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OMB157G/Ofatumumab

Synopsis/Clinical Trial Protocol COMB157GUS12 / NCT04667117

An open-label multicenter study to assess response to influenza vaccine in participants with multiple sclerosis treated with ofatumumab 20 mg subcutaneously

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List of abbreviations

AE	Adverse Event
CMO&PS	Chief Medical Office and Patient Safety
CQA	Clinical Quality Assurance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Terminology Criteria
EDC	Electronic Data Capture
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HI	Hemagglutination Inhibition
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
iDMT	Injectable Disease Modifying Therapy
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
mg	milligram(s)
mL	milliliter(s)
QMS	Quality Management System
sc	subcutaneous
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction

[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 specific group of participants fulfilling certain criteria and generally treated at the same 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
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 paper source forms 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 or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	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
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
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

[redacted]

Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
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.
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

[redacted]

Amendment 3

Amendment Rationale

By the time of this amendment, it is projected that the study will not be able to enroll all planned number of patients in all three cohorts. Thus, the protocol is modified by extending the study to the next flu season (2022-2023) to allow for completing the enrollment. In addition, to continue with annual monitoring of safety and efficacy, the second interim analysis is included in this amendment.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 2 (15-Mar-2021)

This protocol has been modified to give participants in Cohort 2 the option to continue taking their prescribed ofatumumab during the open-label extension period of the study, correct inconsistencies related to when study drug should be administered in relation to the titer sample and to update inclusion criteria from planning to receive a 2020-2021 flu vaccine to willing to receive the 2020-2021 flu vaccine.

Amendment 1 (13-Jan-2021)

The protocol was modified to exclude participants with a history of Guillain-Barre syndrome within 6 weeks of receiving the influenza vaccination as recommended by the FDA. Additional modifications included permitting sites to administer the quadrivalent influenza vaccine from their site supply in lieu of a participant receiving it from a local pharmacy.

[redacted]

Protocol summary

Protocol number	COMB157GUS12
Full Title	An open-label multicenter study to assess response to influenza vaccine in multiple sclerosis participants treated with ofatumumab 20 mg subcutaneously
Brief title	A multicenter study to assess response to influenza vaccine in multiple sclerosis participants treated with ofatumumab
Sponsor and Clinical Phase	Novartis Clinical phase IV
Investigation type	Biological/Vaccine
Study type	Interventional, 3-cohort arm
Purpose and rationale	The objective of this study is to assess whether participants treated with ofatumumab 20 mg subcutaneous (s.c.) administered once every 4 weeks (q4) can mount an adequate immune response to inactivated influenza vaccine as measured by humoral responses compared to participants on an iDMT.
Primary Objective(s)	To characterize those achieving seroprotection to the 2020-2021, 2021-2022, or 2022-2023 seasonal quadrivalent influenza vaccine in participants treated with ofatumumab 20 mg sc once every 4 weeks.
Secondary Objectives	• To characterize those achieving seroconversion after receiving the 2020-2021, 2021-2022, or 2022-2023 seasonal quadrivalent influenza vaccine in participants treated with ofatumumab 20 mg sc once every 4 weeks • Safety
Study design	This is a three cohort, multicenter, prospective study of up to 66 relapsing MS participants. The first cohort will be participants who will received 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine at least two weeks prior to ofatumumab start. The second cohort will be participants who will receive a 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine at least four weeks after beginning ofatumumab. The third cohort will be participants currently on an iDMT who will receive a 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine. All groups will undergo an HI titer prior to vaccination and then again four weeks after vaccination. Upon completing the study, participants in cohort 1 and 2 will have the option to continue into a 6 month open-label Extension Period. Participants will obtain the quadrivalent influenza vaccine at no cost from their local pharmacy using a pharmacy card supplied by Novartis or from investigational site supply. Participants should receive the vaccine within 9 calendar days after the Screening Visit, before the Week 0 Visit occurs.
Study population	Adult (ages 18-55) relapsing MS participants
Key Inclusion criteria	1. Written informed consent for the study must be obtained before any study assessment is performed 2. Age 18-55 years old 3. Diagnosis of relapsing MS by 2017 revised McDonald criteria

[redacted]

	4. Must be willing to comply with the study schedule 5. Willing to receive a 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine 6. Planning to start treatment with ofatumumab or already on commercially prescribed ofatumumab for at least 2 weeks prior to the screening visit Participants in Cohort 3 must fulfill criteria 1-5 above in addition to the following: 7. Participant must currently be receiving iDMT
Key Exclusion criteria	1. Already has received the 2020-2021 season influenza vaccine 2. Known hypersensitivity to any component of the influenza vaccine 3. Any safety finding including low IgG and/or low IgM levels requiring an ofatumumab treatment interruption within the 12 weeks immediately prior to Week 0 4. Any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 weeks prior to the first vaccination or oral antibiotics within two weeks prior to Week 0 5. Known clinical diagnosis of influenza infection during the 2020-2021 influenza season prior to starting the study based on investigator's or subject's personal physician's judgement (laboratory report of confirmed influenza infection is not required) 6. Prior treatment with B-cell targeted therapies (e.g., rituximab or ocrelizumab), lymphocyte-trafficking blockers, alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, bone marrow transplantation. Treatment with a natalizumab within 6 months of week 0 7. Treatment with an S1P modulator within 60 days prior to Week 0 8. Participants with any known active systemic bacterial, fungal or viral or fungal infections (such as hepatitis, progressive multifocal leukocencephalopathy, COVID-19 or HIV), or known to have acquired immunodeficiency syndrome (AIDS) 9. Participation in another interventional clinical trial within 14 days prior to the Screening Visit/Week -1
Study treatment	Participants in Cohort 1: Initial dosing includes 20 mg sc ofatumumab administered at Week 2, 3 and 4. Subsequent dosing includes 20 mg sc administered monthly starting at Week 6. Participants in Cohort 2: Will continue to take prescribed ofatumumab as per their current dosing schedule. Participants in Cohort 3: Will continue to take iDMT as per their current dosing schedule. During the Investigational Period, open-label ofatumumab will be provided for Cohort 1. Open-label ofatumumab will be provided during the optional 6-month Extension Period for both Cohort 1 and 2.
Treatment of interest	Inactivated influenza vaccine

[redacted]

Efficacy assessments	None
Key safety assessments	Primary: Seroprotection as defined by a postvaccination antibody titer ≥ 40 (yes/no) Secondary: 1. Seroconversion as defined by either: • ≥ 4-fold increase in HI titers after vaccination (in participants with prevaccination HI titers ≥10) (yes/no) or • postvaccination HI titers ≥40 (in participants with prevaccination HI titers < 10) (yes/no) 2. Change in HI titers 3. AEs, SAEs, events leading to discontinuation
Data analysis	Sample size calculations were based on the proportion of subjects who responded to influenza vaccination. The sample size of 20 participants per arm is selected based on budget and need for early availability of results. The sample size of 20 subjects will provide estimates with margin of error (half-width of a 95% confidence interval) of 20.1%, 19%, and 17.5% corresponding to response rates of 70%, 75%, and 80%, respectively. Adjusting for 10% drop-out, 22 subjects will be enrolled in each arm.
Key words	Influenza, vaccine, ofatumumab, HI titer, open-label

[redacted]

1 Introduction

1.1 Background

Multiple sclerosis (MS) is a common cause of neurologic disability in young adults. In this disease, damage is caused by an autoimmune attack of the central nervous system. Recent phase 3 trials have demonstrated that antibodies that bind and cause CD20 B cells apoptosis have a powerful anti-inflammatory effect as measured by relapse and MRI activity, and leave participants with less disability than active comparators (Hauser et al 2020 and Hauser et al 2017).

