Official Title of Study:

A Phase 3b, Multicenter, Open-label Study to Evaluate the Immune Response to, and the Safety of, Vaccines in Participants With Relapsing Forms of Multiple Sclerosis Who Receive Oral Ozanimod Compared to Non-pegylated Interferon (IFN)-β or No Disease Modifying Therapy

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A PHASE 3B, MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE IMMUNE RESPONSE TO, AND THE SAFETY OF, VACCINES IN PARTICIPANTS WITH RELAPSING FORMS OF MULTIPLE SCLEROSIS WHO RECEIVE ORAL OZANIMOD COMPARED TO NON-PEGYLATED INTERFERON-B OR NO DISEASE MODIFYING THERAPY

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**

Printed Name of Site Principal Investigator

Institution Name:_____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

OVERALL RATIONALE FOR THE PROTOCOL AMENDMENT 1.0

The main rationale for this amendment is to revise the age of participants to be enrolled in the study. The table below highlights the key changes made to the protocol.

SUMMARY OF CHANGES OF PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Protocol Summary Section 4.2: Inclusion Criteria for All Subjects	Changed the age range of participants to be enrolled from "18 to 55, inclusive" to "18 to 65, inclusive".	To include a wider range of participants based on feedback received from sites and enrollment challenges. There is no sufficient immune response data to exclude subjects 55-65 years old.
Section 6.7: Additional and Optional Research	Added section with template language.	Template language was added, which had previously been inadvertently removed during the approval process.

PROTOCOL SUMMARY

Study Title

A Phase 3b, multicenter, open-label study to evaluate the immune response to, and the safety of, vaccines in participants with relapsing forms of multiple sclerosis who receive oral ozanimod compared to non-pegylated interferon (IFN)-β or no disease modifying therapy.

Indication

Relapsing forms of multiple sclerosis

Background

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system (CNS) characterized by inflammation, demyelination, neuronal and oligodendrocyte loss, and disruption of the blood-brain barrier, leading to irreversible deficits in physical function and cognition and an impaired quality of life (Lassmann, 2019). The prevalence of MS is increasing and is currently estimated to affect 2.3 million individuals worldwide (Multiple Sclerosis International Foundation, 2013).

Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator, which binds with high affinity selectively to sphingosine 1-phosphate receptor subtypes 1 and 5 (S1P1 and S1P5). Ozanimod causes lymphocyte retention in lymphoid tissues. The mechanism by which ozanimod exerts therapeutic effects in MS is unknown but may involve reduction of lymphocyte migration into the CNS (Scott, 2016; Chaudry, 2017). Ozanimod is approved for the treatment of relapsing forms of multiple sclerosis (RMS) in adults in the United States (US) and for the treatment of adult subjects with relapsing-remitting MS (RRMS) with active disease as defined by clinical or imaging features in European Medicines Agency (EMA) jurisdictions.

Based on its mechanism of action ozanimod has the potential to reduce the immune response to vaccinations; however, the effect of ozanimod on vaccination response has not been measured. Because many subjects with MS receive disease modifying therapies (DMT) chronically and receive vaccinations while being treated with DMTs, the effect of ozanimod on the vaccination response of MS subjects is of interest to patients and prescribers. This study will evaluate the immune response to vaccines in subjects with RMS taking ozanimod compared to RMS subjects not taking ozanimod.

The vaccines chosen to investigate in this study allow for the assessment of the humoral immune response and are of clinical relevance to MS populations.

Objectives

Primary Objective

To evaluate the proportion of subjects meeting serologic response criteria against the tetanus toxoid antigen after vaccination with the Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis, Adsorbed (Tdap) vaccine in subjects with RMS receiving ozanimod or receiving non-pegylated interferon-β (IFN-β) or no DMT.

