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Novartis Research and Development

OMB157/Ofatumumab

Clinical Trial Protocol COMB157G2402 / NCT05199571

A 12-month, open-label, prospective, multicenter, interventional, single-arm study assessing the efficacy and safety of ofatumumab 20mg s.c. injection in relapsing multiple sclerosis (RMS) patients in China

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List of abbreviations

[redacted]	[redacted]
AE	Adverse Event
AEP	Accelerated Elimination Procedure
AIDS	Acquired Immune Deficiency Syndrome
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BIL	Bilirubin
BL	Baseline
BTK	Bruton's Tyrosine Kinase
BUN	Blood Urea Nitrogen
CDP	Confirmed Disability Progression
CFR	Code of Federal Regulations
CIS	Clinically Isolated Syndrome
CK	Creatine Kinase
CKD	Chronic Kidney Disease
cm	centimeter
CMO&PS	Chief Medical Office and Patient Safety
CNS	Central Nervous System
CO	Country Organization
COA	Clinical Outcome Assessment
COVID	Corona Virus Disease
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDE	Direct Data Entry
DMTs	Disease-Modifying Therapies
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End of Study
eSAE	electronic Serious Adverse Event
eSource	electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration
FS	Functional Systems
FSH	Follicle Stimulating Hormone

GBCA	Gadolinium-Based Contrast Agent
GCP	Good Clinical Practice
Gd	Gadolinium
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
HA	Health Authority
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
hCG	human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
i.v.	intravenous
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IEC	Independent Ethics Committee
IFNβ-1a	Interferon β-1a
IFNβ-1b	Interferon β-1b
IgG	Immunoglobin G
IgM	Immunoglobin M
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
kg	kilogram
LFT	Liver Function Test
LLN	Lower Limit of Normal
M	Month
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mL	milliliter
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
MS	Multiple Sclerosis
NFS	Nephrogenic Systemic Fibrosis
NMOSD	Neuromyelitis Optica Spectrum Disorder
NMPA	National Medical Products Administration
Nrf2	Nuclear Factor (erythroid-derived 2)-like 2
NYHA	New York Heart Association
PAC	Post-Approval Commitment
PCR	Protein-creatinine Ratio
PML	Progressive Multifocal Leukoencephalopathy
PMS	Progressive Multiple Sclerosis

PPMS	Primary Progressive Multiple Sclerosis
PRO	Patient Reported Outcome
PT	Prothrombin Time
PT FU	Post-treatment Follow-up
PTA	Post Trial Access
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
Sars-CoV-2	Severe acute respiratory syndrome Coronavirus 2
SD	Standard Deviation
SOP	Standard Operating Procedure
SPMS	Secondary Progressive Multiple Sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TBL	Total Bilirubin Level
TFQ	Trial Feedback Questionnaire
UK	United Kingdom
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
W	Week
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis

Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Variable (or endpoint)	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Protocol summary

Protocol number	COMB157G2402
Full Title	A 12-month, open-label, prospective, multicenter, interventional, single-arm study assessing the efficacy and safety of ofatumumab 20 mg subcutaneous (s.c.) injection in relapsing multiple sclerosis (RMS) patients in China
Brief title	Study of efficacy and safety of ofatumumab in relapsing multiple sclerosis (RMS) patients in China
Sponsor and Clinical phase	Novartis; Phase IV
Investigation type	Biological
Study type	Interventional
Purpose	The purpose of this study is to evaluate the efficacy and safety of ofatumumab s.c. in adult participants with relapsing multiple sclerosis (RMS) in China, as part of a post-approval commitment to the Health Autorithy in China. The study will also be used for ofatumumab's license renewal.
Primary Objective(s)	The primary objective of this trial is to evaluate the effect of ofatumumab 20 mg monthly s.c. on annualized relapse rate (ARR) in participants with RMS
Secondary Objectives	● To evaluate the safety and tolerability of ofatumumab 20 mg monthly s.c. in participants with RMS ● To evaluate the effect of ofatumumab 20 mg monthly s.c. on MRI lesions in participants with RMS
Study design	Prospective, open-label, single arm, multi-center, interventional study. The study is composed of 3 periods with around 100 enrolled participants: ● Screening period (up to 30 days) ● Treatment period (12 months) ● Post-treatment Follow-up period (6 months)
Rationale	The clinical development program of ofatumumab has demonstrated efficacy and safety of ofatumumab 20 mg monthly s.c. for the treatment of participants with RMS globally in two pivotal clinical studies, COMB157G2301 and COMB157G2302. Chinese participants were not enrolled into these studies. To support the local approval of ofatumumab as a treatment for RMS in China, the National Medical Products Administration (NMPA) in China requested a post-approval study to collect efficacy and safety data of ofatumumab 20 mg monthly s.c. in adult Chinese RMS participants.
Study population	Adult participants with RMS
Key Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study. 2. Male or female Chinese aged 18-55 years (inclusive) at their enrollment of the study (signing the study consent form). 3. Clinical definite diagnosis of RMS according to the 2017 Revised McDonald criteria (Thompson et al 2018）， and the documentation prior to their enrollment to the study (signing the study consent form) of: ● Two documented relapses during the past 2 years, or ● One documented relapse during the last year, or ● A positive Gd-enhancing MRI scan during the year prior to Screening. Note: Screening MRI scan may be used if no positive Gd-enhancing scan exists from prior year. 4. Disability status with an EDSS score of 0 - 5.5 (inclusive) at Screening. 5. Neurologically stable within 1 month prior to both Screening and Baseline (including no MS relapse in this period).
Key Exclusion criteria	1. Participants with primary progressive MS (PPMS) or secondary progressive MS (SPMS) without disease activity 2. Participants meeting criteria for neuromyelitis optica spectrum disorder (NMOSD) 3. Pregnant or nursing (lactating) women 4. Women of child-bearing potential unless using effective methods of contraception while

	taking study treatment and for at least 6 months after stopping medication 5. Participants with an active chronic disease of the immune system other than MS 6. Participants with neurological findings consistent with PML or confirmed PML 7. Participants with active hepatitis B disease 8. Participants with active systemic infections (including but not limited to active COVID-19 infection) or known to have AIDS or to test positive for HIV antibody at Screening 9. Participants at high risk of developing or having reactivation of syphilis or tuberculosis 10. Have received any live or live-attenuated vaccines within four weeks prior to first study drug administration 11. Have been treated with medications as specified or within timeframes specified in the protocol 12. Any other disease or condition that could interfere with participation in the study according to the study protocol, or with the ability of the participants to cooperate and comply with the study procedures.
Study treatment	Ofatumumab 20 mg sc injections at Week 0, 1, 2 and monthly thereafter starting at Week 4, administered using an autoinjector
Efficacy assessments	● MS relapse ● Expanded Disability Status Scale (EDSS) ● Magnetic Resonance Imaging (MRI)
Key safety assessments	● Adverse events ● Physical/neurological examinations (including skin) ● Vital signs ● Laboratory evaluations (blood and urine)
Other assessment	Trial Feedback Questionnaire (TFQ) (optional)
Data analysis	Data will be analyzed using summaries and/or statistical models on different analysis sets as appropriate. Annualized relapse rate (ARR) will be analyzed using a negative binomial model. The number of Gd-enhancing T1 lesions per MRI scan as well as the annualized rate of new or enlarging T2 lesions will also be analyzed using a negative binomial model. Change in T2 lesion volume will be summarized by visit. All safety endpoints as well as the [redacted] will be statistically summarized appropriately.
Key words	Relapsing multiple sclerosis, open-label, interventional, efficacy and safety, ofatumumab.

1 Introduction

1.1 Background

The disease: relapsing multiple sclerosis (RMS)

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 is the most common autoimmune demyelinating disorder of the CNS, affecting approximately 2.8 million individuals worldwide (MSIF 2020). MS typically affects young adults (mean age at onset 30 years) and women are affected more often than men.

Reflecting the current understanding of MS, the disease course is traditionally grouped into 2 main categories:

1. Relapsing MS (RMS): clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), active secondary progressive MS (SPMS)
2. Progressive MS (PMS): SPMS without relapses and primary progressive MS (PPMS)

At the time of their first MS diagnosis, approximately 80% to 85% of patients present initially with RRMS, characterized by recurrent acute exacerbations (relapses) of neurological dysfunction followed by a variable state of recovery. Most patients with RRMS may progress to SPMS, which is a stage of the disease that is characterized by continuous worsening of disability independent of relapses. Approximately 10% of patients suffer from PPMS, characterized by accumulation of disability since the beginning of the disease with or without superimposed relapses (MSIF 2020, Claes et al 2015, D'Amico et al 2019). MS prevalence in China is lower than that in western countries, with approximately 3 cases per 100,000 people in China comparing to >200 cases per 100,000 people in North America (MSIF 2020). In recent years, with increased awareness and revisions to the diagnostic criteria, there are more patients being diagnosed and treated in China. Further, the MS phenotypes, gender ratio and age range are comparable to Caucasian MS patients (Lau et al 2008, Cheng et al 2010, Chan et al 2011).

Although there is currently no cure for MS, several disease-modifying therapies (DMTs) have been approved globally including in China. As of May 2021, there are 6 approved DMTs in China, including interferon β-1b (IFNβ-1b, Betaseron®), interferon β-1a (IFNβ-1a, Rebif®), teriflunomide (Aubagio®), fingolimod (Gilenya®), siponimod (Mayzent®) and dimethyl fumarate (Tecfidera®). Beta interferons have multiple immune actions but the means by which the drugs are effective in MS remains unknown. High-dosage IFNβ-1b showed modest (~34%) effect on relapses compared to placebo in RRMS patients (Goodin et al 2002). Teriflunomide, an orally active drug that inhibits lymphocyte proliferation, showed moderate reduction in disease activity (~30%) and disability (~20%) compared to placebo in RMS patients (O'Connor et al 2011, Gold et al 2012); fingolimod, a sphingosine-1 phosphate receptor modulator, and dimethyl fumarate, which has anti-inflammatory immune response by the Nuclear Factor (erythroid-derived 2)-like 2 (Nrf2) dependent and independent pathways (Yadav et al 2019), both showed marked effect on relapse rate (~50%) and moderate effect on disability (~30%) compared to placebo in RMS patients (Kappos et al 2010, Calabresi et al 2014;Gold et al 2012, Arnold et al 2014). Siponimod, a selective sphingosine-1-

phosphate (S1P) receptors modulator, showed significant effect on active MRI lesions (~70%) compared to placebo at the approved dose in a Phase 2 study in RRMS patients (Selmaj et al 2013), marked reduction of ARR (55%) and some effect on disability (~20%) relatieve to placebo in SPMS patients in a large Phase 3 trial (Kappos et al 2018).