The US Centers for Disease Control recommends that all persons aged > 6 months who do not have contraindications receive an influenza vaccination. MS is not considered a contraindication. Instead, it is considered important for people with MS to receive vaccination to prevent the sequelae of influenza infection, including possible relapse for MS participants.

MS disease modifying treatments target the immune system and in so doing may diminish vaccine efficacy (Farez et al 2019). Questions have arisen whether therapies that affect B cells might also abrogate vaccine response. Though other medications also impact B cells, anti-CD20 antibodies have the most selective and potent impact on B cells. These antibodies impact memory B cells which are believed to be an important component in maintaining immunologic memory but also preserve immunoglobulin secreting plasma cells which function to recognize and remove pathogens.

Research with an anti-CD20 B cell agent, ocrelizumab, indicates that an immune response can occur after influenza vaccination but that the proportion of participants with an adequate response is diminished relative to a control group (Bar-Or et al 2020). Specifically, seroprotection rates against five influenza strains ranged from 55.5-80% and 75-97% in healthy controls.

Ofatumumab is a subcutaneously administered anti-CD20 therapy that received FDA approval for treatment of relapsing forms of MS in August 2020. Data is currently lacking regarding whether MS participants on ofatumumab can mount an appropriate immune response to vaccines, including the influenza vaccine. In this study, MS participants will receive the influenza vaccination and follow-up titers to assess whether they are able to mount a response to influenza vaccine. Because the ability to mount an immune response varies depending on the influenza strain administered, a reference cohort of participants on injectable disease modifying treatments (interferon or glatiramer acetate) is included. In a prior study, interferon and glatiramer acetate did not diminish influenza vaccine response (Olberg et al 2018.)

1.2 Purpose

Vaccinations against influenza comprise an important strategy for effective management of participants with MS. Ofatumumab is a human anti-CD20 monoclonal antibody (mAb) that induces B-cell depletion. Considering the role of B-cells in immune-mediated responses, participants treated with ofatumumab may be at an increased risk of developing influenza. They also may incur an increased chance of morbidity and mortality should they become infected. Therefore, it is important to assess if participants treated with ofatumumab are able to mount protective immune responses against the influenza vaccine.

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To characterize those achieving seroprotection after receiving the 2020-2021, 2021-2022, or 2022-2023 seasonal quadrivalent influenza vaccine in participants treated with ofatumumab 20 mg sc once every 4 weeks	**Endpoint(s) for primary objective(s)** • Achieving seroprotection as defined by a postvaccination antibody titer ≥ 40 (yes/no)
Secondary Objective(s) • To characterize those achieving seroconversion after receiving the 2020-2021, 2021-2022, or 2022-2023 seasonal quadrivalent influenza vaccine in participants treated with ofatumumab 20 mg sc once every 4 weeks • Safety	**Endpoint(s) for secondary objective(s)** • Achieving seroconversion as defined by either: (a) a ≥4-fold increase in Hemagglutination Inhibition (HI) titers after vaccination (in participants with prevaccination HI titers ≥10) or (b) postvaccination HI titers ≥40 (in participants with prevaccination HI titers <10) (yes/no) • Change in HI titers • AEs, SAEs, events leading to discontinuation

2.1 Primary estimands

The primary clinical question of interest is: Do relapsing MS participants who receive ofatumumab treatment mount an immune response to the 2020-2021, 2021-2022, or 2022-2023 influenza vaccine?

The justification for the primary estimand is that it will capture whether ofatumumab treated participants generate antibodies to influenza vaccine as assessed by HI titers.

The primary estimand is described by the following attributes:

- **Population:** Relapsing MS participants subdivided into three cohorts. (1) Receiving inactive influenza vaccine two weeks prior to starting ofatumumab 20 mg subcutaneous treatment; (2) Receiving inactive influenza vaccine after at least 4 weeks of commercial ofatumumab 20 mg subcutaneous treatment (3) receiving inactive influenza vaccine while on injectable disease modifying therapy (iDMT).
- **Variable:** Achieving seroprotection as defined by a postvaccination antibody titer ≥ 40 (yes/no) at Week 4
- **Treatment of interest**: Inactivated influenza vaccination either two weeks prior to ofatumumab start or at least 4 weeks after ofatumumab start or while on iDMT.
- **Intercurrent event:** None
- **Summary measure:** Proportion of subjects achieving seroprotection

[redacted]

2.2 Secondary estimands

Not applicable.

3 Study design

This is a three-cohort, multicenter prospective study in up to 66 participants with relapsing multiple sclerosis. Up to 44 of the participants will begin treatment with ofatumumab or already be on commercial ofatumumab, the remaining 22 participants will remain on their iDMT. In this study, participants must receive the 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine. Participants also must meet inclusion criteria and not meet exclusion criteria.

There are 3 study periods:

1. Screening Period:

Participants will enter a Screening Period of up to 1 week to assess eligibility requirements. Participants in Cohort 1 without Hepatitis B virus (HBV) and serum immunoglobulin results within the past 6 months prior to screening will require central labs drawn. Participants with Hepatitis B virus (HBV) and serum immunoglobulin results within the past 6 months prior to screening will not require the labs to be drawn.

2. Investigational Period:

All participants should receive an inactivated influenza vaccine within 9 calendar days after the Screening Visit, before the Week 0 Visit occurs. Participants will obtain the quadrivalent influenza vaccine at no cost to them from their local pharmacy using a pharmacy card supplied by Novartis or from the investigational site supply. Patients should be instructed to provide pharmacy documentation of vaccine administration to the Study Doctor at the next scheduled on-site study visit.

Participants in Cohort 1: Loading doses of 20 mg sc ofatumumab will be administered at Week 2, 3 and 4.

Participants in Cohort 2: Will continue taking their prescribed ofatumumab as per their dosing schedule throughout the Investigational Period.

Participants in Cohort 3: Will continue administration of their prescribed iDMT as per their dosing schedule in the Investigational Period.

3. Optional, 6-month open-label Extension Period:

The optional, 6-month open-label extension is designed to continue to observe the immune response.

Participants in Cohort 1 will administer their first dose of ofatumumab in the open-label Extension Period at Week 6. Thereinafter, they will continue monthly dosing until the final dose at Week 26. Novartis will supply ofatumumab to participants in Cohort 1 for the Extension Period.

Participants in Cohort 2 will continue to administer ofatumumab monthly until the final dose at Week 28. Novartis will supply ofatumumab to participants in Cohort 2 for the Extension Period.

[redacted]

Cohort 2 participants may either remain on their commercially prescribed ofatumumab or switch to study supplied ofatumumab.