Secondary Objectives

To evaluate the following in subjects with RMS undergoing vaccination and receiving ozanimod or receiving non-pegylated IFN-β or no DMT:

- Proportion of subjects meeting tetanus seroprotective criteria
- Proportion of subjects meeting pneumococcus serologic response and seroprotective criteria
- Safety and tolerability

Exploratory Objectives

To evaluate the following in subjects with RMS undergoing vaccination and receiving ozanimod or receiving non-pegylated IFN-β or no DMT:

- Immune response to the seasonal inactivated influenza vaccine
- Proportion of subjects meeting diphtheria serologic response, seroprotective criteria, and the Geometric Mean Concentration (GMC) ratio of anti-diphtheria immunoglobulin G (IgG) and immunoglobulin M (IgM)
- Proportion of subjects meeting pertussis serologic response, seroprotective criteria, and the GMC ratio of anti-pertussis IgG and IgM
- GMC ratios of IgG and IgM against tetanus antigens
- GMC ratios of IgG and IgM against antigens contained in the pneumococcal polysaccharide vaccine (PPSV23)
- Pharmacokinetic (PK) and pharmacodynamic (PD) parameters of ozanimod and its active metabolites (ie, CC112273) in subjects who receive ozanimod as their standard of care

Study Design

The proposed study is a Phase 3b, multicenter, open-label study to evaluate the immune response to and the safety of vaccines administered in subjects with RMS who receive either oral ozanimod 0.92 mg or IFN-β or no DMT.

All enrolled subjects will be vaccinated on Day 1 and followed until Day 28 (±3 days) to evaluate immune response via serological endpoints.

The study will include two cohorts differentiated by the vaccines administered. Cohort 1 comprises subjects who receive Tdap, PPSV23, and the seasonal inactivated influenza vaccine. Cohort 2 comprises subjects who have already received the seasonal inactivated influenza vaccine and will therefore receive Tdap and PPSV23 only. Initiation of Cohort 2 will be based on the availability of eligible subjects who have not previously been vaccinated with the seasonal inactivated influenza vaccine. Cohort 2 may be opened for enrollment at any time determined by the Sponsor but is estimated to occur after no less than 60% of subjects of the planned total enrollment have been recruited into Cohort 1. Subjects who meet all eligibility criteria will continue to be enrolled in Cohort 1 throughout the time both cohorts are open for enrollment at the discretion of the Sponsor.

The study will be conducted in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Approximately 60 ambulatory subjects between the ages of 18 to 65, inclusive, with RMS will be enrolled. Approximately 30 of these subjects will have been continuously treated with ozanimod at least [redacted] days prior to the Day 1 (Baseline) Visit, and approximately 30 subjects will either be treated with a non-pegylated IFN-β or will not be receiving any DMT.

Length of Study

This study will include a screening period of up to 14 days. The study period is from Day 1 vaccination to the 28-day assessment visit. The maximum potential length from screening to end of trial is 45 days. Screening and Day 1 may occur on the same day in eligible subjects.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Tdap, Influenza Vaccine, and Pneumococcal Vaccine, Polyvalent

For all vaccines the pre-filled syringe (0.5 ml) dosage form must be used.

Ozanimod and Non-pegylated IFN-β

Ozanimod and non-pegylated IFN-β will be considered standard of care DMT medications prescribed by the Investigator in this study. Standard of care DMTs are not provided as part of this study, and the Sponsor will not reimburse sites or subjects for the cost of the standard of care medication. During the study, subjects should continue their medication according to their regular schedule and as prescribed in the label of their respective countries.

Overview of Key Efficacy Assessments

This study will evaluate immune response, measured by comparing post-vaccination to pre-vaccination titers or concentrations of IgG and IgM antibodies against the Tdap, PPSV23, and seasonal influenza vaccines in serum samples.

