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Ofatumumab

Clinical Trial Protocol COMB157GUS10 / NCT05084638

AGNOS: An 18-month, Open-label, Multi-Center Phase IV Study to Assess the Effect of Ofatumumab 20mg SC Monthly in Treatment Naïve, Very Early Relapsing Remitting Multiple Sclerosis Patients Benchmarked Against Healthy Controls on Select Outcomes.

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List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
b.i.d.	bis in die/twice a day
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
[redacted]	[redacted]
CD-ROM	Compact Disc – Read Only Memory
CDP	Clinical Development Plan
CDS	Core Data Sheet
CK	Creatine Kinase
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
CO_2	carbon dioxide
COA	Clinical Outcome Assessment
CQA	Clinical Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSF	Cerebral Spinal Fluid
CSR	Clinical study report
CTC	Common Terminology Criteria
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DIN	Drug Inducted Nephrotoxicity
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DMT	Disease Modifying Therapy
DQF	Data Query Form
DSMB	Data Safety Monitoring Board
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-linked immunosorbent assay
EOI	End of Infusion
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source

[redacted]

FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
h	Hour
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HC	Healthy controls
HED	Human Equivalent Dose
HEOR	Health Economics & Outcomes Research
HIV	Human immunodeficiency virus
HNSTD	Highest Non-Severely Toxic Dose
HRQoL	Health-Related Quality of Life
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
Nab	Neutralizing antibody
NCDS	Novartis Clinical Data Standards
NEDA	No Evidence of Disease Activity
NOVDD	Novartis Data Dictionary
ObsRO	Observer Reported Outcomes
OMB	Ofatumumab
p.o.	oral(ly)
PA	posteroanterior
PD	Pharmacodynamic(s)
PDDS	Patient Determine Disease Steps

[redacted]

PerfO	Performance Outcomes
PK	Pharmacokinetic(s)
PPD	Premature Participant Discontinuation
PRO	Patient Reported Outcomes
PSD	Premature Subject Discontinuation
PT	prothrombin time
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RAP	The Report and Analysis Plan
RBC	red blood cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
RoW	Rest of World
RU	Resource Utilization
sc	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	standard deviation
[redacted]	[redacted]
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TD	Study Treatment Discontinuation
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 days)
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits

[redacted]

Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued, and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy

[redacted]

Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Tele-visit	Procedures or communications conducted using technology such as telephone or videoconference, whereby the participant is not at the investigative site where the investigator will conduct the trial
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent (WoC) / Opposition to use of data / biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent

[redacted]

Amendment 03

Rationale for Amendment

The purpose of Amendment 3 is to make editorial modifications and amend study design items that required updates to provide further clarification.

Changes throughout protocol:

- [redacted]
- [redacted]
- Updated contraception options to include a single barrier method as acceptable
- Updated figure 3-1 to clarify 2 distinct time periods for healthy control arm since reconsenting after the first 18 months will be required
- Clarification on use of plasmapheresis for the treatment of a relapse
- Clarified MRI timeframe and Migraine criteria

[redacted]

Amendment 02.01

Rationale for Amendment

Administrative change on the protocol cover page 1 and the protocol summary page 17, to update the protocol title to reflect the trial phase (Phase IV):

- "An 18 month, Open-label, Multi-Center Phase IV Study to Assess the Effect of Ofatumumab 20mg SC Monthly in Treatment Naïve, Very Early Relapsing Remitting Multiple Sclerosis Patients Benchmarked Against Healthy Controls on Select Outcomes."

[redacted]

Amendment 02

Rationale for Amendment

The purpose of Amendment 2 is to amend additional items that were not clear in the assessment schedule and study design.

Changes throughout protocol:

- [redacted]
- Clarified 100-day Safety Follow-up data with further details on different patient groups and that it will only be captured in the Source Document, not the EDC
- Clarified use of blood vs serum for cell level determination in Table 8-1 and throughout protocol

[redacted]

Amendment 01

Rationale for Amendment

The purpose of Amendment 1 is to amend items that were not clear in the assessment schedule and study design.

Changes in Table 8-1

- PROs will be captured at on-site visits only, not monthly as per previous footnote in Table 8-1
- C-SSRS will now be captured at every screening or baseline, and every on-site visit thereafter, up until EOS
- Study Design has been updated to show 100-day Safety Follow-up visit separate from M21 visit for clarification
- Clarified assessments for Healthy Control participants

Change in Section 6.3.2

- Updated language regarding timing of assessment and drug administration if occurring on same day

Changes throughout protocol

- Clarified the period for NEDA-3 measurement is month 6-18
- Clarified that month 18 will have an interim analysis conducted as the primary endpoint will be measured at this time
- Clarified 100-day Safety Follow-up data will only be captured in the Source Document, not the EDC

[redacted]

Protocol summary

Protocol number	COMB157GUS10
Full Title	An 18 month, Open-label, Multi-Center Phase IV Study to Assess the Effect of Ofatumumab 20mg SC Monthly in Treatment Naïve, Very Early Relapsing Remitting Multiple Sclerosis Patients Benchmarked Against Healthy Controls on Select Outcomes.
Brief title	Study to Assess the Effect of Ofatumumab in Treatment Naïve, Very Early Relapsing Remitting Multiple Sclerosis Patients Benchmarked Against Healthy Controls.
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug vs Healthy Control
Study type	Interventional
Purpose	To complement the ofatumumab clinical development pivotal trials by demonstrating clinical and MRI efficacy (both conventional and non-conventional) in a young adult, treatment naïve, very early MS patient population; patients earlier in the MS disease continuum than those in ASCLEPIOS I and II.
Primary Objective(s)	The primary objective is to explore the impact of ofatumumab (OMB) on the ability to achieve No Evidence of Disease Activity (NEDA-3) status in treatment-naïve, very early RRMS patients over an 18-month, open-label study period after a re-baseline of MRI at 6 months.
Secondary Objectives	**Secondary objectives:** Secondary objectives include additional efficacy outcomes after treatment with ofatumumab in a very early RRMS population, as well as comparison to HC on non-conventional MRI measures and adverse events. • Evaluate the effect of ofatumumab on various clinical (NEDA, disability, relapse) metrics • Evaluate the efficacy of ofatumumab on conventional MRI metrics • Evaluate the efficacy of ofatumumab on patient reported outcomes (PROs) (NeuroQOL™, Patient Determined Disease Steps [PDDS]) • Evaluate the effect of ofatumumab vs healthy controls on whole brain and regional atrophy • Evaluate the safety and tolerability of ofatumumab
[redacted]	[redacted]

[redacted]

	[redacted]
Study design	The study is an open-label, multi-center, prospective 18-month study in 118 MS patients with early RRMS (defined as within 6 months of diagnosis of clinically definite RRMS) and who are treatment naïve. RRMS patients will be benchmarked against age- and sex-matched healthy controls (n=50) for select secondary [redacted] Primary analysis will be conducted at Month 18. MRI data will be re-baselined at Month 6 to account for treatment-related pseudo atrophy. Additional efficacy and safety assessments will be evaluated during an optional 12-month open-label extension period to further elucidate the long-term clinical and radiological effect of ofatumumab.
Rationale	The proposed study would provide rigorous clinical, MRI, digital and biomarker data demonstrating the efficacy, safety and tolerability of ofatumumab in a naïve RRMS population at first diagnosis and would provide the first data relative to healthy controls, identified data gaps in the US.
Study population	The study population will consist of young adult participants, male and female, 18-35 years of age, with an EDSS (0-3.0 inclusive), and very early RRMS (defined as within six months of diagnosis of clinically definite RRMS) that are disease modifying therapy treatment naïve. Approximately 168 (118 ofatumumab and 50 healthy control) participants. These participants will be recruited from approximately 40 centers within the United States.
Key Inclusion criteria	Participants eligible for inclusion in this study must meet **all** of the following criteria: 1. Signed informed consent must be obtained prior to participation in the study 2. Age 18-35 years Patients in the healthy control arm eligible for inclusion must fulfill the following criteria: 3. Able to obtain MRI (HC with abnormal MRI at Screening will be excluded) and use wearable device 4. Able to provide blood sample (no CSF will be collected in HC) Patients in the ofatumumab-treated arm eligible for inclusion must fulfill the following criteria:

[redacted]

	5. Diagnosis of RRMS per McDonald Criteria (2010/2017) 6. Within 6 months of diagnosis of clinically definite MS (CDMS) 7. EDSS 0-3.0 (Inclusive) at both screening and baseline 8. Treatment-naïve to MS DMT 9. Able to obtain MRI and attend study visits at sites 10. Able to use wearable device 11. Able to provide blood sample (and CSF for sub-group n=15) 12. If a participant is receiving dalfampridine (Ampyra®/Fampyra®) concomitantly with study treatment, the participant 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 wherever possible
Key Exclusion criteria	Participants in the healthy control arm meeting any of the following criteria are not eligible for inclusion in this study: 1. Confounding medical condition as determined by the investigator RRMS patients fulfilling any of the following exclusion criteria are not eligible for inclusion in this study: 2. Diseases other than multiple sclerosis responsible for the clinical or MRI presentation 3. Patients with neuromyelitis optica, Radiologic/Clinically Isolated Syndrome, Secondary Progressive or Primary Progressive MS diagnosis 4. Use of experimental or investigational drugs for MS 5. Previous use of Disease Modifying Therapy (DMT) or chemotherapeutic medications for MS 6. Relapse between screening and Baseline visits 7. Known sensitivity to gadolinium; patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m2) or acute kidney injury (contraindicated with use of gadolinium) 8. Known history of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes 9. CNS anomalies that are better accounted for by another disease process (e.g., traumatic brain injury) or MRI anomalies causing clinically apparent impairments in social, occupational, or generalized areas of functioning, due to the direct physiologic effects of substances (recreational drug abuse, toxic exposure, etc) or a medical condition 10. Known active malignancies 11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test 12. Females of childbearing potential (all women physiologically capable of becoming pregnant) should use effective contraception while receiving ofatumumab and for 6 months after the last treatment of ofatumumab Effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the participant, if accepted by the local regulation). **NOTE:** Periodic abstinence (e.g. calendar, ovulation, symptothermal,

[redacted]

	post-ovulation methods) and withdrawal **ARE NOT** acceptable methods of contraception • Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment • Single barrier methods of contraception: male or female condom or occlusive cap, diaphragm, or cervical/vault caps. • For female participants on the study, the vasectomized male partner should be the sole male 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 investigational drug. Oral contraceptive may be switched during the trial, if participant is able to maintain stable dose during course of participation In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF Note: Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential 13. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g. rheumatoid arthritis, scleroderma, Sjögren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with immunodeficiency syndrome (e.g., hereditary immune deficiency, drug-induced immune deficiency) 14. Patients with active infections including systemic bacterial, viral (including SARS-CoV-2/COVID-19) or fungal infections, or known to have AIDS or to test positive for HIV antibody at Screening 15. Patients with neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML), or confirmed PML 16. Patients with IgG or IgM levels below LLN at Screening 17. Patients that have received any live or live-attenuated vaccines within 4 weeks prior to first dose of study drug administration 18. Patients at risk of developing or having reactivation of hepatitis: Positive results at Screening for serological markers for hepatitis (H) B indicating acute or chronic infection:

[redacted]

	a. HBs Ag and/or anti-HBc IgM and/or HB virus deoxyribonucleic acid (DNA) b. anti-HBs negative and Anti-HBc positive NOTE: If the Investigator suspects false positive hepatitis serology results, such as an antibody pattern indicating acute hepatitis infection but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, an infectious disease expert may be consulted. If the infectious disease expert finds no evidence of acute or chronic hepatitis infection and considers the serology results false positive and not clinically relevant, the Investigator must document (in source data) that the serology results are considered false positive and may then enroll the patient.
Study treatment	The investigational treatment, ofatumumab will be provided in an auto injector for subcutaneous administration containing 20mg ofatumumab (20mg/0.4ml). Participants with RRMS will be assigned at their Baseline visit to ofatumumab.
Treatment of interest	The treatment of interest is ofatumumab and is the same as the investigational treatment. The dose regimen for ofatumumab, for this study, is an initial dose regimen of 20mg at Baseline/Week 0, followed by Week 1, 2 and every month thereafter, beginning at Week 4 (Month 1) until Month 18. There will be an optional extension of dosing through month 30.
Efficacy assessments	The treatment period includes assessing the effectiveness of ofatumumab: • Number of relapses • 3-month Disability Worsening-free (yes/no) • NEDA clinical in Months 6 to 18 (yes/no) • NEDA radiological in Months 6 to 18 (yes/no) • Conventional MRI metrics (Gd+ lesion number, new Gd+ lesion number, Gd+ lesion volume, T2 lesion number (Baseline), New/enlarging T2 lesion number (post-Baseline), T2 lesion volume, new unenhancing T1 lesion number, T1 unenhancing lesion volume) • Brain volume loss (BVL) assessment (whole brain and regional) • Patient Reported Outcomes (NeuroQOL™, PDDS) • Safety and tolerability of ofatumumab
Key safety assessments	• Physical examination • Vital signs • Laboratory evaluations • Adverse Event monitoring
[redacted]	[redacted]

[redacted]

	[redacted]
Data analysis	The primary objective is to explore the impact of ofatumumab on the ability to achieve No Evidence of Disease Activity (NEDA) status in treatment-naïve to MS DMT, very early RRMS patients over an 18 month, open-label study period after a re-baseline of MRI at 6 months. The primary endpoint will be NEDA-3 (Relapse-free, 3-month clinical disability progression-free, MRI activity-free) in Months 6 to 18 (yes/no). Ofatumumab sample size calculations were based on the proportion of participants with NEDA-3 in Months 6 to 18. A sample size of 100 participants will provide a 7.8% precision (half-width of 95% confidence interval), or a 7.0% precision corresponding to estimated proportions of 80% and 85% of participants achieving NEDA-3. Adjusting for a 15% drop out rate, 118 participants will be enrolled to the study. The number (and percentage) of participants achieving NEDA-3 will be presented. The 95% confidence interval for the proportion of NEDA-3 will be calculated by using exact method. The full analysis set will used for those analyses.
Key words	*early relapsing multiple sclerosis, ofatumumab, healthy control, treatment naïve, young adult population, disability, biomarker, MRI*

[redacted]

1 Introduction

1.1 Background

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

The McDonald Criteria (McDonald et al., 2001) was the first diagnostic criteria for MS to employ MRI measures alongside clinical assessments. As more data and experience with MRI were acquired (Tintore et al., 2000; Swanton et al., 2006, 2007; Montalban et al., 2010), the criteria evolved further with two subsequent revisions (Polman et al., 2005, 2011). Currently, the 2010 revision of the McDonald Criteria is utilized to characterize the patients' clinical stage and determine the patients' eligibility to participate in the trial.

Several disease modifying treatments have been approved for relapsing MS over the past decade, which has led to improved outcomes over the short term. However, many individual patients do not tolerate these (newer) approved drugs which forces them to discontinue the treatment (Merkel et al., 2017). Further, long term disability resulting from relapse independent progression, even in patients thought to have relapsing MS, demonstrates that an underlying progression occurs in most MS patients from disease onset (Cree et al., 2019). For example, in a study by (Cree et al., 2016), follow-up data from 471 patients over 10 years demonstrated clinically significant disability accrued in 59% of the patients. This illustrates that an unmet need remains for highly effective disease-modifying therapies (DMTs) with acceptable safety profiles in early relapsing MS patients and that those treatments should be used at first diagnosis to reduce the burden of long-term accrual of disability as there are no limitations based on the prescribing information and decisions are generally made based on HCP preference.

While traditional research has focused on the role of T cells for MS, pathogenic B cells are known to play an early role in the immune-mediated pathogenesis of MS (Archelos et al., 2000, Frohman et al., 2006, McFarland, 2008). B cells, acting in concert with T cells, have been found to be required for full disease expression (Genain and Hauser, 1996) and have been shown to be essential in regulating immune response. B cells may contribute to disease pathogenesis by self-antigen presentation, promoting CD4+ T-cell activation (Bouaziz et al., 2007), regulating T-cell function/inflammation via cytokine production (Lund, 2008) and producing autoantibodies. B-cells are present in chronic MS plaques, areas of demyelination, and in the cerebrospinal fluid of MS patients (Lehmann-Horn et al., 2013). These observations have provided a new framework for the importance of B cells in MS pathogenesis and validate the use of B□cell□based therapeutics in the disease.

Ofatumumab (also known as Kesimpta®, OMB157, GSK1841157 and HuMax-CD20) is a human type 1 immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) which targets the CD20 molecule on cell surfaces. Ofatumumab (20mg subcutaneous [sc]) is available for commercial use in the US with an indication of "the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults" (Kesimpta®, PI).

[redacted]

Ofatumumab binds specifically to two distinct epitopes on the receptor, encompassing both the small and large extracellular loops of the CD20 molecule. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the late pre-B to mature B lymphocyte stage but is not expressed in stem cells or in plasma cells. Once bound to cell surface CD20, ofatumumab induces B-cell lysis via complement dependent cytotoxicity (CDC) and antibody dependent T-cell-mediated cytotoxicity (ADCC). The pharmacokinetics (PK) of ofatumumab are typical of a mAb with low clearance, a small volume of distribution, and a relatively long half-life (T1/2). Since ofatumumab is a mAb, conventional studies to investigate protein binding, whole body distribution, metabolism, excretion, and the potential for pharmacokinetic drug-drug interactions, are not appropriate and have therefore not been conducted.

A comprehensive package of nonclinical toxicology studies with toxicokinetic evaluation has been conducted to support the intravenous (iv) and sc administration of ofatumumab in humans. Intravenous administration for up to 7 months duration and a repeat dose toxicity study of 2 weeks duration by the sc route in cynomolgus monkeys resulted in the expected depletion of peripheral and lymphoid tissue B-cells with no associated toxicological findings. Studies conducted to investigate human tissue cross reactivity *in vitro*, inflammatory and coagulation parameters in cynomolgus monkeys, and local tolerance evaluation as part of repeat dose toxicity studies in cynomolgus monkeys revealed no adverse or unexpected findings. No maternal toxicity or adverse effects on embryo fetal development effects were noted in cynomolgus monkeys (refer to Kesimpta®, PI, COMB157G2301 and COMB157G2302--clinical-study-report here and below for further information on the pivotal trial program).

Efficacy data for ofatumumab in MS was obtained from two completed Phase 2 studies in patients with RRMS: one study with iv administration (OMS115102) and one study with sc administration (OMS112831). Ofatumumab administered iv (100, 300, 700mg) and sc (3mg, 30mg, 60mg every 12 weeks [q12w], 60mg every 4 weeks [q4w]) demonstrated profound, dose-dependent B-cell depletion and beneficial clinical effects compared to placebo (Sorensen et al., 2014, Bar-Or et al., 2018). Analysis of peripheral B-cell counts in the iv Phase 2 study showed that ofatumumab caused CD19+ and CD20+ cells at all dose levels studied to decrease below the detectable limit within one week (Sorensen et al 2014). Analysis of peripheral B-cell counts in the sc Phase 2 also demonstrated a rapid, dose and dose frequency dependent reduction in B-cell counts, the effect being less pronounced with the 3mg q12w regimen compared to the higher dose regimens studied. In the sc Phase 2 study, dosing every 4 weeks showed no signs of B-cell repletion during the inter-dosing interval. Both 30mg and 60mg q12w showed approximately 75% decrease of B-cell counts compared to baseline prior to re-dosing. Once dosing was ceased, all treatments showed a similar rate of B-cell repletion over up to 60 weeks of follow up (Bar-Or et al., 2018).

Ofatumumab also demonstrated strong suppression of inflammatory activity on magnetic resonance imaging (MRI). Only one of three subjects in the iv Phase 2 study dosed with ofatumumab (active/placebo treatment in the 100mg dose cohort) had a single new Gd-enhancing lesion detected up to Week 24 (Sorensen et al., 2014). In the sc Phase 2 study, ofatumumab reduced the mean cumulative number of new Gd-enhancing lesions by 65% vs placebo during weeks 0-12 ($p<0.001$) (Bar-Or et al., 2018). Disease activity that occurred before

[redacted]

onset of action of ofatumumab was captured in this analysis, and therefore a post hoc analysis of cumulative ofatumumab doses of 30mg and 60mg dose groups during weeks 4-12 was done; it demonstrated a reduction in the mean cumulative number of new Gd-enhancing lesions by >90% vs placebo. Reductions were maintained up to the last observation at week 48, even though last dosing of ofatumumab was at week 20 (Bar-Or et al., 2018).

Based on the promising Phase 2 results, Novartis continued the development of ofatumumab for the treatment of patients with relapsing MS using a large Phase 3 pivotal trial program named ASCLEPIOS. This clinical program comprised of two worldwide, randomized, double-blind, double-dummy, active comparator-controlled, parallel-group studies of identical design (COMB157G2301 and COMB157G2302; also referred to as ASCLEPIOS I and II). The ofatumumab Phase III studies (ASCLEPIOS I and II) were designed in accordance with the recommendations from the FDA and EMA during end-of-Phase 2 meetings. The purpose of ASCLEPIOS I and II were to provide efficacy, safety and tolerability data for ofatumumab sc compared to oral (po) teriflunomide (Aubagio®) in patients with relapsing MS.

In ASCLEPIOS I and II, monthly subcutaneous ofatumumab 20mg demonstrated superiority over once daily oral teriflunomide 14mg in participants with relapsing forms of MS (Hauser et al., 2020, Kesimpta®, PI). 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 participants 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 teriflunomide (both studies $p<0.001$) in ASCLEPIOS I and II studies respectively (Hauser et al., 2020). Key secondary endpoints were also met, with ofatumumab showing a relative risk reduction of 34.4% in 3-month confirmed disability (CDW) ($p=0.002$) and 32.5% in 6-month CDW ($p=0.012$) versus teriflunomide in a pre-specified pooled analyses (Hauser et al., 2020). The results from the pooled safety analyses from the two pivotal Phase 3 studies showed no new or unexpected safety signals for ofatumumab, as compared to earlier MS clinical studies.