Participants in Cohort 3 will not enter the open-label Extension Period.

Study design schematics for Cohorts 1, 2 and 3 are shown in Figure 3-1, Figure 3-2 and Figure 3-3 respectively.

Figure 3-1 Study Design (Cohort 1)

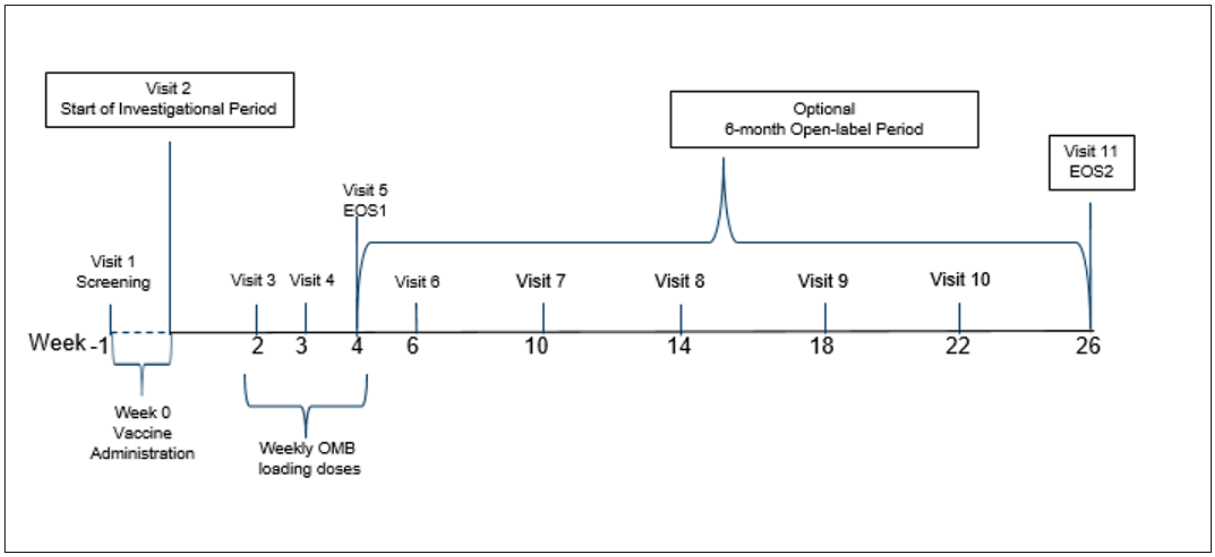
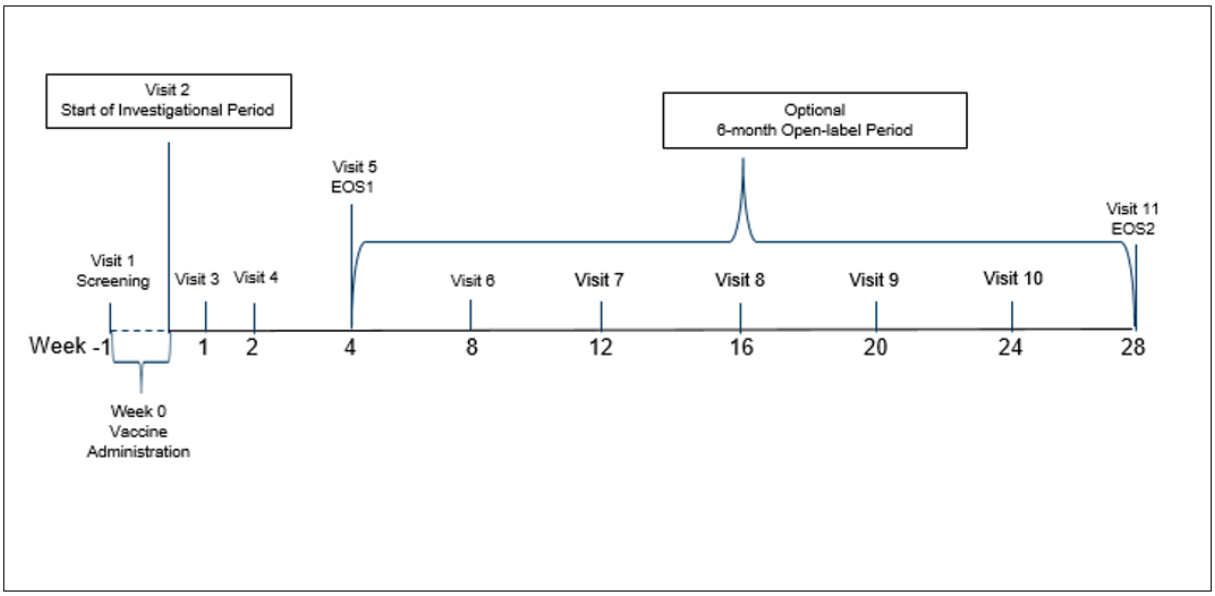
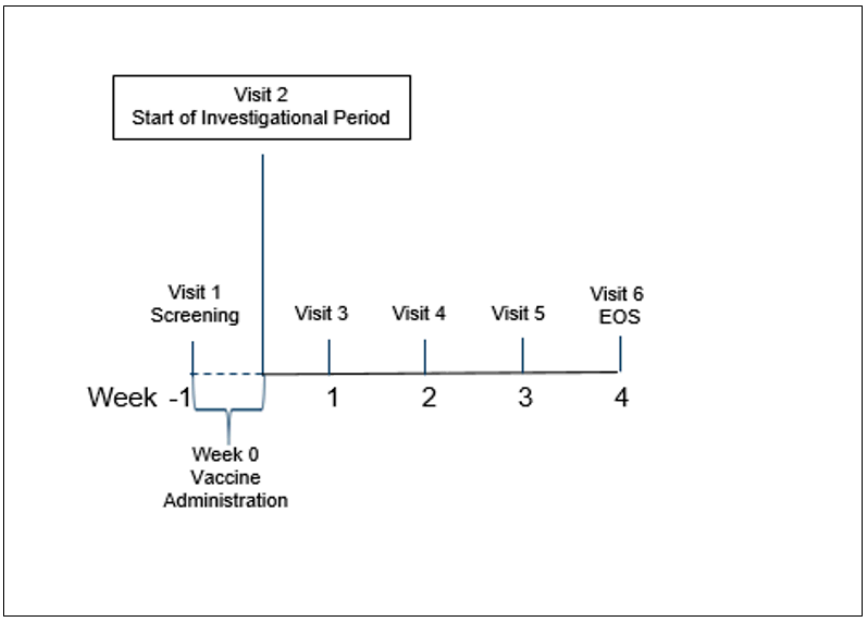


Figure 3-2 Study Design (Cohort 2)



[redacted]

Figure 3-3 Study Design (Cohort 3)



4 Rationale

4.1 Rationale for study design

A multicenter, multi-cohort, open-label, comparator design has been selected in order to render feasible recruitment before the end of the 2021-2022 or 2022-2023 , vaccine season and study completion. The study will address two questions:

1. Can participants treated with ofatumumab develop influenza antibodies if receiving influenza vaccine two weeks prior to ofatumumab start?
2. If receiving influenza vaccine after introduction of ofatumumab treatment, can participants develop influenza antibodies?