<u>Primary Endpoint:</u>

- Proportion of subjects with serologic response to tetanus toxoid

<u>Secondary Endpoints:</u>

- Tetanus:
  - Proportion of subjects with serological protection against tetanus toxoid
- Pneumococcus
  - Proportion of subjects with serologic response to at least 5 of the following pneumococcal serotypes: 3, 6B, 9N, 11A, 14, 19A, 19F, 22F and 23F
  - Proportion of subjects with serological protection against the following pneumococcal serotypes: 3, 6B, 9N, 11A, 14, 19A, 19F, 22F and 23F

Exploratory Endpoints:

- Influenza
  - Proportion of subjects with serologic response to the seasonal influenza vaccine
  - Proportion of subjects with serological protection against seasonal influenza
  - Geometric Mean Titer (GMT) ratio of anti-influenza antibodies
  - Assessment if at least one of the specified criteria is met for each treatment arm for each influenza strain
- GMC ratio of anti-tetanus toxoid IgG and IgM
- GMC ratio of anti-pneumococcus IgG and IgM for each pneumococcal serotype in PPSV23
- Diphtheria
  - Proportion of subjects with serologic response to reduced diphtheria toxoid
  - Proportion of subjects with serological protection against reduced diphtheria toxoid
  - GMC ratio of anti-diphtheria toxoid IgG and IgM
- Pertussis
  - Proportion of subjects with serologic response to pertussis
  - Proportion of subjects with serological protection against pertussis
  - GMC ratio of anti-pertussis IgG and IgM
- PK/PD sampling to determine plasma concentration of ozanimod and active metabolites

Overview of Key Safety Assessments

Safety assessments in the study include adverse events (AE), vital signs, physical examination, clinical laboratory evaluations, and relapses. The incidence, severity, relationship, and type of treatment-emergent AEs, serious adverse events (SAEs), AEs leading to study discontinuation, and relapses will be summarized, as well as clinically meaningful changes from baseline for clinical laboratory measures, vital signs, and physical examinations.

Statistical Methods

This is a non-randomized, open-label study in which all subjects remain on their pre-study (baseline) treatment per protocol. Subjects will be recruited by investigators from MS clinical practice patients and prospectively assessed for immune response to vaccination. The statistical analyses will focus on estimating immune response rates, adjusting for baseline subject-level characteristics. No formal statistical hypothesis is evaluated. To mitigate for potential differences in the recruited subject population in the ozanimod and non-ozanimod arms that potentially could affect immune response, response rates will be estimated based on a logistic regression model adjusting for several factors, eg, age, sex, body mass index (BMI), and baseline absolute lymphocyte count (ALC). The results of the statistical analyses for immune response endpoints will be summarized for subjects receiving ozanimod (ozanimod arm) and subjects not receiving

ozanimod (non-ozanimod arm) as their standard of care DMT for MS. Analyses of safety will be summarized by descriptive statistics separately for the ozanimod and non-ozanimod arms.

The primary endpoint is the proportion of subjects with serologic response to vaccination with tetanus toxoid. The primary endpoint analysis and all analyses for immune response to vaccination will be performed in the per-protocol population, ie, in subjects who received the correctly assigned vaccinations, had no systemic use of corticosteroids, and did not receive any other vaccines throughout the study. Sensitivity analyses will be conducted within the modified intent-to-treat population consisting of all subjects who received at least one vaccination and summarized according to their initial arm status (ozanimod vs. non-ozanimod) regardless of steroid use.

The sample size of the study is 60 subjects with an estimated 30 subjects expected to have received ozanimod and 30 subjects expected to not have received ozanimod as standard of care DMT. It is expected that approximately 60% of the subjects in the IFN-β or no DMT control group will have a serologic response to vaccination with Tdap (Kappos, 2015).

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1 INTRODUCTION

1.1 MS Disease Background

Multiple Sclerosis

Multiple sclerosis (MS) is an idiopathic, chronic inflammatory demyelinating disease of the Central Nervous System (CNS). The disease is characterized pathologically by inflammatory lesions of CNS myelin with resultant edema, demyelination, and oligodendrocyte and neuronal loss. Acute inflammatory lesions are initiated by activated peripheral lymphocytes that enter the CNS through a breached blood-brain barrier (Lucchenetti, 2000; Popescu, 2012; Lassmann 2007, Lassman, 2019; Frisher, 2015)