Recently, with the discovery of the roles of B-cells in the contribution to the immune-mediated histopathology in MS (Archelos et al 2000, Frohman et al 2006, McFarland 2008), B-cell targeted therapies have drawn some attention and are regarded as high-efficacy treatments that can be applied as first-line therapy early in the disease course. The first FDA-approved, humanized anti-CD20 monoclonal antibody, ocrelizumab, for RMS showed that B-cell depletion led to significantly reduced relapse rates, reduced MRI disease activity, and delayed the time to disability worsening vs interferon β-1a over 2 years in RMS patients. With ocrelizumab being administrated via intravenous route with relatively high drug dose and volume, the risk of infusion-related reactions and potentially limited access to infusion facilities need to be considered when choosing ocrelizumab as a treatment option (Hauser et al 2017). Ocrelizumab has not been approved by National Medical Products Administration (NMPA) in China.

Ofatumumab

Ofatumumab (OMB157) is a fully human monoclonal antibody (mAb), which targets CD20 expressed on B-cells and a subset of T-cells. To date, ofatumumab is approved for the treatment of relapsing forms of MS (RMS) (Kesimpta®) in the US, European Union, Japan, Singapore and other countries and is among the highly effective MS DMTs (Samjoo et al 2020).

Ofatumumab specifically recognizes a unique conformational epitope encompassing both the large and small extracellular loops on the human CD20 molecule, which allows ofatumumab binding very close to the plasma membrane. This unique composite epitope is separate from the epitopes on the large loop of CD20 that other anti-CD20 mAbs bind (e.g. rituximab and ocrelizumab) (Teeling et al 2006, Bleeker et al 2008).

In a human CD20 transgenic mouse model, subcutaneous administration of ofatumumab resulted in a more direct access to lymph nodes as compared to intravenous administration of the drug. It is expected that the direct access to the lymphatic system, a primary location of MS pathology and target for MS therapies (Sabatino et al 2019), may contribute to a lower required dose to achieve clinical efficacy, with a corresponding better tolerability and an expected lower clinical risk (i.e. fewer adverse drug reactions) when compared to an intravenous route of administration.

The efficacy and safety profile of ofatumumab in MS has been evaluated in different clinical studies. The two confirmatory Phase 3 pivotal trials (COMB157G2301 and COMB157G2302) consisted of randomized, double-blind, double-dummy, active comparator controlled, parallel-group, multi-center studies of identical design in a total of 1882 RMS participants. Superiority of ofatumumab over teriflunomide was demonstrated independently in the two pivotal trials. The annualized relapse rate (ARR) was significantly reduced by >50% in both trials, leading to very low annualized relapse rates in participants treated with ofatumumab (ARR of 0.11 and 0.10, respectively). Further, treatment with ofatumumab compared with teriflunomide significantly reduced the mean number of gadolinium (Gd)-enhancing T1 lesions per scan

by >90% in each of the trials. A significant reduction in the rate of new or enlarging T2 lesions per year by >80% was also observed. Compared to teriflunomide, ofatumumab significantly reduced the risk for 3-month confirmed disability progression and 6-month confirmed disability progression by >30% in pre-specified pooled analyses of the two trials. The results for the two pivotal Phase 3 studies showed that treatment with ofatumumab was well tolerated and the safety profile observed for ofatumumab was consistent with the expected risks associated with anti-CD20 antibody therapy, but with low rates and with primarily mild to moderate severity grades for injection-related reactions including the first injection (Hauser et al 2020).

In a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 2 registry study in participants with RMS in Japan and Russia (COMB157G1301), ofatumumab demonstrated superior efficacy versus placebo, meeting the primary endpoint with a statistically significant reduction in the mean number of Gd-enhancing T1 lesions per scan up to Week 24 of 94% and a consistent effect across regions (Japan/Russia). The overall safety observations were consistent with the known safety profile of ofatumumab in RMS patients based on the global pivotal Phase 3 trials (publication under journal review).

For further details about ofatumumab and an overview of all completed and ongoing studies, please refer to the Investigator's Brochure.

As part of a post-approval commitment to the Health Authority in China, as China did not join previous global studies, Novartis is conducting this post-approval commitment study (PAC) in order to evaluate the efficacy and safety profile of ofatumumab in RMS patients in China.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of ofatumumab 20 mg monthly s.c. in adult participants with relapsing multiple sclerosis (RMS) in China, as part of a post-approval commitment to the Health Authority in China. The study will also be used for ofatumumab's license renewal.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the effect of ofatumumab 20 mg monthly s.c. on annualized relapse rate (ARR) in participants with RMS	• Annualized relapse rate (ARR, based on frequencies of confirmed relapses)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of ofatumumab 20 mg monthly s.c. in participants with RMS	• Adverse events, including injection-related reactions; • Laboratory data and vital signs.
• To evaluate the effect of ofatumumab 20 mg monthly s.c. on MRI lesions in participants with RMS	• Number of Gd-enhancing T1 lesions per MRI scan ; • Number of new/enlarging T2 lesion per year (annualized T2 lesion rate);

Objective(s)	Endpoint(s)
	• Change in T2 lesion volume compared to baseline.
[redacted]	

3 Study design

This is a 12-month, open-label, prospective, multi-center, single-arm, interventional study to evaluate the efficacy and safety of ofatumumab (OMB157) in approximately 100 adult participants with RMS in China.

The study consists of three periods (see Figure 3-1): Screening, Treatment, and Post-treatment Follow-up.

Screening (up to 30 days):

After signing the informed consent, participants will enter the Screening period to determine eligibility according to the inclusion and exclusion criteria. The Investigator must ensure that participants meet all the inclusion and none of the exclusion criteria to be eligible for the study. If a participant is declared a screen failure, he/she may be re-screened and all assessments must be repeated, with the possible exception of the MRI (if the initial screening MRI was completed within the last 3 months). For details, refer to Section 8.1.

Treatment (12 months):

During the Treatment period, all eligible participants will receive initial dosing with ofatumumab 20 mg s.c. injection at Baseline/Week 0 (BL/W0), W1 and W2, followed by subsequent monthly dosing starting at W4 (Month 1/M1; a study month is defined as 28 days). The first s.c. injection at W0 will be administered [redacted].

All participants will have an End of Study (EOS) visit at the end of the Treatment period, when a participant has reached the maximum of 12-month treatment, or at the time a participant prematurely discontinues study treatment. After study treatment discontinuation, participants may initiate alternative MS therapy according to local standard of care if clinically indicated (refer to Section 9.3).

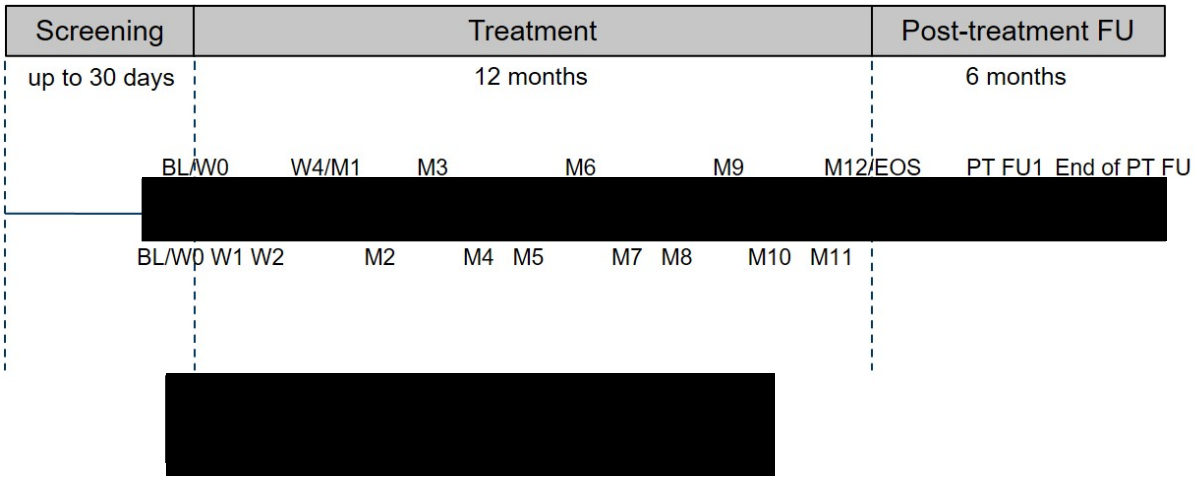
Post-treatment Follow-up (6 months):

All participants, except for completers who decide to continue with commercially available ofatumumab treatment, will be followed up in the Post-treatment Follow-up period for 6 months after last study drug dose (Table 8-2). The Post-treatment Follow-up visits should be scheduled relative to the EOS visit and will occur at EOS+3 months and EOS+6 months (End of Post-treatment Follow-up). If a participant prematurely discontinues from Post-treatment Follow-up, the End of Post-treatment Follow-up visit should be arranged as soon as possible. Investigators

may continue to follow participants outside of this study at his/her discretion (for example, if participants have not repleted their B-cells at the end of Post-treatment Follow-up).

Throughout the study periods, participants may have unscheduled visits due to a suspected MS relapse, an acute illness of undetermined cause, for other reasons, or at the discretion of the Investigator (refer to Section 8.3.1).

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

The clinical development program of ofatumumab in MS has demonstrated efficacy and safety of ofatumumab 20 mg monthly s.c. for the treatment of patients with RMS globally in two pivotal clinical studies, COMB157G2301 and COMB157G2302. As Chinese patients were not enrolled into these studies, the NMPA in China requested a post-approval study to collect the efficacy and safety data of ofatumumab 20 mg monthly s.c. in adult Chinese RMS patients.

This study is designed with the aim to obtain efficacy and safety data in Chinese RMS participants treated with ofatumumab for up to 12 months. Given the limited population size of RMS participants in China and as ofatumumab is an approved RMS therapy and continues to be effective and safe for RMS patients across various countries in the world, an open-label, single arm design is considered to be adequate for this study.

Upon the requirement of license renewal in 2026, an interim analysis (IA) based on data collected up to the IA cut-off (around Q1 2025) will be performed, unless the final analysis has already been completed prior to the license renewal, and the results will be reported to NMPA.

4.2 Rationale for dose/regimen and duration of treatment

The dose regimen for ofatumumab for this study is an initial dosing of 20 mg at BL/W0, W1 and W2, followed by subsequent monthly dosing of 20 mg starting at W4.

This dose regimen is consistent with the dose and regimen in the global Phase 3 development program of ofatumumab in RMS and with the approved dosage in the various countries worldwide, including China before this study is initiated.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

One interim analysis is planned around Q1 2025. The efficacy and safety data of IA will be submitted to NMPA for local license renewal.

4.5 Risks and benefits

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and avoidance of prohibited treatments and adherence to investigator guidance regarding specific safety areas.

