rituximab or ocrelizumab, ublituximab, or obinutuzumab	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, stem cell therapy Other strongly immunosuppressive treatments (with effects potentially lasting over 6 months) Ofatumumab	Any time

14. 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
15. 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 eg completely excised with clear margins), within the past 5 years, regardless of whether or not there is evidence of local recurrence or metastases
16. Any of the following conditions or treatments that may impact the safety of the patient:
    - History of, or current, significant cardiac disease including cardiac failure (NYHA functional class II-IV), myocardial infarction (within 6 months), unstable

[redacted]

angina(within 6 months), transient ischemic attack (within 6 months), stroke, cardiac arrhythmias requiring treatment or uncontrolled arterial hypertension.

- Concomitant clinically significant cardiac arrhythmias, eg, sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker on screening electrocardiogram (ECG).
- History of familial long QT syndrome or known family history of Torsades de Pointe.
- History of or active severe respiratory disease, including Chronic Obstructive Pulmonary Disease, interstitial lung disease or pulmonary fibrosis.
- Patients with asthma requiring regular treatment with oral steroids.
- Severe hepatic impairment (Child-Pugh class C) or any chronic liver or biliary disease.
- Patients with severe renal impairment (Glomerular Filtration Rate < 30 ml/min/1.73m^2).
- Any medically unstable condition as determined by the Investigator

17. Any of the following abnormal laboratory values prior to randomization
    - Total or conjugated bilirubin (BIL) greater than 1.5 times upper limit of normal (ULN) range, unless in the context of Gilbert's syndrome.
    - Alkaline phosphatase (ALP) greater than 1.5 times the ULN range.
    - AST or ALT greater than 1.5 times ULN or gamma-glutamyl transferase (GGT) greater than 2 times ULN range.
    - White blood cell (WBC) count < 3500/mm3 (< 3.5 x 109/L) Lymphocyte count < 800/mm3 (< 0.8 x 109/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 (eg significant anemia, neutropenia, thrombocytopenia, signs of impaired bone marrow function)
18. Patients with severe hypoproteinaemia eg in nephrotic syndrome
19. 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 (eCSSRS), 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 (ie 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 (eg stroke, traumatic brain or spinal injury, history or presence of myelopathy) or neurological disorders which may mimic MS
20. Patients unable or unwilling to undergo MRI scans
21. History of hypersensitivity to the study drug or excipients or to drugs of similar chemical classes

[redacted]

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 (eg in regards to a higher legal age for study participation) or regulatory (eg in regards to compliance with local prescribing information) requirements, the local requirements must be followed. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Investigational drug will be provided in pre-filled syringes containing 20 mg ofatumumab (50 mg/ml, 0.4 ml content) or autoinjector containing 20 mg ofatumumab (50 mg/ml, 0.4 ml content) for subcutaneous administration. Ofatumumab is a clear to opalescent, colorless to pale yellow, essentially particle-free liquid.

Study drug will be supplied by Novartis.

5.1.2 Additional treatment

No additional treatment beyond investigational drug is included in this trial.

5.2 Treatment arms

Subjects will be assigned at visit Day 1 to one of the following 4 treatment arms in a ratio of 5:5:1:1

- PFS (abdomen): ofatumumab 20 mg sc. injection with PFS administrated on abdomen
- AI (abdomen): ofatumumab 20 mg sc. injection with AI administrated on abdomen
- PFS (thigh): ofatumumab 20 mg sc. injection with PFS administrated on thigh
- AI (thigh): ofatumumab 20 mg sc. injection with AI administrated on thigh

5.3 Treatment assignment and randomization

On Day 1 all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the IRT

[redacted]

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 devices as well as the assigned injection location.

Randomization will be stratified by body weight (< 60 kg, 60-90 kg, > 90 kg).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

Not applicable for this trial.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise 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 the electronic data capture (EDC) system.

If an enrolled patient fails to be randomized or treated for any reason, the reason will be entered on the appropriate screening period CRF.

Upon signing the informed consent form, the patient is assigned the next sequential number available in the 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 Screening period CRF.

5.5.2 Dispensing the study drug

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 4 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). 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.

