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Clinical Trial Protocol COMB157G23101 / NCT04353492

A single-arm, prospective, multicentre, open-label study to evaluate ofatumumab treatment effectiveness and patient-reported outcomes in patients with relapsing multiple sclerosis (RMS) transitioning from fumarate-based RMS approved therapies or fingolimod

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List of abbreviations

CCI	[redacted]
3mCDW	3-month Confirmed Disability Worsening
6mCCD	6-month Confirmed Cognitive Decline
6mCDW	6-month Confirmed Disability Worsening
9HPT	Nine Hole Peg Test
ACR	Albumin/Creatinine Ratio
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AI	Autoinjector
AIDS	Acquired Immunodeficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARR	Annual Relapse Rate
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	blood urea nitrogen
C-CASA	Columbia Classification Algorithm for Suicide assessment
C-SSRS	Columbia Suicide Severity Rating Scale
CCI	[redacted]
CDC	Complement-Dependent Cytotoxicity
CDW	Confirmed Disability Worsening
CFR	Code of Federal Regulation
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central Nervous System
CO	Country Organization
COVID-19	Coronavirus disease 2019, an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
CRF	Case Report/Record Form (paper or electronic)
CSF	Cerebrospinal Fluid
CTCAE	Common Toxicity Criteria for Adverse Events
CTT	Clinical Trial Team
DDE	Drug Data Entry
DMF	Dimethyl Fumarate
CCI	[redacted]
DMT	Disease Modifying Therapy
DNA	Deoxyribonucleic Acid
DRF	Diroximel Fumarate
DWI	Diffusion-weighted Imaging
EAE	Experimental Autoimmune Encephalitis
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDD	Expected Delivery Date

EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FS	Functional Score
CCI	CCI [redacted]
FU	Follow-up
GCP	Good Clinical Practice
Gd	Gadolinium
CCI	CCI [redacted]
GGT	Gamma-Glutamyl Transferase
CCI	CCI [redacted]
HB	Hepatitis B
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HC	Hepatitis C
HCV	Hepatitis C Virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
CCI	[redacted]
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
iv	intravenous
KM	Kaplan-Meier
LCVA	Low Contrast Visual Acuity
LDL	Low Density Lipoprotein
LFT	Liver function test
LLN	lower limit of normal
LSLV	Last Subject Last Visit
MAA	Marketing Authorization Application
mAb	Monoclonal Antibody
MedDRA	Medical dictionary for regulatory activities

MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
CCI	CCI
CCI	
NCI	National Cancer Institute
NEDA	No Evidence of Disease Activity
NfL	Neurofilament Light Chain
NYHA	New York Heart Association
OMB	Ofatumumab
PCR	Polymerase Chain Reaction
PD	pharmacodynamic(s)
PFS	Pre-filled Syringe
PML	Progressive Multifocal Leukoencephalopathy
PRO	Patient Reported Outcome
PTA	Post-Trial Access
QMS	Quality Management System
RBC	red blood cell(s)
RMS	Relapsing multiple sclerosis
RNA	Ribonucleic acid
CCI	
RPR	Rapid Plasma Reagin
RRMS	Relapse Remitting Multiple Sclerosis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome, coronavirus 2 (Coronavirus disease 2019)
CCI	
s.c.	subcutaneous
sCR	serum creatinine
CCI	
SFU	Safety Follow-Up
SPMS	Secondary Progressive Multiple Sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reactions
T25FW	Timed 25-Foot Walk
TB	Tuberculosis
TBL	total bilirubin
CCI	CCI
ULN	upper limit of normal
US	United States
CCI	
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Part	A single component of a study, which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study (participant). The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol Amendment 03 (18-Aug-2023)

Amendment Rationale

The main purpose of this amendment is to address comments received by the CCI

[redacted]

[redacted]

[redacted]

Changes to the protocol:

[redacted]


CCI


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Protocol Amendment 02 (15-Nov-2021)

Amendment rationale

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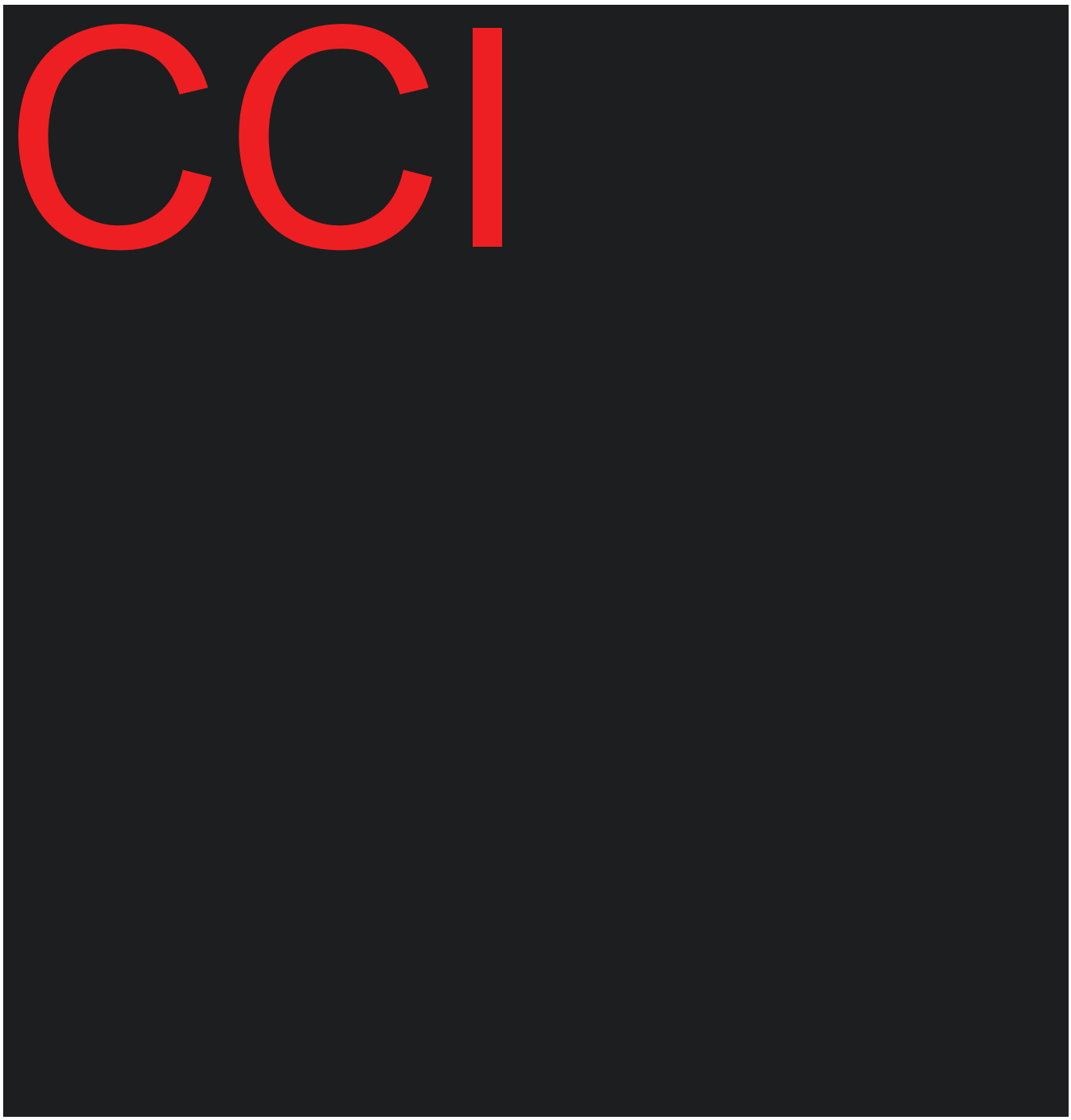

CCI

Approvals of IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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

Protocol Amendment 01 (05-Nov-2020)

Amendment rationale

Changes to the protocol:


CCI


CCI

Approvals of IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

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

Protocol summary

Protocol number	COMB157G23101
Full Title	A single-arm, prospective, multicentre, open-label study to evaluate ofatumumab treatment effectiveness and patient-reported outcomes (PRO) in patients with relapsing multiple sclerosis (RMS) transitioning from fumarate-based RMS approved therapies or fingolimod
Brief title	An open-label study evaluating ofatumumab treatment effectiveness and PROs in subjects with RMS transitioning from fumarate-based RMS approved therapies or fingolimod to ofatumumab
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of the study is to complement the ofatumumab pivotal Phase 3 program by exploring outcomes of patients transitioning from commonly used oral therapies, fumarates or fingolimod, to ofatumumab due to breakthrough disease (defined as relapse, Gd+, or new/enlarging T2 lesions)
Primary Objective(s)	Demonstrate the effectiveness of ofatumumab 20 mg subcutaneous (s.c.) administered every 4 weeks in subjects with relapsing forms of multiple sclerosis (MS) who had breakthrough disease on fumarates or fingolimod, as measured by Annual Relapse Rate (ARR) at the 96 weeks endpoint
Secondary Objectives	Evaluate the safety of ofatumumab 20 mg s.c. administered every 4 weeks in subjects with relapsing forms of MS who had breakthrough disease on fumarates or fingolimod using assessment of adverse events (AEs), proportion of patients with laboratory or vital signs results meeting abnormal criteria and the proportion of subjects discontinuing treatment
Study design	This study uses a prospective, single arm, open-label, multicentre treatment design, enrolling subjects who are transitioning from fumarates or fingolimod
Population	Approximately 555 adult (ages 18 to 60) subjects with RMS
Key Inclusion criteria	• Diagnosis of MS according to the 2017 Revised McDonald criteria • Relapsing MS: relapsing forms of MS (RMS) including RMS and secondary progressive MS (SPMS) (Lublin et al 2014) • Disability status at screening defined by Expanded Disability Status Scale (EDSS) score of 0 to 4 (inclusive) • MS treatment history with a maximum of 3 Disease Modifying Therapies (DMTs), where all fumarates are considered as one DMT • Subject transitioning from either any fumarate-based RMS approved therapies, such as dimethyl fumarate (DMF) or diroximel fumarate (DRF), or fingolimod which was administered for a period of at least 6 months, as their last DMT before first study drug administration • Breakthrough disease activity while the participant was adequately using fumarates or fingolimod prior to transitioning for a minimum of 6 months as evidenced by one or more clinically reported relapses or one or more signs of Magnetic Resonance Imaging (MRI) activity (e.g. Gd+ enhancement, new or enlarging T2 lesions) • Neurologically stable within one month prior to first study drug administration
Key Exclusion criteria	• Subjects with primary progressive MS (Polman et al 2011) or SPMS without disease activity (Lublin et al 2014) • Subjects meeting criteria for neuromyelitis optica (Wingerchuk et al 2015) • Disease duration of more than 10 years since diagnosis • Pregnant or nursing (lactating) women • Women of child-bearing potential unless they are using highly effective forms of contraception during dosing and for at least 6 months after stopping study medication

	• Subjects with active chronic disease of the immune system other than MS or with immunodeficiency syndrome • Subjects with active systemic bacterial, fungal or viral infections (such as hepatitis, HIV, COVID-19), or known to have Acquired Immunodeficiency Syndrome (AIDS) • Subjects with neurological symptoms consistent with Progressive Multifocal Leukoencephalopathy (PML) or with confirmed PML • Subjects at risk of developing or having reactivation of syphilis or tuberculosis (e.g. subjects with known exposure to, or history of syphilis, or active or latent tuberculosis, even if previously treated), as confirmed by medical history or per local practice • Subjects with active hepatitis B and C disease, assessed locally • Have received any live or live-attenuated vaccines within 4 weeks prior to first study drug administration • Have been treated with medications as specified or within timeframes specified (e.g. corticosteroids, ofatumumab, rituximab, ocrelizumab, alemtuzumab, natalizumab, daclizumab, cyclophosphamide, teriflunomide etc.) • Subjects suspected of not being able or willing to cooperate or comply with study protocol requirements in the opinion of the investigator
Study treatment	Ofatumumab 20 mg s.c. injection once every 4 weeks (following initial loading dose regimen of three 20 mg s.c. doses in the first 14 days)
Efficacy assessment	• MS relapse expressed as Annualized Relapse Rate (ARR) • Expanded Disability Status Scale (EDSS) • Magnetic Resonance Imaging (MRI) • Timed 25-foot walk (T25FW) • Nine-hole peg test (9HPT) • CCI [redacted] • Low Contrast Visual Acuity (LCVA) • No Evidence of Disease Activity (NEDA-3) • Neurofilament light chain (NfL) • CCI [redacted]
Key safety assessments	• Adverse events • Vital signs • Laboratory evaluations (blood and urine) • Columbia Suicide Severity Rating Scale (C-SSRS) • Electrocardiogram (ECG)

Other assessments	• Patient reported outcomes (PROs)
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI

Data analysis	All efficacy data will be analyzed according to the intent-to-treat principle. The primary analysis for the ARR is estimated based on the FAS using individual relapse count as the response variable with time in study as an offset variable. Secondary analysis includes AE safety related endpoints. Exploratory endpoints will be presented descriptively.
Key words	Interventional, transitioning, clinical trial, effectiveness, safety, open-label, ofatumumab, relapsing multiple sclerosis, treatment satisfaction, patient reported outcomes

1 Introduction

1.1 Background

Multiple sclerosis (MS), one of the most common causes of neurological disability in young adults, is the prototypic acquired inflammatory demyelinating condition of the central nervous system (CNS), characterized by inflammation, demyelination and axonal/neuronal destruction, ultimately leading to severe disability in the majority of patients.

Traditional research has focused on the role of T-cells for MS. This focus is based on the results of murine models of MS, known as experimental autoimmune encephalitis (EAE), where pathogenic T-cells mediate the pathology of MS with little or no participation of B-cells.

A modern reassessment of the potential role of humoral immunity (B-cell mediated immunity) in EAE began with a search to replicate a more distinctive pattern of demyelination present in MS lesions and not found in T-cell-mediated EAE models, e.g. the inflammatory cortical demyelination in early multiple sclerosis (Magliozzi et al 2007; for further reference Epstein et al 1983, Lucchinetti et al 2011) or the presence of meningeal B-cell follicles in SPMS associated with early onset of disease and severe cortical pathology.

In these MS -like models, antibodies and B-cells, acting in concert with T-cells, were found to be required for full disease expression (Genain and Hauser 1996). These observations provided a new theoretical framework for the use of B-cell-based therapeutics in MS (Ray et al 2011).

Indeed, anti CD20+ B-cell antibodies have now emerged as one of the most the important targets given their high preclinical and clinical efficacy. The recently reported trials of the humanized anti-CD20 monoclonal antibody (mAb) ocrelizumab revealed dramatic effects on all key clinical and magnetic resonance imaging (MRI) outcomes in relapsing MS (RMS) (Hauser et al 2017), and also demonstrated clear benefits for the previously untreatable form of the disease, namely primary progressive MS (PPMS) (Montalban et al 2017).

Ofatumumab, a fully human mAb approved for treatment of multiple sclerosis (as a subcutaneous, low dose regimen) (Prescribing information Kesimpta 2020), and for refractory chronic lymphocytic leukemia in United States (US), Australia and Japan (as solution for intravenous (iv) infusion) (Prescribing information Arzerra 2016), has greater complement-dependent cytotoxicity (CDC) than antibody-dependent cell-mediated cytotoxicity (ADCC) activity compared to ocrelizumab (Teeling et al 2006). Ofatumumab is the only anti CD20 therapy administered as a subcutaneous, low dose regimen. Ofatumumab recognizes an epitope localized close to the cell membrane on the 2 extracellular domains of the CD20+ molecule, N-proximal of the epitope for the anti–CD20 mAb rituximab. CD20-binding of ofatumumab induces B-cell lysis primarily through CDC and ADCC.