Ofatumumab is approved for the treatment of RMS in several countries. In the pivotal Phase 3 studies COMB157G2301 and COMB157G2302, treatment with ofatumumab significantly lowered the annualized relapse rate (ARR; primary endpoint) compared to the active comparator teriflunomide by >50%. Ofatumumab also significantly reduced the risk of disability progression by >30% and showed significant suppression of both Gd-enhancing T1 lesions (>90%) and new/enlarging T2 lesions (>80%) on brain MRI compared to teriflunomide.

The data from the global ofatumumab MS program indicate ofatumumab has an acceptable safety profile and is well tolerated at the recommended subcutaneous dose of 20 mg.

Reported adverse reactions included upper respiratory tract infections, decreased immunoglobulin M, injection site reaction, and injection-related reactions. For further details about ofatumumab, please refer to the Investigator's Brochure.

Overall, the balance of benefit and risk supports the proposed clinical study to evaluate the use of ofatumumab sc as an effective and safe therapy in Chinese participants with RMS.

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 requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

In the context of a Public Health Emergency, additional risks exist for participants taking part in any clinical trial cannot be excluded. Eligibility criteria for the study requires the Investigator to evaluate infections and exclude participants with ongoing infection. The protocol also includes guidance on immunization (see Section 16.4.4). Additionally, this protocol has been adapted to include the option to allow for remote visits (on a case-by-case basis), to minimize unnecessary risk that would be associated with on-site visits. Other options like home nursing and shipment of study drug directly to participants' home may be considered on case-by-case

basis. Participants receiving ofatumumab, who may have been exposed to individuals with COVID-19, who are experiencing protracted flu-like symptoms (particularly shortness of breath) consistent with COVID-19, or are confirmed to have COVID-19, should inform their treatment physician as soon as possible. Whether there will be interruption of the use of ofatumumab will be based on Investigator's judgement.

4.5.1 Imaging Risk

A gadolinium-based contrast agent (GBCA) will be administered as an i.v. bolus during each MRI session. There is recent evidence of gadolinium deposition in brain tissues following use of GBCAs. Although no symptoms or diseases linked to gadolinium accumulation in the brain have been identified, health authorities took a precautionary approach (e.g., GBCA EMA restriction re brain deposit), noting that data on the long-term effects in the brain are limited. This led to the suspension of several linear GBCAs and the recommendation that another class of GBCAs known as macrocyclic agents be used as an alternative solution, as they are deemed more stable and have a lower propensity to release gadolinium than linear agents. Although this is highly debated, the current belief is that such agents, especially the linear gadolinium agents, may also increase the risk of a rare but serious disease called nephrogenic systemic fibrosis (NFS). Few studies showed that use of linear agents in participants with normal kidney function or mild-to-moderate CKD (stage 3; eGFR 30-59 ml/min per 1.73 m^2) is without clinically significant risk of nephrogenic systemic fibrosis (NFS) (Goldstein et al 2019), however they should remain contraindicated in participants with acute kidney injury (AKI) or severe renal disease (stage 4 or 5 chronic kidney disease, CKD) (eGFR <30 ml/ min per 1.73 m^2). To prevent this risk and in accordance with health authority guidance (e.g. GBCA FDA guidance re NFS, GBCA MHRA guidance re NFS), people with severe kidney failure, participants with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent; participants with severe renal disease (eGFR <30 mL/min/1.73 m^2), or acutely deteriorating renal function, who would be at risk of nephrogenic systemic fibrosis should be excluded from participating in this study as stipulated in the exclusion criterion.

4.6 Rationale for Public Health Emergency mitigation procedures

In the event of a Public Health Emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures may be required to ensure participants' safety and trial integrity are listed in relevant sections of the study protocol. Notification of the Public Health Emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by local or regional health authorities and ethics committees as appropriate.

5 Study Population

The study population will consist of adult relapsing multiple sclerosis (RMS) participants aged 18-55 years (inclusive) fulfilling all the eligibility criteria listed below. No additional inclusion/exclusion criteria may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible participants.

Approximately 100 participants will be enrolled from study sites in China.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female Chinese aged 18-55 years (inclusive) at their enrollment of the study (signing the study consent form).
3. Clinical definite diagnosis of RMS according to the 2017 revised McDonald criteria (Thompson et al 2018, refer to Section 16.3), and
   with the documentation prior to their enrollment to the study (signing the study consent form) of:
   - Two documented relapses during the past 2 years, or
   - One documented relapse during the last year, or
   - A positive Gd-enhancing MRI scan during the year prior to Screening. Note: Screening MRI scan may be used if no positive Gd-enhancing scan exists from prior year.
4. Disability status with an EDSS score of 0 - 5.5 (inclusive) at Screening.
5. Neurologically stable within 1 month prior to both Screening and Baseline (including no MS relapse in this period).

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Participants suspected of not being able or willing to cooperate or comply with study protocol requirements in the opinion of the Investigator.
2. Participants with primary progressive MS (PPMS) (Thompson et al 2018) or secondary progressive MS (SPMS) without disease activity (Lublin et al 2014).
3. Participants meeting criteria for neuromyelitis optica spectrum disorder (NMOSD; Wingerchuk et al 2015).
4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
5. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective contraception while taking study treatment and for at least 6 months after stopping medication.
   Note: Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6. Participants at high risk of developing or having reactivation of syphilis or tuberculosis. Testing for syphilis and tuberculosis will be done by the central lab at Screening for eligibility.

   NOTE: If test results are suspected to be false positive/negative, an infectious disease expert should be consulted. The Investigator must document that the test results are considered false positive/negative and may then enroll/exclude the participant.

   For participants with positive or uncertain results but no overall disease activity as evaluated by an infectious disease expert and have low risk of disease reactivation, the Investigator may consider enrolling such a participant. In this case, the investigator must document the assessments by the infectious disease expert, and give appropriate treatment and/or monitoring as per local clinical practice.
7. Participants with active hepatitis B disease:

   Hepatitis B virus (HBV) screening is required in all participants, including hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local practice.

   Participants with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent HBV infection or reactivation.
8. Participants with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g. rheumatoid arthritis, scleroderma, Sjögren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with immunodeficiency syndrome (hereditary immune deficiency, drug-induced immune deficiency).
9. Participants with active systemic infections (including but not limited to active COVID-19 infection) or known to have AIDS or to test positive for HIV antibody at Screening.
10. Participants with neurological findings consistent with PML or confirmed PML.
11. 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 or the uterus that have been radically treated e.g. completely excised with clear margins), within the past 5 years, regardless of whether or not there is evidence of local recurrence or metastases.
12. History of hypersensitivity to the study treatment or its excipients or to drugs of similar chemical classes.
13. Use of other investigational drugs at the time of enrollment (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; or longer if required by local regulations.
14. Have received live or live-attenuated vaccines (including but not limited to live or live-attenuated Sars-CoV-2 vaccines, if any) within 4 weeks prior to first study drug administration.

    Note 1: Inactivated vaccines, whenever possible, should be administered at least 2 weeks prior to the initiation of study drug.

    Note 2: At the time of development of this protocol, there is no efficacy or safety data on Sars-CoV-2 vaccines in immunocompromised persons. Though immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Sars-CoV-2 vaccines, there is presently no

contraindication for the use of an inactivated, viral-vector-, or mRNA based Sars-CoV-2 vaccine in participants who are immunocompromised. However, different Sars-CoV-2 vaccines may have various mechanisms of action and different associated potential risks. Local prescribing information of any specific Sars-CoV-2 vaccine must be reviewed and local prescribing information requirements for specific contraindications and special warnings and precautions for use must be followed. Vaccination against Sars-CoV-2 during whole study course should be considered on a case-by-case basis at the discretion of the treating physician taking into account the individual benefit-risk assessment and local vaccination recommendations. For details, refer to Section 16.4.4.

15. Have been treated with any other MS DMT within 5 elimination half-lives (according to their labels) or within expected pharmacodynamic effect window. For the medications commonly used in MS treatment, wash-out period is suggested to be:

Medication	**Exclusionary if used/used within required wash-out period**
Systemic corticosteroids, adrenocorticotropic hormone	30 days prior to Screening MRI scan
interferon-β or glatiramer acetate	none
Intravenous immunoglobulin	8 weeks prior to baseline
Plasmapheresis	8 weeks prior to baseline
Siponimod and ponesimod	4 weeks prior to baseline
Fingolimod	8 weeks prior to baseline
Teriflunomide	3.5 months prior to baseline or 1 month prior to baseline if participant undergoes AEP (Accelerated Elimination Procedure) before baseline
B-cell targeted therapies (e.g., rituximab, ocrelizumab, obinutuzumab)	Prior to consideration for trial/at Screening, B-cell recovery (LLN as per central lab) needs to be verified and documented by the investigator Or 2 years prior to baseline
BTK inhibitors	2 weeks prior to baseline
Natalizumab (Participants who have discontinued natalizumab in the 6 months prior to randomization should be evaluated to rule out PML)	12 weeks prior to baseline
Mild to moderately immunosuppressive/chemotherapeutic medications (e.g. azathioprine, methotrexate)	24 weeks prior to baseline
Highly immunosuppressive/chemotherapeutic medications (e.g., mitoxantrone, cyclophosphamide, cladribine)	48 weeks prior to baseline
Alemtuzumab	Anytime
Lymphoid irradiation or bone marrow transplantation	Any time
Mitoxantrone (with evidence of cardiotoxicity following treatment or cumulative life-time dose > 60 mg/m2)	Anytime
Ofatumumab	Anytime

16. Any of the following chronic, severe conditions that may impact compliance:
    - History of, or current, significant cardiac disease including cardiac failure (NYHA functional class II-IV), myocardial infarction (within 6 months prior to Screening), unstable angina (within 6 months prior to Screening), transient ischemic attack

(within 6 months prior to Screening), stroke, cardiac arrhythmias requiring treatment or uncontrolled arterial hypertension

- Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia and clinically significant second or third degree AV block without a pacemaker on screening electrocardiogram (ECG)
- History of familial long QT syndrome or known family history of Torsades de Pointes
- History of or active severe respiratory disease, including Chronic Obstructive Pulmonary Disease, interstitial lung disease or pulmonary fibrosis
- Participants with asthma requiring regular treatment with oral steroids
- Severe hepatic impairment (Child-Pugh class C) or any chronic liver or biliary disease
- Participants with severe renal impairment (Glomerular Filtration Rate < 30 ml/min/1.73 m2) or severe hypoproteinemia (e.g. in nephrotic syndrome)
- Any medically unstable condition as determined by the Investigator

17. Any of the following abnormal laboratory values as confirmed by the central laboratory prior to first study drug administration:
    - Lymphocyte count < 800/mm3 (< 0.8 x 10^9/L).
    - B-cell count < lower limit of normal (LLN, as per central laboratory range) if participants had a history of receiving a B-cell targeted therapy and did not meet the suggested wash-out period as detailed in exclusion criterion #15.
    - Serum IgG and/or serum IgM < LLN (according to central laboratory range)
    - Any other clinically significant laboratory assessment as determined by the Investigator (e.g. significant anemia, neutropenia, thrombocytopenia, signs of impaired bone marrow function)
18. Current medical or neurological condition that might impact efficacy assessments e.g. dementia, schizophrenia, bipolar disorder, major depression, history of multiple traumatic brain injuries, alcohol/drug abuse or dependence currently, or dependence within the last two years.
19. Participants intolerant to undergo MRI or presents contraindications to MRI (e.g. metallic implants, metallic foreign bodies, pacemaker, defibrillator) and the use of gadolinium-based agents (e.g. people with severe kidney failure, participants with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent; participants with severe renal disease (eGFR<30 mL/min/1.73 m^2), or acutely deteriorating renal function, who would be at risk of nephrogenic systemic fibrosis).