A 3rd cohort of participants on iDMT is included to provide a comparison that would be useful to investigative sites since the influenza vaccine is in limited supply.

Rationale of study population:

The included population is selected to be consistent with the phase 3 trial program and within the parameters of use specified by FDA approval and United States Prescribing Information (USPI). The population included is also within CDC recommendations to receive the influenza vaccine as part of routine clinical care. Screening participants will be excluded if they possess contraindications to either receiving ofatumumab per prescribing information or they possess contraindications to receiving the influenza vaccine. Participants will also be excluded if there is clinical or serologic evidence they have already contracted a 2020-2021, 2021-2022, or 2022-

2023 influenza strain. This is appropriate because the aim of the study is to assess whether a non-vaccinated ofatumumab treated individual can mount a response after influenza vaccine.

Rationale of chosen endpoints:

The proposed study primary endpoints are widely accepted as measures of influenza vaccine efficacy and consistent with FDA and European guidelines establishing effect. The endpoints will provide evidence addressing whether ofatumumab participants can mount an adequate immune response to the influenza vaccine.

4.2 Rationale for dose/regimen and duration of treatment

Ofatumumab dose

The dose regimen for ofatumumab in this study is consistent with the FDA approved regimen in the prescribing information.

In the Investigational Period, participants assigned to Cohort 1 will receive their first of three loading doses at Week 2. The second and third loading doses will be administered at Week 3 and Week 4. If participants in Cohort 1 opt to continue into the Extension Period, they will begin their monthly dose of ofatumumab starting at Week 6 and will continue receiving additional monthly doses until Week 26.

In the Investigational Period, participants assigned to Cohort 2 will continue to take ofatumumab as prescribed from their personal supply. Participants in Cohort 2 that continue into the Extension Period will continue taking ofatumumab monthly until Week 28 from a study-provided supply.

Vaccine Administration

Cohorts 1 – 3: Participants will need to receive an inactive influenza vaccine from their local pharmacy within 9 calendar days after the Screening Visit, before the Week 0 Visit occurs. Participants will obtain the quadrivalent influenza vaccine at no cost using a pharmacy card supplied by Novartis or will receive the vaccine from investigational site supply. Patients should be instructed to provide pharmacy documentation of vaccine administration to the Study Doctor at the next scheduled on-site study visit.

Duration of treatment:

Cohort 1: The treatment duration is 26 weeks (inclusive of a 6-month extension).

Cohort 2: The treatment duration is 28 weeks (inclusive of a 6-month extension).

Cohort 3: The treatment duration is 5 weeks. Participants in Cohort 3 will not enter the extension.

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

Since the ability to mount an immune response varies depending on the influenza strain administered, a reference cohort of participants on iDMTs (interferon or glatiramer acetate) is included. In a prior study, interferon and glatiramer acetate did not diminish influenza vaccine response (Olberg et al 2018.)

[redacted]

4.4 Purpose and timing of interim analyses/design adaptations

For the purpose of earlier dissemination of results, an interim analysis will be performed after either all enrolled participants have completed or discontinued the Investigational Period or on/around March 31, 2022, whichever comes first.

4.5 Risks and benefits

There is no benefit expected for participants in this study. Their participation will help contribute to a better understanding of the immune response that occurs when participants receiving ofatumumab are given the influenza vaccine. The ability to mount an immune response on ofatumumab will also be important to understand in response to any potential COVID vaccine. Though this study will not directly address COVID or potential COVID vaccines, it will provide some basic information about response to inactivated vaccine in ofatumumab treated participants.

Participants will obtain the quadrivalent influenza vaccine at no cost to them from their local pharmacy using a pharmacy card supplied by Novartis or will receive the vaccine from investigational site supply.

Novartis will supply participants in Cohort 1 with ofatumumab treatment in the Investigational Period and the optional Extension Period as per the assessment schedule (Table 8-1). Novartis will provide participants in Cohort 2 with ofatumumab treatment from study supplies in the optional Extension Period as per the assessment schedule or they may remain on their prescribed supply (Table 8-2).

Ocrelizumab safety data has been previously published (Hauser et al 2020) demonstrating infusion related reactions occur in 34.3%, serious infections occurred in 1.3%, and neoplasms occurred in 0.5% of participants. The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Over 1500 RMS participants have been exposed to ofatumumab across phase 2 and phase 3 studies. No unexpected safety findings were observed in MS participants who received ofatumumab in the completed studies (Hauser et al 2020).

Men and women of child-bearing potential must use a highly-effective method of birth control method during the study. 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.

5 Study Population

The study population will consist of male and female participants, ≥ 18 years of age to 55 years of age inclusive, with a diagnosis of relapsing MS.

The study aims to enroll up to 66 participants (up to 22 participants per cohort) at approximately 12 centers in the United States. Since a 25% screen failure rate is expected, approximately 88 participants will be screened.

[redacted]

The last day to screen a patient for this study will be when Cohort 1 and Cohort 3 each have 22 participants enrolled, or at the end of Q1 2023, whichever comes first.

5.1 Inclusion criteria

Participants eligible for inclusion in Cohorts 1 and 2 must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Age 18-55 years old
3. Diagnosis of relapsing MS by 2017 revised McDonald criteria
4. Must be willing to comply with the study schedule
5. Willing to receive a 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine
6. Planning to start treatment with ofatumumab or already on commercially prescribed ofatumumab for at least 2 weeks prior to the screening visit

Participants in Cohort 3 must fulfill criteria 1-5 above in addition to the following:

7. Participant must currently be receiving iDMT

5.2 Exclusion criteria

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

1. Already has received the 2020-2021, 2021-2022 or 2022-2023 season influenza vaccine
2. Known hypersensitivity to any component of the influenza vaccine
3. Any safety finding including low IgG and/or low IgM levels requiring an ofatumumab treatment interruption within the 12 weeks immediately prior to Week 0
4. Any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 weeks prior to or oral antibiotics within two weeks prior to Week 0
5. Known clinical diagnosis of influenza infection during the 2020-2021, 2021-2022 or 2022-2023 influenza season prior to starting the study based on investigator's or subject's personal physician's judgement (laboratory report of confirmed influenza infection is not required)
6. Prior treatment with B-cell targeted therapies (e.g., rituximab or ocrelizumab), lymphocyte-trafficking blockers, alemtuzumab, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, bone marrow transplantation. Treatment with a natalizumab within 6 months of week 0
7. Treatment with an S1P modulator within 60 days prior to Week 0
8. Participants with any known active systemic bacterial, fungal or viral or fungal infections (such as hepatitis, progressive multifocal leukocencephalopathy, COVID-19 or HIV), or known to have acquired immunodeficiency syndrome (AIDS)
9. Participation in another interventional clinical trial within 14 days prior to the screening visit

[redacted]

10. 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
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for at least 6 months after stopping study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the 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
    - For female participants on the study, the vasectomized male partner should be the sole partner
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug

    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 child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks. 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.
12. Patients with a history of Guillain-Barre syndrome within 6 weeks of receiving the influenza vaccination.