Preclinical differentiation amongst aCD20+ mAb suggests a favorable profile of ofatumumab including higher CDC, direct lymph node targeting and potential sparing of marginal zone B-cells, which are relevant for host defense. The clinical correlates of these preclinical findings remain to be explored in Ph3b/4 studies.

Ofatumumab has been evaluated in two Phase II studies in patients with RMS (OMS115102 and OMS112831). Study OMS115102 was a 48-week (24-week cross-over), double-blind, placebo-controlled study that evaluated the effects of ofatumumab administered *intravenously*

in 38 patients with Relapse Remitting Multiple Sclerosis (RRMS) (Sorensen et al 2014). The study showed that iv administration of ofatumumab resulted in a profound reduction in circulating B-cell counts and suppression of MRI lesion activity at each dose level evaluated in both treatment periods (Week 0-24 and Week 24-48).

Study OMS112831 was a randomized, placebo-controlled, dose-ranging, 48-week study (24-week double-blind treatment phase, then 24-week follow-up phase) that examined the efficacy and safety of repeat-dose *subcutaneous* ofatumumab in RRMS. The primary endpoint was met in the study, demonstrating that ofatumumab reduced the mean cumulative number of new gadolinium-enhancing lesions by 65% vs placebo during Weeks 0-12 ($p < 0.001$), and by ≥ 90% during Weeks 4-12 vs placebo in a post hoc analysis of cumulative ofatumumab doses ≥ 30 mg ($p < 0.001$) (Bar-Or et al 2018).

In the head-to-head Phase III clinical trials, ASCLEPIOS I and II (COMB157G2301 and COMB157G2302, respectively), monthly subcutaneous ofatumumab 20mg demonstrated superiority over once daily oral teriflunomide 14mg in patients with relapsing forms of multiple sclerosis. Both studies met the primary endpoints where ofatumumab showed a highly significant and clinically meaningful reduction in the number of confirmed relapses, evaluated as the annualized relapse rate (ARR). Specifically, RMS patients on ofatumumab had a reduction in annualized relapse rate (ARR) by 50.5% (0.11 vs. 0.22) and 58.5% (0.10 vs. 0.25) compared to Aubagio® (teriflunomide) (both studies $p<0.001$) in ASCLEPIOS I and II studies respectively (Hauser et al 2019). Key secondary endpoints were also met, where ofatumumab showed a relative risk reduction of 34.4% in 3-month confirmed disability worsening (CDW) ($p=0.002$) and 32.5% in 6-month CDW ($p=0.012$) versus teriflunomide in a pre-specified pooled analyses.

In the ASCLEPIOS studies the ofatumumab was subcutaneously administered via pre-filled syringe (PFS). In the APLIOS Phase II study (OMB157G2102), the autoinjector (AI) was compared with the pre-filled syringe (PFS) in a 12-week randomized open-label multicentre bioequivalence study. The study concluded that the PFS and AI were bioequivalent. The AI facilitates improved self- and home-administration and hence reduces the burden of treatment on the patient.

Despite increasing evidence that high efficacy treatment targeting B-cells benefits patients early on (Hauser et al 2017), in clinical practice, interferon and glatiramer acetate or oral drugs such as dimethyl fumarate (Tecfidera®) are used as first line treatment (Multiple sclerosis disease modifying drugs first line treatments 2017). Dimethyl fumarate was introduced in 2013 (US, (Prescribing Information Tecfidera 2021) and 2014 (European Union (EU), (Summary of Product Characteristics Tecfidera INN-dimethyl fumarate)) and many patients have received the drug in first line therapy since. In real world setting, more than 50% of patients discontinue dimethyl fumarate (DMF) within 2 years due to lack of efficacy and/or tolerability (Eriksson et al 2018). In addition, generic DMF is now approved and available in many countries around the world (approved by Food and Drug administration (FDA) in August 2020) (Office of Generic Drugs 2020 Annual Report 2021), as is diroximel fumarate (Vumerity®), which was approved by the FDA in 2019 (Approval Package: Vumerity 2019) and submitted for review by European Medicines Agency (EMA) in 2021. Diroximel fumarate is approved in US for use in relapsing forms of MS. The approval of Vumerity® is based upon bioavailability studies in patients and healthy subjects, comparing dimethyl fumarate to

diroximel fumarate, bridging to the efficacy and safety of dimethyl fumarate in RMS (Prescribing Information Vumerity 2019). In light of chronic treatment needs for people with MS, exploring treatment outcomes after DMF and DRF discontinuation fills a relevant clinical gap. There are no clinical data available to describe effectiveness of transitioning in terms of safety, efficacy and patient reported outcomes.

In 2010, fingolimod, a sphingosine 1-phosphate receptor modulator, was the first US Food and Drug Administration-approved oral treatment for RRMS (United States Food and Drug Administration FDA Approves First Oral Drug to Reduce MS Relapses 2010). Fingolimod is frequently used as high efficacy oral second line therapy when therapy with interferons / glatiramer acetate failed. Discontinuation rates on fingolimod based on one-year studies are around 10% only, likely due to good tolerability and efficacy demonstrated in clinical trials as well as in real world settings. Treatment choices after fingolimod failure are limited and transitioning carries a risk of breakthrough disease (Switching to Alemtuzumab in MS, Keep Washout to a Minimum 2018).

The ofatumumab Phase 3 program provides only limited data on transitioning from dimethyl fumarate (Tecfidera®) or fingolimod (Gilenya®) to ofatumumab given that patients needed to have discontinued 1 month or 2 months, respectively, prior to study randomization, and constitute only a minority of the study patients (~5%) (Hauser et al 2019). Ofatumumab has been approved for relapsing forms for MS by several Health Authorities, including the FDA in August 2020 (FDA approves Novartis Kesimpta® (ofatumumab), the first and only self-administered, targeted B-cell therapy for patients with relapsing multiple sclerosis 2020), and the European Commission in March 2021 (Novartis receives EU approval for Kesimpta® (ofatumumab), the first and only self-administered, targeted B-cell therapy for adult patients with relapsing multiple sclerosis, 2021).

The current study will address relevant clinical practice questions on the effectiveness, safety, and PRO of patients who are transitioning from fumarates or fingolimod onto ofatumumab. In addition, we explore the utility of Neurofilament light chain (NfL) and CCI as wet biomarkers of disease progression and for treatment monitoring in MS. Finally, this study will also compare the added benefit of CCI in the assessment and management of people living with MS over in-clinic assessments alone.

1.2 Purpose

The purpose of the study is to complement the ofatumumab Phase 3 program by exploring outcomes of patients transitioning from any fumarate-based RMS approved therapy, such as dimethyl fumarate (DMF generic or branded) or diroximel fumarate (DRF), or fingolimod (generic or branded) to ofatumumab due to breakthrough disease in a specialized clinical practice and tertiary care settings.

Breakthrough disease has been defined as:

- At least one documented relapse during previous year OR two relapses during previous two years prior to inclusion
- Or presence of at least one Gd+ lesion on an MRI scan within the last 12 months
- Or presence of new or enlarging T2 lesions within the last 12 months

A combination of clinical and/or imaging findings is also accepted for inclusion.

The primary outcome will be to demonstrate the treatment effectiveness of ofatumumab in subjects with relapsing forms of MS as measured by ARR at 96 weeks. This Phase IIIb study will provide additional data on patient reported outcomes, biomarker outcomes and explore the utility of digital tools for patient assessments and treatment persistence / adherence.

Exploratory outcomes include assessments of processing speed, daily activity, physical functioning, and patient reported outcomes. Outcomes will be captured digitally and compared to clinical assessments wherever possible. NfL and CCI monitoring during the trial will better elucidate the underlying disease activity during RMS.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Demonstrate the effectiveness of ofatumumab 20 mg s.c. administered every 4 weeks in subjects with relapsing forms of MS who had breakthrough disease on fumarates or fingolimod	• Annual relapse rate (ARR, based on confirmed relapses) measured over the 96 weeks
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Evaluate the safety of ofatumumab 20 mg s.c. administrated every 4 weeks in subjects with relapsing forms of MS who had breakthrough disease on fumarates or fingolimod	• Proportion of subjects with adverse events, including injection related reactions • Proportion of patients with laboratory or vital signs results meeting abnormal criteria • The proportion of subjects discontinuing treatment due to insufficient effectiveness (lack of efficacy) or tolerability/safety reasons
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

• Demonstrate effectiveness of ofatumumab 20 mg s.c. administered every 4 weeks	• Change from Baseline during the treatment period, of the following Assessments:
	  • EDSS
	  • Timed 25-Foot Walk (T25FW)
	  • Nine-Hole Peg Test (9HPT)
	  • CCI
	  • Low Contrast Visual Acuity (LCVA)
	  • T2 lesion volume
	• Time to 6-month Confirmed Disability Worsening (6mCDW) based on EDSS
	• Time to a 6-month confirmed cognitive decline (6mCCD), defined as a 4-point worsening on CCI
	• Number of T1 Gd+ lesions per scan
	• Number of new or enlarging T2 lesions on MRI per year (annualized T2 lesion rate)
	• Proportion of patients without MRI activity
	• Proportion of subjects with No Evidence of Disease Activity (NEDA-3) as per protocol defined events during a 96-week period

Objective(s)	Endpoint(s)

• Explore patient reported outcomes in subjects treated with ofatumumab 20 mg s.c. administered every 4 weeks	• Change from Baseline during the treatment period of the following Assessments:
	  • The impact of MS disease as measured by the CCI
	  • CCI
	  • CCI
	  • CCI

• Explore Neurofilament (NfL) light chain as a biomarker for MS in terms of prognosis and disease activity monitoring	• Change from baseline in serum NfL light chain concentration • Relationship between baseline serum NfL and disease activity, disease course and treatment response • Correlation of serum NfL measures and MRI activity signs /Gd+ or new / enlarging T2 lesions) for disease activity monitoring
• Explore serum CCI for MS progression	• Change from baseline in serum CCI • Relationship between baseline serum CCI and disease progression (EDSS) and treatment response • Correlation of serum CCI measures and MRI activity signs /Gd+ or new / enlarging T2 lesions) for disease activity monitoring • Correlation between serum CCI levels and NfL serum levels in the course of MS disease

• Explore the utility of CCI using the CCI application	• Adherence to CCI assessments quantified as CCI
	• Correlation between CCI assessments and other assessments performed in the study
	• CCI CCI CCI includes the following:
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI
	  • CCI

• Explore daily activity and sleep patterns via CCI	• Change from Baseline in CCI derived metrics

3 Study design

This is a single arm, prospective, multicentre and open-label, 96-week study to evaluate the treatment effectiveness of ofatumumab (OMB157) in subjects with relapsing MS transitioning from any fumarate-based RMS approved therapy, such as DMF or DRF, or fingolimod due to breakthrough disease activity. A total of approximately 555 eligible subjects will receive open-label ofatumumab 20 mg s.c. every 4 weeks (after an initial loading dose regimen of three weekly 20 mg doses in the first 14 days).

The study is divided into three parts: Part 1 - Screening period, Part 2 - Treatment period, Part 3 - Safety follow-up

Part 1 - Screening (and transition) period

The Screening period can last up to 60 days and consists of two sections; namely Screening section and Baseline section. The Screening period will include the transition period (see Section 6.6.1 for details around subjects transitioning from either a fumarate therapy or fingolimod as per clinical practice). Baseline section can last up to the point of first study drug administration (Day -7 to Day 1). Patient eligibility will be determined based on the Screening and Baseline assessments.

Part 2 - Treatment period

Treatment period will consists of an initial induction phase (Week 1 to Week 4) with 20 mg s.c. ofatumumab during visits at Day 1, Day 7 and Day 14 followed by a monthly maintenance dose regimen of 20 mg s.c. ofatumumab every 4 weeks starting at Week 4. During the treatment period, the subjects will have the assessments as per Table 8-1. All visits should be performed in the morning whenever possible to reduce the impact of fatigue on the scheduled assessments.

Part 3 - Safety follow-up period

Safety follow-up:

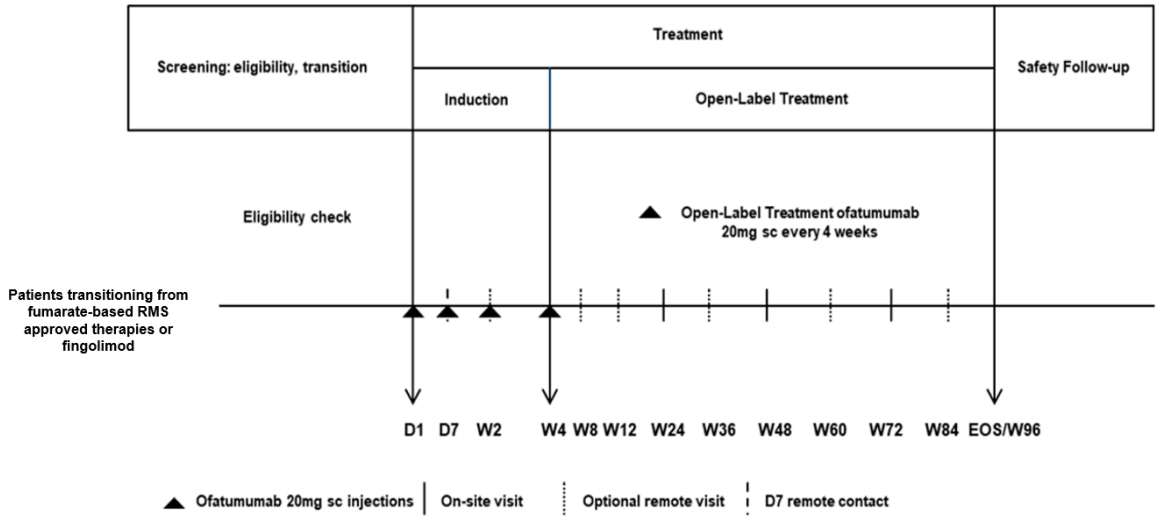
- The Safety follow-up (FU) period will be applicable for the following subjects:
  - Subjects who complete the Treatment period on the study drug and do not continue ofatumumab treatment (either commercial ofatumumab via prescription or via Post-Trial Access mechanisms*)
  - Subjects who prematurely discontinue study drug
- All Safety FU visits must be scheduled relative to the End of Study (EOS) Visit.

***Post-Trial Access**

In the countries where ofatumumab is not approved by Health Authorities, not launched or reimbursed, subjects participating in the current study with a clinical benefit in the opinion of the Investigator at the completion of the Treatment period may continue to receive ofatumumab via a Post-Trial Access (PTA) mechanism until ofatumumab becomes commercially available and it is reimbursed in the particular country or until the PTA program ends, whichever occurs first. Reimbursement refers to country level and not individual reimbursement, if there are multiple reimbursement channels in a country the date of reimbursement is when the first major reimbursement is in place. Post Study Drug Supply (PSDS) is the first option for PTA. If PSDS cannot be implemented in a country due to the local legislation, the clinical trial team will work with the Investigator to assess other PTA possibilities.

All patients continuing ofatumumab after the study completion (either commercial ofatumumab via prescription or via Post-Trial Access mechanisms), must complete the EOS visit of this study first.

Figure 3-1 Study Design



Transition period is described in Section 6.6.1

4 Rationale

4.1 Rationale for study design

The study is a Phase IIIb open-label, single arm, non-comparative study evaluating effectiveness of ofatumumab after transitioning from fumarate-based RMS approved therapies or fingolimod in subjects with relapsing forms of multiple sclerosis who have breakthrough disease as evaluated by the annualized relapse rate (ARR), Gd+, or new/increasing T2 lesions.