[redacted]

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 Novartis CPO Quality Assurance.

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. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

5.5.3.2 Handling of additional treatment

Not applicable to this trial.

5.5.4 Instructions for prescribing and taking study treatment

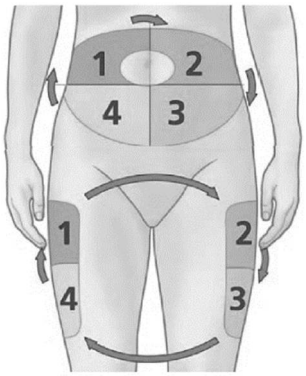
The study medication (ofatumumab injections) will be dispensed starting at the Randomization Visit (Day 1). Drug will then be dispensed at planned visits throughout the treatment period according to Table 6-1. On Day 7 and Day 14, the same time-window (+/− 1 day) as for study visit applies. Starting at Week 4, the subcutaneous injections should be administered at 4-Week (28 days) intervals (+/− 3 days).

All investigational drugs will be administered at site by a HCP/study nurse. The study medication will be administered as subcutaneous injections either to the abdomen or to the thigh depending on the randomization. For each of the two injection areas, study medication should be administered in an alternating fashion in accordance with the graphics in Figure 5-1 Alternation of injection areas for abdomen and thigh.

In order to assess tolerability of the initial dose of study medication 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. Vital signs should be obtained 30-60 minute 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 and 8.

[redacted]

Figure 5-1 Alternation of injection areas for abdomen and thigh



5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and interruptions are not permitted during the study.

Should the patient interrupt the study drug for whatever reason, re-start decision should be made on a case-by-case basis.

5.5.6 Recommendations for the treatment of MS relapses

MS relapses may be treated with a standard short course of corticosteroids (eg 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 CRF.

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, 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 Novartis medical monitor 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 treatment period (Day 1), the addition of premedication with steroids (methylprednisolone 100 mg iv or

[redacted]

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.

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. 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 and washout periods 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	Action taken
Immunosuppressive/chemotherapeutic medications (including herbal) or procedures, including but not limited to cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, cladribine, lymphoid irradiation and hematopoietic/other 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, ublituximab 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, siponimod, ozanimod, laquinimod, interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide, leflunomide, 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.
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

Not applicable for this trial.

[redacted]

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.

The Safety FU will complete when all patients who entered have been followed for the stipulated period of time (for at least 9 months after study drug discontinuation) (see Section 3.3) 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 6.6.6 and Section 7.6)
- Use of prohibited treatment (Table 5-1)
- Diagnosis of PML
- Patient with active serious infections or reactivation (eg 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)

[redacted]

- Laboratory abnormalities (eg 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

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

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 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.

5.6.3 Withdrawal of informed consent

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

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

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

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

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

[redacted]

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

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, eg 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 end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis 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. The Investigator may delegate this responsibility to the Study Nurse/Study Coordinator as appropriate and permissible by local regulation
- Confirmation of patient's eligibility for randomization
- [redacted]
- Administration of EDSS
- Management of adverse events and MS relapses
- Ensuring that all site personnel are informed of concomitant medications excluded per protocol (eg 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 (eg, a back-up physician or Study Nurse/Study Coordinator) at the study site to

[redacted]

perform some of the tests and evaluations listed above. The Investigator is also responsible for ensuring access to appropriate expertise for consultation (eg infectious disease, ECG interpretation, mental health care) during the study as needed.

EDSS Rater – Investigator or delegate

The 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
- EDSS is not blinded and therefore the investigator can serve as the EDSS rater

The 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.

To ensure consistency in the EDSS scoring across Raters, the 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 EDSS Rater should remain the same throughout the study, whenever possible.

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
- Administration of injections
- [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
- Providing patient with a Patient Information Card identifying patients as study participant in a clinical trial with pertinent information and site contact information.