6 Treatment

6.1 Study Treatment

6.1.1 Investigational and control drugs

Novartis will supply the following study treatments:

[redacted]

- Open-label ofatumumab will be provided in an auto-injector containing 20 mg sc ofatumumab (20 mg/0.4ml) for subcutaneous administration.
  - Novartis will supply participants in Cohort 1 with ofatumumab treatment in the Investigational Period and the optional 6-month Extension Period as per the assessment schedule in Table 8-1.
  - Participants in Cohort 2 will continue on their commercially prescribed ofatumumab treatment during the Investigational Period. Novartis will supply participants in Cohort 2 with ofatumumab treatment in the optional 6-month Extension Period as per the assessment schedule in Table 8-2. Cohort 2 participants may either remain on their prescribed ofatumumab or switch to study supplied ofatumumab.
- Participants will obtain the quadrivalent influenza vaccine at no cost to them from their local pharmacy using a pharmacy card supplied by Novartis or will receive the vaccine from investigational site supply.

Participants enrolled in Cohort 3 will continue on their commercially prescribed iDMT.

Table 6-1 Investigational and control drugs

Investigational/ Control Drug	Route of Administration	Supply Type	Supplied by
OMB157 20mg/0.4mL	Subcutaneous Use	Open-label commercial supply; vials	Sponsor or commercially prescribed
iDMT	Subcutaneous or intramuscular use	Commercially prescribed	NA
Quadrivalent influenza vaccine	Intramuscular	Commercially supplied	Participants to obtain from their local pharmacy via pharmacy card or from investigational site supply

6.1.1.1 Decentralized Clinical Trial Model

The study medication and all required clinical study supplies may be distributed via direct-to-participant shipment utilizing an extension of the IND for compliance purposes.

6.1.2 Treatment cohorts/group

- Cohort 1: RMS participants receiving a 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine at least two week prior to ofatumumab start.
- Cohort 2: RMS participants receiving a 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine at least 4 weeks after ofatumumab start.
- Cohort 3: RMS participants currently on a prescribed iDMT receiving a 2020-2021, 2021-2022, or 2022-2023 inactivated influenza vaccine.

[redacted]

6.1.3 Post-Trial Access

Participants in Cohort 1 and 2 that successfully complete the Investigational Period may either continue into the optional, 6-month open-label Extension Period or will be referred to the commercial participant services hub for post-trial continuity of treatment, where the benefit/risk is acceptable and discussed with the participant, investigator and if applicable, the participant's treating physician. Participants who do not complete the study or withdraw due to an ofatumumab related AE or SAE should follow-up with their treating physician for continued treatment options.

6.2 Other treatments

6.2.1 Concomitant therapy

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.

Premedication prior to subcutaneous injection

Premedication is not required. Premedication with acetaminophen and/or antihistamines (or equivalent) is optional and may be administered at the discretion of the Investigator. For participants in Cohort 1, the addition of premedication per normal clinical practice is an additional consideration for the first injection of the Investigational Period (Week 2). If Investigators choose to administer premedication, it should be administered 30 to 60 minutes prior to study drug injection.

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis 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.

6.2.2 Prohibited medication

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.

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

[redacted]

Table 6-2 Prohibited medication at enrollment

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 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 the Sponsor.
Any other immunomodulatory or disease modifying MS treatment, including but not limited to fingolimod, interferon beta, glatiramer acetate, dimethyl fumarate, intravenous immunoglobulin, plasmapheresis or systemic corticosteroids (except for when given for MS relapse treatment as defined in Section 6.2.3)	Interrupt or 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 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 when participants are no longer exposed to study drug. Consider risk/benefit and follow local labels.

6.2.3 Recommended treatment of MS Relapse

The decision to treat MS relapses should be based on the Investigator's judgement and/or local clinical practice. 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 for treatment of MS attack/relapse must be recorded on the Concomitant Medications eCRF.

[redacted]

6.3 Participant numbering, treatment assignment

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation 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. At the Screening Visit (Visit 1/Week -1), the Investigator or his/her staff will contact the Interactive Response Technology (IRT) system 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.

Once assigned to a participant, a participant number will not be reused. If a participant fails to be enrolled for any reason, the IRT system must be notified within 2 days and the reason for not being enrolled will be entered on the Screening Phase Disposition Form and the appropriate eCRF(s) pages should also be completed.

6.3.2 Treatment assignment

An IRT system will be used to track patient visits, patient status and dispense open-label treatment to Cohort 1 when indicated in the assessment schedule (Table 8-1). The system will also be used to dispense treatment to participants in both Cohort 1 and Cohort 2 during the optional, 6-month open-label Extension Period.

At dosing visits, the system will specify unique medication numbers that will correspond to open-label treatment to be dispensed.

6.4 Treatment blinding

Not applicable.

6.5 Dose escalation and dose modification

Dose escalation and modifications are not permitted in this study.

6.6 Additional treatment guidance

Not applicable.

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

[redacted]

Compliance will be assessed by the investigator and/or study personnel at each visit using information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Emergency breaking of assigned treatment code

Since this study is open-label, emergency breaking of assigned treatment codes is not applicable.

6.7 Preparation and dispensation

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

Each study site will be supplied with study drug in packaging as described under investigational and control drugs 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).

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in English and comply with legal requirements in the U.S. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a Drug Accountability Log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. 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 treatment, packaging, drug labels, and a copy of the completed drug accountability log to Novartis or its agents.

Destruction of the unused drug should be done according to local requirements and after approval by Novartis clinical team.

6.7.2 Instruction for prescribing and taking study treatment

All investigational medication will be provided by Novartis. Ofatumumab treatment should be administered after study assessments have been completed for the visit.

[redacted]

Influenza Vaccine

The quadrivalent vaccine should be obtained at the patient's preferred pharmacy using the Novartis supplied pharmacy card or will receive the vaccine from the investigational site supply within 9 days of the screening visit.

Ofatumumab

Site staff should remove the study treatment from the refrigerator and allow the auto injector pen to reach room temperature in their unopened box (approximately 15-30 minutes) before self-injection by the participant. Used syringes 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.

Participants in Cohort 1

The patients in Cohort 1 will receive their first loading dose of ofatumumab at the study site at Week 2 (2 weeks after receiving the influenza vaccine). The next loading dose of study drug will be dispensed to the participant at this visit to take home for administration at Week 3. The Week 4 dose will be administered in the clinic after the post-vaccine titer is drawn. Doses at Week 3 (dose #2) and Week 4 (dose #3) should be administered +/- 1 day from when they are scheduled to be administered. If the dose on Week 3 (dose #2) is missed, the dose due on Week 4 (dose #3) should be adjusted to 7 days after dose #2 was given.

If participants in Cohort 1 opt to participate in the Extension Period, at Week 4, sufficient study drug will be supplied to the participant to cover monthly home administrations of study drug until the Week 18 clinic visit which should take place in the clinic. At Week 18, sufficient study drug will be supplied to the participant to cover the Week 22 dose. The Week 26 dose will be administered in-clinic. **Note: At Week 26, sites must perform a study drug dispensation transaction in IRT before the transaction to register study completion is performed.**

Participants will be asked to complete a patient diary to record doses of study treatment administered at home study visits.