The efficacy and safety of ofatumumab have been demonstrated in pivotal Phase III clinical studies (COMB157G2301 (ASCLEPIOS I) and COMB157G2302 (ASCLEPIOS II)) in which teriflunomide was used as a comparator. It is important to understand if ofatumumab may provide clinical benefit in these patients with breakthrough disease activity, switching from other oral treatments, specifically fumarate-based RMS approved therapies, such as DMF and DRF, or fingolimod, which are some of the most prevalent oral MS DMTs prescribed globally.

Baseline characteristics from ASCLEPIOS I and II demonstrate that only 5% or less of RMS patients randomized in study were transitioning from DMF or fingolimod (note: ASCLEPIOS I and II exclusion criteria prohibited patients that had been previously treated with teriflunomide). Therefore, this Phase IIIb clinical study aims to bridge the gap and to provide complimentary effectiveness and safety data to the development program of ofatumumab. The current study design supports generation of clinically relevant evidence in a chosen patient population that was less represented in the pivotal trial program or in other ofatumumab studies – patients who are switched to ofatumumab from either any fumarate or fingolimod, and have breakthrough disease before the switch.

The single arm, open label design has been selected to more closely reflect routine clinical setting and care, especially for RMS patients transitioning from any fumarate or fingolimod to

ofatumumab. It is especially relevant to reflect real-world clinical settings in the context of ofatumumab use, considering the availability of ofatumumab in countries worldwide, including US (approved 20-Aug-2020), EU (approved in March 2021), as well as the timelines of the study and the time when study data will be available.

Subjects eligible for participation in this trial will have breakthrough disease activity despite their previous treatment with fumarates or fingolimod. Therefore, a placebo arm was not considered due to the safety risk it would impose. With the current single-arm, open-label design, all subjects included in the trial will receive ofatumumab, which has demonstrated superior efficacy compared to teriflunomide and a good safety profile in ASCLEPIOS I and II trials (COMB157G2301 and COMB157G2302). To further elucidate the effectiveness of transitioning to ofatumumab, additional data from patient registries or other data sources may be utilized.

T2 enlarging lesions have been included in the definition of breakthrough disease beyond the Phase 3 program. It is recognized that T2 enlarging lesions highly correlate with brain tissue loss and loss of brain tissue integrity, hence providing a somewhat different, and equally meaningful, measure compared to Gd+ enhanced images.

Since ofatumumab demonstrated a strong reduction of disease activity (relapses and MRI lesions) versus an active comparator in Phase 3, very low disease activity is expected in patients after transitioning from fumarates or fingolimod to ofatumumab. It is therefore possible to conduct the study as a single arm open-label study.

This study aims to provide clinical evidence supplementing the Phase 3 program by providing effectiveness and safety data of ofatumumab in a patient population having suboptimal response to oral DMTs. This evidence is highly relevant for neurologists and treating healthcare practitioners in the real world setting.

4.2 Rationale for dose/regimen and duration of treatment

Ofatumumab dose

The dose regimen for ofatumumab for this study is a *loading dose regimen* of 20 mg at Day 1, Day 7 and Day 14, followed by a monthly *maintenance dose regimen* of 20 mg administered every 4 weeks, starting at week 4.

This dose regimen is consistent with the dose and regimen in the Phase 3 development program of ofatumumab in RMS.

Duration of treatment

Treatment duration within the study will be 96 weeks with the primary endpoint being at 96 weeks.

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

No comparator arm will be implemented.

4.4 Purpose and timing of interim analyses/design adaptations

The sponsor reserves the right to conduct periodic interim analysis (es) as needed (e.g. to support regulatory updates).

4.5 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with eligibility criteria, close clinical monitoring, avoidance of prohibited treatments, adherence to protocol requirements and Investigator guidance regarding specific safety areas. In addition, safety data from the pivotal Phase 3 program are available and the benefit/risk profile for ofatumumab treated patients with RMS is assessed as favorable.

Clinical experience with ofatumumab in RMS patients comes from completed Phase 2 and Phase 3 studies, as well as ongoing studies, including a long term extension study, with approximately 3020 RMS patients who have been exposed to ofatumumab in these studies (cut off 25-Sep-2022). No unexpected safety findings were observed in MS patients who received ofatumumab in the two completed Phase 2 studies, OMS115102 and OMS112831, and two ASCLEPIOS Phase 3 studies. Briefly, in the 48-week, placebo-controlled, cross-over study (cross-over at 24 weeks) of intravenous doses of ofatumumab up to 700 mg, adverse events reported more frequently on ofatumumab vs placebo included: rash, throat irritation, erythema, fatigue, viral infection and flushing. In the placebo-controlled, dose-ranging study of ofatumumab administered at s.c. doses up to 60 mg every 4 weeks for up to 24 weeks, injection related reactions were observed more frequently in the overall ofatumumab group. In the ASCLEPIOS I and II studies, ofatumumab demonstrated a favorable safety profile with no unexpected safety signals, no imbalance in adverse events or serious adverse events (SAEs), the rates of infection (including serious infection) or malignancy when compared to teriflunomide. In the studies, systemic injection-related reactions were reported in 20.6% of patients on ofatumumab and in 15.3% of patients on teriflunomide. 99% of all reported systemic injection reactions were mild to moderate (Grade 1-2) and limited to the first injection.

Ofatumumab s.c. has demonstrated profound suppression of new MRI lesion activity (≥ 90% versus placebo over Weeks 4-12) in relapsing MS patients in a Phase 2 study (OMS112831). In the Phase 3 studies, ofatumumab has shown a highly significant and clinically meaningful reduction in the number of confirmed relapses, evaluated as the annualized relapse rate (ARR). Patients treated with ofatumumab had an ARR of 0.11 and 0.10 compared to teriflunomide (ARR of 0.22 and 0.25) in ASCLEPIOS I and II respectively, corresponding to a reduction in ARR by 50.5% and 58.8% with ofatumumab ($p<0.001$ in both studies). Ofatumumab showed highly significant suppression of both Gd+ T1 lesions and new or enlarging T2 lesions compared to teriflunomide, demonstrating a profound suppression of new inflammatory activity. Additionally, ofatumumab showed a relative risk reduction of 34.4% ($p=0.002$) in 3-month confirmed disability worsening (CDW†) and 32.5% ($p=0.012$) in 6-month CDW versus teriflunomide in pre-specified pooled analyses (Hauser et al 2019). Taken together, available information of relevant clinical and MRI outcome supports the potential efficacy of ofatumumab in patients with relapsing MS.

Overall, data acquired to date supports the rationale of this study to evaluate the efficacy and safety of ofatumumab s.c. to address the unmet medical need of patients with relapsing MS and breakthrough disease on commonly used oral therapies.

Women of child-bearing potential must be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and must 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 subject will not reliably comply with the study procedures, they should not be entered or continue in the study.

It is realized, in the context of COVID-19 pandemic, that additional risks might exist for patients taking part in any clinical trial. Eligibility criteria for the study already require investigator to evaluate infections and exclude patients with ongoing infection, which would include COVID-19. The protocol also includes guidance on immunization in case a COVID-19 vaccine is utilized during the course of the study (see Section 16.1.3). Additionally, this protocol has been adapted to include the option to reduce the number of on-site visits, to minimize unnecessary risk that would be associated with the on-site visits and allow shipment of the IMP directly to patient's home.

4.6 Rationale for public health emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic, or natural disaster, mitigation procedures to ensure subject safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Population

The study population will consist of adult subjects with RMS fulfilling all the eligibility criteria listed below. The study is planned to be conducted in approximately 120-170 centers worldwide. It is aimed to enroll a total of approximately 555 subjects. Subjects who enroll and prematurely discontinue study will not be replaced.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Adult subjects aged 18 to 60 years (inclusive) at Screening.
3. Diagnosis of MS according to the 2017 Revised McDonald criteria (Thompson et al 2018)
4. Relapsing MS: relapsing forms of MS (RMS) including RMS and secondary progressive MS (SPMS) (Lublin et al 2014).
5. Disability status at Screening with an EDSS score of 0 to 4 (inclusive).
6. MS treatment history with a maximum of 3 DMTs, where all fumarates are considered as one DMT
7. Subject transitioning from either any fumarate-based RMS approved therapies, such as dimethyl fumarate (DMF) or diroximel fumarate (DRF), or fingolimod which was administered for a period of at least 6 months, as their last DMT before first study drug administration

8. Breakthrough disease activity while the participant was adequately using fumarates or fingolimod prior to transitioning for a minimum of 6 months as evidenced by one or more clinically reported relapses or one or more signs of MRI activity (e.g. Gd+ enhancement, new or enlarging T2 lesions)
9. Neurologically stable within one month prior to first study drug administration.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study:

1. Subjects suspected of not being able or willing to cooperate or comply with study protocol requirements in the opinion of the investigator.
2. Subjects with primary progressive MS (Polman et al 2011) or SPMS without disease activity (Lublin et al 2014).
3. Subjects meeting criteria for neuromyelitis optica (Wingerchuk et al 2015).
4. Disease duration of more than 10 years since diagnosis.
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive Human Chorionic Gonadotropin (hCG) laboratory test.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for at least 6 months after stopping study medication. Highly effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject, if accepted by the local regulation). **NOTE:** Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal **ARE NOT** acceptable methods of contraception
   - Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male partner sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner
   - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

   In case local regulations are more stringent than the contraception methods listed above, local regulations apply and will be described in the ICF.

   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 prior to enrollment on study. 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 to be not of child-bearing potential.

7. Subjects with 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)
8. Subjects with active systemic bacterial, fungal or viral infections (such as HIV or COVID-19), or known to have acquired immunodeficiency syndrome (AIDS). Where local regulation requires it, SARS-CoV-2 must be ruled out by the Polymerase Chain Reaction (PCR) test.
9. Subjects with neurological symptoms consistent with PML or with confirmed PML.
10. Subjects at risk of developing or having reactivation of syphilis or tuberculosis (e.g. subjects with known exposure to, or history of syphilis, or active or latent tuberculosis, even if previously treated), as confirmed by medical history or per local practice.
11. Subjects with active hepatitis B or C disease, assessed locally.
    - Hepatitis B virus (HBV) screening should be performed before initiation of treatment. At a minimum, screening should include hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) testing. These can be complemented with other appropriate markers as per local guidelines. Subjects with positive hepatitis B serology (either HBsAg or anti-HBc) should perform HBV DNA test. If HBV DNA test is positive, the subject is not eligible. If HBV DNA test is negative, the subject should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation (Section 16.1.2).
    - Hepatitis C risk must be ruled out via anti-HC IgG (if positive IgG, HCV-RNA PCR will be performed and if negative, subject can be enrolled)

      NOTE: If the Investigator suspects false positive hepatitis serology results such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, an infectious disease expert may be consulted. In the case the patient has a record of vaccination including HB, and there is no evidence of acute or chronic hepatitis infection (confirmed by an infectious disease expert), the Investigator must document (in source data and as a comment in the electronic Case Report Form (eCRF) that the serology results are considered false positive and may then enroll the subject.

12. Have received any live or live-attenuated vaccines (including for varicella-zoster virus or measles) within 4 weeks prior to first study drug administration
13. Have been treated with any of the medications listed below within the time specified

Table 5-1 Exclusionary Medicine

Medication	Exclusionary if used within the timeframe specified below
Systemic corticosteroids, adrenocorticotropic hormone	30 days prior to Screening MRI scan
Teriflunomide (unless rapid elimination procedure was performed)	9 months prior to first study drug administration
Natalizumab	6 months prior to first study drug administration
Highly immunosuppressive/chemotherapeutic medications (e.g. mitoxantrone, cyclophosphamide, cladribine, daclizumab) B-cell targeted therapies (e.g. rituximab, ocrelizumab) Laquinimod	2 years prior to first study drug administration
Mitoxantrone (with evidence of cardiotoxicity following treatment or cumulative life-time dose > 60mg/m^2) Alemtuzumab Lymphoid irradiation; bone marrow transplantation Other strongly immunosuppressive treatments (with effects potentially lasting over 6 months) Ofatumumab aCD20+ monoclonal antibodies in development (e.g. ublituximab or obinutuzumab)	Any time

14. 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.
15. History of malignancy of any organ system (other than basal cell carcinoma, in situ squamous cell carcinoma of skin, or in situ carcinoma of cervix 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.
16. Any of the following chronic, severe conditions or treatments that may impact the compliance of the study:
    - 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 or active severe respiratory disease, including Chronic Obstructive Pulmonary Disease, interstitial lung disease or pulmonary fibrosis
    - Subjects with asthma requiring regular treatment with oral steroids
    - Severe hepatic impairment (Child-Pugh class C) or any chronic liver or biliary disease

- Subjects with severe renal impairment (Glomerular Filtration Rate < 30 ml/min/ 1.73 m^2)
- Any medically unstable condition as determined by the Investigator
- severe hypoproteinaemia e.g. in nephrotic syndrome

17. Any of the following abnormal laboratory values as confirmed by the central laboratory prior to first study drug administration:
    - Lymphocyte count <500/mm^3 (<0.5 x 10^9/L) in patients discontinuing fumarates
    - Serum IgG < 500 mg/dL (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. Subjects with any of the following neurologic/psychiatric disorders prior to first study drug administration:
    - Score "yes" on item 4 or item 5 of the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS), if this ideation occurred in the past 6 months, or "yes" on any item of the Suicidal Behavior section, except for the "Non-Suicidal Self-Injurious Behavior" (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.
19. History of hypersensitivity to the study drug or any of the excipients or to drugs of similar chemical classes

6 Treatment

6.1 Study treatment

6.1.1 Investigational drugs

Table 6-1 Investigational Drug

Treatment Title	OMB157
Treatment Description	Investigational drug will be provided in an autoinjector (AI) for subcutaneous administration containing 20 mg ofatumumab (50 mg/ml, 0.4 ml content). Ofatumumab (OMB157) is clear to opalescent, colorless to pale yellow, essentially particle-free liquid.
Type	Drug
Dose Formulation	Autoinjector
Unit Dose Strength(s)	20 mg (50 mg/ml, 0.4 ml)
Dosage Level(s)	20 mg (50 mg/ml, 0.4 ml)
Route of Administration	Subcutaneous injection
Use	Experimental
IMP	Yes

Sourcing	Study drug will be supplied by Novartis.
Packaging and Labeling	Study treatment will be provided in an autoinjector. Each autoinjector will be labeled as required per country requirement.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

This is a single arm open-label treatment study.

6.1.4 Treatment duration

The planned duration of treatment is 96 weeks. Subjects may be discontinued from treatment earlier as per criteria in Section 9.1.1.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The Investigator should instruct the subject 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 subject was enrolled into the study must be recorded on the appropriate CRFs.

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 enrolling a subject or allowing a new medication to be started. If the subject is already enrolled, the investigator should contact Novartis to determine if the subject should continue participation in the study.

If a patient is receiving dalfampridine (Ampyra®/Fampyra®) concomitantly with study treatment, the subject should have been on a stable dose at least 30 days prior to first study drug administration and remain on that dose throughout the study whenever possible.