The prevalence of MS is increasing and is currently estimated to affect 2.3 million individuals worldwide (Multiple Sclerosis International Foundation, 2013). In Europe (EU), the highest prevalence of MS occurs in countries with high latitude, including Sweden (188.9 per 100,000), Norway (203 per 100,000), and Denmark (232 per 100,000) (Ahlgren, 2011; Grytten, 2015; Koch-Henriksen, 2015). Estimates that 300,000 to 400,000 individuals have MS in the United States (US) are based largely on revisions of estimates from older data (Baum, 1981; Anderson, 1992; Evans, 2013). In an algorithm applied to private, military, and public Administrative Health Claims datasets, the estimated 2010 prevalence of MS in the US was 727,344 cases and may have been as high as 913,925 in 2017 (Wallin, 2019). The median age at onset is approximately 30 years of age and there is a consistent, 3:1 female to male ratio (McKay, 2015; Ribbons, 2015).

Relapsing MS (RMS) has an initial presentation of an acute attack which accounts for the initial presentation of approximately 85% of all subjects with MS (Confavreux, 2003; Reich, 2018). Typical symptoms include numbness and weakness in the legs leading to difficulty walking, vision loss, incoordination, cognitive dysfunction, fatigue, and pain. Almost half of relapses may result in incomplete recovery of function and leave permanent disability and impairment that accumulates over time (Lublin, 2003).

There are several Disease Modifying Therapies (DMTs) available for the treatment of MS with different mechanisms of action and differentiated efficacy and safety profiles. These include (1) the first-approved DMTs (interferon [IFN] β-1a, IFN β-1b, glatiramer acetate [GA]), (2) oral therapies (fingolimod, siponimod, ozanimod, dimethyl fumarate, teriflunomide, and cladribine), and (3) monoclonal antibodies (alemtuzumab, ocrelizumab, ofatumumab, and natalizumab).

1.2 Compound Background

Ozanimod

Ozanimod is approved for the treatment of RMS in adults in the US and for the treatment of adult subjects with relapsing-remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features in European Medicines Agency (EMA) jurisdictions.

Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator, which binds with high affinity selectively to sphingosine 1-phosphate receptor subtypes 1 and 5 (S1P1 and S1P5). This leads to reversible sequestration of lymphocytes in lymphoid tissues. The mechanism by which ozanimod

exerts therapeutic effects in MS is unknown but may involve the reduction of lymphocyte migration into the CNS (Scott, 2016; Chaudry, 2017).

Ozanimod was evaluated in two large, randomized, double-blind, double-dummy, parallel-group, active controlled clinical trials of similar design and endpoints, in subjects with RMS. SUNBEAM was a 1-year study with subjects continuing assigned treatment beyond month 12 until the last enrolled subject completed the study (Comi, 2019). RADIANCE was a 2-year study (Cohen, 2019). The active comparator was IFN β-1a 30 µg intramuscularly (IM) once a week in both studies. The primary endpoint, annualized relapse rate (ARR), was met for ozanimod 1 mg versus IFN-β-1a in each study. In Study RPC01-301, a statistically significantly ($p < 0.0001$) lower adjusted ARR was observed for ozanimod 1 mg (0.181; [95% confidence interval (CI): 0.140, 0.236]) compared with IFN-β-1a (0.350; [95% CI: 0.279, 0.440]), corresponding to a 48.2% reduction in ARR over 12+ months. In Study RPC01-201B, a statistically significantly ($p < 0.0001$) lower adjusted ARR was observed for the ozanimod 1 mg group (0.172; [95 % CI: 0.142, 0.208]) compared with the IFN-β-1a group (0.276; [95% CI: 0.234, 0.324]), corresponding to a 37.7% reduction in ARR over 24 months. Key secondary endpoints of new or enlarging T2 lesions and the number of gadolinium-enhancing (GdE) lesions were met for ozanimod 1mg versus IFN β-1a.