Data from ASCLEPIOS I and II supported the US regulatory filing and approval of ofatumumab for the treatment of patients with relapsing MS. Ofatumumab was approved by the FDA with an indication of treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults (Kesimpta®, PI).

1.2 Purpose

This study is meant to complement the ofatumumab clinical development pivotal trials by demonstrating clinical and MRI efficacy (both conventional and non-conventional) in a young adult, treatment naïve, very early MS patient population. The focus will be on patients earlier in the MS disease continuum than the average patient studied in ASCLEPIOS I and II. The baseline characteristics for ASCLEPIOS I and II included: mean ages of 38.9 years and 38.0 years, mean duration from first symptoms of 8.36 years and 8.2 years, and mean EDSS scores of 2.97 and 2.90 years, respectively. In the ASCLEPIOS I and II studies, only ~30% of ofatumumab patients were treatment-naïve and ~24% were under the age of 30, leading to an

identified data gap for ofatumumab in the United States for the treatment of young adult, treatment naïve and very early MS patients (Hauser et al., 2020).

Because the ASCLEPIOS I and II studies had relatively small numbers of treatment-naïve patients compared to similar regulatory trials for competitor products and did not specifically address the very early MS patient population, the current proposed study intends to address these groups. The ASCLEPIOS I and II trials used an active comparator (as required by regulatory authorities) and therefore did not compare ofatumumab to healthy control (HC) patients. This type of HC comparator data can provide important information on safety outcomes (e.g., infections) and the ability of ofatumumab to normalize CNS pathology as measured by biomarkers and MRI. Additionally, there remains a data gap for patient reported outcomes (PRO), digital monitoring and biomarker work, which was either not or incompletely addressed in the ASCLEPIOS study program.

The proposed study would provide rigorous clinical, MRI, digital and biomarker data demonstrating the effect of ofatumumab in a naïve RRMS population at first diagnosis and would provide the first data relative to healthy controls, identified data gaps in the US. The very early MS young adult population in this study will consist of treatment naïve RRMS patients that are within 6 months of diagnosis at the time of study entry. Detailed data will be collected within the first month to document a rapid response to therapy. Further, a HC group will be used to analyze select endpoints vs ofatumumab (e.g., brain atrophy) with the strategy of showing normalization of brain structural/functional changes. This would also highlight the need for high efficacy therapy very early in the course of the disease as the extension data of up to 30 months would potentially show stabilization long term.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• The primary objective is to explore the impact of ofatumumab (OMB) on the ability to achieve No Evidence of Disease Activity (NEDA-3) status in treatment-naïve, very early RRMS patients over an 18 month, open-label study period after a re-baseline of MRI at 6 months	• NEDA-3 (Relapse-free, 3-month clinical disability progression-free, MRI activity-free) in Months 6 to 18 (yes/no)
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
Evaluate the effect of ofatumumab on various clinical (NEDA, disability, relapse) metrics at 18 months	Baseline and months 6, 12, 18, 30 (T1 Gd
• Evaluate the effect of ofatumumab on conventional MRI metrics, with MRIs at	

[redacted]

- Number of relapses
- 3-month Disability Worsening-free (yes/no)
- NEDA clinical in Months 6 to 18 (yes/no)
- NEDA radiological in Months 6 to 18 (yes/no)
- Change from Baseline in Conventional MRI metrics (Gd+ lesion number, new Gd+ lesion number, Gd+ lesion volume, T2 lesion

[redacted]

Objective(s)	Endpoint(s)
@ Baseline, month 6, 18 and T1/T2 @ every timepoint)	number (Baseline), New/enlarging T2 lesion number (post-Baseline), T2 lesion volume, new unenhancing T1 lesion number, T1 unenhancing lesion volume)
• Evaluate the effect of ofatumumab on patient reported outcomes (PROs) (NeuroQOL™, Patient Determined Disease Steps [PDDS])	• Change from Baseline in Patient Reported Outcomes (NeuroQOL™, PDDS) (also obtained in HC)
• Evaluate the effect of ofatumumab vs healthy controls on 1) whole brain and regional atrophy measured at month 18/30 after re-baseline at 6 months; and 2) regional atrophy measured 18/30 months from Baseline	• Brain volume loss (BVL) assessment (whole brain and regional) (also obtained in HC)
• Evaluate the safety and tolerability of ofatumumab	• Adverse events, laboratory data, physical examination, and vital signs (also obtained in HC)

[redacted]

[redacted]

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during the trial conduct which could impact the interpretation of the trial results (e.g. premature discontinuation of treatment).

The primary clinical question of interest is: will treatment with ofatumumab allow young and very early RRMS patients to achieve No Evidence of Disease Activity (NEDA-3) at 18 months and what changes occur in these patients as measured by innovative methods such as non-conventional MRI, patient reported outcomes (PRO), biomarker and digital monitoring technologies?

The justification for the primary estimand is that it will capture the effect of ofatumumab on shutting down MS inflammatory and associated clinical disease activity within the CNS in a RRMS population that is at first diagnosis.

The primary estimand is described by the following attributes:

- **Population:** Defined through appropriate inclusion/exclusion criteria to reflect the targeted population. Young adult and very early RRMS (defined as within six months of diagnosis of clinically definite RRMS) patients that are disease modifying therapy treatment naïve. Further details about the population are provided in Section 5.
- **Variable:** No evidence of Disease Activity (NEDA-3) [Relapse-free, clinical disability progression-free, MRI activity-free] in Months 6 to 18 (yes/no).
- **Treatment of interest:** an initial dose regimen consisting of doses administered at Baseline/Week 0 (Day 1), followed by Week 1 (Day 7), Week 2 (Day 14), and then every month thereafter, beginning at Week 4 (Month 1) until Month 18 (see Figure 3-1). All doses of ofatumumab will be given subcutaneously via an auto-injector at a dose of 20mg. Further details about the investigational treatment are provided in Section 6. Healthy controls will be used for comparison purposes and will not receive study treatment.
- **Intercurrent event:** Death or treatment/study discontinuation.
- **Summary measure:** Proportion of participants achieving NEDA-3 in Months 6 to 18.

2.2 Secondary estimands

Not applicable.

3 Study design

This study is an open-label, multi-center, prospective eighteen-month study in a minimum of

[redacted]

118 MS patients with early RRMS (defined as within 6 months of diagnosis of clinically

[redacted]

definite RRMS) and who are disease modifying therapy (DMT) treatment naïve. RRMS patients will be benchmarked against age- and sex-matched healthy controls (n=50) for select secondary [redacted]. A screening period of 4 weeks will be used to assess eligibility and the assessment to address the primary objective will be performed at the end of the maintenance period (Month 18). There will be one interim analysis after the last participant completes his/her Month 18 (primary analysis time point) visit. Participants who complete the treatment period or who prematurely discontinue study drug and the study, and do not continue on any MS DMT, will undergo a safety evaluation 100 days following last dose of study treatment (captured only in source documents and only for ofatumumab treated participants), and will be discharged from the study if they choose to not be included in the optional extension portion of the trial for an additional 12 months (up to 30 months total in trial). Healthy control participants will not have a safety evaluation post end of study. Additional efficacy and safety assessments will be evaluated during the optional open-label extension to further elucidate the long-term clinical and radiological effects of ofatumumab (Figure 3-1). Of note, MRI data will be re-baselined at month 6 to account for treatment-related pseudo atrophy.

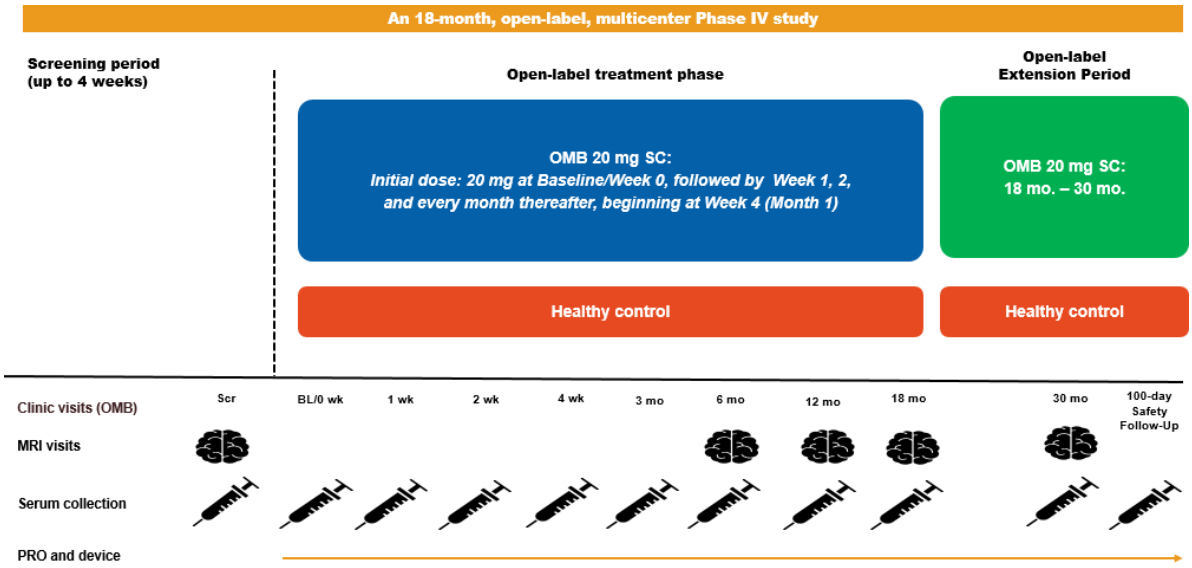
Eligible participants with RRMS will receive ofatumumab 20mg subcutaneous doses at Baseline/Week 0 (Day 1), followed by Week 1 (Day 7), Week 2 (Day 14) and then every month thereafter, beginning at Week 4 (Month 1) until Month 18 (see Figure 3-1). Additional efficacy and safety assessments will be evaluated up to 30 months, necessitating ofatumumab monotherapy over the course of up to 30 months. Ofatumumab will be administered according to the United States Prescribing Information (USPI). RRMS patients must remain on ofatumumab monotherapy to remain in the trial, with no DMT switching or combination DMT therapy allowed. Healthy controls will not be given a therapy.

Assessments will be performed per the assessment schedule found in Table 8-1.

Figure 3-1 Study design

There are 3 periods to this trial: Screening (up to 4 weeks), open-label active treatment (from Baseline to month 18), and optional 12-month open-label extension (from month 18 to 30).

[redacted]



For participants who discontinue study treatment and study participation prematurely for any reason before the end of the treatment phase, an End of Study visit must be performed within 7 days of study discontinuation.

Upon completing the trial, study patients can continue ofatumumab therapy on commercial drug.

Safety follow-up:

The Safety follow-up (FU) period will be applicable for the following participants:

- participants who complete the Treatment period on the study drug and do not continue on any MS DMT.
- participants who prematurely discontinue study drug and study participation, and do not continue on any MS DMT.

All Safety FU visits must be scheduled relative to the End of Study (EOS) Visit.

Any RRMS patient starting another MS DMT post-trial discontinuation will not have a FU visit performed.