Premedication prior to s.c. injection

If investigators choose to administer premedication, oral premedication should be administered 30 to 60 mins prior to study drug injection. Premedication with acetaminophen and/or antihistamines (or equivalent) is optional and may be administered at the discretion of the Investigator. Premedication with steroids is not recommended based on findings from the pivotal clinical trials where only limited benefit of premedication with steroids was seen (Bar Or et al 2020, Ofatumumab Investigator Brochure Edition 16 Autoimmune Diseases, Version 07 Nov 2022)

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

After the initial dose of study medication, subjects may inject study medication at home at Day 7 and onwards (refer to Section 6.7.2). Based on the experience with the injections administered at the site and with the use of any premedication, the Investigator will evaluate whether or not

premedication (such as acetaminophen and/or antihistamines) should be used before injections administered at home. If premedication is prescribed, the study staff must ensure that the subject will receive a sufficient supply of premedication for home-use (i.e. to last at least until the next visit) and clear instructions (oral and written) about type and dose of premedication, and when to take it (i.e. 30-60 min before the injection for oral premedication). The Investigator will evaluate the need for premedication, or a change in the prescription, at each visit (scheduled and unscheduled) including at the monthly subject contacts during the study (contact should gather details on any injection-related symptoms and the use of premedication). If, based on the remote contacts, a change in pre-medication is needed, the subject should be asked to return to the site for an unscheduled visit.

The subjects must be comprehensively informed (through the patient information and consent process) about the possibility that injection related reactions might occur despite use of premedications and about the possible symptoms of a systemic injection reaction and their management. Furthermore, subjects must be reminded to always carry their Patient Card, which includes the Investigator and site telephone contact numbers in case of an emergency.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-2 is NOT allowed in combination with study drug, due to increased risk of immunosuppression and confounding of efficacy evaluations.

Exclusionary medications for study eligibility are listed in the exclusion criteria (Section 5.2). Use of excluded medications is not allowed while the subject is on study medication.

Table 6-2 Prohibited medication

Medication	Action taken
Immunosuppressive/chemotherapeutic medications (including herbal) or procedures, including but not limited to cyclosporine, azathioprine, leflunomide, methotrexate, cyclophosphamide, mitoxantrone, lymphoid irradiation and hematopoietic stem cell transplantation	Discontinue study drug, increase vigilance regarding infections. NOTE: Restarting study drug in subjects exposed to these medications is not permitted.
Monoclonal antibodies targeting the immune system, including but not limited to natalizumab, alemtuzumab, daclizumab and B-cell depleting agents such as but not limited to rituximab, ocrelizumab and obinutuzumab	Discontinue study drug, increase vigilance regarding infections. NOTE: Restarting study drug after exposure to B-cell depleting agents is not permitted. For others only after consultation with the Sponsor.
Any other immunomodulatory or disease-modifying MS treatment, including but not limited to fingolimod, interferon beta, teriflunomide glatiramer acetate, fumarate-based RMS approved therapies, intravenous immunoglobulin, plasmapheresis or systemic corticosteroids (except for when given for MS relapse treatment as defined in Section 6.2.3).	Interrupt or discontinue study drug, increase vigilance regarding infections.
Administration of any live or live-attenuated vaccine (including for measles) is prohibited while subjects are exposed to study drug (long lasting effects of the study drugs should be taken into consideration)	They may be administered when subjects are no longer exposed to study drug Section 16.1.3 Consider risk/benefit and follow local labels.

6.2.3 Recommended treatment of MS Relapse

The decision to treat MS relapses should be based on the Investigator's judgement and/or local clinical practice. If MS relapses require treatment, the standard treatment should consist of a short course of corticosteroids of 3-5 days and up to 1000mg methylprednisolone/day or equivalent on an inpatient or outpatient basis. Standard of care will be followed during treatment as per local clinical practice.

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 MS attack/relapse must be recorded on the Concomitant Medications eCRF. Please refer to restrictions for MRI in Section 8.3.4 concerning the use of steroids and performing the MRI.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), which is assigned at the Screening visit and retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it by the Interactive Response Technology (IRT) system, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available. The site must use the eCRF with the matching subject number from the electronic data capture (EDC) system to enter data.

If an enrolled subject fails to be treated for any reason, the reason will be entered on the Screening Subject Status eCRF. If the subject is re-screened later on, a new Subject No. will be assigned.

6.3.2 Treatment assignment, randomization

Not applicable.

6.4 Treatment blinding

Not applicable.

6.5 Dose escalation and dose modification

Dose escalation and modifications are not permitted in this study.

6.5.1 Dose modifications

Not applicable.

6.5.2 Follow-up for toxicities

Not applicable.

6.5.3 Drug Interruptions

Conditions/events that may lead to 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 subject interrupt the study drug for whatever reason, the re-start decision should be made on a case-by-case basis (refer to Section 6.7.2). Should the Investigator decide, after informing the Sponsor, to re-initiate treatment with study drug, depending on the duration of the interruption, the first dose at re-start may need to take place at the study site to ensure observation in a similar manner as on Day 1.

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

6.6 Additional treatment guidance

6.6.1 Transition period following treatment with prior DMT

Evidence-based recommendations on transitioning between DMTs are lacking. Hence, only general recommendations apply for sequential administration of immunosuppressive therapies. The risk of additive immune system effects when switching from drugs with immune effects such as fumarate-based RMS approved therapies or fingolimod needs to be considered and balanced against the risk of rebound or recurrent disease activity.

For the purpose of this study, we define the transitioning period as the time between stopping the current treatment (fumarates or fingolimod) and starting ofatumumab treatment. The exact timing of the transitioning is based on the clinical judgment of the investigator.

During the transition period, the subject may not receive any other DMT for the treatment of MS.

The transition procedure should be documented in the appropriate eCRF and any AEs reported during the procedure must be recorded on the AE eCRF.

6.6.2 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study drug exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using AI counts and information provided by the subject. This information should be captured in the source document at each visit. All study drug dispensed and returned must be recorded in the Drug Accountability Log.

6.6.3 Emergency breaking of assigned treatment code

Emergency breaking of assigned treatment code is not applicable to this study as this is an open-label study.

6.7 Preparation and dispensation

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

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT system and obtaining the medication number(s). Drug accountability and reconciliation data is recorded in the IRT system.

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 subject'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 subject is no longer appropriate or possible, and that it is in the interest of the subject's health to administer the study treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis. The dispatch of IMP from the Investigator site to the subject's home remains under the accountability of the Investigator, and will be done from third study injection onwards. Each shipment/provisioning will be for a maximum of 3 home injections. In this case, documented regular phone calls or, virtual contacts (at least every 4 weeks or more frequently if needed) will occur between the site and the subject for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring subjects continue to benefit from treatment and discussion of the subject´s health status until the subjects can again visit the site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study drug must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study drug must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (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 drug but no information about the subject except for the medication number.

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

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study drug, 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.

6.7.1.2 Handling of additional treatment

Not applicable to this trial.

6.7.2 Instruction for prescribing and taking study treatment

The study drug (ofatumumab injections) will be administered starting at Visit 1. Drug will then be dispensed at scheduled visits throughout the treatment period. Starting at week 4, the subcutaneous injections should be administered at 4-week intervals (+/- 3 days).

Site personnel will provide training to subjects on the correct procedure for self-administration of s.c. injections. At Visit 1, subjects will receive the s.c. injection at site, where tolerability and vital signs will be assessed. Should the subject experience any tolerability event or post dose vital signs are not within reasonable limits, subject may remain at site until symptoms resolve or vital signs are within reasonable limits of baseline values.

In certain countries, e.g. Czech Republic, the local health authority requires subjects to remain at the site under observation for approximately 1 hour following first study drug dosing at Visit 1, where post vital signs will be collected. A longer observational period may be required if per investigator judgement these vital signs are not within reasonable limits of subject's baseline values. Subject or caregiver will inject the study medication under supervision of the study staff.

Following Visit 1, subjects may inject the study medication at home by themselves or have a caregiver who has been trained by the study staff on the proper technique and safety precautions, inject the study medication. Ability to self-administer injections must be demonstrated and documented before home-administration is permitted. Injection 2 (Day 7) will be overseen remotely by the designated site personnel to support the self/home administration and provide additional training as needed. Subjects will return to the site for the week 2 and 4 administrations. If a subject is unable/unwilling to self-administer injections, home-administration may be performed by another individual (e.g. partner, relative or a healthcare professional) who has accompanied the subject to the site and has been trained on and demonstrated ability to correctly administer the s.c. injections. In the exceptional circumstances, the subject may receive injections at the site, for example, subjects with severe neurological deficits should not self-administer injections.

Subjects should be instructed to record any missed doses in the subject diary provided for the study and to inform the study staff of any missed s.c. injection(s). This can be done at the visits and/or during the monthly remote contacts that are scheduled throughout the study during which, the study site staff will inquire about the subject's status and compliance with study treatment administration or issues related to the home administration.

Subjects 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 followed:

- If one monthly injection is missed by 1 week or less, the subject should take injection as soon as possible. The next injection should then be administered according to the original schedule.
- If one monthly injection is missed by more than 1 week, the subject 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 Sponsor before re-starting dosing.

Information about all kits of study medication assigned by the IRT will be recorded in the IRT system.

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

7 Informed consent procedures

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the subject or their legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

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 subject source documents.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the subject or their legally authorized representative. Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each subject the objectives of the additional research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for additional research. Subjects who decline to participate in this optional additional research will document this.

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed, this includes changes in available standard of care if 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 subject.

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.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research using your Personal Data’ to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Follow-up consent for female subjects
- Optional informed consent for Home Nursing visits

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

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, the 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, and ECs/IRBs 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.).

In case Home Nursing is implemented during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic, or natural disaster, or to reduce burden related to an on-site visits, a separate Home Nursing consent document must be used in addition to the main ICF.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments and indicates with an "x" when they are performed. All data obtained from these assessments must be supported by the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. In case a visit is performed outside of the schedule, subsequent visits shall be performed in keeping with the original visit schedule. In addition to the scheduled visits, subjects may have unscheduled visits due to a MS relapse, an acute illness of undetermined cause, for other reasons, or at the discretion of the Investigator. Data collected during unscheduled visits will be recorded in the unscheduled visits CRF.

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 local health authority, national and local regulations, and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultations) or visits by site staff/off-site healthcare professional(s) to the subject´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the subject to visit the site again. The subject may also opt to have some of the on-site visits performed by home nursing service at home as defined in the Table 8-1. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Subjects who prematurely discontinue the study for any reason should be scheduled for the EOS visit as soon as possible and then enter the Safety Follow-up period according to the schedule in Table 8-2. At this final visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications recorded on the CRF.

Table 8-1 Assessment Schedule, Treatment

Period	Screening		Treatment												
Visit Name	**Screening**	**Baseline**	**Visit 1[2]**	**Visit 2 (Remote contact Visit)[3]**	**Visit 3 Week 2[24]**	**Visit 4 Week 4**	**Visit 5 Week 8[24]**	**Visit 6 Week 12[24]**	**Visit 7 Week 24**	**Visit 8 Week 36[24]**	**Visit 9 Week 48**	**Visit 10 Week 60[24]**	**Visit 11 Week 72**	**Visit 12 Week 84[24]**	**EOS/Visit 13 Week 96[4]**
Visit Numbers[1]	**1**	**20**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**
Days	**-60 to -8**	**-7 to 1 (Prior to 1st dose/visit 1 start)**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**56 ±7**	**84 ±7**	**168 ±14**	**252 ±14**	**336 ±14**	**420 ±14**	**504 ±14**	**588 ±14**	**672 ±14**
Informed Consents[24]	X														
Demography, Height	X														
Medical History	X														
MS History/Treatments[5]	X														
Inclusion / Exclusion criteria	X	X													
Patient Training[6,7]		X	X												
Drug dispensation			X		X	X	X	X	X	X	X	X	X	X[28]	
Site contact with subjects[8]				X				Monthly between scheduled visits							
MS Relapse	X[27]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EDSS	X	X[20]							X		X		X		X
MRI[9]	X[10]								X		X				X[11]
Office examinations [12]			X[13]						X		X		X		X
CCI															
LCVA			X[13]								X				X
PROs [14]			X [13]			X			X		X		X		X
CCI			X [13]								X				X

Period	**Screening**		**Treatment**												
Visit Name	**Screening**	**Baseline**	**Visit 1[2]**	**Visit 2 (Remote contact Visit)[3]**	**Visit 3 Week 2[24]**	**Visit 4 Week 4**	**Visit 5 Week 8[24]**	**Visit 6 Week 12[24]**	**Visit 7 Week 24**	**Visit 8 Week 36[24]**	**Visit 9 Week 48**	**Visit 10 Week 60[24]**	**Visit 11 Week 72**	**Visit 12 Week 84[24]**	**EOS/Visit 13 Week 96[4]**
Visit Numbers[1]	**1**	**20**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**
Days	**-60 to -8**	**-7 to 1 (Prior to 1st dose/visit 1 start)**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**56 ±7**	**84 ±7**	**168 ±14**	**252 ±14**	**336 ±14**	**420 ±14**	**504 ±14**	**588 ±14**	**672 ±14**
CCI [redacted]		X[25]	X		X	X	X	X	X	X	X	X	X	X	X
CCI [redacted] review[16]		X[25]	X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X[17]			X			X		X		X		X
Physical Exam (including weight)[6]	X					X			X		X		X		X
Electrocardiogram (ECG)	X														X
Biomarker sampling[18,19]	X					X		X	X	X	X	X	X	X	X
Total IgG, IgM levels	X					X			X		X		X		X
Routine lab samples including urine	X	X[20]				X		X	X		X		X		X
Sample for CD19+ B-cells (all sites)		X				X			X		X		X		X
Sample for B-cell and T-cell subset testing (US sites only)		X				X			X		X		X		X
Serological markers for hepatitis B and C[26]	X														
Syphilis/Tuberculosis Assessment[26]	X														
Pregnancy Test (serum)[21]	X										X				X

Period	Screening		Treatment												
Visit Name	**Screening**	**Baseline**	**Visit 1[2]**	**Visit 2 (Remote contact Visit)[3]**	**Visit 3 Week 2[24]**	**Visit 4 Week 4**	**Visit 5 Week 8[24]**	**Visit 6 Week 12[24]**	**Visit 7 Week 24**	**Visit 8 Week 36[24]**	**Visit 9 Week 48**	**Visit 10 Week 60[24]**	**Visit 11 Week 72**	**Visit 12 Week 84[24]**	**EOS/Visit 13 Week 96[4]**
Visit Numbers[1]	**1**	**20**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**
Days	**-60 to -8**	**-7 to 1 (Prior to 1st dose/visit 1 start)**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**56 ±7**	**84 ±7**	**168 ±14**	**252 ±14**	**336 ±14**	**420 ±14**	**504 ±14**	**588 ±14**	**672 ±14**
Urine Pregnancy Test[21]			X[13]			X	X	X	X	X	X	X	X	X	X
C-SSRS	X		X[13]		X	X	X	X	X	X	X	X	X	X	X
Contraception Status[6,22]	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Diary Review[6]			X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Disposition															X

X Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Visit structure given for internal programming purpose only
[2] Enrollment and first dose (usually expected on the same day). If first dose occurs on a different day after enrollment, the day of the first dose should be considered as Day 1
[3] Remote contact visit to support home/self-administration of the study drug, support compliance with the diary and provide additional training as needed. An on-site visit is permitted in case the subject is unable/unwilling to self-administer injections.
[4] EOS visit will be required for all subjects (subjects who permanently discontinue study drug and subjects who complete the study).
[5] MS history including number of relapses in previous year and number of relapses in previous two years
[6] Assessments captured as source data
[7] At Baseline visit, patient training on CCI and CCI (as required) CCI 's functionality and use. At day 1 patient training on study requirements including study drug administration using the autoinjector, ePRO, urine pregnancy tests used at home
[8] Remote contact with subjects by site staff around the time of administration of ofatumumab self/home-injection. The contact should query about any new or worsening symptoms warranting an unscheduled visit, compliance with study treatment, injection reactions, results of home pregnancy testing and compliance with contraception requirements (when applicable). Method of contact can be via telephone, email or text message depending on the preference of each subject.
[9] Restrictions may apply to MRI concerning steroid use, please refer to Section 8.3.4.
[10] Screening MRI should be completed once all other screening eligibility assessments have been completed and confirmed to meet eligibility criteria
[11] MRI scan at the EOS visit is needed if there was no MRI scan in the previous 3 months.