The safety profile of ozanimod is well-characterized by a phase 2 and two large phase 3 studies and their ongoing open label extension and is consistent with the known safety profile of S1P modulators (Novartis Pharmaceuticals Corporation, 2010; 2019). Treatment initiation with S1P receptor modulators results in a transient, dose-dependent bradyarrhythmia in both healthy subjects and in subjects with RMS mediated through the S1P1 receptor in humans (Gergely, 2009; Horga, 2010; Juif, 2016; Scott, 2016). Ozanimod treatment requires a dose escalation regimen at treatment initiation, to minimize transient reduction in heart rate (Celgene Corporation, 2020).

IFN-β

Interferons are naturally occurring proteins produced by eukaryotic cells in response to viral infection and other agents. The type I family of interferons includes the IFN-βs, which are used to treat MS; however, the mechanism of action of IFN-β in the treatment of MS is not completely understood.

After the Interferon Beta Study Group demonstrated IFN β-1b efficacy (INFB SG, 1993), the drug was approved for the treatment of RMS in the US almost 30 years ago and is approved for the treatment of RRMS in EMA jurisdictions. Forms of IFN-β for the treatment of MS include IFN β-1a (administered IM once per week or subcutaneously [SC] 3 times per week) and IFN β-1b (administered SC every other day).

Tdap

In this study BOOSTRIX®, a booster vaccine containing tetanus toxoid, reduced diphtheria toxoid and acellular pertussis antigens (Tdap), that confer protection against tetanus, diphtheria, and pertussis diseases, will be administered. The acellular pertussis vaccine adsorbed component of the Tdap vaccine contains 5 bacterial antigens: pertussis toxoid and 4 adhesion proteins of filamentous hemagglutinin, pertactin and fimbriae types 2 and 3 (Dewan, 2020).

The Centers for Disease Control (CDC) in the US recommends receiving the Tdap vaccine every 10 years for adults, or more frequently if clinically indicated. The Tdap vaccine can be safety administered at the same time as other vaccines. Additional information about the tetanus vaccine can be found at https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/index.html. The World Health Organization (WHO) currently recommends primary vaccination against tetanus during childhood administering 3-4 doses of the tetanus vaccine in the first 2 years of life, followed by booster vaccinations throughout adulthood every 10-20 years (Weinberger, 2017). Most European countries follow the WHO recommendations. For example, in Germany, the Tdap vaccine is recommended every 10 years in adults and should be administered as a vaccine that also vaccinates against diphtheria and pertussis (https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2019/Ausgaben/34_19.pdf?__blob=publicationFile).

PPSV23

In this study the PNEUMOVAX23® vaccine will be used. PNEUMOVAX23® is a sterile, liquid vaccine consisting of a mixture of purified capsular polysaccharides from Streptococcus pneumoniae types (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) (Merck & Co., Inc, 1983). Pneumococcal polysaccharide vaccine (PPSV23) contains antigens to 23 pneumococcal serotypes providing protection against 80-90% of capsular serotypes causing disease (Daniels, 2016). The CDC recommends routine PPSV23 in all adults 65 years and older and in adults 19 through 64 years of age with certain medical conditions. (https://www.cdc.gov/vaccines/vpd/pneumo/hcp/index.html.) In Germany, PPSV23 vaccine is recommended in adults ≥ 60 years of age and in adults with chronic diseases including neurological diseases (https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2019/ Ausgaben/34_19.pdf?__blob= publication File) (https://www.rki.de/EN/Content/infections/Vaccination/recommandations/34_2017_engl.pdf?__blob=publicationFile). Additionally, routine booster vaccination for the PPSV23 vaccine can be considered in immunocompromised and at-risk subjects with repeat vaccinations of intervals of at least 6 years in Germany and 5 years in the US after the last vaccination for subjects with increased risk for pneumococcal disease.

Seasonal influenza vaccine

In this study a seasonal inactivated influenza vaccine will be administered.

The CDC recommends that people 6 months and older should receive a licensed age-appropriate influenza vaccine each year at the start of the influenza season. Vaccination is particularly important in subjects who are at high risk of developing influenza complications. These subjects include those with neurologic conditions and subjects requiring chronic medications that suppress the immune system. The CDC recommends that the influenza vaccine is administered by end of October in the US; however, getting vaccinated later can still be beneficial and vaccination should continue to be offered throughout the influenza season (https://www.cdc.gov/vaccines/vpd/flu/hcp/index.html.)