6 Treatment

6.1 Study treatment

This is a single-arm, open-label study. The study treatment is 20 mg ofatumumab for subcutaneous injection.

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
ofatumumab 20mg	solution for injection	subcutaneous use	Open label; autoinjector	Sponsor (global)

Ofatumumab (OMB157) will be provided as solution for injection in an autoinjector (also called pre-filled pen) 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-fee liquid.

There is no control drug in this study.

6.1.2 Additional study treatment

No other treatments beyond investigational drug are included in this trial.

6.1.3 Treatment arms

This is an open-label study with one treatment arm (ofatumumab 20 mg s.c. injections at Week 0, Week 1, Week 2, Week 4 and every month thereafter).

6.1.4 Treatment duration

The planned duration of treatment is 12 months. Participants may be discontinued from treatment earlier due to unacceptable toxicity (whether it is related to study drug or not), disease progression or serious non-compliance to study protocol, and/or treatment is discontinued at the discretion of the Investigator or the participant. For participants who in the opinion of the Investigator are still deriving clinical benefit from ofatumumab, every effort will be made to continue provision of study treatment.

Post Trial Access (PTA) is not planned for this study, because this is a PAC study and by the time when the first participant completes the 12-month treatment, ofatumumab will have been launched and commercially accessible in China.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The Investigator should instruct the participant to notify the study site about any new medications he/she takes after study enrollment.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate electronic Case Report Forms (eCRFs).

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

dosing with study drug or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Only limited benefit of premedication with steroids, antihistamines, or acetaminophen was seen in RMS clinical studies (refer also to the Investigator's Brochure). Injection-related reactions (systemic or local reactions) can be managed with symptomatic treatment, should they occur. If Investigators choose to administer premedication, it should be administered 30 to 60 min prior to study drug injection. Any administrations of premedication must be recorded in the appropriate eCRF.

A standard short course of intravenous corticosteroids (methylprednisolone) is allowed for the treatment of MS relapses (refer to Section 6.2.3). In addition, the restrictions regarding MRI assessments during, or within 30 days after termination of steroid therapy, must be followed (Section 8.3.2)

The medications allowed for treatment of adverse reactions and MS relapses are not considered study supplies, and therefore, need to be supplied by the study site.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table is not allowed concomitantly with study treatment.

Exclusionary medications for study eligibility are listed in the exclusion criteria (Section 5.2).

Use of excluded medications is not allowed while the participant is on study treatment.

Table 6-2 Prohibited medication

Medication	Action taken
Any immunosuppressive/ chemotherapeutic medications or procedures including but not limited to cyclosporine, azathioprine, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and hematopoietic stem cell transplantation; 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, obinutuzumab and BTK inhibitors.	Discontinue study treatment; increase vigilance regarding infections. NOTE: Restarting study treatment is not permitted.
Systemic corticosteroids except when given for symptomatic treatment of MS relapses or as pre-medication Immunoglobulins	Interrupt study treatment; increase vigilance regarding infections.
Any other immunomodulatory or disease-modifying MS treatment, including but not limited to fingolimod, siponimod, interferon beta, glatiramer acetate, dimethyl fumarate	Discontinue study treatment; increase vigilance regarding infections. NOTE: Restarting study treatment is not permitted.

Medication	Action taken
Any other investigational drugs	Discontinue study treatment; increase vigilance regarding infections. NOTE: Restarting study treatment is not permitted.
Administration of any live or live-attenuated vaccine on study drug (long-lasting effects of ofatumumab should be taken into consideration; refer to Investigator's Brochure).	They may be administered when participants are no longer exposed to study drug (Section 16.4.4). Consider risk/benefit and follow local labels. Note: Restarting study treatment is not permitted.

6.2.3 Recommended treatment for MS relapses

The decision to treat MS relapses should be based on the Investigator's judgement and/or local clinical practices. If MS relapses require treatment, the standard treatment should consist of a short course of corticosteroids (methylprednisolone). Standard of care will be followed during treatment.

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

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

Use of steroids for treatment of relapses must be recorded on the Concomitant medications eCRF.

Please refer to restrictions for MRI in Section 8.3.2 concerning the use of steroids and performing the MRI.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in Section 6.1.1.

Ofatumumab is commercially available and will be supplied locally by the Novartis Country Organization (CO). Preparation and dispensation should follow the locally approved package insert and local practice.

As per Section 4.6, during a Public Health Emergency as declared by local or regional authorities, i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 4 months' supply. In this case, additional phone calls or virtual contacts to replace scheduled on-site visits will occur between the site and their participants for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants

continue to benefit from treatment and discussion of the participants' health status until the participants can resume visits at the study site.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received [redacted], handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the approved label.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO 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 participant 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 field monitors during site or remote monitoring visits, and at the completion of the trial.

If study treatment is administered at home, participants 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.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, 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.

6.3.2 Instruction for prescribing and taking study treatment

Ofatumumab will be dispensed starting at W0, and then at scheduled visits throughout the Treatment period according to Table 8-1.

Participants will receive 3 initial s.c. injections of ofatumumab at W0, W1 and W2, followed by subsequent regular monthly dosing starting at W4 (a month is defined as 28 days).

The first s.c. injection at W0 will be administered [redacted]

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

- If one monthly injection is missed by more than 1 week, the participant should skip the dose and take the next dose at the time when the next injection would be due according to the original schedule.
- If two or more consecutive monthly injections are missed, the Investigator should inform the local Sponsor Medical Advisor before re-starting dosing.
- If any initial dose (at W0, W1 or W2), or the W4 dose is missed, then the injection should be administered as soon as possible. The next injection should then be administered according to the original schedule.

All dosages prescribed to the participant and all dose administrations and interruptions during the study must be recorded on the eCRF.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential Participant No. suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form (ICF), the participant is assigned to the next sequential Participant No. available.

6.4.2 Treatment assignment, randomization

This is a single-arm study and all participants will receive the same treatment (ofatumumab 20 mg s.c.).

6.5 Treatment blinding

Not applicable.

6.6 Dose escalation and dose modification

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

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

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

Should the participant interrupt the study drug for whatever reason, re-start decision should be made on a case-by-case basis. Should the Investigator decide, after informing the Sponsor, to re-initiate treatment with study drug, depending on the duration of the interruption, the first s.c. dose at re-start may need to take place [redacted] to ensure observation in a similar manner as W0.

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

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed. A monitor will perform and document drug accountability during site visits and at the end of the study. All study treatment dispensed and returned must be recorded in the drug accountability log.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation) IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she

must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form (ICF) that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) and the approved label. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug 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 then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

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 requirements.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

As per Section 4.6, during a Public Health Emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1 and Table 8-2) lists all of the assessments and indicates with "X" or "S" when they are performed. The “X” in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The “S” in the table denotes the assessments that are only in the participant’s source documentation and do not need to be recorded in the clinical database. All data obtained from these assessments must be supported in the participant’s source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1 and Table 8-2) or as close to the designated day/time as possible, with an allowed “injection window” as described in Section 6.3.2. Missed or rescheduled visits should not lead to automatic discontinuation. In the study, one month is defined as 28 calendar days.

For all scheduled visits, any AE or SAE reported by the participant will be recorded according to Section 10.1.1 and Section 10.1.2. For women of childbearing potential, urine or serum pregnancy test is required prior to each administration of study drug, and drug administration can only be conducted with negative pregnancy test result (refer to Section 8.4.3).

EOS visit is mandatory for all participants. The EOS visit is conducted at the end of the Treatment period (i.e. M12), or when participants prematurely discontinue study treatment before M12, whether they plan to enter Post-treatment Follow-up period or withdraw from the study. Participants who prematurely discontinue study treatment will have their EOS visit as soon as possible. At the EOS visit, AEs and concomitant medications not previously reported must be recorded on the eCRFs.

Participant diaries

During the study, participants will be asked to complete a diary from BL/W0 onwards till EOS to record information pertinent to study treatment administration (including date and time of s.c. injections), home pregnancy testing (date and results) for women of childbearing potential and other information (e.g. AEs). The participant is requested to bring the completed diaries with them to each visit and the Investigator/Study Coordinator/Nurse must review these for completeness and for potential AEs, injection-related reactions, study treatment interruptions etc. and record information obtained from the diaries into the relevant eCRFs.

Telephone or virtual interviews

Site personnel will conduct a structured telephone interview (script provided) for W1 and W2 initial doses, and then every month in between the scheduled site visits following the W4 site visit (Table 8-1 and Table 8-2). During the Treatment period, the interview should take place around time of the monthly s.c. self/home-injections to query about any new or worsening symptoms warranting an unscheduled visit, compliance with study treatment, changes in concomitant medication, injection reactions, results of home pregnancy testing and compliance with contraception requirements when applicable. During the Post-treatment Follow-up period, the interview should take place regularly every month between scheduled visits to query about any new or worsening symptoms warranting an unscheduled visit, changes in MS treatment and concomitant medication, compliance with contraception requirements and potential AEs etc.

Participants, except for those who will continue with commercially available ofatumumab treatment, will enter the 6-month Post-treatment Follow-up period after EOS as described in Table 8-2.