All patients who elect to not be included in the 12-month extension will be followed for an additional 100 days following the EOS timing for that individual patient. A shorter follow-up time is acceptable if patients select a different approved MS DMT (injectable, infusion or oral) treatment during this period. Patients who do not have access to commercial drug within one day of the EOS Visit must continue into the safety FU phase until they are able to access commercial drug or decline DMT therapy moving forward (up to 100 days maximum).

Safety assessments will include standard clinical laboratory evaluations (hematology), [redacted], adverse event, and serious adverse event monitoring. Participants that elect to not continue on a DMT after study and have low levels of quantitative

[redacted]

serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections, should have immunoglobulins monitored by the trial site until B-cell repletion occurs.

4 Rationale

4.1 Rationale for study design

This study is an open-label, multi-center, prospective eighteen-month study in a minimum of 118 MS patients with early RRMS (defined as within 6 months of diagnosis of clinically definite RRMS) and who are DMT treatment naïve. RMS patients will be benchmarked against age- and sex-matched healthy controls (n=50) for select secondary [redacted]. The concept herein will expand on previous ofatumumab studies and provide important clinical and safety data in an earlier RRMS population than studied in ASCLEPIOS I and II. Further, this study will investigate multiple secondary [redacted] (over the course of up to 30 months; all patients are in trial for 18 months, but the optional extension period extends to 30 months) to build the data sets on early use of ofatumumab using MRI metrics, patient reported outcomes (PRO), biomarker and digital monitoring technologies. Finally, the study will compare select endpoints vs age- and sex-matched HC patients to provide first evidence of safety and disease stabilization measured by MRI/[redacted] vs non-MS patients.

Due to the limited time from diagnosis and lack of experience with B cell depleting therapies that this population will have, an open-label, multi-center design was selected to facilitate recruitment. Further, the clinical trial space is very active with numerous therapies under development and therefore careful consideration was taken regarding impact on the patient when designing monitoring outcomes. The design limited the number of clinic visits and MRIs to minimum acceptable levels and focused on using "at home" digital technology for monitoring when available.

Finally, the use of a HC group for comparison is novel in the clinical trial program for ofatumumab. In the Phase 2 APOLITOS trial, a Japanese/Russian population was studied to evaluate the efficacy and safety of ofatumumab versus placebo in RMS patients. Although this study included RMS placebo-treated patients, no study has compared ofatumumab treated patients to non-MS HCs. The HC comparator data can provide important information on safety outcomes (e.g., infections) and the ability of ofatumumab to normalize CNS pathology as measured by MRI and [redacted] of disease.

Rationale of chosen endpoints:

The proposed study endpoints are widely accepted as clinically relevant and have been used in numerous pivotal clinical trials in RRMS. The primary endpoint for the study will be no evidence of disease activity as defined by NEDA-3 criteria (relapse-free, clinical disability progression-free, MRI activity-free). Secondary endpoints will include relapse-related endpoints, conventional and non-conventional MRI-related endpoints, safety endpoints, digital biometric and physical/cognitive function endpoints, [redacted], and patient reported outcomes (PROs). In two large phase 3 studies, ofatumumab demonstrated significant reductions in disease activity (reductions in relapses, Gd T1 lesions and new and/or enlarging T2 lesions)

[redacted]

versus an active comparator. This study will expand on those data and focus on patient centric outcomes and novel ways of measuring changes in patients with early/mild disease. This evidence is highly relevant for patients, neurologists, treating healthcare practitioners in the real-world setting, and payers.

4.2 Rationale for dose/regimen and duration of treatment

Ofatumumab dose

The dose regimen for ofatumumab, for this study is an initial dose regimen of 20mg at Baseline/Week 0 (Day 1), followed by Week 1 (Day 7), Week 2 (Day 14) and every month thereafter, beginning at Week 4 (Month 1), until Month 18 (see Figure 3-1).

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

Duration of treatment

Treatment duration within the primary study will be 18 months. RRMS patients must remain on ofatumumab monotherapy to remain in trial, with no DMT switching or combination therapy allowed. Additional efficacy and safety assessments will be evaluated during an optional 12-month open-label extension necessitating ofatumumab monotherapy over the course of up to 30 months (see Figure 3-1).

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

Not Applicable

4.4 Purpose and timing of interim analyses/design adaptations

Not Applicable

4.5 Risks and benefits

The risk to participants 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, the study has been designed to minimize site visits (during COVID pandemic) and reduce the number of MRI scans using gadolinium. 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 RRMS patients comes from four Phase 2 studies and the two Phase 3 clinical trials, where a total of 1537 RMS patients have been exposed to ofatumumab (Phase 2 studies: iv: N=38; and sc: N=553; Phase 3 studies sc N=946). No unexpected safety findings were observed in MS patients who received ofatumumab in the two completed Phase 2 studies and two ASCLEPIOS Phase 3 studies.

[redacted]

Briefly, in the 48-week, placebo-controlled, cross-over study (cross-over at 24 weeks) of iv doses of ofatumumab up to 700mg, adverse events reported more frequently on ofatumumab vs placebo included: rash, throat irritation, erythema, fatigue, viral infection and flushing (Sorensen et al., 2014). In the placebo-controlled, dose-ranging study of ofatumumab administered at sc doses up to 60mg every 4 weeks for up to 24 weeks, injection related reactions were observed more frequently in the overall ofatumumab group (Bar-Or et al 2018). 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), rates of infection (including serious infection), or malignancy when compared to teriflunomide. In these 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 (Hauser et al., 2020, Kesimpta®, PI).

Ofatumumab sc has demonstrated benefit on disease activity in the pivotal trial program, with profound suppression of new MRI lesion activity (≥ 90% versus placebo over Weeks 4-12) in RMS patients in a Phase 2 study (Bar-Or et al., 2018). 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 progression (CDP) and 32.5% ($p=0.012$) in 6-month CDP versus teriflunomide in a pre-specified pooled analyses (Hauser et al., 2020, Kesimpta®, PI). Taken together, available information of relevant clinical and MRI outcome supports the potential efficacy of ofatumumab in patients with RRMS.

Overall, data acquired to date supports the rationale of this study to evaluate the efficacy and safety of ofatumumab sc to address the unmet medical need of early, treatment naïve RRMS patients.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

There is no benefit expected for healthy control participants in this study. Similar to ofatumumab treated patients, the study has been designed to minimize site visits (during COVID pandemic) and to reduce the number of MRI scans.

[redacted]

In the context of the COVID-19 pandemic, additional risks for participants taking part in any clinical trial cannot be excluded. Eligibility criteria for the study requires the investigator to evaluate infections and exclude patients with ongoing infection. The protocol also includes general guidance on immunization (see Section 16.1.4).

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over the period of the study with blood draws from each participant. Additional samples may be required for safety monitoring. Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

See the Section 8.5.2 on the potential use of residual samples.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

The study population will consist of adult participants with RRMS fulfilling all the eligibility criteria listed below. The study is planned to be conducted in approximately 40 centers within the United States. It is aimed to enroll a minimum of 168 (118 ofatumumab, 50 HC) participants. Participants who enroll and prematurely discontinue study will not be replaced.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-35 years

Patients in the healthy control arm eligible for inclusion must fulfill the following criteria:

3. Able to obtain MRI (HC with abnormal MRI at Screening will be excluded) and use wearable device
4. Able to provide blood sample (no CSF will be collected in HC)

[redacted]

Patients in the ofatumumab-treated arm eligible for inclusion must fulfill the following criteria:

5. Diagnosis of RRMS per McDonald Criteria (2010/2017)
6. Within 6 months of diagnosis of clinically definite MS (CDMS)
7. EDSS 0-3.0 (Inclusive) at both screening and baseline
8. Treatment-naïve to MS DMT
9. Able to obtain MRI and attend study visits at sites
10. Able to use wearable device
11. Able to provide blood sample (and CSF for sub-group n=15)
12. If a participant is receiving dalfampridine (Ampyra®/Fampyra®) concomitantly with study treatment, the participant 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 wherever possible

5.2 Exclusion criteria

Participants in the healthy control arm meeting any of the following criteria are not eligible for inclusion in this study:

1. Confounding medical condition as determined by the investigator

Participants in the ofatumumab-treated arm meeting any of the following criteria are not eligible for inclusion in this study:

2. Diseases other than multiple sclerosis responsible for the clinical or MRI presentation
3. Patients with neuromyelitis optica, Radiologic/Clinically Isolated Syndrome, Secondary Progressive or Primary Progressive MS diagnosis
4. Use of experimental or investigational drugs for MS. Use of other investigational drugs within 5 half-lives of enrollment/initiation of study treatment (select as appropriate) within 30 days (e.g. small molecules) / or until the expected pharmacodynamic effect has returned to baseline (e.g. biologics), whichever is longer; or longer if required by local regulations
5. Previous use of Disease Modifying Therapy (DMT) or chemotherapeutic medications for MS
6. Relapse between screening and Baseline visits
7. Known sensitivity to gadolinium; patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2) or acute kidney injury (contraindicated with use of gadolinium)
8. Known history of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes
9. CNS anomalies that are better accounted for by another disease process (e.g. traumatic brain injury) or MRI anomalies causing clinically apparent impairments in social, occupational, or generalized areas of functioning, due to the direct physiologic effects of substances (recreational drug abuse, toxic exposure, etc) or a medical condition

[redacted]

10. Known active malignancies
11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
12. Females of childbearing potential (all women physiologically capable of becoming pregnant) **unless** they are using effective contraception while receiving ofatumumab, and for 6 months after the last treatment of ofatumumab

    Effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant, 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 sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Single barrier methods of contraception: male or female condom or occlusive cap, diaphragm, or cervical/vault caps
    - For female participants on the study, the vasectomized male partner should be the sole male 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 investigational drug. Oral contraceptive may be switched during the trial, if participant is able to maintain stable dose during course of participation

    In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

    Note: Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.
13. Patients with an active chronic disease (or stable but treated with immune therapy) of the immune system other than MS (e.g. rheumatoid arthritis, scleroderma, Sjögren's syndrome, Crohn's disease, ulcerative colitis, etc.) or with immunodeficiency syndrome (e.g., hereditary immune deficiency, drug-induced immune deficiency)

[redacted]

14. Patients with active infections including systemic bacterial, viral (including SARS-CoV-2/COVID-19) or fungal infections, or known to have AIDS or to test positive for HIV antibody at Screening
15. Patients with neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML), or confirmed PML
16. Patients with IgG or IgM levels below LLN at Screening
17. Patients that have received any live or live-attenuated vaccines within 4 weeks prior to first dose of study drug administration
18. Patients at risk of developing or having reactivation of hepatitis: Positive results at Screening for serological markers for hepatitis (H) B indicating acute or chronic infection:
    a. HBs Ag and/or anti-HBc IgM and/or HB virus deoxyribonucleic acid (DNA)
    b. anti-HBs negative and Anti-HBc positive

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

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Investigational drug will be provided in an auto-injector pen for subcutaneous administration containing 20mg ofatumumab (20mg/0.4 ml). Study drug will be supplied by Novartis.