Participants in Cohort 2

Upon enrollment, participants already receiving prescribed ofatumumab will continue to take prescribed treatment as per their current dosing schedule during the Investigational Period. If participants in Cohort 2 opt to participate in the Extension Period, at Week 4, the participant will be supplied with study drug to cover monthly administrations in the Extension Period of the study until the Week 16 clinic visit. At Week 16, sufficient study drug will be supplied to the participant to cover monthly doses up to and including Week 24. The Week 28 dose will be

[redacted]

administered in-clinic. **Note: At Week 28, sites must be sure to perform a study drug dispensation transaction in IRT before the transaction to register study completion is performed.**

Participants will be asked to complete a patient diary to record doses of ofatumumab taken during the Investigational Period and during the Extension Period, if applicable.

Participants in Cohort 3

Upon enrollment, participants in Cohort 3 will continue to take their iDMT as per their current dosing schedule.

Participants will be asked to complete a patient diary to record doses of their iDMT taken during the Investigational Period.

Table 6-3 Dose and treatment schedule

	Investigational Drug	Frequency and/or Regimen
Cohort 1	OMB157 20mg/0.4mL	*Week 2, Week 3, Week 4, Week 6, and then monthly*
Cohort 2	OMB157 20mg/0.4mL	*Monthly as prescribed*
Cohort 3	iDMT	*As prescribed*

As patients must administer ofatumumab from home at certain visits, site personnel will provide training on the correct procedure for self-administration of the ofatumumab subcutaneous injections to enable the participant and/or a caregiver to administer treatment on the day of home visits. Documentation of the participant or caregiver understanding the correct administration procedure must be documented in the source document.

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 in a Participant Diary.

Site personnel will make remote contact with participants on/around the time of the 2nd loading dose to query about any new or worsening symptoms warranting an unscheduled visit, compliance with study treatment, injection reactions, and compliance with contraception requirements when applicable. Additional remote contacts should be conducted on/around the time patients are due to administer treatment at home. The method of contact with each participant can be the personal preference of the individual between telephone contacts, email contact or text messages, however, the site staff must be able to provide suitable source documentation of each contact regardless of the method of contact.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB) 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 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 International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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.

Information about common side effects already known about the investigational drug 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 included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

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

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

8 Visit schedule and assessments

The below Assessment Schedules (Table 8-1, Table 8-2, Table 8-3) list all assessments with an X when they are performed. Assessments that will only be reported in the source documentation are marked with an 'S'.

Participants should be seen for all visits/assessments as outlined in the assessment schedules or as close to the designated day/time as possible with an allowed visit window of ±3 days. The Investigator should promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity of the study. Missed or rescheduled visits should not lead to automatic discontinuation. The subject should be instructed to contact the Investigator if he/she is unable for any reason to

[redacted]

attend a study visit as scheduled or if he/she is unable for any reason to take the study treatment as prescribed.

Cohort 1: At Week 0, the study site will perform a Vaccine Status Check-in via remote contact to confirm participant has received the influenza vaccine. At-home study visits will be performed at Week 2, 3, 6, 10, 14, and Week 22. Patients and/or caregivers trained to administer the ofatumumab subcutaneous injections will need to administer treatment at home study visits. At Week 4, sufficient study drug will be supplied to the participant to cover all home administrations of study drug until the Week 18 clinic visit. At Week 18, sufficient study drug will be supplied to the participant to cover dosing up at Week 22. The last dose of study drug will be administered at the Week 26 visit at the site. Refer to Table 8-1.

Cohort 2: At Week 0, the study site will perform a Vaccine Status Check-in via remote contact to confirm participant has received the influenza vaccine. At-home study visits will be performed at Week 1, 2, 8, 12, 20, and Week 24. At Week 4, sufficient study drug will be supplied to the participant to cover all home until the next clinic visit (Week 16). At Week 16, sufficient study drug will be supplied to the participant to cover dosing up to and including the Week 24 dose. The last dispensation of ofatumumab supplied in the study will occur at the Week 28 visit at the site. Refer to Table 8-2.

Cohort 3: At Week 0, the study site will perform a Vaccine Status Check-in via remote contact to confirm participant has received the influenza vaccine. At-home study visits will be performed at Week 1, 2 and 3. Refer to Table 8-3.

Cohort 1 and 2 participants who prematurely discontinue the study while in the Investigational Period should be scheduled for the End of Study (EOS1) visit within 7 days. At this final visit, all the assessments mentioned under EOS1 visit should be performed except for study drug administration. Cohort 3 participants who prematurely discontinue the study while in the Investigational Period should be scheduled for the End of Study (EOS) visit within 7 days.

Cohort 1 and 2 participants who prematurely discontinue the study while in the Extension Period should be scheduled for the final visit of the Extension Period (EOS2) within 7 days. All EOS2 assessments should be performed except study drug administration.

In addition to the scheduled visits, participants may have unscheduled visits due to a MS relapse, an acute illness of undetermined cause, for other reasons, or at the discretion of the Investigator. Data collected during unscheduled visits will be recorded in the unscheduled visits CRF.

[redacted]

Table 8-1 Assessment schedule for participants (cohort 1)

Period	Screening	Investigational Period				6-month Extension Period						Unscheduled
Visit Name	Visit 1 Screening	Visit 2 (vaccine status check-in)	Visit 3	Visit 4 (home visit)	Visit 5 EOS1	Visit 6 (home visit)	Visit 7 (home visit)	Visit 8 (home visit)	Visit 9	Visit 10 (home visit)	Visit 11 EOS2	Unscheduled
Day/Week/Month	Week -1	Week 0	Week 2	Week 3	Week 4	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26	
Visit Window Days (d)			± 1d	± 1d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	
Obtain informed consent	X											
Inclusion/exclusion criteria	X											
Demography	X											
Relevant medical history/current medical history	X											
Prior/Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X
MS Relapse	X		X	X	X	X	X	X	X	X	X	X
Hepatitis B virus (HBV)	X[1]											
Serum immunoglobulins	X[1]											
Local Serum Pregnancy Test	S											
Screening / Pre-vaccine HI titer	X											
Dispense pharmacy card	S[2]											
Self-injection training			S									
IRT transaction	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Period	Screening	Investigational Period				6-month Extension Period						Unscheduled
Visit Name	Visit 1 Screening	Visit 2 (vaccine status check-in)	Visit 3	Visit 4 (home visit)	Visit 5 EOS1	Visit 6 (home visit)	Visit 7 (home visit)	Visit 8 (home visit)	Visit 9	Visit 10 (home visit)	Visit 11 EOS2	Unscheduled
Day/Week/Month	Week -1	Week 0	Week 2	Week 3	Week 4	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26	
Visit Window Days (d)			± 1d	± 1d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	
Post vaccine Serum HI titers					X[3]							
Administration of study drug			X	X	X	X	X	X	X	X	X	
Drug Accountability	S				S				S		S	
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Subject disposition	X				X						X	
Remote Contact		X[4]	S[5]	S[5]		S[5]	S[5]	S[5]		S[5]	S[5]	

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

S = assessment to be recorded in the source documentation only

[1] Participants with lab results within the past 6 months prior to screening will not require labs drawn at screening visit. Local labs should be documented in the source. Participants without lab results from the past 6 months prior to screening will require central labs drawn at the screening visit to be entered into the clinical database.