In Europe, the seasonal influenza vaccine is recommended in all individuals older than 6 months of age with certain chronic diseases. Administration of a tetravalent vaccine is recommended before the influenza season begins (World Health Organization, 2021).

1.3 Rationale

1.3.1 Purpose of Study

Based on its mechanism of action, ozanimod has the potential to reduce the immune response to vaccinations. However, the effect of ozanimod on vaccination response has not been assessed. This study is designed to provide data on the immune response and safety of administering vaccines to RMS subjects taking ozanimod compared to controls taking IFN-βs or receiving no DMT. The data of this study will support the labels for ozanimod in MS because the effect of ozanimod on the vaccination response of MS subjects is of interest to patients and prescribers.

In this study, we do not anticipate the risks of receiving vaccines to be different than the risks of receiving vaccines in the general population. Several clinical studies have been conducted using multiple vaccines in MS subjects, providing no evidence that receiving multiple vaccinations is unsafe for MS subjects (Ufer, 2017; Bar-Or, 2020; Ciotti, 2020)

1.3.2 Rationale to Study Vaccine Response in Ozanimod Subjects

Persons with MS should receive vaccinations to avoid preventable diseases (Reyes, 2020; Riva, 2021). In persons with MS not receiving immunotherapy, the disease itself does not appear to affect the ability of individuals to mount an immune response to antigenic stimulation, and the vaccine response is similar to those who do not have MS (Moriabadi, 2001). Infections may trigger MS relapses, increase MS radiologic and immunologic activity, and accelerate disease progression (Pannitch, 1994; Buljevac, 2002; Correale, 2006; Farez, 2019). Multiple sclerosis subjects receiving immunotherapies as part of MS treatment may be at an increased risk of infection, including pneumococcal pneumonia and influenza infection, which carry the potential to cause significant morbidity and mortality in individuals with chronic debilitating diseases (De Keyser, 1998; Noseworthy, 2000). The vaccines administered in this study have not been associated with an increased risk of developing MS, with an increased risk of relapse, or with an increased risk of MS disease activity in MS subjects; however, MS subjects are not recommended to receive vaccines during a relapse (Confavreux, 2001; Farez, 2019; DeStefano, 2003; Loebermann, 2013). The availability of vaccine immune response and safety data in subjects treated with ozanimod will help guide practitioners on the impact of ozanimod on vaccine responses in MS subjects.

1.3.3 Effects of DMTs on Vaccine Response

Several studies have evaluated the impact of DMTs on vaccine response, including studies of two other S1P modulators, fingolimod and siponimod. Multiple sclerosis subjects and healthy volunteers treated with fingolimod showed significantly lower response rates to influenza, PPSV23, and tetanus toxoid vaccines at multiple timepoints post-vaccination compared to placebo (Boulton, 2012; Kappos, 2015). Healthy volunteers treated with siponimod met seroprotective criteria similar to those in other treatment groups to influenza after vaccination, but titer ratios were generally lower in siponimod groups (Ufer, 2017).

Non-pegylated IFN-βs in MS subjects produce immune responses comparable to controls and do not reduce response to vaccination (Schwid, 2005; Olberg 2014; Bar-Or, 2013; von Hehn, 2017). A few studies suggest a trend of potential increased humoral immune response in MS subjects

treated with IFN-βs compared to controls (Mehling 2013; Olberg, 2014). However, this trend is not consistent across studies, and IFN-β has not proven to be a vaccine adjuvant (Toporovski, 2010; Rizza, 2011; Ye, 2019). Pegylated IFN-β has not been studied for effect on vaccine response in MS subjects.

Ocrelizumab demonstrated a significantly reduced immune response to several vaccines with some subjects not achieving seroprotection (Bar-Or, 2020). Both dimethyl fumarate and teriflunomide showed no significant differences in response rates; similarly, natalizumab-treated subjects showed no significant differences in antigen-specific immunoglobulin G (IgG) response, but generally had lower titers, leading to an inadequate response in some subjects (von Hehn, 2017; Bar-Or, 2013; Kaufman, 2014). Glatiramer acetate vaccine studies show mixed results on immune response (Olberg 2014; Olberg, 2018).