Table 6-1 Investigational drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Ofatumumab 20mg	Solution for injection	Subcutaneous pen	Commercial	Sponsor (local)

6.1.1.1 Decentralized Clinical Trial Model

The study medication and all required clinical study supplies could possibly be distributed via

[redacted]

direct-to-patient shipment utilizing an extension of the IND for compliance purposes. Remote

[redacted]

study visit options may be available and need to be discussed with Novartis prior to implementation.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

This study is an open-label, multi-center, prospective eighteen-month study in a minimum of 118 MS patients with early RRMS (defined as within 6 months of diagnosis of clinically definite RRMS) and who are treatment naïve.

Participants with RRMS will be assigned at Baseline visit to ofatumumab. The dose regimen for ofatumumab for this study is an initial dose regimen of 20mg at Baseline/Week 0 (Day 1), followed by Week 1 (Day 7), Week 2 (Day 14) and every month thereafter, beginning at Week 4 (Month 1) until Month 18 (see Figure 3-1). Additional efficacy and safety assessments will be evaluated during an optional 12-month open-label extension, necessitating ofatumumab monotherapy over the course of up to 30 months.

Table 6-2 Treatment arms/group

Treatment Arm	# of Patients Entered Treatment	Type of Study Drug	Compound	Min Dose	Max Dose	Frequency	Admin. Route	Generic Acceptable? (applies only for comparator)
Arm 1	**118**	Commercial	Ofatumumab	20mg	20mg	Monthly	Subcutaneous pen	NA
Arm 2	**50**	N/A Healthy Control	N/A	N/A	N/A	N/A	N/A	N/A

6.1.4 Treatment duration

The planned duration of treatment is 18 months and participants will continue on ofatumumab treatment arm for 18 months. Once a participant is started on ofatumumab, they must remain on ofatumumab throughout the duration of the study and switching to a different DMT therapy will not be permitted. Participants may be discontinued from treatment earlier due to unacceptable adverse events, disease progression and/or at the discretion of the Investigator or the participant. Additional efficacy and safety assessments will be evaluated during an optional 12-month open-label extension, necessitating ofatumumab monotherapy over the course of up to 30 months in patients that choose to enter the extension.

6.1.5 Post-Trial Access

Participants who have completed the treatment period successfully will be given the option to terminate from the study or will be referred to the ofatumumab commercial patient services hub for post-trial continuity of treatment programs, where the benefit/risk is acceptable and discussed with the participant and investigator. Participants who terminate prior to the end of

[redacted]

the treatment period or who withdraw permanently due to an ofatumumab related AE or SAE should follow up with their primary neurologist or treating physician for continued treatment options as quickly as possible.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The Investigator should instruct the participant to notify the study site about any new medications he/she takes after study enrollment. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

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

If a participant is receiving dalfampridine (Ampyra®/Fampyra®) concomitantly with study treatment, the participant 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 wherever possible.

Premedication prior to subcutaneous injection

Premedication is not required in this study. Premedication with acetaminophen and/or antihistamines (or equivalent) is optional for ofatumumab treated patients and may be administered at the discretion of the Investigator.

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

After the initial dose of study medication, which should be given under the guidance of a healthcare professional, participants may inject study medication at home at Week 1 (Day 7) and onwards if they have demonstrated the ability to self-inject (refer to Section 6.3.2). Based on the experience with the injection(s) 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 participant will receive a sufficient supply of premedication for home-use (i.e., to last at least until the next study office visit) and clear instructions (oral and written) about type and dose of premedication, and when to take it (i.e., 30-60 min before the injection). The Investigator will evaluate the need for premedication, or a change in the prescription, at each visit (scheduled and unscheduled) including at the participant contacts during the study (contact should include specific questions about any injection-related symptoms and the use of premedication). If, based on the remote contacts, a change in premedication is needed, the participant should be asked to return to the site for an unscheduled visit.

The participants must be informed (through the participant information and consent process) about the possibility that injection related reactions might occur despite use of premedications

[redacted]

and about the possible symptoms of a systemic injection reaction and their management. Participants must be reminded to always carry their Participant 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 6-1 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 participant is on study medication.

Table 6-3 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 participants exposed to these medications is not permitted.
Monoclonal antibodies targeting the immune system, including but not limited to natalizumab, alemtuzumab, daclizumab ocrelizumab and rituximab and B-cell depleting agents under investigation, such as but not limited to ublituximab 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 Novartis.
Any other immunomodulatory or disease-modifying MS treatment, including but not limited to fingolimod, interferon beta, glatiramer acetate, dimethyl fumarate, intravenous immunoglobulin, plasmapheresis or systemic corticosteroids (except for when given for MS relapse treatment as defined in Section 6.2.3)	Discontinue study drug, increase vigilance regarding infections. NOTE: Restarting study drug in participants exposed to these medications is not permitted.
Administration of any live or live-attenuated (does not apply to non-live, inactivated, mRNA, adenovirus vector vaccines) vaccine (including for measles) is prohibited while participants are exposed to study drug (long lasting effects of the study drugs should be taken into consideration)	They may be administered 4 weeks prior to first administration of ofatumumab in the study or when participants are no longer exposed to study drug with documented B cell repletion. Consider risk/benefit and follow local labels.

6.2.3 Recommended treatment of MS Relapse

Prior to screening and study entry, use of corticosteroids or plasmapheresis is allowed to treat relapses per Investigator's judgement and/or local clinical practice, however there is a minimum time from last treatment to screening MRI of ≥30 days. The decision to treat MS relapses during the study should be based on the Investigator's judgement and/or local clinical practice. If

[redacted]

MS relapses require treatment, the standard tretament should consist of a short course of

[redacted]

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 participant 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 or plasmapheresis for treatment of MS attack/relapse must be recorded on the Concomitant Medications eCRF. Please refer to restrictions for MRI in Section 8.3.6 concerning the use of steroids and performing the MRI.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational drug section. A unique medication number is printed on the study medication label. Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s).

6.3.1 Handling of study treatment and other treatment

6.3.1.1 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 CO Quality Assurance.

The Investigator 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 field monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study drug and packaging at the end of the study or at the time of discontinuation of treatment.

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 according to the instructions provided by Novartis or its agents.

6.3.2 Instruction for prescribing and taking study treatment

All eligible RRMS participants will receive treatment with open label ofatumumab; no randomization will be performed in this study. In general, administration instructions contained within the USPI for Kesimpta® should be followed. Administration of ofatumumab (at study site or at home) should occur after the study visit assessments are performed, if on the same day of the study visit.

[redacted]

Drug will be dispensed at scheduled visits throughout the treatment period. Ofatumumab injection will be administered via an initial dose regimen of 20mg at Baseline/Week 0 (Day 1), followed by Week 1 (Day 7), Week 2 (Day 14) and every month thereafter, beginning at Week 4 (Month 1) until Month 18. Additional efficacy and safety assessments will be evaluated during an optional 12-month open-label extension, necessitating ofatumumab monotherapy over the course of up to 30 months (see Figure 3-1).

At the Baseline/Week 0 visit, participants will receive the subcutaneous injection at the study site. Site personnel will provide training to the participants on the correct procedure for self-administration of the subcutaneous injections. The participant or a caregiver may inject the study medication under supervision of a healthcare professional. Documentation of injection procedure understanding by the participant and/or the caregiver must be documented in the source document. Participants should remain at study site under observation for approximately 1 hour following dosing at the Baseline/Week 0 visit, where post-dose vital signs will be collected. A longer observation period may be required if these vital signs are not within reasonable limits of the participant's baseline values.

Site staff should remove the study treatment from the refrigerator and allow the AI pen to reach room temperature in the unopened box (approximately 15-30 minutes) before self-injection by the participant. Used AI pens should be disposed of immediately after use in a sharps container.

A different body site (front of thighs, lower abdomen) should be chosen each time a dose is administered to reduce the risk of an injection-site reaction; investigator/qualified site staff/caregiver can also inject the study treatment in the outer upper arms. Each new injection should be given at least one inch from the previously used site. If administration is in the abdomen, the 2-inch area around navel should be avoided. Study treatment should also not be injected into areas where the skin is tender, bruised, red, or hard, or where the participant has scars or stretch marks.

Following the Baseline/Week 0 visit, sufficient study drug will be supplied to the participant to cover all home administrations. Participants may inject the study medication at home, if they demonstrated ability to self-administer injections. If a participant is unable/unwilling to self-administer injections, another individual (e.g. partner, caregiver, relative or a healthcare professional) may perform home-administration who has accompanied the participant to the site and has been trained on and demonstrated ability to correctly administer the subcutaneous injections. The participant may also continue to have injections at the site if this is the participant's preference.

If a participant is unable to travel to the investigative site for their study visit, shipment of study treatment from the site to the participant's home may be available in cases of a pandemic or a national and/or global emergency.

Doses on Week 1 (dose #2) and Week 2 (dose #3) should be administered no more than +/- 1 day. If the dose on Week 1 (dose #2) is missed, the dose due on Week 2 (dose #3) should be adjusted to 7 days after dose #2 was given.

If a monthly injection of ofatumumab is missed, it should be administered as soon as possible without waiting until the next scheduled dose. Subsequent doses should be administered at the recommended intervals (+/- 3 days).

[redacted]

Participants will be instructed to contact the investigator/site staff prior to self-administration at home if they are experiencing any AE/SAEs or have any concerns. Participants will record the dates of all at-home study treatment doses.

Participants will be provided with the following items to facilitate the at-home injections of study treatment: an insulated bag with cool gel packs to transport the study treatment from the site to the participant's home; alcohol swabs and gauze pads; a sharps container for immediate disposal of the used syringes; monthly home urine pregnancy test; ofatumumab dose administration and pregnancy test diaries; and a copy of the AI instruction leaflet will be provided which includes detailed information, precautions and instructions for administering subcutaneous injections using the AI pen. This information should be reviewed with the participant (and his/her partner/relative as applicable) to ensure that they understand the correct procedure for self/home administration.

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

Table 6-4 Arm 1 treatment schedule

Ofatumumab 20mg	BL	D 7	D 14	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	M 13	M 14	M 15	M 16	M 17

Key

BL = Baseline
D = Day
M = Month

Table 6-5 Extension treatment schedule

Ofatumumab 20mg	M 18	M 19	M 20	M 21	M 22	M 23	M 24	M 25	M 26	M 27	M 28	M 29	M 30

Key

M = Month

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The participant no. consists of the Center Number (Center No.) (assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available by the Investigator. The Investigator or his/her staff will contact the IRT and provide the assigned participant study identification number along with the requested identifying information to register the participant into IRT. The site must use the eCRF with the matching participant number from the electronic data capture (EDC) system to enter data.

[redacted]

If an enrolled participant fails to be assigned to treatment for any reason, the IRT must be notified within 2 days that the participant was not assigned to treatment. The reason for not being assigned to treatment will be entered into the appropriate eCRFs. If the participant is re-screened at a later date, a new Participant No. will be assigned.

6.4.2 Treatment assignment, randomization

This is an open label study. There will be no treatment blinding.

6.5 Dose escalation and dose modification

Dose escalation and modifications are not permitted in this study.