As per Section 4.6, during a Public Health Emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local health authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule, Screening and treatment

Period	Screening	Treatment								Treatment
Visit Name	Screening	BL/W0	W1 (Phone Interview)	W2 (Phone Interview)	W4	M3	M6	M9	M12/EOS	Unscheduled Visit[1]
Days	-30 to -1	-	7	14	28	84	168	252	336	-
Informed consent	X									
Demography, Height	X									
Inclusion / Exclusion criteria	X	X[2]								
Medical history/current medical conditions	X									
MS History/Treatments	X									
COVID-19 vaccination status	X	X[3]	X	X	X	X	X	X	X	
Physical Examination	S	S[3]			S		S		S	S
Weight, Vital Signs	X	X[4]			X	X	X	X	X	X
Electrocardiogram (ECG)	X									
Hematology	X[5]				X	X	X	X	X	
Clinical Chemistry	X[5]				X	X	X	X	X	
Urinalysis	X[5]				X		X		X	
Serological markers for hepatitis B[6]	X[5]									
HIV antibody screen[7]	X[5]									
Syphilis screen[7]	X[5]									
Tuberculosis screen [7]	X[5]									
Pregnancy and assessments of fertility [8]	X[5]	X[3]			X	X	X	X	X	
Contraception Status[9]	X	X[3]	X	X	X	X	X	X	X	
MS relapse	X	X[3]	X	X	X	X	X	X	X	X
MRI	X					X			X[10]	

Period	Screening	Treatment								Treatment
Visit Name	Screening	BL/W0	W1 (Phone Interview)	W2 (Phone Interview)	W4	M3	M6	M9	M12/EOS	Unscheduled Visit[1]
Days	-30 to -1	-	7	14	28	84	168	252	336	-
Adverse Events	X	X[3]	X	X	X	X	X	X	X	X
Prior/Concomitant Medications [11]	X	X[3]	X	X	X	X	X	X	X	X
Surgical/medical procedures	X	X[3]	X	X	X	X	X	X	X	X
Sample for B-cells[12]	X	X[3]			X	X	X		X	
Sample for IgG and IgM[12]	X						X		X	
Drug dispensation		S			S	S	S	S		
Drug administration [13]		X	X	X	Monthly, except for M12/EOS					
Participant diaries[14]			X							
Participant Diary Review					X	X	X	X	X	
Phone interview/virtual visit[15,16]			X	X	Monthly between scheduled visits					
Treatment Phase Completion									X	

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Unscheduled visit: assessments performed as unscheduled visits will depend on the clinical needs of the participant. All participants with neurological symptoms suggestive of an MS relapse should at least have the mentioned assessments in table 8-1 performed. Other assessments may be done as appropriate.
[2] Inclusion/exclusion criteria need to be checked again before first dose of study drug.
[3] Assessments to be completed prior to first study drug administration.
[4] 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).
[5] Laboratory results must be available prior to Baseline/Week 0 (BL/W0) to evaluate the Inclusion/Exclusion criteria.
[6] Hepatitis B screening is required in all study participants, including hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. For detailed guidance, refer to Section 16.4.2.
[7] HIV, Syphilis and Tuberculosis testing must be done at central lab as part of eligibility check (Exclusion criterion #6 and #9) for all participants.
[8] Women of childbearing potential only -For Screening and EOS visits, serum pregnancy test will be conducted in central lab. Monthly urine pregnancy tests will be conducted between scheduled visits(starting after W4) at home or at site prior to the administration of study treatment. In case of a positive test result, the participant must contact the investigator immediately and confirmatory testing should be performed at the investigator's discretion.
[9] Contraception MUST be used during the study treatment period and for at least 6 months after the last dose of study drug. Participant's contraception status must be reviewed and documented to ensure method of contraception continues to be appropriate per protocol requirement for effective contraception.

Period	Screening	Treatment								Treatment
Visit Name	Screening	BL/W0	W1 (Phone Interview)	W2 (Phone Interview)	W4	M3	M6	M9	M12/EOS	Unscheduled Visit[1]
Days	-30 to -1	-	7	14	28	84	168	252	336	-

[10] MRI scan at the End of Study (EOS) is needed if there was no MRI scan in the last 3 months.
[11] Including corticosteroids used to treat MS relapse; any newly started MS treatment as applicable (for participants who have discontinued study medication).
[12] The assessments (samples taken for IgG and IgM, B-cells) should be completed prior to study drug administration.
[13] The first s.c. injection at W0 will be administered [redacted].
[14] Study treatment administration (including date and time of s.c. injections) and home pregnancy testing (date and results) for women of childbearing potential will be recorded for each home injection. Other information (e.g. AEs) will be recorded continuously.
[15] Phone interview will be performed by site staff for W1 and W2, and then every month starting from W4 between scheduled visits. The interview should take place around time of the monthly s.c. self/home injection to query about any new or worsening symptoms warranting an unscheduled visit, injection reactions, results of home pregnancy testing and compliance with contraception requirements.
[16] Phone interview/virtual visits are also applicable to the scheduled visits for participants who exceptionally cannot come to the study site for a face-to-face examination due to a Public Health Emergency (e.g. restricting the subject's general access to sites).

Table 8-2 Assessment Schedule, Post-Treatment Follow-up

Period	**Post-Treatment Follow-Up**		
Visit Name	**V1**[1]	**End of FU**[1,2]	**Unscheduled Visit**[3]
Days	**EOS+3 months**	**EOS+6 months**	**NA**
Weight, Vital Signs	X	X	X
COVID-19 vaccination status	X	X	
Physical Examination	S	S	S
Clinical Chemistry	X	X	
Hematology	X	X	
Urinalysis	X	X	
Pregnancy Test (serum)[4]	X	X	
Contraception Status[5]	X	X	
Sample for B-cells	X	X	
Sample for IgG and IgM	X	X	
MS relapse	X	X	X
MRI		X[6]	
Concomitant medications[7]	X	X	X
Surgical/medical procedures	X	X	X
Adverse Events	X	X	X
Phone interview/virtual visit[8,9]	Monthly between scheduled visits		
Post Treatment Part Completion		X	

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Visits 1 and end of FU are applicable to all participants, except for completers of the Treatment period who decide to continue with commercially available ofatumumab treatment.
[2] If a participant prematurely discontinues from the Post-Treatment Follow-up (PT FU), the End of PT FU should be done as soon as possible. If scheduled PT FU1 visit and the end of PT FU visit occur around the same time, only end of PT FU should be done.
[3] Unscheduled visit: assessments performed at unscheduled visits depend on the clinical needs of the participant. All participants with neurological symptoms suggestive of an MS relapse should have an EDSS evaluation. Other assessments may be done as appropriate.
[4] Women of childbearing potential only. Serum pregnancy tests will be conducted on scheduled visits every 3 months by central lab.

Period	**Post-Treatment Follow-Up**		
Visit Name	**V1**[1]	**End of FU**[1,2]	**Unscheduled Visit**[3]
Days	**EOS+3 months**	**EOS+6 months**	**NA**

[5] Contraception MUST be used during the study and for at least 6 months after stopping study drug. Participant's contraception status must be reviewed and documented to ensure method of contraception continues to be appropriate per protocol requirement for highly effective contraception.
[6] For treatment period completers, MRI at the end of PT FU is not needed. For participants that prematurely discontinue from study treatment, MRI scan at the End of FU is needed if there has been no MRI scan in the last 3 months.
[7] Including corticosteroids used to treat MS relapse; any newly started MS treatment as applicable (for participants who have discontinued study medication).
[8] Phone interview/virtual visits are also applicable to the scheduled visits for participants who exceptionally cannot come to the study site for a face-to-face examination due to a Public Health Emergency (e.g. restricting the subject's general access to sites).
[9] Phone interview will be performed by site staff regularly every month between scheduled visits to query about any new or worsening symptoms warranting an unscheduled visit, changes in MS treatment and concomitant medication, compliance with contraception requirements and potential AEs.

8.1 Screening

Screening

If a participant does not meet Inclusion/Exclusion criteria, he/she may be re-screened. In general, a participant may not be re-screened more than once. All assessments must be repeated at re-screening, with the possible exception of MRI if the previous screening MRI scan was performed within 3 months of re-screening. If a participant is re-screened, a new ICF must be obtained and re-screening will be documented in the participant's source documents.

A new participant ID will be allocated and the site will record the data in a new eCRF.

In the case where a laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated at the discretion of the Investigator within the Screening period time window, and the participant may be included if the criteria are then met. In this instance, it is not considered as re-screening; the participant will not be required to sign another ICF and the original Participant Number assigned by the Investigator will be used. In the event that the laboratory tests cannot be performed within the Screening visit window, or the re-tests do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screen failure.

8.1.1 Information to be collected on screening failures

Participants who sign an ICF and are subsequently found to be ineligible prior to starting treatment will be considered as a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The disposition, demographic information, informed consent, and inclusion/exclusion, withdrawal of consent (if the participant withdrew consent) pages must also be completed for screen failure participants. No other data is required to be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event (SAE) during the screening phase (see Section 10.1.3 for SAE reporting details).

Adverse events that are not SAEs will be followed by the Investigator and recorded only in the source data.

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition eCRF.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data to be collected on the appropriate eCRF from the participant will include age, race, sex, ethnicity, height and weight.

Relevant medical history (including alcohol and smoking history), current medical conditions present before signing informed consent and any medication taken to treat these conditions will be captured on the corresponding eCRF. Where possible, the diagnosis and not symptoms should be recorded. Investigators will have discretion to record abnormal test findings on the

eCRF capturing medical history whenever in their medical judgment, the test abnormality occurred prior to the informed consent signature.

MS disease history including date of diagnosis, history of relapses and previous MS treatment will also be collected on the corresponding eCRFs.

8.3 Efficacy

MS relapse activity and neurological impairment of MS as measured by Expanded Disability Status Scale (EDSS) will be obtained in order to characterize the clinical disease activity. Brain MRI will be used to assess radiological disease activity.

8.3.1 Efficacy assessment 1

Annualized relapse rate (ARR)

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

Diagnosing MS relapses during the study: The assessment, management and reporting of MS relapse is made by the Treating Investigator. A participant may report symptoms indicative of a relapse at a scheduled visit or at any other time. Participants will be instructed to immediately contact the Investigator if he/she develops new or re-occurring or worsening neurological symptoms. At each scheduled visit, the participant will also be asked whether any such symptoms have occurred. If a participant reports new neurological symptoms or worsening of previous symptoms, an unscheduled visit should be performed as soon as possible, ideally within 7 days. During this visit, the Investigator will first assess whether the new/worsening neurological abnormality is consistent with the definition of MS relapse above. If so, the standard neurological examination (for the EDSS score) should be performed by the Investigator or a qualified designator. If fever or infection cannot be excluded, the neurological examination will be postponed until the fever or the infection has ceased (provided that the symptoms indicative of a relapse are still present). Treatment with steroids should not begin prior to the assessment by the Investigator.

Confirmation of MS relapse: A relapse is confirmed when it is accompanied by an increase of at least half a step (0.5) on the EDSS score or an increase of 1 point on two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS) compared to the previously available rating (the last EDSS rating that did not occur during a relapse).

All MS relapses, regardless if they meet definition for confirmation based on EDSS or not, are reported on the appropriate eCRF.

8.3.2 Efficacy assessment 2

MRI parameters: Gd- enhancing T1 lesions; new or enlarging T2 lesions; T2 lesion volume

All participants will undergo MRI scanning of the brain according to the schedule in the schedule of assessment (Table 8-1 and Table 8-2). MRI scans will be read by the central MRI reading center as part of the efficacy analysis (central reading not needed for eligibility). Each site Investigator will be responsible to have a qualified neuro-radiologist review each MRI scan to determine if there may be any incidental findings unrelated to the planned observations within the study protocol detected on the images. Refer to Section 16.4.1 for Guidance on safety monitoring.