1.3.4 Rationale for Selected Study Design

This study will use a prospective, open-label design with subjects receiving vaccines at a single visit followed by immune response and safety assessments 28 days later in subjects on steady state ozanimod compared to subjects receiving IFN-β as a reference control or not receiving DMT treatment. Using a control group of subjects treated with IFN-β is supported by vaccination studies in MS subjects on IFN-βs which show similar post-vaccination immune responses to MS subjects receiving no DMT (Olberg, 2014; Olberg, 2018; Mehling, 2013) and subjects on IFN-βs have been successfully used as controls in other MS DMT vaccine response studies (Bar-Or, 2013; Olberg, 2020; Von Hehn, 2018). Multiple vaccines administered during a single visit are well established in children and recommended for adults as safe, tolerable, and are not likely to reduce immune response (King, 1994; Broderick, 2016; Ferlito, 2021). Open-label designs are acceptable to assess the effects of immune modulating therapies on vaccine response and by vaccine manufacturers to assess vaccine immunogenicity (Schwid, 2005; Bar-Or, 2013; Olberg, 2018; Von Hehn, 2018). Laboratory studies, including the immunological correlates that assess the humoral response to vaccines (eg, serum antibody concentrations or antibody titers) provide objective assessments of vaccine response as substitute endpoints for longer term studies that measure clinical protective effect (Madore, 2010). The specific laboratory criteria used to establish vaccine immunogenicity is vaccine dependent. In general, vaccine responses are assessed by comparing post-vaccination to pre-vaccination antibody levels and by determining whether responses surpass a minimum threshold for seroprotection or an increase in antibody titers/concentrations to produce a serologic response (WHO, 2013). The laboratory criteria used in this study are based on guideline recommendations and correlates of humoral immunity (EMA, 1997; Qin, 2007; FDA, 2007; Plotkin, 2008). To mitigate the differences in the recruited subject population, this study will define eligibility criteria to reduce potential confounding variables affecting immune response to vaccination. Despite well-defined eligibility criteria, to account for potential confounders that could affect immune responses, serological response criteria will be compared based on a model adjusting for appropriate factors (eg, age, sex, body mass index [BMI], and baseline absolute lymphocyte count [ALC]).

To mitigate the risk of potential enrollment challenges surrounding influenza season, the study is designed to allow the addition of a second cohort of subjects that may have already received the seasonal influenza vaccine. Subjects in Cohort 2 will only receive Tdap and PPSV23. As of 13 May 2022, Cohort 1 is closed, and study subjects are only able to enroll in Cohort 2.

Some subjects in either treatment arm may have discontinued S1P modulators due to lymphopenia and may have ongoing profound lymphopenia that could affect immune response to vaccination. To avoid skewing the recruited subject population, no greater than 25% of enrolled subjects who discontinued any S1P modulator due to associated lymphopenia can have an ALC <0.5 x 10^9/L on steady state ozanimod or in the control group prior to Day 1. This threshold corresponds to approximately the 25th percentile of ALC levels observed in the ozanimod pivotal trials. Subjects enrolled who discontinued any S1P modulator due to associated lymphopenia must have an ALC assessment performed within the 6 months prior to enrollment (and if on ozanimod, the lab must have been performed after being on ozanimod for a minimum of [redacted] days). Subsequent subjects enrolled who discontinued an S1P modulator due to associated lymphopenia must have an ALC ≥ 0.5 x 10^9/L within 6 months prior to enrollment.

1.3.5 Rationale for Selected Vaccines

This study will examine response to Tdap, PPSV23, and seasonal influenza vaccines by measuring responses that act through different immune response pathways. Both T cell-dependent and T cell-independent humoral responses will be assessed in this study.