6.5.1 Dose escalation guidelines

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 participant interrupt the study drug for whatever reason, the re-start decision should be made on a case-by-case basis (refer to Section 6.6.1). 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 Baseline/Week 0 (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 Treatment compliance

The Investigator must promote compliance by instructing the participant to take the study drug exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study drug as prescribed. Compliance will be assessed by the Investigator and/or study personnel at each visit. Participant compliance should be at least 80%. The Investigator and/or study personnel will counsel the participant if compliance is below 80% and will determine (in consultation with Novartis) if the participant will be removed

[redacted]

from the study due to lack of compliance with study drug. Study drug accountability will also be determined by the site monitor while performing routine site/virtual visits and at the completion of the study. 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.

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs) beyond standard clinical care.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code.

Not applicable.

7 Informed consent procedures

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

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

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

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

Information about common side effects already known about the investigational treatment can be found in the USPI and Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples (e.g. additional new [redacted], MRI scans) collected during this study

[redacted]

  - Potential for additional efficacy and safety assessments that will be evaluated during the optional 12-month open-label extension for up to 30 months
- An Optional Biomarker Consent for those participants who opt into additional biomarker sample analysis provided from cerebral spinal fluid (CSF)
- As applicable, Pregnancy Outcomes Reporting Consent for female subjects who took study treatment
- As applicable, Pregnancy Outcomes Reporting Consent for the female partners of male participants who took study treatment

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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

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

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

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

8 Assessment schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment and study participation, and do not continue on any MS DMT, are to return for the end of study visit as soon as possible and attend safety follow-up visits as indicated in the Assessment Schedule (Table 8-1). Healthy control participants will not have a safety evaluation post end of study.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

[redacted]

The “X” in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The “S” in the table denotes the assessments that are only in the participant’s source documentation and do not need to be recorded in the clinical database.

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

[redacted]

Table 8-1 Assessment Schedule

Name	Scr	BSL/ Wk0	Wk 1	Wk 2	Wk 4	M3	M6	M9[6]	M12	M15[6]	M18	M21[6]	M24[6]	M27[6]	M30/ EOS	100-day Safety Follow-up[12]	USV[4]
Days: Window:	**-28**	**1 (+3)**	**7 (±1)**	**14 (±1)**	**28 (±3)**	**90 (±3)**	**180 (±3)**	**270 (±3)**	**360 (±3)**	**450 (±3)**	**540 (±3)**	**630 (±3)**	**720 (±3)**	**810 (±3)**	**900 (±3)**		
Informed Consent[x]	O,H										O,H[13]						
Patient Demographics[x]	O,H																
Medical History[x]	O,H																
Smoking Status	O,H										O,H				O,H		
MS History[x]	O																
Inclusion/ Exclusion Criteria[x]	O,H	O															
Height/ Weight[x]	O,H	O															
Dispense Study Drug[x]		O[7]	O	O	O	O	O	O	O	O	O	O	O	O			
Collect Study Drug/ Drug Account-ability			O	O	O	O	O	O	O	O	O	O	O	O	O		O

[redacted]

Name	**Scr**	**BSL/ Wk0**	**Wk 1**	**Wk 2**	**Wk 4**	**M3**	**M6**	**M9[6]**	**M12**	**M15[6]**	**M18**	**M21[6]**	**M24[6]**	**M27[6]**	**M30/ EOS**	**100-day Safety Follow-up[12]**	**USV[4]**
Days: **Window:**	**-28**	**1 (+3)**	**7 (±1)**	**14 (±1)**	**28 (±3)**	**90 (±3)**	**180 (±3)**	**270 (±3)**	**360 (±3)**	**450 (±3)**	**540 (±3)**	**630 (±3)**	**720 (±3)**	**810 (±3)**	**900 (±3)**		
Sc Self-injection Training (participant and/or caregiver)[S]		O															
Study drug self-injection (at-home or at site)[X, 16, 17]			O	O	O	O	O	O	O	O	O	O	O	O	O		
Prior and Concomitant Meds[X]	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O	O,H
Non-drug therapies[X]	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O	O,H
Vital Signs[X, 7]	O,H	O,H	O,H	O,H	O,H	O,H	O,H		O,H		O,H				O,H		O,H
Physical Exam[S]	O[3],H	O,H	O,H	O,H	O,H	O,H	O,H		O,H		O,H				O,H		O,H
Adverse Events[X, 4]	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O,H	O	O,H
[redacted]																	

Name	**Scr**	**BSL/ Wk0**	**Wk 1**	**Wk 2**	**Wk 4**	**M3**	**M6**	**M9[6]**	**M12**	**M15[6]**	**M18**	**M21[6]**	**M24[6]**	**M27[6]**	**M30/ EOS**	**100-day Safety Follow-up[12]**	**USV[4]**
Days: **Window:**	**-28**	**1 (+3)**	**7 (±1)**	**14 (±1)**	**28 (±3)**	**90 (±3)**	**180 (±3)**	**270 (±3)**	**360 (±3)**	**450 (±3)**	**540 (±3)**	**630 (±3)**	**720 (±3)**	**810 (±3)**	**900 (±3)**		
MS Relapse Assessment[X, 2]	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Labs (hematology, biochemistry) [X]	O										O				O	O	O

[redacted]

[redacted]

Name	Scr	BSL/ Wk0	Wk 1	Wk 2	Wk 4	M3	M6	M9[6]	M12	M15[6]	M18	M21[6]	M24[6]	M27[6]	M30/ EOS	100-day Safety Follow-up[12]	USV[4]
Days: **Window:**	**-28**	**1 (+3)**	**7 (±1)**	**14 (±1)**	**28 (±3)**	**90 (±3)**	**180 (±3)**	**270 (±3)**	**360 (±3)**	**450 (±3)**	**540 (±3)**	**630 (±3)**	**720 (±3)**	**810 (±3)**	**900 (±3)**		
Hepatitis B[S, 9]	O																
HIV[S, 9]	O																
Coagulation[S, 9]	O	O									O				O		O
Dipstick urinalysis[X, 10]	O	O									O				O		O
Serum β-hCG in women of childbearing potential[S, 3]	O	O															O
Urine β-hCG in women of childbearing potential[S, 3]			O	O	O	O	O	O	O	O	O	O	O	O	O		O
MRI[X, 14, 18]	O,H						O,H		O,H		O,H				O,H		O
Columbia Suicide Severity Scale (C-SSRS)[X, 15]	O	O	O	O	O	O	O		O		O				O		
PROs[X] (NeuroQOL™, PDDS)		O,H	O,H	O,H	O,H	O,H	O,H		O,H		O,H				O,H		
[redacted]																	

[redacted]

Name	Scr	BSL/ Wk0	Wk 1	Wk 2	Wk 4	M3	M6	M9[6]	M12	M15[6]	M18	M21[6]	M24[6]	M27[6]	M30/ EOS	100-day Safety Follow-up[12]	USV[4]
Days: **Window:**	**-28**	**1 (+3)**	**7 (±1)**	**14 (±1)**	**28 (±3)**	**90 (±3)**	**180 (±3)**	**270 (±3)**	**360 (±3)**	**450 (±3)**	**540 (±3)**	**630 (±3)**	**720 (±3)**	**810 (±3)**	**900 (±3)**		
[redacted]																	
Optional Trial Feedback Questionnaire[S]		O,H					O,H				O,H				O,H		
Participant Thank You Letter[S]		O,H									O,H				O,H		

O = Ofatumumab participant

H = Healthy Control

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

S = assessment to be recorded in the source documentation only

[redacted]

[2] Relapse assessment will be performed in scheduled, as well as unscheduled visits as deemed necessary by the Investigator or designee. Assessment can be done on site or via remote procedures

[3] Urine β-hCG will be conducted monthly, at home, as well as, at defined clinical visits (scheduled and unscheduled)

[redacted]

[4] Assessment during an unscheduled visit will be performed as deemed necessary by the investigator, **except** for vital signs and evaluation of AE, which are mandatory at each visit

[redacted]

[6] Participants are not required to come to the study site. Remote contact with participants, by site staff around the time of at-home, self-administration of ofatumumab should query about any new or worsening symptoms warranting an unscheduled visit, MS relapse, compliance with study treatment [redacted], adverse events, and compliance with contraception requirements (when applicable). The method of contact can be via telephone, email, video conference or text message depending on the preference of each participant

[7] For the first injection, vital signs should be obtained 30-60 minutes before sc injection and again approximately 60 minutes post-injection

[8] All lab assessments should be taken prior to dosing at the Day 1 visit. For any later biomarker visits, if the visit coincides with the day the monthly injection is scheduled, the subject should not take the injection in the morning before coming to the site so that the biomarker sample can be drawn before the injection

[9] Labs must be drawn to allow adequate time for results to be obtained before first study drug administration to ensure participant's eligibility

[10] Urine dipstick: If abnormal send full urinalysis to central laboratory

[redacted]

[12] Data for safety follow-up visit will be captured in source documentation **only**. Safety follow-up participants are not required to come to study site and lab assessments should be done locally

[13] Only for participants continuing onto the 12-month open-label extension period

[14] Gadolinium will not be given to healthy controls and gadolinium enhanced T1 MRI imaging will not be conducted in healthy controls

[15] The C-SSRS must be administered at either screening or baseline, then at every on-site visit thereafter until End of Study (EOS)

[16] Administration of ofatumumab (at study site or at home) should occur after the study visit assessments are performed, if on the same day of the study visit

[17] Study drug self-injection (at-home or on-site) will be performed **monthly,** beginning at Week 4, by all ofatumumab participants

[18] MRI assessment must be completed within +/-7 days of the visit

[redacted]

8.1 Screening

Screening

A participant who enters screening but is determined not to be eligible will be considered a screen failure. The Investigator may consider re-screening the participant later if he/she believes that the participant's condition has changed, and he/she may potentially be eligible. In this case, a new participant number will be allocated to the participant and he/she will need to re-perform all screening procedures except for MRI. The original MRI may be used during rescreening if the rescreening occurs within 3 months of the original MRI date. Requests from the investigator/site staff to rescreen patients will be handled on a case-by-case basis, with Clinical Trial Lead approval required, prior to rescreening. A participant may be re-screened only once. A minimum of 24 hours must elapse between screen failure and re-screening. If a participant is re-screened, a new ICF must be obtained, and a new participant number issued prior to conducting any screening assessments. This must be documented in the participant's source documents with the new participant number assigned.

8.1.1 Eligibility screening

8.1.1.1 Hepatitis screen, HIV screen

All ofatumumab treated participants will be screened for Hepatitis B surface antigen (HBsAg) and, if standard local practice, Hepatitis B core antigen (HBcAg).

Evaluation for HIV seropositivity will be performed in ofatumumab treated participants, and, if positive, confirmation by a second technique available at the laboratory site (e.g. Western blot). Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator. This will be recorded as source data only by the use of an "S" for the corresponding criteria in Table 8-1 (Assessment Schedule) of the protocol.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details).

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

8.2 Participant demographics/other baseline characteristics

Participant demographic data and baseline characteristics to be collected on the participants include age, sex, race and ethnicity. Relevant medical history/current medical condition data

[redacted]

includes data collected up to the point in which informed consent is signed. Where possible, diagnoses, and not symptoms will 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.