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

[redacted]

- 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. Subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. In case a visit is performed outside the schedule, subsequent visits shall be performed in keeping with the original visit schedule. In addition to the scheduled 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. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

[redacted]

Table 6-1 Assessment schedule

Period	Screening/Pretreatment		Induction						Pharmacokinetics						
Visit	**SCR D-30 to D-8**	**BL D-7 to D1**	**D1[1]**	**D4**	**D7**	**D14**	**W4 D28**	**W6 D42**	**W8 D56**	**W8 D57**	**W8 D59**	**W9 D63**	**W10 D70**	**W11 D77**	**EOS[2]/W12 D84**
Visit No.	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**1999**
Visit Window (hours or days)	**n.a.**	**n.a.**	**n.a.**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±2d**	**±2d**	**±2d**	**±2d**
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
Dispense study drug			X		X	X	X		X						X
Premedication[4]			X		X	X	X		X						X
Vital signs[5]	X	X	X[5]		X[5]	X[5]	X[5]		X[5]						X
Weight		X													
Routine lab samples including urine	X	X[13]					X								X
Physical Exam[6]	X[9a]	X[9a]													
ECG	X[9a]	X[9a]													X
Sample for $CD19^+$ B-cells and $CD3^+CD20^+$ T-cells		X	X	X	X	X	X	X	X						X
Pregnancy test[7]	X		X				X		X						X
Contraception status[8]	X	X	X				X		X						X
PK sampling prior to dosing		X	X	X[10]	X	X	X	X	X	X[10]	X[10]	X[10]	X[10]	X[10]	X
[redacted]															
ADA sampling prior to dosing		X					X		X						X
[redacted]															
Total IgM, IgG levels	X[9a]	X[9a13]					X								X
Serological markers for hepatitis A, B, C, and E	X														

[redacted]

Period	Screening/Pretreatment		Induction						Pharmacokinetics						
Visit	**SCR D-30 to D-8**	**BL D-7 to D1**	**D1[1]**	**D4**	**D7**	**D14**	**W4 D28**	**W6 D42**	**W8 D56**	**W8 D57**	**W8 D59**	**W9 D63**	**W10 D70**	**W11 D77**	**EOS[2]/W12 D84**
Visit No.	**1**	**20**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**1999**
Visit Window (hours or days)	**n.a.**	**n.a.**	**n.a.**	**±1d**	**±1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±1d**	**±2d**	**±2d**	**±2d**	**±2d**
HIV test	X														
[redacted]															
eCSSRS	X[9a]	X[9a]	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
[redacted]															
Prior/Con Meds[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Disposition															X

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). Patients waiting for open label extension study to open can continue to receive study drug. Patients should return every 12 Weeks and complete all EOS assessments with the exception of PK, [redacted] and ECG.
3. Syphilis and Tuberculosis testing must be done as part of eligibility check (Exclusion criterion #10) unless completed in the last 6 months prior to screening with documented negative results. For tuberculosis testing, QuantiFERON®-TB Gold test can be done by the local lab to assess patient's eligibility at Screening.
4. For the first injection (Day 1), the addition of premedication with steroids (methylprednisolone 100 mg iv. or equivalent) is recommended. Premedication with acetaminophen and/or antihistamines (or equivalent) is recommended and may be administered at the discretion of the Investigator. Premedication should be administered 30 to 60 min prior to study drug injection.
5. 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 and 8.
6. 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.

[redacted]

7. 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 scheduled visits as indicated in Table 6-1 prior to dosing. The results will be captured in source documents.
8. Patient's contraception status must be reviewed and documented in source to ensure method of contraception continues to be appropriate per protocol requirement for highly effective contraception.
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. Labs must be drawn to allow adequate time for results to be obtained before randomization to ensure patient's eligibility
10. On non-injection visits the PK (Plasma) [redacted] samples can be drawn at any time during the visit.

[redacted]

12. Including corticosteroids used to treat MS relapse.
13. Labs must be drawn to allow adequate time for results to be obtained before randomization to ensure patient's eligibility.

[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
[redacted]					
Sample for Total IgG, IgM	X	X	X	X	X
Routine Labs	X	X	X	X	X
[redacted]					
Follow up Disposition					X

W=week.