[2] Participants will use the pharmacy card to cover the cost of the influenza vaccine. Participants administered the vaccine from investigator site supply will not receive a pharmacy card. All participants should receive the vaccine within 9 calendar days after the Screening Visit, before the Week 0 visit occurs.

[3] Post vaccine titer to be drawn before administration of ofatumumab.

[4] Remote contact to perform a Vaccine Status Check-in by site staff to confirm participant has received the influenza vaccine and to collect any AEs/SAEs.

[5] Remote contact with participants by site staff. The contact should query about any new AEs or SAEs, changes in con meds and compliance with current treatment. Method of contact can be via telephone, email or text message depending on the preference of each participant.

[redacted]

Table 8-2 Assessment schedule for participants (cohort 2)

Period	Screening	Investigational Period				6-month Extension Period						Unscheduled
Visit Name	Visit 1 Screening	Visit 2 (vaccine status check-in)	Visit 3 (home visit)	Visit 4 (home visit)	Visit 5 EOS1	Visit 6 (home visit)	Visit 7 (home visit)	Visit 8	Visit 9 (home visit)	Visit 10 (home visit)	Visit 11 EOS2	Unscheduled
Day/Week/Month	Week -1	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	
Visit Window Days (d)			± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	
Obtain informed consent	X											
Inclusion/exclusion criteria	X											
Demography	X											
Relevant medical history/current medical history	X											
Prior/Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X
MS Relapse	X		X	X	X	X	X	X	X	X	X	X
Local Serum Pregnancy Test	S											
Screening / Pre-vaccine HI titer	X											
Dispense pharmacy card	S[1]											
IRT transaction	X	X	X	X	X	X	X	X	X	X	X	
Administration of study drug						X	X	X	X	X	X	
Post vaccine Serum HI titers					X[2]							
Drug Accountability Log	S				S			S			S	
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Subject disposition	X				X						X	

[redacted]

Period	Screening	Investigational Period				6-month Extension Period						Unscheduled
Visit Name	Visit 1 Screening	Visit 2 (vaccine status check-in)	Visit 3 (home visit)	Visit 4 (home visit)	Visit 5 EOS1	Visit 6 (home visit)	Visit 7 (home visit)	Visit 8	Visit 9 (home visit)	Visit 10 (home visit)	Visit 11 EOS2	Unscheduled
Day/Week/Month	Week -1	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	
Visit Window Days (d)			± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	± 3d	
Remote Contact		X[3]	S[4]	S[4]		S[4]	S[4]		S[4]	S[4]		

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

S = assessment to be recorded in the source documentation only

[1] Participants will use the pharmacy card to cover the cost of the influenza vaccine. Participants administered the vaccine from investigator site supply will not receive a pharmacy card. All participants should receive the vaccine within 9 calendar days after the Screening Visit, before the Week 0 visit occurs.

[2] Post vaccine titer to be drawn before administration of ofatumumab.

[3] Remote contact to perform Vaccine Status Check-in by site staff to confirm participant has received the influenza vaccine and to collect any AEs/SAEs.

[4] Remote contact with participants by site staff. The contact should query about any new AEs or SAEs, changes in con meds and compliance with current treatment. Method of contact can be via telephone, email or text message depending on the preference of each participant

[redacted]

Table 8-3 Assessment schedule for participants (cohort 3)

Period	Screening	Investigational Period					Unscheduled
Visit Name	Visit 1 Screening	Visit 2 (vaccine status check-in)	Visit 3 (home visit)	Visit 4 (home visit)	Visit 5 (home visit)	Visit 6 EOS	Unscheduled
Day/Week/Month	Week -1	Week 0	Week 1	Week 2	Week 3	Week 4	
Visit Window Days (d)			± 3d	± 3d	± 3d	± 3d	
Obtain informed consent	X						
Inclusion/exclusion criteria	X						
Demography	X						
Relevant medical history/current medical history	X						
Prior/Concomitant Medications	X		X	X	X	X	X
MS Relapse	X		X	X	X	X	X
Local Serum Pregnancy Test	S						
Screening / Pre-vaccine HI titer	X						
Dispense pharmacy card	S[1]						
IRT Transaction	X	X	X	X	X	X	
iDMT administration log	X					X	
Post vaccine Serum HI titers						X	
Drug Accountability log	S					S	
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X
Subject disposition	X					X	
Remote Contact		X[2]	S[3]	S[3]	S[3]		

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

[1] Participants will use the pharmacy card to cover the cost of the influenza vaccine. Participants administered the vaccine from investigator site supply will not receive a pharmacy card. All participants should receive the vaccine within 9 calendar days after the Screening Visit, before the Week 0 visit occurs.

[2] Remote contact to perform a Vaccine Status Check-in by site staff to confirm participant has received the influenza vaccine and to collect any AEs/SAEs.

[3] Remote contact with participants by site staff. The contact should query about any new AEs or SAEs, changes in con meds and compliance with current treatment. Method of contact can be via telephone, email or text message depending on the preference of each participant.

[redacted]

8.1 Rescreening

Rescreening is not permitted.

8.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to enrollment will be considered a screen failure. The reason for screen failure should be recorded on the appropriate 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). If the participant fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the participant was not enrolled.

Participants who are enrolled and fail to start treatment, e.g. participants enrolled in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.3 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 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.

8.4 Efficacy

Not applicable.

8.5 MS Relapse

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 relapse, an unscheduled visit to the Investigator must be scheduled as soon as possible (whenever possible within 7 days of onset of the symptoms). Confirmed relapses should be recorded on the Summary of MS Relapse eCRF.

MS relapse definition

An MS relapse is defined as an 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.

[redacted]

8.5.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected listed below with the exception of the serum pregnancy test. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

8.5.1.1 Hepatitis B virus (HBV)

Hepatitis B virus (HBV) will be performed at Visit 1/Screening for participants in Cohort 1 that do not have test results in their medical history within 6 months prior to the Screening Visit/Week -1.

8.5.1.2 Serum Immunoglobulins

Serum immunoglobulins will be performed at Visit 1/Screening for participants in Cohort 1 that do not have test results in their medical history within 6 months prior to the Screening Visit/Week -1.

8.5.2 Pregnancy and assessments of fertility

A local, serum pregnancy test will be performed for all women of child-bearing potential at Screening Visit/Week -1.

The Investigator should review the contraception status with the participant at the Screening Visit/Week -1 to ascertain if the participant will comply with protocol requirements for highly effective contraception.

All pre-menopausal women who are not surgically sterile will have pregnancy testing.