8.3 Efficacy

The study includes the following efficacy assessments which are conducted at visits as shown in Assessment Schedule, Table 8-1:

Clinical

- MS Relapse Assessment
- Vitals

Laboratory

Patient Reported Outcomes

- NeuroQOL™
- PDDS

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

8.3.1 MS Relapse Assessment

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

The assessment, management and reporting of MS relapse is made by the Investigator. Confirmation of MS relapse and severity grading is based on the

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 participant may report symptoms indicative of a relapse at a planned visit or at any other time. Participants 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 participant will also be asked whether any such symptoms have occurred between scheduled visits. If a participant 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 participant'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 participant status in between the initial assessment by the Investigator and the EDSS rating by the EDSS rater. [redacted]

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 previously available rating (the last EDSS rating that did not occur during a relapse). Confirmation of MS relapse, based on these definitions, will be done using the EDSS score (provided by the EDSS Rater with level B).

All MS relapses, regardless of 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 8-2 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 8-2 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

[redacted]

	1 point change in four or more systems	Exceeding Moderate criteria

[redacted]

[redacted]

8.3.6 Magnetic Resonance Imaging (MRI)

All participants will undergo MRI scanning of the brain, within +/- 7 days of the visit, according to the assessment schedule in Table 8.1.

MRI scans will be read by the central MRI reading center. Prior to the start of the study, the MRI technician from each study site will receive an MRI Manual, outlining the minimum criteria needed for MRI capabilities, 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 participants. 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 neuroradiologist. 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 regard to Gd+-enhancing lesions) for the treatment of MS relapse and diagnostic challenges with concomitant participant migraines, the following restrictions apply for this study:

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

[redacted]

- Participant cannot have an ongoing migraine during MRI scan (migraine diagnosis needs to be episodic or less in frequency).

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 assessment schedule.

Scanning

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

Sequences will include T2-weighted images, T1-weighted images (with and without Gd-based contrast), [redacted] measures in regions of interest. Gadolinium will not be given to healthy controls and gadolinium enhanced T1 MRI imaging will not be conducted in healthy controls. 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.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

[redacted]

[redacted]

8.3.8 Quality of Life in Neurological Disorders (NeuroQOL™)

The NeuroQOL™ is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with neurological conditions (https://www.healthmeasures.net/explore-measurement-systems/neuro-qol; Miller et al., 2016). The following domains will be measured:

Physical Health: Fatigue, Sleep disturbance, Lower Extremity function (mobility), Upper Extremity Function (Fine motor, ADL), Urinary/Bladder Function and Bowel Function

Mental Health: Anxiety, Depression, Cognitive Function, Communication, Positive Affect and Well-Being

Social Health: Ability to Participate in Social Role and Activities

The NeuroQOL™ will be used to assess health-related quality of life and will be evaluated according to the assessment schedule in Table 8-1.

[redacted]

8.3.9 Patient Determined Disease Steps (PDDS)

The PDDS is a standardized rating scale developed by Hohol et al. in 1995, which is a self-assessment scale of functional disability in multiple sclerosis patients primarily based on ambulation. The questionnaire contains 1 question which is scored ranging from 0 (normal) to 8 (bedridden) (https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Disease-Steps-(DS)). A score of 0 to 2 indicates mild disability; a score of 3 to 5 indicates moderate disability; a score of 6 to 8 indicates severe disability (Hohol et al., 1995).

[redacted]

8.3.11 Appropriateness of efficacy assessments

The relapse, disability [redacted] 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 participant population in terms of their MS disease status.

The patient reported outcomes will assess important outcomes that impact people living with MS but are otherwise not captured with efficacy assessments. The NeuroQOL™ and the PDDS will assess the physical, mental, and social effects experienced by MS patients, and functional disability respectively. These assessments have been used in RRMS studies.

8.4 Safety

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

- Physical examination
- Vital signs
- Height and Weight
- Laboratory evaluations
- Pregnancy testing
- Columbia Suicide Severity Rating Scale (C-SSRS)

For details on AE collection and reporting, refer to AE section.

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 telephone or virtual contacts can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again. These contacts should be done at the times when study on-site visits would be due as per assessment schedule,

[redacted]

Table 8-1, and will be in addition to the regular monthly telephone interview between scheduled visits detailed in the assessment schedule Table 8-1.

Table 8-3 Safety assessments and specifications

Assessment	Specification
Physical examination	A complete physical examination will be performed at the visits indicated in assessment schedule, Table 8-1 and will include an assessment of skin, head and neck, lymph nodes, heart, lungs, abdomen, back, neurological function and comments on general appearance. A complete neurological examination will be part of the initial physical examination at Screening. Information for all physical examinations (including skin 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 as an adverse event.
Vital signs	Vital signs will include the collection of sitting pulse rate, sitting systolic and diastolic blood pressure, and body temperature (oral, or per local practice; recorded in °C). After the subject has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. For the first injection, vital signs should be obtained 30-60 minutes before sc injection and again approximately 60 minutes post-injection. If premedication is administered, the vital signs should be taken prior to pre-medication administration.
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 as specified in Table 8-1.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in

[redacted]

consultation with the sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, total white blood cell count and differential counts (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils).
Chemistry	Albumin, ALP, ALT, AST, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), calcium, magnesium, phosphorus, sodium, potassium, creatinine, total and conjugated bilirubin (BIL), blood urea nitrogen (BUN), uric acid, amylase, lipase, glucose (non-fasting).
Urinalysis	Dipstick parameters assessed will include pH, blood, glucose, specific gravity, WBC, Nitrite, Bilirubin, Ketones and protein. In case of an abnormal dipstick test, a urine sample will be sent to the central laboratory for testing including additional parameters such as microscopy and white blood cell and red blood cell sediments.
Coagulation	Prothrombin time (PT), international normalized ratio [INR]), activated partial thromboplastin time (APTT).
[redacted]	[redacted]
[redacted]	[redacted]
Hepatitis markers	HBV screening is required in all participants, including Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing. Participants with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent HBV infection or reactivation. NOTE: If the infectious disease expert finds no evidence of acute or chronic hepatitis infection and considers the serology results false positive and not clinically relevant, the Investigator must document (in source data) that the serology results are considered false positive and may then enroll the participant.
Pregnancy Test	Serum / Urine pregnancy test (refer to Section 8.4.2).

8.4.2 Pregnancy and assessments of fertility

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

Serum pregnancy tests will be conducted at Screening and Baseline visits. Urine pregnancy tests will be conducted for all women who are of childbearing potential at all other planned clinic visits prior to study drug administration. In addition, participants will be provided with urinary pregnancy test kits for monthly home pregnancy testing required between the scheduled

[redacted]

clinic visits prior to study drug administration. The participants will document the date and result of each home pregnancy test in a diary provided for the study. In case of a positive test result, the participant must contact the Investigator immediately for confirmatory testing at the Investigator's discretion.

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

Contraception must be used during the study and for at least 6 months after stopping study drug.

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

8.4.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire that prospectively assesses suicidal ideation and suicidal behavior. The C-SSRS must be administered at either Screening or Baseline/week 0 (day 1), then at every on-site visit thereafter until end of study (EOS).

The electronic version of the C-SSRS (eC-SSRS) will be administered by the Investigator. A completed pC-SSRS must be filed in the participant's source documents.

If, at any time after Screening, 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 participant must be referred to a mental healthcare 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 participant is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a participant 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.

8.4.4 Appropriateness of safety measurements

The safety assessments included in this study (see Table 8-1, Table 8-3 and Table 8-4) are standard for the MS indication and study participant 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) or Kesimpta® USPI for more information.

The use of C-SSRS to detect suicidal ideation behavior is currently mandated in studies of CNS active drugs.

[redacted]

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

Patient reported outcome (PRO) measures included in this study are the NeuroQOL™ (Quality of Life in Neurological Disorders) (Section 8.3.8) and the PDDS (Patient Determined Disease Steps) (Section 8.3.9).

The participant must be given the PRO measure(s) to be completed as per the assessment schedule (Table 8-1). Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

The site personnel should check electronic PRO measure(s) for completeness and ask the participant to complete any missing responses. The responses stored electronically in the database will be considered the source file. Site personnel will be trained on appropriate instructions for any digital devices use to collect PRO information virtually.

Trial Feedback

At Baseline, month 6, month 18 and month 30 (EOS), patients might be asked to complete an optional anonymized questionnaire, "Trial Feedback Questionnaire" to provide feedback on their clinical trial experience. Responses would be used to understand where improvements can be made in the clinical trial process. This questionnaire is not meant to collect data about the patient's disease, symptoms or adverse events and therefore would not be considered trial data. Should any spontaneous information be collected about AEs, it would be transferred to the safety database. Patients may opt in or opt out of completing this questionnaire. The data will be used to help understand and conduct clinical trials better in the future.

[redacted]

[redacted]

[redacted]

8.6 Remote visits in case of Public Health Emergency

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, remote study visits may be allowed for participants unable to travel to the clinic for their study visits on a case-by-case basis. This would provide the opportunity for participants, if desired, to continue their participation in the study. Remote visits can only be performed after agreement with the Global Sponsor team based on the Public Health Emergency situation.

If allowed by local health authority and depending on operational capabilities, telephone calls and virtual contacts or visits by site staff/home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

If participants cannot visit the site for protocol-specified safety laboratory assessments, an alternative (local) laboratory collection site may be used.

Additional details may be shared in a site guide.

9 Study discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

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

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

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision (Section 9.2)
- Pregnancy (Section 8.4.2 and Section 10.1.4)
- Use of prohibited treatment as per recommendations in the prohibited treatment section (Section 6.2.2)
- Diagnosis of PML (Section 16.1.1)
- Hypersensitivity to the study drug
- Protocol violation that results in a significant risk to the patient's safety
- Emergence of certain adverse events, such as malignancy (except successfully treated basal cell carcinoma, *in situ* squamous cell carcinoma and *in situ* carcinoma of cervix of uterus), liver failure or, serious chronic infection (such as HIV)

[redacted]

- Laboratory abnormalities requiring the action of study drug discontinuation as defined in Appendix 16.1 and abnormal test procedure as defined in Appendix 16.1.3
  - Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- Any situation in which continued study participation might result in a safety risk to the participant
- Non-compliance with study drug or study procedures

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.2). Where possible, they should return for the assessments indicated in the visit assessment schedule (Table 8-1). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, certified letter) should be made to contact the participant/pre-designated contact as specified in the 'Lost to Follow-up' Section 9.1.3. This contact should preferably be done according to the study visit assessment schedule.

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

After discontinuation from study treatment, 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 participant's discontinuation from study treatment.

9.1.2 Discontinuation from study

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

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

Discontinued patients will not be replaced in this trial.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g.

[redacted]

dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

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

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

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

and

- No longer wishes to receive study treatment

and

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

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

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment schedule Table 8-1.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study completion and post-study treatment

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

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

1. Subject has completed the study in its entirety according to the approved duration of the study

[redacted]

2. Subject is eligible for commercially available ofatumumab after completing the minimum duration of 18 months in the study

3. The subject has not stopped the study due to one or more of the following reasons:

- Study discontinuation (Section 9.1.1)
- Withdrawal of informed consent (Section 9.2)
- Lost to follow-up (Section 9.1.3)

End of Study (EOS) visit is mandatory for all subjects. The EOS visit is conducted at the end of the Open-label Treatment at Month 18 unless the patient continues into the extension period (as stipulated above). EOS will be done 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 assessment schedule rhythm. Subjects who prematurely discontinue study treatment, and study participation, will have their EOS visit as soon as possible and continue into the Safety Follow-up for 100 days according to assessment schedule Table 8-1. 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.