1. Time measured from the EOS visit
2. As needed for the patients requiring [redacted] (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 the 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

[redacted]

6.1 Information to be collected on screening failures

For sites using RAVE for data collection, all patients who have signed informed consent and who have agreed to participate in the trial will fully complete Screening CRFs. Additionally all adverse events occurring after informed consent is signed will be recorded on the AE form. Investigators will have the discretion to record abnormal test findings on the medical history form whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

All subjects who have signed informed consent but not entered into the next period will have the disposition, demographics, inclusion/exclusion, informed consent, rescreening (only in case it is applicable for OMB study) withdrawal of consent (if subject withdrew consent) and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator or primary care physician and collected only in the source data.

6.2 Pharmacokinetics sampling

The primary objectives of this trial are depending upon the pharmacokinetics assessment of the study drug. Bioequivalence will be evaluated statistically based on AUCtau and Cmax values from individual patient time-concentration profiles of ofatumumab. Data from patients randomized to group 1 and 2 will be used for the bioequivalence assessment. Hence, it is of key importance that the dosing instructions, samples collection procedures and timing of visits during the study are followed closely. The dosing interval between Week 8 and Week 12 is of particular importance to obtaining accurately assessed bioequivalence data. Pharmacokinetics sampling has been scheduled prior to dosing on all dosing visits. The time window in which the respective visits should occur, is also specified in the assessment schedule (see Table 6-1). If, for some reason, the visit cannot be completed within the specified time window, the planned dose administration and associated blood sampling should still be carried out as close as possible to the originally planning time points. In all cases, the PK sample collection date and time must be recorded as instructed in the lab manual and entered in the appropriate CRF.

6.3 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), and previous MS treatment and will also be collected on the corresponding CRFs.

6.4 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

[redacted]

administered and intervals between visits. These data should be transcribed on the appropriate CRFs.

All study treatment dispensed must be recorded in the Drug Accountability Log.

6.5 Efficacy

The primary objective of this study is to demonstrate pharmacokinetic bioequivalence of 20 mg ofatumumab injected by the PFS or AI devices, as assessed by AUCtau and Cmax. MS efficacy assessments [redacted] will not be included in the CSR, but reported in a separate document at a later date. This data will be used to inform the Open-label Extension study for patients who continue into that study. This study includes the following efficacy assessments conducted at visits as shown in Table 6-1:

- [redacted]
- [redacted]
- [redacted]
- [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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.5.5 Appropriateness of efficacy assessments

The [redacted], [redacted] 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]

6.6 Safety

Safety assessments will include:

- Adverse events
- Physical examination (including skin)
- Vital signs
- Laboratory Evaluations
- Pregnancy testing (females of childbearing potential)
- ECG
- Columbia Suicide Severity Rating Scale (eCSSRS) (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).

[redacted]

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.

6.6.1 Physical examination

A complete physical examination will be performed at the visits indicated in the Study Assessments (Table 6-1) and will include an assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, neurological function and comments on general appearance. A complete neurological examination will be part of the initial physical examination at Screening. Information for all physical examinations (including skin exams) must be included in the source documentation at the study site. All significant findings that are present prior to signing informed consent must be reported on the relevant medical history/current medical conditions CRF. Significant findings seen after signing the informed consent and being randomized meet the definition of an AE and must be recorded on the adverse events CRF.

6.6.2 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.

Vital signs should be obtained 30-60 min before sc injection and again approximately 60 min post-injection on Day 1, Day 7, Day 14, Week 4 and 8. 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.

6.6.3 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.

6.6.4 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.

[redacted]

6.6.4.1 Hematology

Blood samples will be collected at the planned visits indicated in Table 6-1. 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.

6.6.4.2 Clinical chemistry

Blood samples will be collected at the planned visits indicated in Table 6-1. 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 (TBL), 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. Appendix 1 refers to liver events and Appendix 2 refers to renal events.

6.6.4.3 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 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.

6.6.4.4 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 10, Section 4.2). QuantiFERON®-TB Gold test can be done locally or by the central lab 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-HA Immunoglobulin (Ig) M (IgM)
- HBs Ag and/or anti-HBc IgM and/or HB virus deoxyribonucleic acid (DNA)
- anti-HBs negative and Anti-HBc positive
- anti-HC IgG (if positive IgG, HCV-RNA PCR will be performed and if negative, patient can be randomized)
- anti-HE IgM (if positive IgG and/or IgM, perform HE-RNA PCR and if negative, patient can be randomized)

[redacted]

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

Additional samples for ADA, [redacted] will be taken (Section 6.6.1, Section 6.6.2, and Section 6.6.3).