Period	Screening		Treatment												
Visit Name	**Screening**	**Baseline**	**Visit 1[2]**	**Visit 2 (Remote contact Visit)[3]**	**Visit 3 Week 2[24]**	**Visit 4 Week 4**	**Visit 5 Week 8[24]**	**Visit 6 Week 12[24]**	**Visit 7 Week 24**	**Visit 8 Week 36[24]**	**Visit 9 Week 48**	**Visit 10 Week 60[24]**	**Visit 11 Week 72**	**Visit 12 Week 84[24]**	**EOS/Visit 13 Week 96[4]**
Visit Numbers[1]	**1**	**20**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**
Days	**-60 to -8**	**-7 to 1 (Prior to 1st dose/visit 1 start)**	**1**	**7 ±1**	**14 ±1**	**28 ±1**	**56 ±7**	**84 ±7**	**168 ±14**	**252 ±14**	**336 ±14**	**420 ±14**	**504 ±14**	**588 ±14**	**672 ±14**

[12] Timed 25-Foot Walk, Nine Hole Peg Test

[13] To be completed prior to first study drug administration

[14] Patient Reported Outcomes: CCI , CCI CCI , CCI

[15] CCI via the CCI application will be conducted in countries where applicable languages are available. Data is collected continuously throughout the study. CCI should be dispensed at Baseline Visit, and given to the patient a minimum of 7 days prior to planned first study drug dose, and returned at EOS/Visit 13. On the days of the scheduled site visits, the CCI CCICCI assessments will be performed under the supervision of trained site staff.

[16] Subject to return CCI CCI for data download and transfer. It's necessary to obtain CCI data at least 1 week before Visit 1. These data will be considered as CCI baseline data. Refer to Section 8.5.1.6 for more information.

[17] Vital signs should be obtained 30-60 minutes before Day 1 s.c. injection (if premedication is administered, pre-injection vital signs should be obtained before premedication is administered), and again approximately 60 minutes post Day 1 s.c. injection

[18] If the scheduled visit coincides with the day that study drug administration is scheduled, the subject should be instructed not to administer the injection before coming to the site so that the assessments can be completed prior to study drug administration.

[19] Additional NfL and CCI sample to be collected in case of any unscheduled visit due to suspected MS relapse

[20] Assessment must be completed to allow adequate time for results to be obtained before first study drug administration to ensure subject's eligibility

[21] Women of childbearing potential only - Serum pregnancy tests will be conducted on an annual basis at site. Monthly urine pregnancy tests will be conducted between scheduled visits at home and on scheduled visits (in the absence of an annual serum pregnancy test) at site prior to the administration of study drug. The subject must contact the Investigator immediately in the case of a positive test for confirmatory testing at the Investigator's discretion.

[22] Subject's contraception status must be reviewed and documented to ensure method of contraception continues to be appropriate per protocol requirement for highly effective contraception.

[23] Including corticosteroids used to treat MS relapse; any new started MS treatment as applicable (for subjects who have discontinued study medications).

[24] Visit can be performed at the site or at subject's home with support of home nursing service. In this case an additional home nursing ICF must be signed.

[25] CCI and CCI CCI should be given to the patient minimum 7 days prior to planned first study drug dose.

[26] To be assessed locally. If local testing is not feasible at a site, then these tests may be done by the Central Laboratory to assess patient's eligibility.

[27] MS relapses occurring after ICF signature should be assessed according to Section 8.3.1 and recorded on the Summary of MS Relapses eCRF.

[28] One additional medication kit can be dispensed at Visit 12/week 84, and taken by the subject prior to or no later than the day of the EOS visit, to ensure the subject does not have an interruption in treatment between study completion and start of commercial ofatumumab via prescription or via PTA mechanisms.

Table 8-2 Assessment Schedule, Safety Follow-up

Period	Post-Treatment Follow-up				
Visit Name	**Safety Follow-up Visit 1**	**Safety Follow-up Visit 2**	**Additional Follow-up Visits[1]**	**End of Safety Follow-up Visit**	
Days	**EOS + 3 Months ±14**	**EOS + 6 Months ±14**	**Every 3 months ±14 after Safety Follow-up Visit 2**	**Early discontinuation**	**Completion[6]**
MS Relapse	X	X	X	X	
EDSS	X	X	X	X	
Physical Exam (including weight)	X	X	X	X	
Vital Signs	X	X	X	X	
Routine lab samples including urine	X	X	X	X	
Sample for CD19+ B-cells (all sites)	X	X	X	X	
Sample for B-cell and T-cell subset testing (US sites only)	X	X	X	X	
Total IgG, IgM levels	X	X	X	X	
Neurofilament and CCI Sampling	X	X	X	X	
Urine Pregnancy Test[2]	X	X		X[7]	
Contraception Status[3,4]	X	X		X[7]	
Concomitant medications[5]	X	X	X	X	X
Adverse Events	X	X	X	X	X
Safety Follow-up Subject Disposition				X	X

X Assessment to be recorded in the clinical database or received electronically from a vendor

1 As needed for the subjects requiring prolonged Immunoglobulin (IgG and IgM) monitoring; refer to Section 9.2.1.

2 Pregnancy test is conducted on female subjects only. Urine pregnancy tests will be conducted at all scheduled visits as indicated in Table 8-2. Monthly urine pregnancy tests will be conducted at home between site visits. The subject must contact the Investigator immediately in the case of a positive test for confirmatory testing at the Investigator's discretion.

3 Subject's contraception status must be reviewed and documented to ensure method of contraception continues to be appropriate per protocol requirement for highly effective contraception.

4 Assessments captured as source data

5 Including corticosteroids used to treat MS relapse; any newly started MS treatment as applicable.

6 For subjects completing Safety Follow-up, the End of Safety Follow-up visit will be performed by telephone contact (after the central laboratory results have confirmed that IgG and IgM results are ≥ screening or LLN) to inform the subject that his or her participation in the Safety Follow-up has ended; the disposition form will be completed at that time and the AE and concomitant medications eCRFs will be updated if necessary to record any new or worsening events or medication changes since the last clinic visit. Please refer to Section 9.2.1.

7 To be performed only if less than 6 months after stopping study medication

8.1 Screening

The Screening period, including baseline visit, can last up to 60 days and consists of assessments used to determine subject eligibility and including the transition period from any fumarate-based RMS approved therapy or fingolimod (Section 6.6.1). In order to allow adequate time to obtain results and confirm subject eligibility, the Baseline and Day 1 visits should not be conducted on the same day.

Subjects may be rescreened if they do not initially meet eligibility criteria. All assessments must be repeated, except for MRI (the original MRI may be used during rescreening if the rescreening occurs within 3 months of the original MRI date). If a subject is re-screened, a new ICF must be obtained and re-screening will be documented in the subject's source documents. A new subject number will be allocated and the site will record the data in a new CRF.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and are subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a SAE during the screening phase (Section 10.1.3).

Subjects 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 CRF.

8.1.2 Subject diaries and site contact with subjects

Subject diaries

During the study, subjects will be asked to complete a diary from Day 1 on a monthly basis to record information pertinent to study drug administration (including date and time of administration). Investigator/Study Coordinator/Nurse will 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.

Site contact with subjects

Site personnel will make remote contact with subjects starting at Day 7 (Week 1) and then on a monthly basis in between scheduled site visits starting at Week 12 and continuing for the remainder of the study. The contact should take place around time of the monthly self/home-administration to ask about any new or worsening symptoms warranting an unscheduled visit, compliance with study treatment, injection reactions, and results of home pregnancy testing and compliance with contraception requirements when applicable. The method of contact with each subject can be the personal preference of the individual between telephone contact, email contact or text messages, however, the site staff must be able to provide suitable source documentation of each contact regardless of the method of contact.

8.2 Subject demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF. Subject demographic data and baseline characteristics to be collected on the appropriate CRF will include age, sex, race and ethnicity. Alcohol and smoking history and relevant medical history/current medical condition present before signing informed consent and any medications taken to treat these conditions will also be captured on the corresponding CRFs. Where possible, diagnoses, and not symptoms should be recorded. Investigators will have the discretion to record abnormal test findings on the CRF capturing medical history whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

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

8.3 Efficacy

This study includes the following efficacy assessments conducted at visits as shown in Table 8-1 and Table 8-2:

- MS Relapse
- EDSS

Exploratory effectiveness assessments:

Laboratory

- Neurofilament (NfL) sampling
- CCI sampling

Imaging

- MRI

Combined endpoint

- No Evidence of Disease Activity - 3(NEDA-3)

Office examinations

- Timed 25-Foot Walk
- Nine-Hole Peg Test (9HPT)
- CCI
- Low Contrast Visual Acuity (LCVA)

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

8.3.1 MS relapse

Subjects must be instructed to immediately report new neurological symptoms, re-occurring or worsening of previous symptoms to the Investigator. If a subject reports symptoms that may be consistent with relapse, an unscheduled visit to the Investigator must be scheduled as soon as

possible (whenever possible within 7 days of onset of the symptoms and always within 30 days from relapse start date and before relapse end date).

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

MS relapse definition

Appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event (Polman et al 2011). The abnormality must have been present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or a known infection.

Diagnosing MS relapses during the study

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

Confirmation of MS relapse

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

All MS relapses, regardless if they meet definition for confirmation based on EDSS or not, are reported on the appropriate CRF. Severity of MS relapse will be calculated centrally per criteria in Table 8-3 below. MS relapse should not be reported as an AE/SAE unless, in the judgment of the Investigator it is unusually severe or medically unexpected and warrants specific notification as an SAE (as described in Section 10.1.2).

Table 8-3 Severity of MS relapse

Mild Relapse	Moderate Relapse	Severe Relapse
EDSS increase of 0.5 points	EDSS increase of 1 or 2 points	Exceeding Moderate criteria
or	or	or
1 point FS change in one to three systems	2 point FS change in one or two systems	Exceeding Moderate criteria
	or	or
	1 point change in four or more systems	Exceeding Moderate criteria

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8.3.2 Expanded Disability Status Scale (EDSS)

Expanded Disability Status Scale (EDSS) will be determined, based on neurological examination, by an Investigator/delegate at planned visits according to 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) and an ambulation score that are then combined to determine the EDSS steps (ranging from 0 (normal) to 10 (death due to MS)). The FSs are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral functions (Fatigue contributes). The FSS and EDSS steps will be assessed in a standardized manner. EDSS is a widely used and accepted instrument to evaluate disability status at a given time and, longitudinally, to assess accumulation of disability in clinical studies in MS. EDSS will be recorded on the tablet and information collected there will be considered source documentation. In the event the EDSS is unavailable on the tablet for the patient during a visit (e.g. technical issue with the tablet), a web backup option can be used to complete the assessment.

Disability worsening should not be reported as an AE/SAE unless, in the judgment of the Investigator it is unusually severe or medically unexpected and warrants specific notification as an SAE (as described in Section 10.1.2).

8.3.3 Neurofilament and CCI sampling

Neurofilament (NfL) is a component of the neuronal cytoskeleton and is released into the cerebrospinal fluid (CSF) and subsequently into blood following neuro-axonal damage. It has been proposed as a biomarker to indicate treatment response and to predict disability worsening in patients with MS (CCI).

CCI is a type III intermediate filament that forms part of the cytoskeleton of mature astrocytes and other CCI but is not found outside the CNS (CCI). CCI is a marker of astroglial injury and found to be upregulated in CSF and serum proceeding CNS injury (CCI). In the context of MS, serum CCI has been found to be expressed in progressive forms of MS (CCI), and may be considered a biomarker of disease severity (CCI). Serum

CCI has also been found to be correlated with serum NfL in progressive MS (CCI).

Samples for biomarker assessment are taken at planned visits according to Table 8-1 and Table 8-2 and in case of a suspected MS relapse and should be taken prior to dosing. If the visit coincides with the day of the monthly injection, the subject should not take the injection in the morning before coming to the site so that the biomarker sample can be drawn prior to administration. The biomarker sample collection date and time must be entered on the appropriate eCRF.

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

8.3.4 Magnetic Resonance Imaging (MRI)

All subjects will undergo MRI scanning of the brain according to the schedules in Table 8-1.

MRI scans will be read by the central MRI reading center. Prior to the start of the study, MRI technician from each center will receive an MRI Manual, outlining technical implementation, image quality requirements and MRI administrative procedures.

The site will be asked to program the MRI scanner that is designated for evaluation of the study subjects. Site will be asked to perform and submit a dummy scan (so called “dummy or dry run”) to the central MRI reading center to assess the image quality and to evaluate the compatibility of the electronic data carrier. Once the dummy run has been accepted, all the parameter settings for the study specific MRI sequences must remain unchanged for the duration of the study. Finally, if the site is already pre-approved for performing conventional MRI scan sequences by the imaging vendor the dummy or dry run may be skipped.

Each MRI scan performed for the study needs to be previewed by a local neuro radiologist. During the study, the quality of each scan performed will be assessed by the central MRI reading center. The MRI scan should be sent to the central MRI reading center upon completion of each individual scan. 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 protocol.

Restrictions to MRI schedule

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

- In case of relapse, if an MRI has been scheduled within 14 days of the initiation of steroid treatment, MRI (with Gd+ enhancement) should be performed **before** steroid treatment is initiated.
- No MRI (with Gd+ enhancement) should be performed while a subject is on steroid therapy for relapse and within the following 14 days upon termination of steroid treatment.

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

Scanning

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

MRI scan sequences including conventional MRI measures of T1 hypointense images (with and without contrast medium, i.e., gadolinium-DTPA) and T2 weighted images will be performed. Additional exploratory MRI scan sequence(s) may be included at selected sites, which will be described in the MRI manual.

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. Any AE experience due to the contrast medium should be recorded on the AE eCRF.

8.3.5 No evidence of disease activity (NEDA-3)

Using combined endpoints to define no evidence of disease activity (NEDA) is becoming increasingly common when setting targets for treatment outcomes in multiple sclerosis (MS).

NEDA takes into account the occurrence of 1) relapses, 2) brain MRI lesions (either T2 or T1 Gd+) and 3) disability worsening confirmed at 6 months (6mCDW), providing a composite endpoint indicative of inflammatory and neurodegenerative activity due to MS. NEDA-3 is relevant to real-world clinical practice, where physicians frequently monitor for disease activity in these three categories (relapses, MRI lesions and confirmed disability worsening). Therefore, NEDA-3 status at one year will be calculated in this study.

8.3.6 Timed 25-Foot Walk

The Timed 25-Foot Walk (T25FW) will be assessed at planned visits according to Table 8-1 when office examinations are planned. The T25FW is an objective quantitative test of neurological function. It is widely used in clinical MS trials. It is an ambulation measurement assessing speed of walking: a timed (in seconds) walk of 25 feet (7.62 meters). The T25FW will be administered according to standardized instructions by the Investigator or by another qualified health care professional experienced with the administration of the T25FW. It should be noted whether the test is performed with/out walking aid(s) and if possible, the same testing condition should be maintained throughout the trial.