At the end of the study, the study team will provide a plan on how subjects will have access to ongoing treatment. Furthermore, if the treatment's risk-benefit ratio has turned negative and/or Novartis discontinues the development of the study treatment 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.

9.4 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 participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study.

[redacted]

Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease. 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 website: ctep.cancer.gov).

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

1. The CTCAE grade (based on most current version)

   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
   - 5 = death
2. Its relationship to the study treatment.

   If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the study drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported

[redacted]

4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
6. Its outcome:
   - Not recovered/not resolved
   - Recovered/resolved
   - Recovering/resolving
   - Recovered/resolved with sequelae
   - Fatal
   - Unknown
   - Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.
   - Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.
   - Adverse event monitoring should be continued for at least 100 days following the last dose of study treatment or until End of Post-Treatment Follow-up for premature withdrawals.
   - Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.
   - Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB) or Kesimpta® USPI.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

[redacted]

- 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 treatment of a clinical event/attack as defined in Section 8.3.1)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 100 days following the last dose of study treatment for study completers or until End of Safety Follow-up for premature withdrawals must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

[redacted]

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 study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the Investigator folder provided to each site.

If the SAE is not previously documented in the Investigator's Brochure or Kesimpta® USPI (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.

Clinical events/attacks as defined in Section 8.3.1 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 corresponding eCRF instead of the SAE form. However, if, in the judgment of the Investigator, a clinical event/attack 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.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis 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.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

[redacted]

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1).

10.2 Additional Safety Monitoring

10.2.1 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is described in Section 8.4.3.

10.3 Committees

10.3.1 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.

10.3.2 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e. not being Novartis representatives.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

[redacted]

11 Data Collection and Database management

11.1 Data collection

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

The investigator/designee is responsible for assuring that the data (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.

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

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events and non-drug therapies will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for 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. 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

[redacted]

visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Study personnel, at minimum, should include the principal investigator or sub-investigator and the study coordinator. 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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

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

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

12.1 Analysis sets

The Full Analysis Set (FAS) will include all participants that received any study drug.

The Safety analysis set (Safety set) will be the same as the FAS.

The healthy-control analysis set will include all participants with at least one valid assessment of variables of interest. This analysis set will be used in the analysis of data collected from healthy-control participants.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for the FAS.

[redacted]

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

12.3 Treatments

The Safety set will be used for the analyses below.

The duration of exposure in days will be summarized by means of descriptive statistics.

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

12.4 Analysis supporting primary objectives

The primary objective is to explore the impact of ofatumumab (OMB) on the ability to achieve No Evidence of Disease Activity (NEDA) status in treatment naïve, very early RRMS patients over an 18 month, open-label study period after a re-baseline of MRI at 6 months.

12.4.1 Definition of primary endpoint(s)

The primary endpoint will be NEDA-3 (Relapse-free, 3-month clinical disability progression-free, MRI activity-free) in Months 6 to 18 (yes/no).

12.4.2 Statistical model, hypothesis, and method of analysis

The number (and percentage) of participants achieving NEDA-3 will be presented. The 95% confidence interval for the proportion of NEDA-3 will be calculated by using exact method. The full analysis set will used for those analyses.

12.4.3 Handling of intercurrent events of primary estimand

Observed case approach (completers) will be used for the analyses of primary endpoint.

12.4.4 Handling of missing values not related to intercurrent event

Observed case approach (completers) will be used for the analyses of primary endpoint.

12.4.5 Sensitivity analyses

Not applicable.

12.4.6 Supplementary analysis

Non-response imputation will be applied to missing data regardless of intercurrent events.

The number (and percentage) of participants achieving NEDA-3 will be presented. The 95% confidence interval for the proportion of NEDA-3 will be calculated by using exact method. The full analysis set will used for those analyses.

[redacted]

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy endpoint(s)

For all efficacy analyses, the FAS will be used. The healthy control set will be used if applicable.

Descriptive statistics will be provided for the following variables:

- Number of relapses during the study
- 3-month disability worsening-free (yes/no) during the study
- NEDA clinical in Months 6 to 18 (yes/no)
- NEDA radiological in Months 6 to 18 (yes/no)
- Change from Baseline in conventional MRI metrics (Gd+ lesion number, new Gd+ lesion number, Gd+ lesion volume, T2 lesion number (Baseline), New/enlarging T2 lesion number (post-Baseline), T2 lesion volume, new unenhancing T1 lesion number, T1 unenhancing lesion volume) by visit/time
- Brain volume loss (BVL) assessment (whole brain and regional) (also obtained in HC for normalization purpose) by visit/time

12.5.2 Safety endpoints

For all safety analyses, the Safety set will be used.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate listing of 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, with a start date during the on-treatment period (treatment-emergent AEs).

Adverse events

All information obtained on adverse events will be displayed by participant.

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

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

Separate summaries will be provided for study medication related adverse events, serious adverse events, other significant adverse events leading to discontinuation.

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

[redacted]

Adverse events which will be counted for a specific treatment period are those which are treatment emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

Vital signs

Change from baseline in vital signs will be summarized descriptively by visit/time.

Clinical laboratory evaluations

All laboratory data and their change from baseline will be summarized 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.

12.5.3 Patient reported outcomes

Change from baseline in NeuroQOL™ and PDDS will be summarized by visit/time using FAS.

[redacted]

[redacted]

12.7 Interim analyses

There will be one interim analysis after the last participant completes his/her Month 18 (primary analysis time point) visit.

The presentation of tables, listings, and figures will include data up to participants' date of Month 18 visit (inclusive). All available data for participants discontinuing the study prior to Month 18 will be included in the interim analysis.

This interim analysis will be the primary analysis. There will be neither hypothesis testing nor estimation at Month 30. Therefore, no statistical adjustment will be made at Month 18.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Ofatumumab sample size calculations were based on the proportion of participants with NEDA-3 in Months 6 to 18.

A sample size of 100 participants will provide a 7.8% precision (half-width of 95% confidence interval), or a 7.0% precision corresponding to estimated proportions of 80% and 85% of participants achieving NEDA-3. Adjusting for a 15% drop out rate, 118 participants will be enrolled to the study.

12.8.2 Secondary endpoint(s)

A sample size of 50 age- and sex-matched healthy controls with no diagnosis of neurologic disease will be enrolled.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

[redacted]

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, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

13.4 Quality Control and Quality Assurance

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

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

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

13.5 Participant Engagement

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

- Thank You letter (beginning and end of study)
- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication

[redacted]

- Trial Feedback Questionnaires (TFQ) – Baseline (week 0), Month 6 and End of Study (EOS)

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

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

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

[redacted]

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16 Appendices

16.1 Appendix 1: Guidance on safety monitoring

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

Should a participant develop any unexpected neurological or psychiatric symptom/signs in the opinion of Investigator (e.g. cognitive deficit, behavioral changes, cortical visual disturbances or any other neurological cortical symptoms/signs any symptom/sign suggestive of an increase of intracranial pressure) or accelerated neurological deterioration, the Investigator should schedule a complete physical and neurological examination and an MRI as soon as possible before beginning any steroid treatment. Conventional MRI, as defined in the protocol, as well as additional scanning such as Fluid-attenuated Inversion Recovery (FLAIR) and Diffusion-weighted imaging (DWI) sequences should be performed to aid in differential diagnosis. The MRI must be evaluated by the local neuroradiologist. The Investigator will contact the Medical Advisor at Novartis and/or a Global Study Team 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) lesions consistent with a clinical event/attack (as defined in Section 8.3.1), assessment and treatment of the clinical event/attack 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 previously available MRI, which are not compatible with lesions consistent with a clinical event/attack, the study drug will be interrupted, and other diagnostic evaluations need to be performed at the discretion of the Investigator. If new lesions are detected on the MRI, which may be infectious in origin, it is recommended to collect a cerebrospinal fluid (CSF) sample if indicated. Analysis of the CSF sample including cellular, biochemical, PCR, and microbiological analysis (e.g. herpes virus, JC virus, cryptococcus) to confirm/exclude an infection should be performed. In the event of suspected CNS infection (PML), a CSF aliquot should be sent to a 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 Global Study Team member, the study drug may be restarted.

16.1.2 Guidance on monitoring participants with infections

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

The Investigator should remind the participant of the risk of infections and instruct them to report any symptoms of infections promptly. The participants must also be reminded to always carry their Participant Information Card (with site contact information and which identifies them as participant in a clinical study with investigational and control agents with potential

[redacted]

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 Global Study Team member of any such cases.

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

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

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

Hepatitis B Virus (HBV)

There were no reports of HBV reactivation in patients with MS treated with ofatumumab. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients being treated with ofatumumab for chronic lymphocytic leukemia (CLL) (at significantly higher intravenous doses than the 20mg dose in MS and in this study) and in patients treated with other anti-CD20 antibodies.

Hepatitis B virus (HBV) screening is required in all study participants, including hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) testing. These can be complemented with other appropriate markers as per local guidelines. Participants with positive hepatitis B serology (either HBsAg or HBcAb) should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent HBV infection or reactivation. In participants with suspicion of HBV infection (active/reactivation) during the study, laboratory testing for HBV should be done. For participants with positive hepatitis B serology (either HBsAg or HBcAb), the Investigator should consult a liver disease expert, and participants should be monitored and managed following local medical standards to prevent HBV infection or reactivation. In participants who develop infection or reactivation of HBV while receiving study drug, immediately discontinue study drug and institute appropriate treatment and follow-up.

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16.1.4 Guidance on immunization

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

It is recommended that the Investigator reviews the participant's immunization history as part of the initial Screening procedure for a participant being considered for treatment with ofatumumab. Because vaccination with live-attenuated or live vaccines is not recommended during treatment with ofatumumab and after treatment discontinuation until B-cell repletion, all immunizations must be administered according to immunization guidelines at least 4 weeks prior to initiation of ofatumumab for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to initiation of ofatumumab for inactivated vaccines (Kesimpta® PI).

Note-mRNA and viral-vector vaccines for SARS-CoV-2 are considered "non-live/inactivated" and therefore should be given per recommendations for "non-live/inactivated" vaccines (Kesimpta® PI). There is presently no contraindication for the use of an inactivated, viral-vector, or mRNA-based SARS-CoV-2 vaccine in patients who are immunocompromised or in patients being treated with ofatumumab (Kesimpta® PI). However, different SARS-CoV-2 vaccines may have various mechanisms of action and different associated potential risks. Please review local prescribing information of any specific SARS-CoV-2 vaccine and comply with local prescribing information requirements for specific contraindications and special warnings and precautions for use. Vaccination (and any booster vaccination) against SARS-CoV-2 should be considered on a case-by-case basis at the discretion of the treating physician taking into account the individual benefit-risk assessment and local vaccination recommendations.

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

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