Additional MRI scans in participants with suspected MS relapse is not required per study protocol and is at the discretion of the Investigator.

Scanning

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

T1-weighted images before and after administration of gadolinium contrast medium as well as T2-weighted images will be performed.

Prior to the start of the study, the neuroradiologist and MRI technician from each center will receive an MRI manual, outlining technical implementation, image quality requirements and MRI administrative procedures. Each site will be asked to program the MRI scanner that is designated for evaluation of the study participants and perform and submit a qualification scan to the MRI reading center to assess the image quality and to evaluate the compatibility of the electronic data carrier. Once the qualification scan has been accepted, all the parameter settings for the study specific MRI sequences must remain unchanged for the duration of the study.

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

As per Section 4.6, during a Public Health Emergency as declared by local or regional authorities i.e. pandemic, epidemic, or natural disaster, that limits or prevents on-site study visits, the collection of images may be modified by Novartis and will be communicated to the Investigator.

Restrictions for MRI schedule

To avoid potential interference caused by steroids used for the treatment of MS relapses, the following restrictions will be applied for this study:

- In case of relapse, if an MRI would have been scheduled within 30 days of the initiation of steroid treatment, this MRI should be performed before steroid treatment is initiated
- No MRI scan should be performed while a participant is on steroid therapy and within 30 days after termination of steroid therapy

8.3.3 Efficacy assessment 3

[redacted]

Expanded Disability Status Scale (EDSS) will be determined, based on neurological examination at scheduled visits (Table 8-1 and Table 8-2) and in case of a suspected MS relapse.

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

[redacted]

8.3.4 Appropriateness of efficacy assessments

MS relapse, EDSS assessments as well as MRI parameters in this patient population are standard efficacy assessments in MS and serve to characterize the patient population included in this study as well as their disease activity and neurological status over the study.

8.4 Safety

Safety assessments are specified as below with the assessment schedule detailing when each assessment is to be performed.

- Physical/neurological examination (including skin)
- Vital signs

- Laboratory evaluations
- Adverse events

For details on AE collection and reporting, refer to Section 10.1.

Table 8-3 Assessments & Specifications

Assessment	Specification
Physical	A physical examination includes an assessment of skin, head and neck, lymph nodes, breast, heart, lungs, abdomen, back and/or comments on general appearance. A neurological examination may also be a part of the physical examination. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.
Vital signs	Vital signs include temperature, blood pressure and pulse measurements. Sitting pulse rate and blood pressure should be obtained after the participant has 5 minutes of rest. The pulse should be measured just prior to obtaining the blood pressure measurement. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using a validated device, e.g. OMRON, with an appropriately sized cuff. For any abnormal reading, the repeated sitting measurements will be made at 1 - 2 minute intervals and the mean of the measurements will be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens (except for urine pregnancy tests) collected as described in Table 8-1 and Table 8-2. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the laboratory manual.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met (see also Section 10.1.1). Clinically significant abnormalities should be recorded in the eCRF as either AEs or as medical history/current medical conditions as appropriate. For AEs related to laboratory abnormalities, repeated evaluations are recommended until normalization of the test result(s) or until the result is no longer considered clinically significant.

In case of increases in liver function test (LFT), refer to Section 16.1.

If a Public Health Emergency as declared by local or regional authorities, i.e. pandemic, epidemic or natural disaster limits or prevents on-site study visits, the method of collection and testing of samples may be modified by Novartis if applicable and if modified, will be communicated to the Investigator.

Table 8-4 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, total white blood cell count and differential counts (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

Test Category	Test Name
Chemistry	Albumin, ALP, ALT, AST, gamma-glutamyl transferase (GGT), sodium, potassium, creatinine, total and conjugated bilirubin (BIL), blood urea nitrogen (BUN)
B-cell	CD19+ B-cell counts
Immunoglobulin	Immunoglobulin (IgG and IgM)
Urinalysis	Macroscopic Panel (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If clinical notable findings of macroscopic panel, then Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells)
Hepatitis markers	HBV screening is required in all participants, including Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing. Participants with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent HBV infection or reactivation. NOTE: 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 that the serology results are considered false positive and may then enroll the participant.
Pregnancy Test[1] (women of childbearing potential)	Serum / Urine pregnancy test (refer to Section 8.4.3)
Additional tests[2]	HIV antibodies, syphilis and TB screening test. Serology markers for other hepatitis, as appropriate; Follicle Stimulating Hormone (FSH) (for female participants with unclear fertility status). Cerebrospinal fluid (CSF) aliquot in the event of suspected CNS infection (PML)

[1] Serum pregnancy test analyzed in Central lab is required for Screening, EOS visits and for scheduled visits during Post-treatment Follow-up period. For the other scheduled visits, urine pregnancy test is to be analyzed with pregnancy kits provided by the central lab; monthly urine pregnancy test is to be conducted with pregnancy kits prior to every study drug administration. Urine pregnancy tests by local lab at site can be considered if pregnancy kit is not allowed per site requirement.
[2] HIV, syphilis and tuberculosis testing must be done as part of eligibility check (Exclusion criterion #6 and #9) for all participants. These screening tests should be done by the central lab.

8.4.2 Electrocardiogram (ECG)

An ECG will be obtained and reviewed locally for the eligibility assessment at Screening. Additional unscheduled ECGs may be performed at Investigator's discretion if clinically indicated.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline/according to the ECG investigator manual. In the case of a series of assessments, ECG should be the first assessment obtained while the participant is at rest (refer to Figure 8-1).

Figure 8-1 Timing of study procedures

The QT interval corrected by Fridericia's formula (QTcF) is suggested for use of clinical decisions. The Investigator should calculate QTcF if it is not auto-calculated by the ECG machine.

Single 12-lead ECGs are collected and results are entered into the appropriate eCRF page. The original ECGs, appropriately signed and labeled, must be collected and archived at the study site. The Investigator should document clinical evaluation in source.

Clinically significant abnormalities must be recorded in the eCRF as either medical history/current medical conditions or AEs as appropriate.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Serum pregnancy tests will be conducted by central lab at Screening, EOS visit and the scheduled visits in the Post-treatment Follow-up period. Urine pregnancy tests will be conducted for all women of childbearing potential at all the remaining scheduled visits and monthly starting after W4 between the scheduled visits (with urine pregnancy testing kits provided by the central lab unless not permitted per site requirement) prior to study drug administration. The participants will document the date and results of each home pregnancy test in a diary provided for the study. A monthly site contact (refer to Table 8-1) will also be conducted with the participants, which includes questions to confirm that the home urine pregnancy testing is done and the result is correctly documented. In case of a positive test result, the participant must contact the Investigator immediately for confirmatory testing at the Investigator's discretion. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative then proceed with the administration of the study treatment. The communication process described above as part of the monthly site contacts with the participant should be followed so that the site is informed and can verify the pregnancy test results.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

In addition, the Investigator will review the contraception status with the participant at each visit to ascertain that the participant continues to comply with protocol requirements for effective contraception as applicable.

Contraception must be used during the study treatment period and for at least 6 months after the last dose of study drug.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population and appropriate based on the current safety profile of ofatumumab (see Investigator's Brochure).

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Trial Feedback

This study is including an optional questionnaire, the “Trial Feedback Questionnaire” for trial participants to provide feedback on their clinical trial experience. Individual trial participant responses will not be reviewed by Investigators. Responses may be used by the Sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not ask questions about the trial participant's disease, symptoms, treatment effect, or adverse events, and therefore is not considered as trial data.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision (Section 9.1.2)
- Pregnancy (Section 8.4.3 and Section 10.1.4)
- Use of prohibited treatment as per recommendations in the prohibited treatment section (Section 6.2.2)
- Diagnosis of PML (Section 16.4.1)
- Hypersensitivity to the study drug

- Protocol violation that results in a significant risk to the participant'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 active hepatitis B, HIV)
- Laboratory abnormalities requiring the action of study drug discontinuation as defined in Section 16.1
- Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- Any situation in which study participation might result in a safety risk to the participant
- Non-compliance with study drug or study procedures

If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.2, 'Withdrawal of Informed Consent' section). Where possible, they should return for the assessments indicated in the Post-treatment Follow-up assessment schedule (Table 8-2). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, the following data should be collected:

- New/concomitant treatments
- Adverse Events/Serious Adverse Events

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due

diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples 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 participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

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Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their end of Post-treatment Follow-up visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

During the Post-treatment Follow-up period, the Investigator should consider the benefit/risk of initiation of alternative MS therapy in terms of the participant's clinical status, local regulations, treatment guidelines and local prescribing information. When initiating other immunosuppressive therapies with prolonged immune effects after study drug, the duration and mode of action should be taken into account because of potential additive immunosuppressive effect.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include the benefit/risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons.

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant's interests. The Investigator or Sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

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

Abnormal laboratory values or test results constitute adverse event 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 non-typical in participants with the underlying disease. Investigators have the responsibility for managing the safety of individual participant and identifying adverse events. Clinically notable laboratory findings are defined according to the Common Terminology Criteria for Adverse Events (CTCAE) (the most current version will be used and can be found on the following web-site: ctep.cancer.gov).

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The CTCAE grade (1-4)

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

- 1 = mild: usually transient in nature and generally not interfering with normal activities
- 2 = moderate: sufficiently discomforting to interfere with normal activities
- 3 = severe: prevents normal activities
- 4 = life-threatening

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of disability) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

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

- No action taken (e.g. further observation only)
- Drug interrupted/permanently discontinued

6. Its outcome

- Not recovered/not resolved
- Recovered/resolved,
- Recovering/resolving,
- Recovered/resolved with sequelae
- Fatal
- Unknown

Conditions that were already present at the time of informed consent should be recorded in the medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

As per the local requirement, non-serious adverse drug reactions will be collected and reported to the health authority in China.

10.1.2 Serious adverse events

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:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant 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 the ICH-E2D Guidelines).

- 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
    - 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
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - 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
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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 participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." 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 the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the End of Post-treatment FU or EOS (if the participant continues with commercial ofatumumab after treatment completion and does not enter Post-treatment FU) must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup SAE Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

Protocol exempt SAEs

MS relapses as defined in Section 8.3.1 are part of one of the effectiveness endpoints in this study; hence, they are exempt from SAE reporting although they may meet the SAE definition on the basis that they are considered medically significant and are frequently associated with hospitalization. These events will therefore be reported on the corresponding eCRF instead of the SAE form. However, if, in the judgment of the Investigator, a MS relapse is unusually severe or medically unexpected and warrants specific notification, then an SAE form should be completed and submitted according to SAE reporting procedures outlined above.