8.3.7 Nine Hole Peg Test

The Nine Hole Peg Test (9HPT) will be assessed at planned visits according to Table 8-1 when office examinations are planned. The 9HPT is an objective quantitative test of neurological function. It is widely used in clinical MS trials to assess upper extremity function. It is measured to assess both right and left arm scores, the metric is the time, in seconds, required to insert and remove nine pegs. The 9HPT will be administered (2 trials per hand) according to standardized instructions by the Investigator or by another qualified health care professional experienced with the administration of the 9HPT.

8.3.8 CCI

CCI will be assessed at planned visits according to Table 8-1 when office examinations are planned. This test can be used in everyday clinical practice, even in small MS centers with few staff members who may not have neuropsychological training.

CCI During the administration of the CCI, only the examiner and the subject should be in the testing room. The CCI will be administered according to standardized instructions by the Investigator or another qualified health care professional experienced with the administration of the CCI

Alternate versions of the CCI

CCI will be completed using a paper format and the total score will be collected and entered into a database.

8.3.9 Low Contrast Visual Acuity (LCVA)

The LCVA will be assessed according to the schedule in Table 8-1 by a qualified individual. Disturbances in visual function are common in patients with MS but these impairments are often not readily apparent on commonly used high-contrast acuity tests. The use of LCVA charts have therefore gained validity in the assessment of visual acuity in patients with MS. Low contrast Sloan letter charts provide a practical, quantitative and standardized assessment of visual function. Each chart consists of rows of gray letters, decreasing in size from the top to the bottom row, on a white background. A complete set consists of 7 charts, each with a different level of contrast ranging from 100% to 0.6%. For this study only the 100% and 2.5% contrast charts will be used. When these charts are being rated it is important that standardized conditions are used (e.g. distance from the chart, lighting conditions). Letter scores indicate the number of letters identified correctly, each chart is scored separately. Low contrast letter acuity testing with Sloan charts is easy to administer and has been shown to have high inter-rater reliability both in patients with MS and in healthy volunteers.

8.3.10 Appropriateness of efficacy assessments

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

The LCVA test is considered by some in the MS scientific community as a potential missing domain, which is not incorporated in the Multiple Sclerosis Functional Composite (MSFC), and has thus also been included in the assessments for this study.

8.4 Safety

Safety assessments are specified below with the assessment schedule (Table 8-1 and Table 8-2) detailing when each assessment is to be performed.

Safety assessments will include:

- Physical examination (including skin)
- ECG
- Vital signs
- Height and Weight
- Laboratory evaluations
- Columbia Suicide Severity Rating Scale (C-SSRS) (Section 10.2.1)
- Pregnancy testing (women of childbearing potential only)
- Adverse events

Additional safety assessments may be conducted should these be requested by the local regulatory authority. Any new or worsening clinically relevant findings from such additional assessments meeting definition of an adverse event (AE) or serious AE should be recorded as AE/SAE. For details on AE collection and reporting, refer to Section 10.1.1.

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 regular phone or virtual calls will occur in place of the schedule on-site visits, for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again.

Safety information from subjects who elect to use home nursing services as per Table 8-1, will be collected by trained medical professional at subject's home.

8.4.1 Physical Examination

A complete physical examination will be performed at the visits indicated in Table 8-1 and Table 8-2 and will include an assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, weight, neurological function and comments on general appearance. A complete neurological examination will be part of the initial physical examination at Screening.

Information for all physical examinations (including skin examination) 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 CRF 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 events eCRF.

8.4.2 Electrocardiogram (ECG)

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

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

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

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

Findings and clinically significant abnormalities must be recorded on the relevant section of the medical history form and AE eCRF page as appropriate.

8.4.3 Vital Signs

Vital signs will include sitting pulse rate (measured three times as radial pulse for 60 seconds), sitting systolic and diastolic blood pressure and body temperature (oral, or per local practice and should be recorded in the relevant CRF page in Celsius) which will be assessed at the visits indicated in Table 8-1 and Table 8-2.

After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Vital signs should be obtained 30-60 minutes before the s.c. injection and again approximately 60 minutes post for the Day 1 administration. If premedication is administered, the vital signs should be taken prior to premedication administration.

8.4.4 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.

8.4.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the laboratory manual. Abnormal laboratory parameters, inconsistent with the clinical presentation of MS or which cause suspicion of an underlying medical condition, should be repeated for confirmation.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory

until normalization of the result(s) or until the result is no longer considered clinically significant.

As per Section 4.6, during a Public Health Emergency, as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, limiting or preventing on-site study visits, alternative methods of providing continuing care may be implemented. Standard safety laboratory testing may be conducted by a local laboratory if it is possible to arrange for the laboratory panels (i.e. scheduled chemistry, hematology and urinalysis) to be performed if subject cannot attend scheduled on-site clinic visit or other issues exist that would either prohibit the collection or shipment of laboratory samples to the central laboratory in accordance with the laboratory manual for the study. A local laboratory may also be used to obtain CD19+ B-cell, IgG and IgM counts at the investigator's discretion. The investigator must assure to collect and file all local laboratory reports, certifications and reference ranges in the subject medical record or chart. Data obtained from local laboratories will be used for the investigator's purposes only (to continue monitoring and following-up on subject safety issues) and will not be included in the study clinical database or study analyses.

Scheduled or unscheduled subject study visits can be performed once feasible and considered safe for subjects to attend the clinical appointments.

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Blood samples will be collected according to the schedule in Table 8-1 and Table 8-2. Hematocrit, Hemoglobin, Platelets, Red blood cell (RBC) count, Total white blood cell (WBC) count and WBC differential counts (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils).
Chemistry	Blood samples will be collected according to the schedule in Table 8-1 and Table 8-2. Electrolytes (Sodium, potassium, chlorine, bicarbonate, calcium, magnesium, phosphorus), random glucose, total protein, blood urea nitrogen (BUN), albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin (TBL), conjugated bilirubin, creatinine, amylase, total cholesterol, triglycerides, high density lipoprotein and low density lipoprotein, C-Reactive protein.
B-cell/T-cell sampling	$CD19^+$ B-cell counts (all sites) and B-cell and T-cell subset counts (US sites only). Samples will be collected according to the schedule in Table 8-1 and Table 8-2. Analyses for the B-cell and T-cell subset testing will be conducted in the United States only and focused on one laboratory highly specialized in the analyses of B-cell and T-cell subsets. The potential number of patients are sufficient for understanding B-cells and T-cells e.g. immunology under treatment with ofatumumab.
Total IgG and IgM levels	Samples will be collected according to the schedule in Table 8-1 and Table 8-2
Biomarker sampling	Refer to Section 8.5.2
Urinalysis	Urine will be collected at the scheduled visits indicated in Table 8-1 and Table 8-2. The dipstick parameters assessed will include blood, glucose, specific gravity and protein. In case of an abnormal dipstick test, a urine sample will be sent to the central laboratory for testing including additional parameters such as microscopy and WBC and RBC sediments.
Additional tests	Testing of lab samples will be conducted at screening to determine the subject's eligibility for inclusion in the study with respect to hepatitis and HIV viruses. Testing for syphilis and tuberculosis at screening is also needed and should be assessed by medical history or per local practice. Subjects with active hepatitis B and C disease, assessed locally.

Test Category	Test Name
	HBV screening should be performed before initiation of treatment. At a minimum, screening should include hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. Subjects 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 hepatitis B reactivation. Hepatitis C risk must be ruled out via anti-HC IgG (if positive IgG, HCV-RNA PCR will be performed and if negative, subject can be enrolled). NOTE: If the Investigator suspects false positive hepatitis serology results such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, an infectious disease expert may be consulted. In the case the patient has a record of vaccination including HB, and there is no evidence of acute or chronic hepatitis infection (confirmed by an infectious disease expert), the Investigator must document (in source data and as a comment in the eCRF that the serology results are considered false positive and may then enroll the subject. SARS-CoV-2 PCR test at screening if required by Health Authorities or in case of patients showing symptoms of COVID-19 during the study.
Pregnancy Test	Serum / Urine pregnancy test (refer to Section 8.4.6).

8.4.6 Pregnancy and assessments of fertility

Serum pregnancy tests will be conducted for all women of childbearing potential at Screening, annually and EOS visits. Urine pregnancy tests will be conducted for all women who are of child bearing potential at all other planned clinic visits as indicated in Table 8-1 and Table 8-2 prior to study drug administration. In addition, the subjects will be provided with urinary pregnancy test kits for monthly home pregnancy testing required between the scheduled clinic visits prior to study drug administration. The subjects will document the date and result of each home pregnancy test. In case of a positive test result, the subject must contact the Investigator immediately for confirmatory testing at the Investigator's discretion.

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

All pre-menopausal women who are not surgically sterile will have pregnancy testing. A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of a medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document. Additional pregnancy testing might be performed if required by local requirements.

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, if subjects cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant subjects can perform the urine pregnancy test at home and report the result to the site.

It is important that subjects 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 subject so that the site is informed and can verify the pregnancy test results (e.g. following country specific measures).

8.4.7 Appropriateness of safety measurements

The safety assessments included in this study (Table 8-1 and Table 8-2) are standard for the MS indication and study subject population and appropriate based on the current safety profile of ofatumumab as seen in both Phase 2 and Phase 3 studies, see Investigator's Brochure (IB) for more information.

The use of C-SSRS to detect suicidal ideation behavior is currently mandated in studies of CNS active drugs, for further details, refer to Section 10.2.1.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported / patient centric outcome (PRO) measures are included in this study to provide an empirical assessment from the subject's perspective of the benefits of treatment that cannot be gained from MRI, EDSS, or relapse measurement. These PROs will be completed according to the schedule in Table 8-1. The CCI , CCI , CCI and CCI will be collected electronically in a handheld CCI . The subject must be given the handheld to be completed at the scheduled visit before any clinical assessments are completed. In the event the questionnaires are unavailable for the subject during a visit (e.g. technical issue with the handheld), there is a web backup option available for the subject to complete. Paper versions for CCI , CCI , CCI and CCI are not available for this study.

8.5.1.1 CCI

The CCI version 2 (Hobart and Cano 2009) will be used to assess health-related quality of life and will be evaluated at planned visits according to Table 8-1 when Patient Reported Outcomes (PROs) are planned. CCI is a CCI , self-administered questionnaire that includes two domains, physical and psychological. Responses are captured on a 4-point scale ranging from “not at all” (1) to “extremely” (4), where higher scores reflect greater impact on day-to-day life.

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

The questions in the scale ask the subject for their views about the impact of MS on their day-to-day life during the past 2 weeks. The CCI takes approximately 5 minutes to complete, and will be translated into the appropriate language of the subject.

8.5.1.2 CCI CCI

The CCI will be used to psychometrically evaluate the patients' satisfaction with ofatumumab treatment and will be recorded at planned visits according to Table 8-1 when Patient Reported Outcomes (PROs) are planned. The CCI is a sound and valid measure of the major dimensions of patients' satisfaction with medication and a good predictor of adherence across different types of medication and patient population.

The CCI Version 1.4 comprises 14 items across four domains focusing on effectiveness (3 items), side effects (5 items), convenience (3 items), and global satisfaction (3 items) of the medication over the previous 2–3 weeks, or since the subject's last use. With the exception of item 4 (presence of side effects; yes or no), all items have 5 or 7 responses, scored from 1 (least satisfied) to 5 or 7 (most satisfied). The 7-item scales had a non-neutral midpoint, such that there were more positive response options than negative response options, to allow precise information to be obtained at the upper end of the score distribution. Item scores are summarized to give four domain scores, which are in turn transformed to a scale of 0–100. For the purpose of the study, medication side effects will be only captured via the AE reporting form to avoid inconsistency in data capture.

8.5.1.3 CCI

Fatigue in the context of multiple sclerosis (MS) is a complex symptom with still unknown pathophysiology. The CCI is a 20 item scale developed as a measure of cognitive and motor fatigue for people with MS. CCI will be assessed at planned visits according to Table 8-1 when Patient Reported Outcomes (PROs) are planned. Sensitivity and specificity scores allow reliable assessment and the statistically identified cutoff values provide detailed quantification of fatigue in clinical routine. The tool has been extensively validated in different languages, and practice settings. Improving fatigue in patients with MS is difficult and drug trials have shown mixed results. Given the high impact on employment and quality of life, the scale will be utilized.

8.5.1.4 CCI

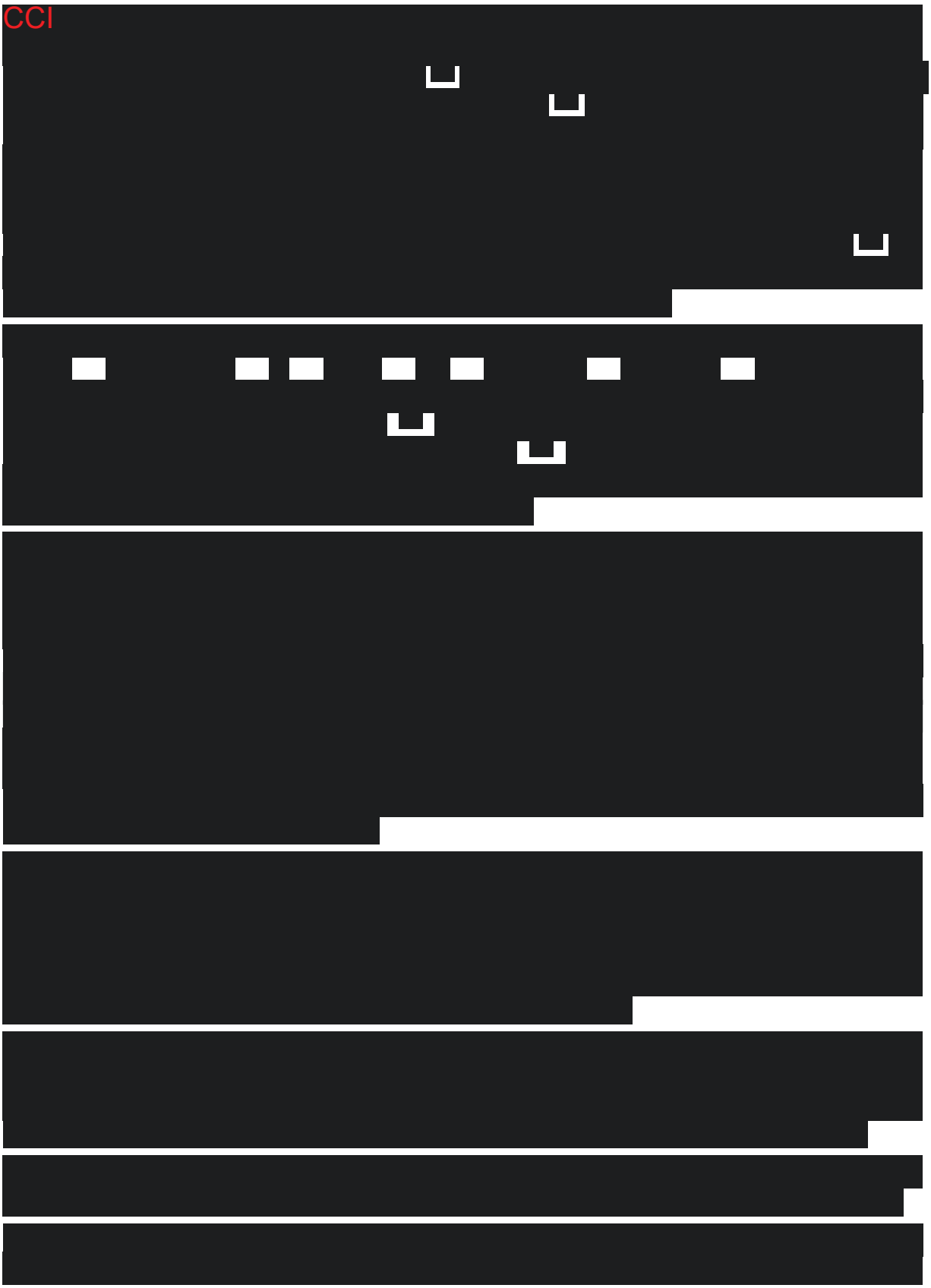
Depression and anxiety are reported to have a severe negative impact on people with MS and are associated with a reduction in health related quality of life.