6.6.5 Electrocardiogram (ECG)

An ECG will be performed at Screening or Baseline and EOS visits. Additional unplanned ECGs may be performed at Investigator's discretion if clinically indicated.

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. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

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

6.6.6 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.

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

6.6.7 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).

[redacted]

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

The safety assessments selected are standard for this indication/patient population.

6.7 Other assessments

6.7.1 Clinical Outcome Assessments (COAs)

Not applicable for this trial.

6.7.1.1 Clinician Reported Outcomes (ClinRO)

Not applicable for this trial.

6.7.1.2 Patient Reported Outcomes (PRO)

Not applicable for this trial.

6.7.1.3 Observer Reported Outcomes (ObsRO)

Not applicable for this trial.

6.7.1.4 Proxy Reported Outcomes

Not applicable for this trial.

6.7.1.5 Resource utilization

Not applicable for this trial.

6.7.2 Pharmacokinetics

Subcutaneous administration of ofatumumab will occur on Day 1, Day 7, Day 14, Week 4, Week 8 and Week 12. [redacted] The secondary objectives include a pharmacokinetics evaluation of the two different injection areas also used in the Phase 3 studies (thigh and abdomen). Data from patients randomized to group 3 and 4 will be used for this assessment through comparison to data obtained from group 1 and 2, respectively (please refer to the study design overview in Figure 3-1). A description of the primary endpoints of the study can be found in Section 6.2.

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

[redacted]

6.7.3 Immunogenicity

ADA will be assessed to evaluate the immunogenicity potential of ofatumumab. Sampling time points are provided in Table 6-1. Samples for ADA assessment should be taken prior to dosing at the visit. 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 (eg, 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 visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

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

[redacted]

- the [severity grade/Common Toxicity Criteria (CTC) AE grade]
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

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

1=mild

2=moderate

3=severe

4=life-threatening (see Section 7.2.1 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 7.2.1 or definition of SAE) and which seriousness criteria have been met.
- action taken regarding (investigational) treatment

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

- no action taken (eg further observation only)
- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2.1 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (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 the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's

[redacted]

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 (specify what this includes)
  - 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, eg 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 (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

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

[redacted]

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days (after the last study visit/ following the last administration of study treatment) if there are post-treatment follow-up visits with no required procedures must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period (after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures) should only be reported to Novartis safety 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, and whether the patient continued or withdrew from study participation.

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

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

7.2.2.1 Reporting of [redacted] as SAE

[redacted] 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 [redacted] instead of the SAE form. However, if, in the judgment of the Investigator, a [redacted] is unusually severe or medically

[redacted]

unexpected and warrants specific notification, then an SAE form must be completed and submitted according to SAE reporting procedures outlined above.

7.2.2.2 Reporting of Disability Worsening as SAE

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

7.3 Liver safety monitoring

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

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

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring 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 of 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.

- 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 (eg, disease, co-medications)

[redacted]

- 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 the appropriate CRFs.

7.4 Renal safety monitoring

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

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine 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.

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

[redacted]

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 and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

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, which uses a semi-structured interview to probe patient responses, will be administered by an individual who has received training and certification in its administration. At the first study visit, the "Baseline/screening" version of the eCSSRS will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the patient's lifetime and during a predefined period. At subsequent visits, the "since last visit" version will be administered.

A validated version of the eCSSRS will be used to capture self-reported eCSSRS data via an interactive voice response telephone system (eCSSRS). The eCSSRS uses a detailed branched logic algorithm to perform the eCSSRS 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 eCSSRS or "yes" on any item of the Suicidal Behavior section, the patient must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the patient is referred.

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

[redacted]

All SAEs relating to suicidal behavior must be reviewed by the Novartis Safety Management team.

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 Novartis representative will review the protocol and data capture requirements (or CRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and 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 data capture / data entry, 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.

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 data capture and/or data entry. 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 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 (CRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

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

[redacted]

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 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 Novartis.