8.6 Additional assessments

No additional tests will be performed on participants entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration 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.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per the USPI

[redacted]

- Any situation in which study participation might result in a safety risk to the participant
- Diagnosis of PML
- Participants with active serious infections or reactivation
- Skin and/or mucosal reactions which raise the suspicion of severe generalized major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome)
- Hypersensitivity to the study medication
- Protocol violation that results in a significant risk to the participant's safety
- Emergence of certain adverse events, such as malignancy (except successfully treated basal cell carcinoma, *in situ* squamous cell carcinoma and *in situ* carcinoma of cervix of uterus), liver failure or serious chronic infection (such as human immunodeficiency virus(HIV))
- Severe hypoproteinemia
- Non-compliance with study drug or study procedures

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2 'Withdrawal of Informed Consent' section). **Where possible, they should return for the EOS Visit applicable to the period in which the patient is currently in. Participants in Cohort 1 that discontinue in the Investigational Period, should return for all assessments indicated for the EOS1 Visit except for study drug administration**. **Participants in Cohort 1 and 2 that discontinue in the Extension Period, should return for all assessments indicated for the EOS2 Visit except for study drug administration**. At EOS visits all dispensed study drug to participants in Cohort 1 and Cohort 2 should be reconciled and the adverse event and concomitant medications should be recorded on the CRF (for participants in both arms). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

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

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

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

[redacted]

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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 his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of 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.

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

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

9.1.4 Study stopping rules

Not applicable.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Inability to complete enrollment by the end of the vaccination season
- Practical reasons

[redacted]

- Regulatory or medical reasons

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible for an end of study visit within 7 calendar days and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant completes the EOS1 Visit if the participant will not continue into the Extension Period, or the EOS2 visit of the Extension Period if the participant continues into the extension.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

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

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 Common Toxicity Criteria (CTC) AE grade (1-4)

   If CTCAE grading does not exist for an adverse event, use:
   - 1 = mild: usually transient in nature and generally not interfering with normal activities
   - 2 = moderate: sufficiently discomforting to interfere with normal activities
   - 3 = severe: prevents normal activities

[redacted]

- 4 = life threatening

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

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

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown).

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

[redacted]

  - 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 *and the malignant neoplasm is not a disease progression of the study indication.*

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 as per Section 10.1.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days *after the last study visit* must be reported to Novartis safety 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.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety 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.

[redacted]

Any SAEs experienced > 30 days after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

Please note: The time of 30 days in the standard text above is the recommended minimum and the SAE form should be submitted to Novartis Safety. A longer duration may be appropriate for drugs with particularly long elimination half-lives or from drug classes with known late occurring effects, or when risk assessment/management objectives require prolonged safety monitoring. Please ensure the Informed Consent Form reflects this 30 day/Post Study Safety Contact.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her 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 on until after the Expected Due Date (EDD) to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Additional follow up will be completed at EDD +1 month, EDD +2 months (in case no answer is received after request at EDD +1 month) and at EDD +3 months. Information on the status of the baby after delivery and information on any development issue or abnormality that would not be seen at birth must be collected.

Pregnancy should be recorded and reported on the Pregnancy Form by the investigator to the Novartis Chief Medical Office and Participant Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

[redacted]

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.

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

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

The investigator/designee is responsible for assuring that the data (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 will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

[redacted]

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

Enrollment and data about all study treatment(s) dispensed to the participant will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. Novartis may request to receive the IRT data electronically 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 visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. 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

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

[redacted]

Categorical variables will be presented as counts and percentages. For continuous variable, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum will be presented.

All summaries will be presented by study arm.

12.1 Analysis sets

The Safety Set comprises all participants who received at least one dose of study drug.

The Safety Set will be used for the summary of demography and baseline characteristics as well as for all safety analyses.

12.2 Participant demographics and other baseline characteristics

Demographics and other baseline characteristics will be summarized descriptively.

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

12.3 Treatment

The duration of exposure in days will be summarized descriptively.

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

12.4 Analysis of primary endpoint(s)/estimand(s)

The primary objective of this study is to characterize those achieving seroprotection after receiving the 2020-2021, 2021-2022, or 2022-2023 seasonal quadrivalent influenza vaccine in subjects treated with ofatumumab 20 mg sc once every 4 weeks. This will be achieved by estimating the seroprotection response rate.

A seroprotection responder is a participant achieving seroprotection as defined by a postvaccination antibody titer ≥ 40.

The seroprotection response rate is defined as the proportion of subjects with seroprotection.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary endpoint is achieving seroprotection as defined by a postvaccination antibody titer ≥ 40 (yes/no) at Week 4.

12.4.2 Statistical model, hypothesis, and method of analysis

The number and percentage of responders by year of enrolment in study and overall will be presented. The 95% confidence interval for the proportion of responders will be calculated by using exact method.

[redacted]

12.4.3 Handling of remaining intercurrent events of primary estimand

Not applicable.

12.4.4 Handling of missing values not related to intercurrent event

Non-responder imputation approach will be applied to missing postvaccination antibody titer.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Not applicable.

12.4.6 Supplementary analysis

12.4.7 Similar analyses will be performed by using observed data.Supportive analyses

Not applicable.

12.5 Analysis of secondary endpoint(s)/estimand(s)

The secondary endpoint is achieving seroconversion defined as meeting one of the following two criteria:

- ≥ 4-fold increase in HI titers after vaccination (in participants with prevaccination HI titers ≥10) (yes/no) or
- postvaccination HI titers ≥40 (in participants with prevaccination HI titers < 10) (yes/no)

Proportion of participants achieved seroconversion at Week 4 will be estimated and the corresponding 95% confidence interval will be calculated using exact method.

Both non-responder imputation and observed case approaches will be applied in the analyses of seroconversion.

To assess the change in HI titers, geometric means will be calculated for pre- and post-vaccination HI titers.

To meet European Medicines Agency guidelines for protection for the Cohort, at least one of the following criteria has to be met:

1. Seroprotection rate is better than 70%;
2. Seroconversion rate is higher than 40%;
3. Ratio of geometric mean of post- to pre-vaccination HI titers ≥ 2.5.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Not applicable.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment arm.

[redacted]

In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, which started or worsened during the on-treatment period (treatment-emergent AEs).

Adverse events

All information obtained on adverse events will be displayed by treatment group and 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 double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, *and adverse events leading to dose adjustment.*

In addition, a separate listing of death including on treatment and post treatment deaths will be provided.

Clinical laboratory evaluations

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

12.6 Analysis of exploratory endpoints

Not applicable.

12.7 Interim analyses

For the purpose of early dissemination of results, two interim analyses will be performed after:

- on/around April 12, 2021, whichever comes first.
- on/around March 31, 2022, whichever comes first.

At the time of each interim analysis, methods proposed in Sections 12.5 and 12.6 for data summary and analyses will be performed. Since there will be no hypothesis testing involved, statistical adjustment for the interim analyses will not be made at the stage of final analyses of efficacy and safety.

[redacted]

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size of 20 participants per arm is selected based on budget and need for early availability of results for the current influenza season. This sample size of 20 subjects will provide estimates of proportion responded with margin of error (half-width of a 95% confidence interval) of 20.1%, 19%, and 17.5% corresponding to response rates of 70%, 75%, and 80%, respectively. Adjusting for 10% drop-out, 22 subjects will be enrolled in each arm.

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.

13.2 Responsibilities of the investigator and IRB

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB 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, 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.

[redacted]

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.

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 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 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 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 at the study site should be informed according to local regulations.

[redacted]

15 References

References are available upon request.

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[redacted]