CCI is a 14-item self-reported measure with two subscales. A score of 8 or above on either subscale indicates possible clinically relevant anxiety or depression. During the study, if the subjects scores 8 or above, the investigator should use the clinical judgment if the subject need additional treatment and document this in the CRF.

The CCI has been found to have high sensitivity and specificity in relation to clinical interview and to other mood rating scales in people with MS. The scale is administered and data captured electronically taking approximately 8 minutes to complete.

8.5.1.5 CCI

CCI


CCI

CCI

8.5.1.6 CCI

CCI

8.5.2 Biomarkers

Blood samples will be drawn for analysis of exploratory biomarkers according to the schedule in Table 8-1 and Table 8-2. These specimens will be used to identify and/or verify potential markers that may be predictive of disease activity, disease course and/or clinical response to treatment. Analysis of these specimens will include NfL and CCI (for both, also refer to Section 8.3.3). Samples for biomarker assessment should be taken prior to dosing at Visit 1. For any later biomarker visits, if the visit coincides with the day of the monthly injection, the subject should not take the injection in the morning before coming to the site so that the biomarker sample can be drawn prior to administration. The biomarker sample collection date and time must be entered on the appropriate eCRF.

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

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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

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

Study drug must be discontinued under the following circumstances:

- Subject/guardian decision (Section 9.1.2)
- Pregnancy (Section 8.4.6 and Section 10.1.6)
- Use of prohibited treatment (Section 6.2.2)
- Diagnosis of PML
- Subjects with active serious infections or reactivation (e.g. tuberculosis, hepatitis B or C)
- Skin and/or mucosal reactions which raise the suspicion of severe generalized major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome)
- Hypersensitivity to the study medication
- Any situation in which study participation might result in a safety risk to the subject
- Protocol violation that results in a significant risk to the subject'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 human immunodeficiency virus (HIV))
- Severe hypoproteinemia
- Interstitial lung disease or new onset or worsening of pulmonary symptoms, such as persistent cough and dyspnea, with or without associated fever, suspicious of interstitial lung disease
- Non-compliance with study drug or study procedures

Study treatment discontinuation should be considered under the following circumstances:

- For subjects who meet the criterion for 6mCDW on EDSS during the study, the investigator must reassess the benefits and risks of continuing study treatment. The investigator will also discuss the further treatment with the subject, including any other MS treatment options that may be available to the subject. The outcome of the discussion with the subject must be documented in the subject's source information
- In case the investigator deems the benefit-risk of continuing study treatment to be unfavorable or if the subject does not wish to continue study treatment, the subject will be discontinued from the study and will enter the Safety Follow-up period (Table 8-2). The investigator will be notified by the Sponsor when a subject meets the criterion for 6mCDW.

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

Subjects who discontinue study drug 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 9.1.2). Subjects that discontinue treatment should complete the EOS visit and move to the Safety Follow-up as per 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 subject/pre-designated contact as specified in Section 9.1.3. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular contact with the subject, or with a person pre-designated by the subject. This contact should preferably be done according to the study visit schedule for up to 6 months post last study drug administration.

After study drug discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

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

The investigator must also contact the IRT to register the subject's discontinuation from study drug.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a subject:

- Explicitly requests to stop use of their data

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 as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the subject, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information. The Investigator shall clearly document if the subject has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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

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

If the subject agrees, a final evaluation at the time of the subject's withdrawal of consent should be made as detailed in the assessment table.

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

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

A subject is considered to have completed the study when they fulfill the following criteria:

- Subject has completed the study in its entirety according to the approved duration of the study within that country
- The subject has **not** stopped the study due to one or more of the following reasons:
  - Discontinuation of study treatment (Section 9.1.1)
  - Withdrawal of informed consent (Section 9.1.2)
  - Lost to follow-up (Section 9.1.3)

End of Study (EOS) visit is mandatory for all subjects. For subjects that complete the study, the next (and last) scheduled visit is the EOS visit and should align with the overall visit schedule. Subjects who prematurely discontinue study treatment will have their EOS visit as soon as possible and continue into the Safety Follow-up according to the assessment schedule in Table 8-2.

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

In the countries where ofatumumab is not approved by Health Authorities, not launched or reimbursed, subjects who participate in Novartis clinical trials and are deriving benefit, based on the investigator's evaluation, from the study drug at the completion of the Treatment period, may continue to receive the study drug (ofatumumab) via a Post-Trial Access (PTA) mechanism until ofatumumab becomes approved by the local Health Authorities, is commercially available, and reimbursed in the particular country or the PTA program ends, whichever occurs first. Reimbursement refers to country level and not individual reimbursement, if there are multiple reimbursement channels in a country the date of reimbursement is when the first major reimbursement is in place. Post Study Drug Supply (PSDS) is the first option for PTA. If PSDS cannot be implemented in a country due to the local legislation, the clinical trial team will work with the Investigator to assess other PTA possibilities.

The PTA program has a maximum duration (program dependent) and will provide the study drug to the subjects until the study drug receives regulatory approval, is commercially available, and reimbursed in the subject's country, or the program ends, whichever occurs first. If the subject is no longer deriving benefit from the study drug (ofatumumab) treatment per the investigator's evaluation, they need to be discontinued from the PTA program. Safety will continue to be monitored in the mechanism that will have been chosen for PTA. The PTA mechanism should comply with the local laws and regulations in the participating trial countries. Furthermore, if the treatment's risk-benefit ratio has turned negative and/or Novartis discontinues the development of the study drug due to lack of efficacy and/or safety reasons, then Novartis will work with the investigators to transition the subjects onto locally available treatment or alternative treatment.

9.2.1 Safety Follow-up

Subjects moving into the Safety Follow-up period, as described in Section 3, will continue for 6 months post last dose of ofatumumab treatment. A shorter follow-up time is acceptable if subjects select a different MS treatment during this period as presented below.

At the EOS + M6 Visit:

- If a subject has IgG and IgM results ≥ screening or LLN, this visit shall be considered final clinic visit for the subject. The End of Safety Follow-up visit will be performed by telephone contact to inform the subject that his or her participation in Safety Follow-up has ended; the disposition form will be completed at that time and the AE and concomitant medications eCRF will be updated if necessary to record any new or worsening events or medication changes since the last clinic visit.
- If a subject has either IgG or IgM results < screening or LLN, Safety Follow-up clinic visits will continue on a plus 3 monthly basis until both IgG and IgM values are ≥ screening or LLN. The End of Safety Follow-up visit will be performed by telephone contact to inform the subject that his or her participation in Safety Follow-up has ended; the disposition form will be completed at that time and the AE and concomitant medications eCRFs will be updated if necessary to record any new or worsening events or medication changes since the last clinic visit; refer to Table 8-2.

- Note: All IgG and IgM results are required to be confirmed by a Central Laboratory result. IgG/IgM assessments performed by a local laboratory under the Public Health Emergency mitigation procedures defined in Section 8.4.5 are not to be used to determine if the subject has met the criterion for their last immunoglobulin follow-up visit. During a Public Health Emergency, subjects should continue to be monitored until it is feasible and safe to schedule a clinic visit to obtain a sample for central laboratory evaluation unless Last Subject Last Visit (LSLV) has already been declared for the study. In such circumstances, please follow the guidance presented below.

Patients starting a different MS treatment during Safety Follow-up:

- During Safety Follow-up subjects may receive any DMT for the treatment of MS as the investigator deems necessary. Prior to starting the MS DMT, subjects will be brought in for their final Safety Follow-up visit. This visit will be the End of Safety Follow-up visit for the subject and the disposition page will be completed at this time.

The study is envisioned to end when the last subject who entered Safety Follow-up completes his or her EOS + M6 clinic visit and the End of Safety Follow-up telephone contact visit defined as LSLV. It is possible that a small subset of subjects may still have low immunoglobulin levels and therefore ongoing in Safety Follow-up as the LSLV date approaches. Study follow-up for these subjects will be truncated so that their final visit will be performed on or prior to the scheduled LSLV date for the study. Subsequent follow-up immunoglobulin monitoring for these subjects, and last subject if necessary, will be performed outside of the study at the discretion of the treatment investigators and documented in subject's medical records only.

10 Safety monitoring and reporting

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 subject or clinical investigation subject 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.

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

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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject 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 subjects with the underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Clinically notable laboratory findings are defined according to the Common Terminology Criteria for Adverse Events (CTCAE) (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):

- The Common Toxicity Criteria (CTC) AE 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

- Its relationship to the study treatment.
- Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
- Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
- 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/withdrawn
- Concomitant medication or non-drug therapy given
- Subject hospitalization/subject's hospitalization prolonged (see Section 10.1.2 for definition of SAE)
- Its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown).

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

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

Adverse event monitoring should be continued for at least 100 days following the last dose of study treatment.

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 (ofatumumab) can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of ofatumumab that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

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

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 subject 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 (e.g. hospitalization for MS relapse treatment)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject'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 subject 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 subject 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 SAE irrespective if a clinical event has occurred, and are to be reported as appropriate according to Section 10.1.7.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 100 days after the final study drug administration for study completers or until the end of Safety Follow-up for premature withdrawals must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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 immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The Investigator must assess the relationship of each SAE to each specific component of study treatment (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form to Novartis Safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements for signature are to be found in the Investigator folder provided to each site.

Follow-up information is submitted as instructed in the Investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has

resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office & Patient Safety (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 100 day period after the final study drug administration or after the end of Safety -Follow-up should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Reporting MS relapse as a SAE

MS relapses are 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 MS relapse 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 must be completed and submitted according to SAE reporting procedures outlined above.

10.1.5 Reporting of Disability Worsening as a SAE

Disability worsening is one of the efficacy endpoints in this study; hence, it is exempt from SAE reporting although it may meet the SAE definition "results in persistent or significant disability/incapacity" (Section 10.1.2). However, if, in the judgment of the Investigator the disability worsening is unusually severe or medically unexpected and warrants specific notification, then a SAE form must be completed and submitted according to SAE reporting procedures outlined above.

10.1.6 Pregnancy reporting

Details of all pregnancies in female subjects will be collected after signing informed consent and until 6 months after stopping study treatment.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis as described in Section 10.1.3. While the

Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Pregnancies

If a female trial subject becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial subject. The subject 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. To ensure subject 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 until after the Expected Delivery Date (EDD) 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. Additional follow up will be completed at EDD +1 month, EDD +2 months (in case no answer is received after request at EDD +1 month), EDD +3 months, EDD + 6 months, and EDD +12 months. Information on the status of the baby after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on a SAE form.

10.1.7 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, subject or consumer (European Medicines Agency (EMA) definition).

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

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

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

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

In certain countries, e.g., Czech Republic, the local health authority requires to ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

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

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 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 16-2 and Table 16-3.

For all liver event triggers, liver chemistry tests (i.e. ALT, AST, TBL, International Normalized Ratio (INR), ALP, albumin, CK, GLDH and GGT) must be repeated according to Table 16-2 and Table 16-3.

- 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 subject.
- 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. Repeat laboratory examinations must then be performed at central laboratory as soon as possible.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- Hospitalization of the subject 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 CRF.

10.2.2 Renal safety monitoring

In certain countries, e.g., Czech Republic, the local health authority requires the following two categories (Serum event and Urine event) of abnormal renal laboratory values that have to be considered during the course of the study:

- Serum creatinine (sCR) increase ≥ 25% compared to baseline during normal hydration status, confirmed after 24 hours
- New onset urine dipstick proteinuria ≥ 3+, confirmed by doubling in the urinary albumin/creatinine ratio (ACR) or urinary protein-creatinine ratio (if applicable).
- New onset (≥ 3+), hematuria or Urine Protein-creatinine ratio ≥ 1g/g

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment. Every renal laboratory trigger or renal event as defined in Table 16-4 should be followed up by the investigator or designated personnel at the trial site.

10.2.3 Prospective suicidality assessment

The C-SSRS is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS can be administered at each visit, including unplanned visits.

At the first study visit, the "baseline/screening" version of the C-SSRS will be administered. This version assesses suicidal ideation and suicidal behavior during the subject's lifetime and during a predefined period. At subsequent visits, the "since last visit" version will be administered.

A validated version of the C-SSRS will be used to capture self-reported C-SSRS data via an electronic device (eC-SSRS). The eC-SSRS uses a detailed branched logic algorithm to perform the C-SSRS subject interview, evaluating each subject's suicidality ideation and behavior in a consistent manner. If the system assesses the subject as having positive suicidal signs, the investigator will be immediately notified by either fax, email, and/or via telephone.

In the event the eC-SSRS is unavailable for the patient during a visit (e.g. technical issue with the tablet), patient should be provided with the web backup version to complete. The paper version of the C-SSRS (C-SSRS) will be administered by the investigator only if the tablet and web backup option is not available. A completed C-SSRS must be filed in the patient's source documents and data transcribed on the eCRF, if completed on paper.

C-SSRS should be also completed during home visits supported by the home nursing service or in case patient is not able to attend on-site visit for any reason and information can only be obtained remotely (e.g. by phone).

If, at any time after screening and/or baseline, the score is "yes" on item 4 or item 5 of the suicidal ideation section of the C-SSRS or "yes" on any item of the suicidal behavior section, the subject must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study drug should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the subject is referred.

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

10.2.4 Data Monitoring Committee

No data monitoring committee will be implemented given that the study is open label. Data will be reviewed on an ongoing basis by the medical monitor and the clinical study team including safety data scientist and statistician.

10.2.5 Steering Committee

A study steering committee will be appointed prior to first patient first visit.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRFs. 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 (recorded on CRFs) (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.

All other data captured for this study will have either the eCRF as source or an external originating source (either written or electronic) with the CRF not being considered as source. In cases where electronic source data capture devices experience faults, for example, digital device used for ePROs, paper back-up source will be permitted.

After final database lock, the investigator will receive copies of the subject 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 Sponsor. MRI scans will be analyzed centrally the derived results will also be sent electronically to Sponsor.

Enrollment codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

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, including determining the occurrence of relevant protocol deviations, and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

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 subject records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full

verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

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 subjects to whom study drug has been assigned and who received at least one dose of study drug. The FAS will be used for the summary of demography and baseline characteristics as well as for all efficacy analyses.

The Safety Set includes all subjects who received at least one dose of study drug. The Safety Set will be used for all safety analyses.

12.2 Subject demographics and other baseline characteristics

Demographics, MS disease history, MRI baseline characteristics and MS medication history will be summarized for the FAS.

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

12.3 Treatments

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 subjects by time category, and with summary statistics of the number of subject years of exposure.

Time-at-risk is defined as the number of days spent in the study, from first dose to the last dose of study medication, plus the safety data cut-off of 100 days. Intermediate treatment interruptions will be included in time-at-risk calculations. Time-at-risk will be summarized in a similar way to exposure to investigational study medication.