ECG readings will be processed locally.

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 Novartis (or a designated CRO).

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 made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

A DMC is not required for this open label study

8.5 Adjudication Committee

Not applicable.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

BE analysis set: All patients randomized to PFS (Abdomen) or AI (Abdomen) treatment arms with PK data during dosing interval starting at Week 8.

PK analysis set: All patients randomized to PFS (Abdomen) or PFS (Thigh) or AI (Abdomen) or AI (Thigh) treatment arms with PK data during dose administrations.

Safety set: All patients randomized and have taken at least one dose of study drug.

[redacted]

9.2 Patient demographics and other baseline characteristics

Demographics, MS disease history, [redacted], and MS medication history will be summarized based on the safety set.

9.3 Treatments

Patients are expected to take a total of 6 injections at Day 1, Day 7, Day 14, Day 28 (Week 4), Week 8 and Week 12. The number of injections actually taken will be summarized descriptively. Duration of exposure to ofatumumab study drug will be summarized by duration category (eg, number of patients exposed to study drug for at least 1 Week, 2 Weeks, 3 Weeks, 4 Weeks, 8 Weeks and 12 Weeks will be provided). The number of patient-years is calculated as (the sum of the number of days of exposure for all patients in the group)/365.25 and will also be summarized. All summaries will be based on the safety set.

9.4 Analysis of the primary variable(s)

To address the primary objectives, comparisons on the primary endpoints from Week 8 to Week 12 between PFS (abdomen) and AI (abdomen) will be made to test bioequivalence in these 2 treatment groups.

9.4.1 Primary Variable(s)

The primary variables are pharmacokinetic endpoints, namely AUCtau and Cmax calculated from data collected in the dosing interval after Week 8 dose administration in accordance with the assessment schedule.

9.4.2 Statistical model, hypothesis, and method of analysis

To address the primary objective of testing bioequivalence at dosing interval after Week 8 between PFS and AI, the primary analysis involves the two groups (PFS (abdomen) and AI (abdomen)). In the following, the PFS (abdomen) group will be referred to as the Reference (or R) group and the AI (abdomen) group as the Test group (or T).

The null hypothesis is that "Mean difference in ln (AUCtau) and/or ln (Cmax) greater than allowed-difference between these 2 groups" (H0:$|\mu_T - \mu_R| > \Delta$). The alternative hypothesis is that "Mean difference in ln (AUCtau) and ln (Cmax) less than allowed-difference between these 2 groups" (Ha: $|\mu_T - \mu_R| \leq \Delta$). Ln refers to the natural log function. The testing procedure is described below.

As the testing for Average Bioequivalence (ABE) will be based on a between-groups comparison, the variabilities of the R and T groups are expected to be high, with a coefficient of variation (CV) greater than 0.3. Hence, the FDA recommended, Reference-scaled average bioequivalence (RSABE) bioequivalence approach for highly variable drugs is proposed.

As there is no FDA guidance for using RSABE in a parallel groups design, the current guidance for cross-over trials (Davit et al, 2012, Draft Guidance on Progesterone, 2011,) has been modified for application in a parallel groups design.

The between-subject variability for the R group will take the place of the within-subject variability for R.

[redacted]

A mixed scaling approach will be used: (1) if the standard deviation of the R group data (on the log scale) exceeds 0.294, the traditional ABE limits of ln(0.8) and ln(1.25) will be scaled by the between-subject variability for the R group, (2) otherwise the standard TOST (two one-sided test) approach for (unscaled) ABE will be used. The regulatory constant used in the linearised criterion for the RSABE approach will be set to $\sigma_0 = 0.25$ (as in the recommended RSABE approach for cross-over trials).