Disability progression as defined in Section 8.3.3 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".

However, if, in the judgment of the Investigator the disability progression is unusually severe or medically unexpected and warrants specific notification, then an SAE form should be completed and submitted according to SAE reporting procedures outlined above.

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.

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 CMO & PS 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.

Any SAEs experienced after the reporting period should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery to collect information about the pregnancy follow up data and the health of the baby (if the pregnancy results in a live birth). To ensure participant 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 should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to ofatumumab any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 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, participant 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 recorded on the appropriate eCRF 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 within 24 hours of Investigator’s awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant 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.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 and Table 16-2 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-1 and Table 16-2. Repeat liver chemistry tests to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1 Discontinuation from study treatment), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+(after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Table 16-3.

10.3 Committees

Not applicable

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The Investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 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 are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical

Therapeutic Chemical classification system. Medical history/current medical conditions 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. MRI scans will be analyzed centrally and the derived results will also be sent electronically to Novartis.

For electronic COAs, devices will be supplied by a vendor, data will be processed centrally, and both raw and processed data will be sent electronically to Novartis (or a designated CRO).

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 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 (i.e. eSource DDE or eCRFs) 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 participant 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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization (or a delegated CRO). Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The Investigator must maintain source documents for each participant 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 eCRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant).

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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The analyses (summaries or listings) will be conducted on all participant data at the time of end of study (i.e. including data from the Post-treatment Follow-up part).

Interim analysis will be performed at the planned time point with details defined in Section 12.7.

There will be no hypothesis testing performed in this study. Data will be summarized descriptively. In general, categorical data will be presented as frequency and percentage; continuous data will be summarized by mean, standard deviation (SD), median, minimum, and maximum. For primary efficacy endpoints, the point estimate and confidence interval will be model-based. Additional analysis populations may be defined and sensitivity analyses may be conducted to evaluate the impact of COVID-19 pandemic.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants who have signed the Informed Consent and who have received at least one dose of study treatment. The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

The Safety Set (SAF) is identical to FAS in this study. The Safety Set will be used for all safety analyses.

12.2 Participant demographics and other baseline characteristics

Demographics, MS disease history, MRI baseline characteristics and MS medication history will be summarized descriptively and/or listed for the FAS as appropriate.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term.

12.3 Treatments

The summary of exposure and time-at-risk will be based on the SAF.

Exposure to investigational study medication is defined as the number of days spent on study treatment divided by 365.25 days. Intermediate treatment interruptions will be subtracted from drug exposure. Exposure to investigational study medication will be summarized with number and percentage of participants by time category, and with summary statistics of the number of participant years of exposure. Further details will be included in the statistical analysis plan (SAP).

Time-at-risk is defined as the number of days spent in the study, from first dose to the last dose of study medication, plus the safety data cut-off of 100 days (or until EOS for participants continue with commercial ofatumumab immediately after EOS, or until last dose of study

medication plus 100 days or one day before switching to another DMT, whichever comes earlier, for participants who have such switch in the PT FU). Intermediate treatment interruptions will be included in time-at-risk calculations. Time-at-risk corresponds to the time window used for adverse event reporting and can serve as a denominator to safety (e.g. in exposure-adjusted incidence rates). Time-at-risk will be summarized in a similar way to exposure to investigational study medication. Further details will be specified in the SAP.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized and/or listed according to the Anatomical Therapeutic Chemical (ATC) classification system.

12.4 Analysis supporting primary objectives

12.4.1 Definition of primary endpoint(s)

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

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

- The cumulative number of confirmed MS relapses by participant is the response variable in the negative binomial model. The confirmation based on EDSS will be derived as defined in Section 8.3.1.
- The time-in-study by participant will be used as an offset variable to adjust for the various length participants have been observed and at-risk of a confirmed MS relapse in the study.

12.4.2 Statistical model, hypothesis, and method of analysis

In the primary analysis, the ARR will be estimated by a negative binomial regression model with log-link function, the cumulative number of confirmed MS relapses per participant as the response variable, number of relapses in the previous year (or two years) before enrollment, baseline EDSS, baseline age and baseline number of Gd-enhancing T1 lesions as continuous covariates. Natural log of time on study in years will be used as the offset variable to account for the varying lengths of participants' time in the study. The adjusted ARR (i.e., model-based estimate adjusted for covariates) and the corresponding 95% confidence interval will be obtained.

The primary analysis will be performed for FAS.

12.4.3 Handling of missing visits/censoring/discontinuation

For participants who withdraw early from the study, the number of relapses up to the study discontinuation will be used for the primary analysis. No imputation will be applied to the incomplete study duration.

The primary negative binomial regression model with an offset for the time in study adjusts for missing information (drop-out) under the assumption of non-informative drop-out, information is missing at random, and constant relapse rate over time.

12.4.4 Supportive analysis

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

A summary of ARR time-based and ARR participant-based will also be given. Time-based ARRs are calculated by taking the total number of relapses observed for all participants in FAS divided by the total number of days in study of those participants and multiplied by 365.25 days. Also, participant-based ARR is presented, where individual ARRs are computed and summarized over participants for FAS population. -For above ARR calculations, the analysis will consider confirmed relapses only.

Additional sensitivity analyses may be defined in the statistical analysis plan.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The following MRI efficacy variables will be analyzed based on FAS:

- The analysis of the number of Gd-enhancing T1 lesions per MRI-scan will be done using a negative binomial regression model with log-link function. The total number of Gd-enhancing lesions (cumulative count of Gd-enhancing lesions across all the MRI-scans per participant) will be used as the response variable, using baseline age and baseline number of Gd-enhancing T1 lesions as continuous covariates. Natural log of the number of MRI-scans will serve as the offset variable to account for the varying lengths of participants' time in the study. The number of Gd-enhancing lesions per scan will be estimated and the corresponding 95% confidence interval will be obtained.
- The analysis of the annualized rate of new or enlarging T2 lesions will be done using a negative binomial regression model with log-link function. The number of new or enlarging T2 lesions on the last available MRI scan relative to baseline will be used as the response variable, using baseline age and baseline volume of T2 lesions as continuous covariates. Natural log of the time (in years) of the MRI-assessment from the baseline/Screening scan will serve as the offset variable to account for the varying lengths of participants' time in the study. The number of new or enlarging T2 lesions per year will be estimated and the corresponding 95% confidence interval will be obtained.
- Change from baseline in T2 lesion volume on MRI will be summarized by visit.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. Unless explicitly stated otherwise, only data up to and including the safety cut-off of 100 days after permanent study treatment discontinuation or treatment completion (or EOS for participants continue with commercial ofatumumab immediately after EOS, or min(last dose of study medication + 100 days, date of switching to another DMT - 1) for participants who have such switch in the PT FU) will be

included in the analysis and data beyond this time point for a participant will be excluded from safety analysis.

The assessment of safety data will be primarily based on the frequency and percentage of adverse events (including death and non-fatal serious adverse events). Additional safety assessments such as laboratory tests, physical examination (including examination of skin), and vital signs will be analyzed. Clinically significant findings in these additional safety assessments will be reported as adverse events and analyzed as such. The detailed analyses of additional safety assessments will be defined in the SAP.

Adverse events

Treatment-emergent adverse events including serious adverse events and deaths will be summarized up to and including the safety cut-off.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

· by primary system organ class and preferred term.

· by primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for adverse events related to study treatment, death, serious adverse events, and other significant adverse events leading to interruption or discontinuation, if appropriate.

Specific risks of interest will be defined by combinations of adverse event and/or other relevant safety data (e.g. lab data). The number (and proportion) of participants fulfilling such risk definitions will be summarized.

A participant with multiple adverse events within a primary system organ class will only be counted once towards the total of the primary system organ class.

Given the flexible follow-up of the study, treatment-emergent adverse events will also be summarized by reporting exposure-adjusted incidence rates (assuming a Poisson-process for adverse events). This will be done for all treatment-emergent adverse events, and for serious treatment-emergent adverse events, by primary system organ class and preferred term.

Vital signs

Vital sign measurements and their change from baseline will be summarized with descriptive statistics (mean, median, standard deviation, min, max) by visit. The number and percentage of participants with clinically notable vital signs will be presented, if appropriate. The clinically notable definitions will be provided in SAP as needed.

Clinical laboratory evaluations

The summary of laboratory evaluations will be presented for 2 groups of laboratory tests: hematology and chemistry.

Laboratory measurements and their change from baseline will be summarized with descriptive statistics (mean, median, standard deviation, min, max) by visit. The number and percentage of participants with clinically notable vital signs will be presented, if appropriate. The clinically notable definitions will be provided in SAP as needed.

Other safety evaluations

All clinically significant safety findings based on additional safety evaluations (e.g. physical examination, urinalysis etc.) must be reported as adverse events on the appropriate eCRF. The statistical analysis of these findings will be done in the analysis of adverse events. Other safety data will be summarized or listed as appropriate.

[redacted]

12.7 Interim analyses

One interim analysis is planned in approximately Q1 2025, unless the final analysis will have already been completed. The efficacy and safety data (including summaries on key efficacy and safety endpoints) will be submitted to NMPA for local license renewal for Kesimpta.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The ARR of Chinese RMS participants treated with ofatumumab is assumed based on the pivotal studies, COMB157G2301 and COMB157G2302. Since the participants are treated up to 12 months in the current study, the cumulative ARR from Month 0 to Month 12 from the pivotal studies is adopted:

	Ofatumumab 20mg	**Teriflunomide 14mg**
Cumulative ARR from Month 0 to Month 12 in COMB157G2301 & COMB157G2302	0.145	0.307

Under the assumption of a negative binomial distribution (~ NB(μ, k)) for the ARR, where μ is the true ARR which we assume to be 0.15 based on the reference above, and k is the dispersion parameter which we assume to be 0.82 based on historical trialdata in MS. For different sample sizes, the following can be calculated using normal approximation: the 95% lower and upper ranges of the estimated ARR (point estimate), and the probability of showing the ARR on ofatumumab is significantly lower than 0.30 (i.e. lower than the historical reference value for the ARR in patients treated with teriflunomide based on the COMB157G2301 & COMB157G2302 trial data)). Note that this probability is equivalent to the probability that the upper limit of 95% CI is lower than 0.3. The results are showed below.