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

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is to determine the effectiveness of ofatumumab 20 mg s.c. administered every 4 weeks in subjects with relapsing forms of MS who have breakthrough treatment response on fumarate-based RMS approved therapies or fingolimod as evaluated by the annualized relapse rate (ARR, based on confirmed relapses) in patients with relapsing MS. The primary analysis will describe the ARR with one-sided 95% confidence bound and test for null hypothesis (H_0): ARR >=0.18 versus alternative hypothesis (H1): ARR<0.18.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is the annualized relapse rate (ARR, based on confirmed relapses), which is defined as the number confirmed MS relapses in a year. In the primary analysis, the ARR is estimated based on the FAS using individual relapse count as the response variable with time in study as an offset variable.

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

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

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will describe the test for null hypothesis (H0): ARR >=0.18 versus

alternative hypothesis (H1): ARR<0.18. The ARR will be estimated for the entire duration by a negative binomial model with log-link and subject's time in study (as natural log of time in years) will be used as an offset with number of relapses in previous year, baseline EDSS, baseline number of T1 Gd enhancing lesions and the patient's age at baseline, prior MS therapies (fumarates or fingolimod) as covariates. The list of covariates in the model can be modified based on convergence of the statistical model. In addition, ARR will be calculated as number of confirmed relapses divided by time in study in year will also be presented for the entire duration. The ARR will also be summarized by yearly interval starting from the first dose of ofatumumab.

12.4.3 Handling of missing values/censoring/discontinuations

CCI [redacted]

12.4.4 Sensitivity and Supportive analyses

CCI [redacted]

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoint(s)

No secondary efficacy endpoint is planned.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented for all subjects in the safety set. Unless explicitly otherwise stated, only data up to and including the safety cutoff of 100 days after permanent study drug discontinuation will be included in the analysis and data beyond this time point for a patient will be excluded from safety analysis. In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, which started or worsened during the on-treatment period (treatment-emergent AEs).

The on-treatment period for safety analysis lasts from the date of first administration of study drug to 100 days after the date of the last actual administration of study drug.

The sensitivity analysis for safety endpoints based on modalities for data collection (on-site or remotely) and based on pandemic phase indicator may be performed if there is sufficient data.

Adverse events

All information obtained on adverse events will be displayed. The number (and proportion) of subjects with AEs of special interest/related to identified and potential risks will be summarized.

A subject with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class. Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of AE, relation to study drug.

Adverse events, Serious AEs and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized. All AEs, death and serious AEs (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

Vital signs data may be listed by subject, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by visit/time.

Clinical laboratory evaluations

All abnormal laboratory values will be listed by subject, and visit/time, if normal ranges are available. Summary statistics will be provided by visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version available at the time of analysis. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE available at the time of analysis, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE available at the time of analysis grades if applicable and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE available at the time of analysis.

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades available at the time of analysis to compare baseline to the worst on-treatment value.
- For laboratory tests where grades are not defined by CTCAE available at the time of analysis

Suicidality evaluations

The C-SSRS data will be mapped to Columbia Classification Algorithm for Suicide assessment (C-CASA) as per FDA guidance on suicidality. The proportion of subjects who have completed suicide, suicide attempt, and preparatory actions toward imminent suicidal behavior, suicidal ideation, and self-injurious behavior without suicidal intent as per the C-CASA scale during the study (safety data cutoff applies) will be summarized.

Other safety evaluations

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

Other safety data will be summarized or listed as appropriate.

12.5.3 Biomarkers

No secondary biomarker analysis is planned.

12.5.4 Patient reported outcomes

No secondary PRO analysis is planned.

12.6 Analysis of exploratory endpoints

Exploratory endpoints will be explored/evaluated through the use of visualization/exploration tools and relevant findings will be provided in the CSR. The details of exploratory endpoints analysis will be provided in a separate statistical analysis plan (SAP).

CCI [redacted]

Long term efficacy of ofatumumab:

The following endpoints will be explored for describing the long-term efficacy of ofatumumab 20 mg s.c. once q4 weeks:

- Change from baseline in Expanded Disability Status Scale (EDSS)
- Change from baseline in Time 25-Foot Walk (T25FW)
- Change from baseline in Nine Hole Peg Test (9HPT)
- Change from baseline in CCI
- Change from baseline in Low Contrast Visual Acuity (LCVA)
- Change from baseline in T2 lesion volume (T2VOL)
- Time to 6-month confirmed Disability Worsening (6mCDW)
- Time to a 6-month confirmed cognitive decline (6mCCD, defined as a 4-point worsening on CCI)
- Number of T1 Gd+ lesions per scan
- Number of new or enlarging T2 lesions on MRI per year (annualized T2 lesion rate)
- Proportions of subjects after 48 and 96 weeks that meet the criteria of No evidence of disease activity three (NEDA-3)

Change from baseline in ARR, EDSS score, T25FW score, 9HPT, CCI , T2VOL and LCVA will be summarized descriptively by visits. Adjusted estimates will be obtained using repeated measures models.

Time to 6mCDW, Time to 6-month confirmed 4-point worsening on CCI will be analyzed by Kaplan-Meier (KM) method. KM curve and KM estimates at each year will be presented.

Number of T1 Gd+ lesions and number of new or enlarging T2 lesions for the entire duration will be summarized descriptively. The proportion of patients with/without MRI lesion activity will also be summarized descriptively.

Proportions of subjects after 48 and 96 weeks that meet the criteria of No evidence of disease activity three (NEDA-3) will be summarized descriptively.

FAS will be used as analysis set for the analysis of all efficacy endpoints.

Biomarker:

The following endpoints will be explored related to biomarker for MS:

- Change from baseline serum Neurofilament (NfL) concentration
- Relationship between baseline serum NfL and disease activity, disease course, treatment response
- Utility of NfL for disease activity monitoring
- Change from baseline serum CCI concentration
- Relationship between baseline serum CCI and disease activity, disease progression and treatment response
- Utility of CCI for disease activity and progression monitoring
- Correlation between CCI and NfL serum levels in the course of MS disease

Change in NfL and CCI concentration will be summarized by visit descriptively. Relationship between NfL and CCI with disease activity, disease course and treatment response will be analyzed along with utility of NfL and CCI for disease activity and progression monitoring. FAS will be used as analysis set. More details will be provided in the SAP.

PROs:

The following endpoints will be explored for the health outcomes in subjects treated with ofatumumab 20 mg s.c. once q4 weeks:

- Change from baseline in CCI
- Change from baseline in CCI
- Change from baseline in CCI
- Change from baseline in CCI

Change from baseline in CCI scores, CCI scores and CCI scores will be summarized by visit descriptively. FAS will be used as analysis set.

The CCI consists of two sub-scores: the CCI for CCI and CCI for CCI. Descriptive statistics for CCI and CCI score at each visit with changes versus baseline will be provided.

CCI:

Adherence to CCI assessments is measured by proportion of study weeks with at least 3 days of completed active testing, and proportion of study weeks with at least 3 days of passive monitoring for ≥ 4 hours/day.

CCI CCI CCI comprises of the following measures:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

The association between CCI [redacted] with CCI [redacted] and other clinical assessments will be evaluated only if a sufficient compliance level is attained.

12.7 Interim analyses

Some interim analysis(es) may be performed periodically as needed (e.g. to support regulatory updates).

12.8 Sample size calculation

The primary analysis (ARR) will use a negative binomial regression model with log-link and time-in-study as offset. The ARR in Phase 3 ofatumumab studies was 0.10 and 0.11 (Hauser et al 2019). In the targeted population of patients with breakthrough activity on either fumarates or fingolimod, an ARR of 0.16 on ofatumumab is assumed (Hauser et al 2015; Kappos et al 2011). CCI [redacted] The study population consists of subjects transitioning from fumarates or fingolimod to ofatumumab. Thus, the sample size of CCI [redacted] is reasonable in order

- to make conclusion on disease control in the overall trial
- to be able to separately analyze effectiveness and safety of ofatumumab in subjects coming from fumarates or fingolimod

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, [IDFU], and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Signing 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
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21, if applicable), 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 informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study

start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is 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 and as required in EudraCT or CTIS public website, if applicable. In addition, after study completion (*defined as last subject 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, EudraCT or CTIS public website, if applicable etc.) .

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.

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

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 Data protection

Subjects will be assigned a unique identifier by Novartis. Any subject records or datasets that are transferred to Novartis will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

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 subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction 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 subject 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 subject 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.

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16 Appendices

16.1 Appendix 1: Safety Monitoring Guidance

16.1.1 Guidance on monitoring of subjects with symptoms of neurological deterioration suggestive of PML

Should a subject 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 FLAIR and Diffusion-weighted imaging (DWI) sequences are recommended to aid in differential diagnosis. The local neuro-radiologist must evaluate the MRI. The Investigator will contact the Medical Advisor at Novartis and a clinical trial team (CTT) member 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. AE/SAEs need to be filed as appropriate.

If the MRI shows new MS lesions consistent with an MS relapse, assessment and treatment of the relapse will be performed as described in the protocol (Section 6.2.3 and Section 8.3.1). In case of new findings in the MRI images in comparison with the previous available MRI, which are not compatible with MS lesions, the study drug will be discontinued and other diagnostic evaluations need to be performed at the discretion of the Investigator. If new lesions are detected on the MRI, which may be infectious in origin, it is recommended to collect a cerebrospinal fluid sample (CSF) if indicated. Analysis of the Cerebrospinal Fluid (CSF) sample including cellular, biochemical, Polymerase Chain Reaction, and microbiological analysis (e.g. herpes virus, JC virus) to confirm/exclude an infection should be performed. In the event of suspected CNS infection (PML), a CSF aliquot should be sent to a central laboratory (designated by 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 CTT member, the study drug may be restarted.

16.1.2 Guidance on monitoring subjects with infections

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

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

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

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

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 CTT of any such cases.

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

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

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

In subjects with suspected COVID-19 infection, the investigator should perform a diagnostic COVID-19 testing. Subjects treated with ofatumumab who are exposed to, or suspected or confirmed positive with COVID-19, should consider treatment interruption after contacting Investigator immediately for further guidance. Investigators are advised to act in accordance with local government and health authority guidance concerning COVID-19 (including guidance on social distancing and self-isolation, as applicable). Study treatment decisions should be made between a subject and Investigator based on a benefit/risk assessment specific to the individual.

16.1.3 Guidance on immunization

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

It is recommended that the Investigator review the subject's immunization history as part of the initial Screening procedure for a subject being considered for treatment with ofatumumab. Vaccination of the subject, in compliance with local area vaccination guidelines for the subject population being treated, is recommended prior to administration of ofatumumab. In particular,

prior to administration of ofatumumab, hepatitis B vaccination, in subjects with risk factors for hepatitis B infection or in areas with a high prevalence of hepatitis B, as per local area treatment guidelines should be considered.

Administer all immunizations according to immunization guidelines. Administration of live or live-attenuated vaccines must be avoided (Section 6.2.2) during treatment and after discontinuation of treatment with ofatumumab until B-cell counts are normalized. Subjects who would like to receive a live or live-attenuated vaccine during the study would discontinue study treatment for vaccination (Section 9.1.1).

Vaccination with inactivated vaccines are permitted during study and there is currently no contraindication for the use of inactivated COVID-19 vaccines. It is recommended not to receive ofatumumab treatment for 2 weeks prior to the administration of inactivated vaccines. The following dose of ofatumumab should not occur until 2 weeks after the final dose administration of the inactivated vaccine regimen.

16.1.4 Guidance on monitoring of subjects with low immunoglobulin levels

During the study, the immunoglobulin levels (IgG and IgM) will be measured according to the schedule in Table 8-1 and Table 8-2. If IgG levels were to drop below 300mg/dL (Agarwal and Cunningham-Rundles 2007), study drug treatment may be interrupted at the discretion of the Investigator and the Investigator should evaluate patient for any potential infections and monitor on a regular basis. Immunoglobulin substitution therapy as per local medical practice is allowed. In case of treatment interruption, re-initiation of the study drug can only be considered once the immunoglobulin levels are back within normal limits.

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

In certain countries, e.g., Czech Republic, the local health authority requires following up on liver events described below:

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5
	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	• Any clinical event of jaundice (or equivalent term)

	Definition/ threshold
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	• Any adverse event potentially indicative of a liver toxicity*
*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal.	

Table 16-2 Follow up requirements for liver events and laboratory triggers

ALT or AST	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase			
ALT or AST	**TBL**	**Liver Symptoms**	
If normal at baseline: · ALT/AST > 3 x ULN	Normal	None	· No change to study treatment · Follow up including measuring ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours, and symptoms/ etiology to establish causality. · Follow-up for symptoms
If elevated at baseline: · ALT/AST > 2 x baseline	No clinically significant change in TBL*		
If normal at baseline: · ALT/AST > 5 x ULN for more than two weeks	Normal	None	· Interrupt study drug · Follow up including measuring ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours, and symptoms/ etiology to establish causality. · Study drug can be restarted only if causality to the study drug is excluded and liver enzymes return to baseline.
If elevated at baseline: · ALT/AST > 3 x baseline for more than two weeks	No clinically significant change in TBL*		
If normal at baseline: · ALT/ AST > 8 x ULN	Normal	None	
ALT/AST increase with bilirubin increase			
ALT or AST	**TBL**	**Liver Symptoms**	
If normal at baseline: · ALT/AST > 3 x ULN	TBL > 2 x ULN (or INR > 1.5)	None	
If elevated at baseline: · ALT/AST > 2 x baseline	Doubling of direct bilirubin at baseline or higher*		
If normal at baseline:	Normal or elevated		

· ALT/AST > 3 x ULN If elevated at baseline: · ALT/AST > 2 x baseline		Severe fatigue, nausea, vomiting, right upper quadrant pain	
Liver events meeting Hy's law (Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 2009). · ALT or AST > 3 x ULN, combined with elevation of serum TBL to > 2 x ULN, without initial findings of cholestasis (no ALP elevation), and · Absence of any alternative cause likely explaining the combination of increased ALT or AST and TBL, such as viral hepatitis B or C; preexisting or acute liver disease; or another drug capable of causing the observed injury			· Interrupt the study drug · Report to Novartis as an SAE · Treating the condition and follow up including measuring ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH at the frequency per investigator's discretion

Table 16-3 Action required for isolated total bilirubin elevation

Abnormality*	**Action required**
Grade 2 (>1.5 - 3.0 ULN)	Repeat liver function test (LFT)s within 48-72 hours, then monitor LFTs weekly until resolution to below Grade 2 or to baseline, if persistent Grade 2, consider drug interruption
Grade 3 (>3.0 – 10 ULN)	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to below Grade 2 or to baseline
Grade 4 (> 10 x ULN)	see footnote** - otherwise discontinue study treatment
*In the absence of Gilbert's syndrome **An isolated bilirubin elevation is not typical for drug-induced liver injury. Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation should therefore, be ruled out before basing dose modification decisions on bilirubin values alone	

16.3 Appendix 3: Specific Renal Alert Criteria and Actions

In certain countries, e.g., Czech Republic, the local health authority requires following up on renal events described below.

Table 16-4 Specific Renal Alert Criteria and Actions

Serum Event	**Actions**
Serum creatinine increase ≥ 25% compared to baseline for participants ≥18 years old during normal hydration status	Consider assessment after 24 hours but within 5 days Consider causes and possible interventions
Urine Event	

New onset urine dipstick proteinuria ≥ 3+ OR New onset hematuria ≥ 3+ on urine dipstick OR Urine Protein-creatinine ratio ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	Consider assessment after 24 hours but within 5 day Consider causes and possible interventions

Additional specialized assessments are available to assess renal function or renal pathology.