The steps in the analysis will therefore be:

1. Calculate s_R the standard deviation of the R group subjects' data on the log-scale (for AUCtau or Cmax).
2. If $s_R < 0.294$ then apply the standard ABE criteria, ie, determine if the 90% confidence interval for the mean difference between T and R on the log-scale, $(\mu_T - \mu_R)$, lies within [-ln(1.25), ln(1.25)].
3. If $s_R \geq 0.294$ then apply the reference scaled ABE criteria, ie, determine if, $-\theta_s \leq \frac{(\mu_T - \mu_R)}{s_R} \leq \theta_s$ where $\theta_s = \frac{\ln(1.25)}{\sigma_0}$, and $\sigma_0 = 0.25$ This is done by calculating an approximate 95% upper confidence bound for the linearised criterion, $(\mu_T - \mu_R)^2 - \theta_s{}^2 \sigma_R{}^2$. If this upper bound is less than or equal to zero and the point estimate of the T/R geometric mean ratio (GMR) falls within (0.8, 1.25), then ABE is declared (ie, the null hypothesis is rejected).

Testing will be performed as above for AUCtau and Cmax separately on the BE analysis set.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed in general for any analyses. Only patients with non-missing data will be included in the relevant analyses. The BE analysis set is defined to include patients randomized to PFS (Abdomen) or AI (Abdomen) treatment arms with PK data during dosing interval starting at Week 8. Patients without PK data during that dosing interval will not be included in the BE analysis.

9.4.4 Sensitivity analyses

No sensitivity analysis is planned.

9.5 Analysis of secondary variables

Summary statistics of AUCtau and Cmax by time point will be provided for each of the four treatment groups on the PK analysis set.

Proportion of patients with positive ADA will be provided by time point and overall for each of the four treatment groups on the safety set. The proportion will be based on patients with non-missing ADA results at the evaluation time point.

9.5.1 Efficacy variables

Efficacy variables include [redacted], [redacted], [redacted], [redacted] Efficacy data are collected in order to evaluate long term treatment effect after patients continue into the open label long term study. Data analyses on efficacy variables are not planned for the CSR of this study.

[redacted]

9.5.2 Safety variables

Safety variables include the number of patients with at least one AE or injection related reaction, the number of patients meeting abnormal criteria and change from baseline in all relevant parameters of lab, vital signs, and ECG evaluations, and the number of patients meeting predefined criteria as collected in eCSSRS. For all safety variables, descriptive statistics will be provided on the safety set.

9.5.3 Resource utilization

Not applicable for this trial.

9.5.4 Pharmacokinetics

The pharmacokinetics parameters will be calculated using the standard NCA module of Winnonlin.

9.5.5 DNA

Not applicable for this trial.

[redacted]

[redacted]

9.7 Interim analyses

As this is an open-label study with primary objective of pharmacokinetic endpoints and no interim analyses on which statistical comparisons will be made is planned, there is no relevance on blinding or alpha-adjustment.

Periodic interim safety analyses to support regulatory updates and interim reports may be warranted.

An interim analysis will be conducted to assess the variability of data as measured by coefficient of variation (CV) when approximately 36 patients total randomized in the PFS (abdomen) and AI (abdomen) treatment groups have completed Week 12. The purpose of this interim analysis is to provide an opportunity to increase the sample size so that sufficient power for the bioequivalence testing can still be achieved in case the estimated CV is larger than the assumed value of 85% at design stage. If deemed necessary, the sample size for the bioequivalence testing can be increased from 120 to a maximum of 250 completed patients.

[redacted]

9.8 Sample size calculation

The grand total sample size of this study is estimated by sum of the estimated sample size in all 4 treatment groups.

Section 9.8.1 provides sample size calculation for groups 1 and 2, which are used to address our primary objective. This sample size may be increased by the results of the interim analysis.

Section 9.8.2 provides sample size calculation for groups 3 and 4. This sample size will not be impacted by the results of the interim analysis.

9.8.1 Sample size calculation for PFS (abdomen) and AI (abdomen)

A total of 120 patients (60 per arm) will be required to achieve 90% power in the testing of bioequivalence between these two groups assuming their geometric mean ratio (GMR) = 1 and the coefficient of variation (CV) = 85%, which are considered reasonable and conservative assumptions according to previous experience with the variability of drug concentration pharmacokinetic parameters. To account for 3% dropout, a total of 124 patients (62 per arm) will be randomized. The dropout rate assumption is based on data observed in the on-going Phase III studies.