μ (true ARR)	**k**	**Sample size**	**95% lower range of estimated ARR**	**95% upper range of estimated ARR**	**Probability that the upper limit of 95% CI is lower than 0.30**
0.15	0.82	60	0.05	0.25	80.8%
0.15	0.82	65	0.05	0.25	83.8%

μ (true ARR)	k	Sample size	95% lower range of estimated ARR	95% upper range of estimated ARR	Probability that the upper limit of 95% CI is lower than 0.30
0.15	0.82	70	0.05	0.25	86.4%
0.15	0.82	75	0.06	0.24	88.6%
0.15	0.82	80	0.06	0.24	90.5%
0.15	0.82	85	0.06	0.24	92.1%
0.15	0.82	90	0.07	0.23	93.4%

Based on the calculation, a sample with 85 participants will provide an estimated ARR in [0.06, 0.24] with 95% probability. In addition, with a probability of 92.1%, a sample with this size will also provide a 95% CI with upper limit lower than 0.30, i.e. it would be strongly suggestive of a higher efficacy of ofatumumab compared with the historical teriflunomide data. Therefore, a sample size of 85 completers is considered adequate. Allowing for a dropout rate of 15% (dropout rate was 10.3% in COMB157G2301 and 17.3% in COMB157G2302), the sample size for this study will be approximately 100 participants.

Sample size calculation was performed in nQuery 8, Version 8.4.1.0, Statistical Solutions Ltd.

13 Ethical considerations and administrative procedures

13.1 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, and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. clinicaltrials.gov) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication
- Trial Feedback Questionnaires (TFQ)

14 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 participants 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 prohibition, 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.

14.1 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 required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Tables below provide the clinically notable liver function test results and the required actions. When the laboratory abnormality is deemed clinically significant, AEs must be reported. Clinical symptoms with a diagnosis must be reported as AEs.

Table 16-1 Follow up requirements for liver laboratory triggers

ALT or AST	TBL	Liver Symptoms	Action
ALT/AST increase without bilirubin increase:			
If normal at baseline: ALT/AST > 3 x ULN **If elevated at baseline:** ALT/AST > 2 x baseline	Normal; For participants with Gilbert's syndrome: No clinically significant change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms/etiology to establish causality
If normal at baseline: ALT/AST > 5 x ULN for more than two weeks **If elevated at baseline:** ALT/AST > 3 x baseline for more than two weeks	Normal; For participants with Gilbert's syndrome: No clinically significant change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms/etiology to establish causality. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT/AST > 8 x ULN	Normal	None	
ALT/AST increase with bilirubin increase:			
If normal at baseline: ALT/AST > 3 x ULN **If elevated at baseline:** ALT/AST > 2 x baseline	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin at baseline	None	
If normal at baseline: ALT/AST > 3 x ULN **If elevated at baseline:** ALT/AST > 2 x baseline	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
Hy's Law cases: - ALT or AST > 3 × ULN and TBL > 2 × ULN, without notable increase in ALP to > 2 × ULN, and - Absence of any alternative cause likely explaining the combination of increased ALT or AST and TBL (such as viral hepatitis A, B, C, or E); pre-existing acute liver disease; or another drug capable of causing the observed injury			• Interrupt study drug • Report to Novartis as SAE • Treat the condition and measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH at the frequency per Investigator's discretion

Table 16-2 Follow up requirements for isolated total bilirubin elevation

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRFs	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate eCRFs	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution* (frequency at investigator discretion)

** 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.*

For any AE potentially indicative of a liver toxicity, consider study drug interruption or discontinuation and hospitalization if clinically appropriate. Establish causality and record the AE and contributing factors in the appropriate eCRFs. Based on Investigator's discretion, investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Serum Event	**Action**
Serum creatinine (sCr) increase ≥25% compared to baseline during normal hydration status	• Confirm 25% increase ≥24 hours but within 5 days • Consider causes and possible interventions (including study drug interruption)
Urine Event	**Action**
Urine protein-creatinine ratio(PCR) ≥1g/g or ≥100 mg/mmol OR New onset dipstick proteinuria ≥ 3+ OR New onset dipstick hematuria ≥ 3+ (after excluding menstruation, urinary tract infection, extreme exercise, or trauma)	• Confirm value* after ≥24 hours but within 5 days • Perform urine microscopy • Consider causes and possible interventions (including study drug interruption/discontinuation)
Follow-up of Renal Events	
• Document contributing factors in the eCRF: co-medication, other comorbid conditions, and additional diagnostic procedures • Monitor participant at Investigator's discretion	

*urine PCR can be used as a follow-up of a positive urine dipstick proteinuria.

16.3 Appendix 3: The 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset

Table 16-4 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset

Number of lesions with objective clinical evidence		**Additional data needed for a diagnosis of multiple sclerosis**
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by

		MRI OR demonstration of CSF-specific oligoclonal bands¶

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis.

*No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for two attacks is

most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed.

¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

16.4 Appendix 4: Guidance on safety monitoring and immunization

16.4.1 Guidance on monitoring of participants with symptoms of neurological deterioration suggestive of PML

Should a participant develop any unexpected neurological or psychiatric symptom/signs in the opinion of Investigator (e.g. cognitive deficit, behavioral changes, cortical visual disturbances or any other neurological cortical symptoms/signs any symptom/sign suggestive of an increase of intracranial pressure) or accelerated neurological deterioration, the Investigator should schedule a complete physical and neurological examination and an MRI as soon as possible before beginning any steroid treatment. Conventional MRI, as defined in the protocol, as well as additional scanning such as Fluid-attenuated Inversion Recovery (FLAIR) and Diffusion weighted imaging (DWI) sequences should be performed to aid in differential diagnosis. The MRI must be evaluated by the local neuroradiologist. The Investigator will contact the Medical Advisor at Novartis to discuss findings and diagnostic possibilities as soon as possible. A copy of the unscheduled MRI should be sent to the MRI Evaluation Center designated by Novartis as soon as possible. SAEs need to be reported and filed as appropriate. If the MRI shows (new) lesions consistent with a MS relapse assessment and treatment of the relapse will be performed as described in the protocol (Section 6.2.3). In case of new findings in the MRI images, in comparison with the previously available MRI, which are not compatible with lesions consistent with a MS relapse, the study drug will be interrupted 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 (CSF) sample if indicated. Analysis of the CSF sample including cellular, biochemical, PCR, and microbiological analysis (e.g. herpes virus, JC virus, cryptococcus) to confirm/exclude an infection should be performed. In the event of suspected CNS infection (PML), a CSF aliquot should be sent to a qualified laboratory (designated by Novartis) for confirmatory testing. Only after the evaluations have excluded diagnoses other than MS and

after discussion with the Medical Advisor at Novartis and a Global Study Team member, the study drug may be restarted.

16.4.2 Guidance on monitoring participants with infections

All infections that develop during the study will be reported as adverse events on the respective eCRF pages. Treatment and additional evaluations will be performed at Investigator discretion. The Investigator should remind the participant of the risk of infections and instruct them to report any symptoms of infections promptly. 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 Novartis Medical Advisor and/or a Study Team member of any such cases. When evaluating a participant with a suspected infection, the most sensitive tests available should be used (i.e. that directly detect the pathogen, as with PCR). The Investigator should consider early treatment with specific antimicrobial therapy based on clinical diagnosis or suspicion thereof in consultation with infectious disease experts, as appropriate. The Investigator should inform the Novartis Medical Advisor and Global Study Team of any such cases. Investigators should consider the added immunosuppressive effects of corticosteroid therapy for treatment of clinical relapses/attack and increase vigilance regarding infections during such therapy and in the weeks following administration.

Hepatitis B Virus (HBV)

There were no reports of HBV reactivation in patients with MS treated with ofatumumab. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (CLL) (at significantly higher intravenous doses than the 20 mg dose in this study) and in patients treated with other anti-CD20 antibodies. HBV screening is required in all study participants, including hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. Participants with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent HBV infection or reactivation. In participants with suspicion of HBV infection (active/reactivation) during the study, laboratory testing for HBV should be done. For participants with positive hepatitis B serology (either HBsAg or HBcAb), the Investigator should consult a liver disease expert and participants should be monitored and managed following local medical standards to prevent HBV infection or reactivation. In participants who develop infection or reactivation of HBV while receiving study drug, immediately discontinue study drug and institute appropriate treatment and follow-up.

16.4.3 Guidance on monitoring of participants with low immunoglobulin levels

During the study, immunoglobulin levels (IgG and IgM) will be measured according to the schedule in Table 8-1. If IgG levels drop below 300mg/dL (Agarwal and Cunningham-Rundles 2007), the Investigator should evaluate participant for any potential infections and monitor on a regular basis (refer to Section 16.4.2). Consider interrupting or discontinuing study treatment if a participant with low IgG as defined above develops a serious opportunistic

infection or recurrent infections, or if prolonged hypogammaglobinemia requires treatment with intravenous immunoglobulins. Immunoglobulin substitution therapy as per local medical practice is allowed and all relevant data must be recorded on the appropriated eCRFs. In case of treatment interruption, re-initiation of the study drug is subject to Investigator's discretion. Care should be taken to re-initiate study treatment according to planned dosing schedule in relation to the participant's W0 injection to ensure continuity and regularity of study visits and assessments. Participants that are prematurely discontinued should have the EOS visit as early as possible and continue into the Post-treatment Follow-up, please refer to assessment schedule Table 8-2.

16.4.4 Guidance on immunization

The safety of and ability to generate a primary or anamnestic response to immunization with live, live-attenuated or inactivated vaccines during ofatumumab treatment has not been investigated. The response to vaccination could be impaired when B-cells are depleted. It is recommended that the Investigator reviews the participant's immunization history as part of the initial Screening procedure for a participant being considered for treatment with ofatumumab. Because vaccination with live-attenuated or live vaccines is not recommended during treatment with ofatumumab and after treatment discontinuation until B-cell repletion, all immunizations must be administered according to immunization guidelines at least 4 weeks prior to initiation of ofatumumab for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to initiation of ofatumumab for inactivated vaccines（including Sars-CoV-2 vaccines）. Hepatitis B vaccination should be considered prior to administration of ofatumumab in participants with risk factors for hepatitis B infection or in areas with a high prevalence of hepatitis B, as per local area treatment guidelines. Immune suppression of B cells is expected to affect the response to vaccination, and thus during treatment with ofatumumab, vaccination (non-live vaccines) may be less effective.

Sars-CoV-2 Vaccinations

SARS-CoV-2 vaccinations (e.g. inactivated, viral-vector-, or mRNA) that have been permitted for use by a local Health Authority are allowed. Permitted use includes full approval, conditional approval, emergency use authorization, provisional/temporary/interim authorization by Health Authority that are administered outside of a SARS-CoV-2 clinical trial to evaluate the effectiveness or safety of a SARS-CoV-2 vaccine.

Additional guidance on permitted use of SARS-CoV-2 vaccinations may be made available separately taking into consideration the SARS-CoV-2 vaccine prescribing information, ofatumumab/SARS-CoV-2 vaccination recommendations and health authority guidance. Risk/benefit ratio for SARS-CoV-2 vaccination must be evaluated on a case-by-case basis by the Investigator.

SARS-CoV-2 vaccination status is to be recorded on appropriate eCRF.