Due to limited PK data in the existing databases, CV can't be assessed accurately. Therefore, an interim analysis is planned to re-assess the CV of Cmax and AUCtau. Details are as described in Section 9.7. If deemed necessary, the sample size for the BE testing can be increased to a maximum of 250 (125 per arm), in which case, the total number of patients to be randomized will be is 258 (129 per arm) accounting for 3% dropout. The maximum sample size will provide approximately 80% power if the true CV is as high as 240%.

The sample size calculation is based on simulation for the testing procedure via a mixed scaling approach as described in Section 9.4.2. Specifically, for a given CV on the natural scale, which is assumed to be the same for the two groups, and an assumed value of the GMR, 10,000 parallel groups trials with a given total sample size n are simulated and the proportion of trials that lead to a decision to declare ABE are recorded. If this value of n does not give a power greater than or equal to 0.9 then the n is increased in steps of 2, until a power of 0.9 is first achieved or exceeded. This n is then taken as the sample size that gives 90% power for the chosen values of CV and GMR. The estimated sample sizes for a range of values of CV and three values assumed for the GMR are given in below table.

[redacted]

Total sample sizes to achieve 90% power for testing for RSABE in a two-group parallel groups design (with $\sigma_0 = 0.25$ and $\theta = \left(\frac{\ln(1.25)}{\sigma_0}\right)$)

CV	GMR=0.95	GMR=1.00	GMR=1.05
0.30	84	66	82
0.35	78	66	78
0.40	74	66	74
0.45	72	66	72
0.50	74	66	72
0.55	76	68	76
0.60	82	72	82
0.65	92	80	90
0.70	102	88	100
0.75	114	98	112
0.80	126	108	126
0.85	138	120	136

As a comparison, the sample sizes required to achieve a power of 0.9, when the standard test (TOST) for ABE is used with a parallel groups design, are given in below table.

Total sample sizes to achieve 90% power for testing for standard ABE in a two-group parallel groups design with equivalence limits $(-\ln(1.25), \ln(1.25))$

CV	GMR=0.95	GMR=1.00	GMR=1.05
0.30	102	78	100
0.35	138	102	134
0.40	176	132	170
0.45	218	162	212
0.50	262	196	256
0.55	310	232	302
0.60	360	270	352
0.65	414	308	402
0.70	468	350	454
0.75	522	390	508
0.80	578	432	564
0.85	636	476	620

For true CV values larger than 0.30, the Type I error rate is controlled at true mean difference values equal to the FDA implied limits [+/- (log(1.25)/0.25)* σ] on the log-transformed scale (see, Davit et. al 2012), where CV=$\sqrt{e^{\sigma^2} - 1}$.

9.8.2 Sample size calculation for PFS (thigh) and AI (thigh)

Sample size requirement is based on a conventional size of studies for an evaluation of pharmacokinetic endpoints in treatment groups with different administration sites (ie, comparing PFS (abdomen) vs. PFS (thigh) or comparing AI (abdomen) vs. AI (thigh)). No formal statistical testing is planned.

[redacted]

A total of 24 patients (12 per arm) will be required for PFS (thigh) and AI (thigh) groups. This is in alignment with sample size often applied to standard pharmacokinetic studies.

For an estimation of mean difference in the two groups of different administration sites (abdomen (n=60) vs. thigh (n=12)), the width of 90% CI will be 0.78 assuming the CV is 85%.

To account for 3% dropout, a total of 26 patients (13 per arm) will be randomized.

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 ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible 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 (eg 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 (eg, advertisements) and any other written information to be provided to 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

[redacted]

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, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of 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 subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the

[redacted]

need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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[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 (eg, 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.	

[redacted]

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 (eg 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 a [redacted]. 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 (eg 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 CRF 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.

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.

[redacted]

When evaluating a patient with a suspected infection, the most sensitive tests available should be used (ie 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 11). 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 and EOS by the central laboratory. They will only be communicated to the site after baseline in case of notably low levels. A notably low IgG level is defined as a level that is 20% below the LLN and a notably low IgM level is defined as a level 10% below the LLN. Following notification, the immunoglobulin level should be repeated within 2 weeks by the central lab to confirm the reading. If the repeated test confirms the immunoglobulin level to be below the threshold, the

[redacted]

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.