Tdap

The tetanus toxoid component of Tdap, which has remained unchanged over time, has been used consistently in trials with other DMTs, including fingolimod, and serves a "benchmark" vaccination (Boulton, 2012; Kappos, 2015). Vaccination against tetanus is recommended on a recurring 10-year basis except following certain potential exposures to *Clostridium tetani* or its toxoid (CDC, 2020; STIKO, 2017). The inactivated tetanus toxoid is a peptide antigen that induces a T-cell dependent response (Lesinski, 2001; Przedpelski, 2020). Most individuals in the US and Germany have been vaccinated with tetanus toxoid (Poethko-Muller, 2013; Williams, 2016). The tetanus vaccine is commonly administered in adults as a booster vaccine along with pertussis and diphtheria vaccines and can be administered as early as 1 year after previous vaccination as well as safely administered at the same time as other vaccines (Halperin 2006; Pool, 2020). Response to tetanus toxoid will serve as the primary endpoint for this study. Information about Tdap can be found at https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/index.html and https://www.who.int/health-topics/tetanus#tab=tab_1.

PPSV23

PPSV23 is a mixture of purified capsular polysaccharides from 23 *Streptococcus pneumoniae* serotypes and allow for assessment of a T-cell independent immune response (Malley, 2005). Immune response to the PPSV23 in this study will be based on response to serotypes that are associated with an increased risk of invasive and/or severe disease (Malley, 2005). In subjects with certain neurological diseases older than 16 and less than 65 years of age, PPSV23 is recommended as a single dose by the Standing Committee on Vaccination at the Robert Koch

Institute (STIKO) vaccination guidelines (https://www.rki.de/EN/Content/infections/Vaccination/recommandations/34_2017_engl.pdf?__blob=publicationFile). Individuals with MS are at increased risk of pneumonia and the American Academy of Neurology (AAN) recommends pneumococcal vaccination in specific subgroups of MS subjects (eg, those with compromised pulmonary function) and those with more severe disease, who may derive greater benefits from pneumococcal vaccination (Reyes, 2020).

Seasonal Influenza Vaccine

Seasonal influenza vaccine generates a T-cell dependent recall for vaccine response (Korenkov, 2018). The seasonal influenza vaccine is recommended for all MS subjects by the AAN and by STIKO guidelines (STIKO, 2017; Farez, 2019).

1.3.6 Rationale for Selected Endpoints

Primary Endpoint

Tetanus Toxoid Immune Response - The proportion of subjects with serologic response to tetanus toxoid in the Tdap vaccine will serve as the primary endpoint in this study. Serologic response to tetanus toxoid is measured by comparing the anti-tetanus toxoid IgG antibody titers at 4 weeks post-vaccination compared to the pre-vaccination titers. The antibody titers will be measured by an ELISA method. Subjects with a pre-vaccination IgG antibody titer level ≤ 0.10 IU/mL will have a serologic response if post-vaccination titer levels are ≥ 0.40 IU/mL. To demonstrate a serologic response if pre-vaccination titer levels are > 0.10 IU/mL and ≤ 2.7 IU/mL, subjects will have at least a 4-fold increase in post-vaccination titers. If subjects have a pre-vaccination titer level > 2.7 IU/mL, they will have at least a 2-fold increase in titers to demonstrate a response. This endpoint is supported by the recommendations to manufactures of tetanus vaccines to establish immune response which stipulates 0.10 IU/mL as a seroprotective level against tetanus and establishes increased Ab titers needed to demonstrate immune response based on pre-vaccination titer level (WHO Technical Report Series, No. 980, Annex 5). The requirement for a serologic response above the upper baseline level of 2.7 IU/mL as a 2-fold increase is supported by the WHO recommendations to establish tetanus vaccine efficacy, as well as by research demonstrating subjects with higher baseline titers are associated with less than a 4-fold response to vaccination (Petras, 2018; Halperin, 2018). Assessing the tetanus toxoid vaccine immune response at 4 weeks is also recommended by the WHO Technical Report Series, No. 980, Annex 5 and coincides with peak humoral immune response in adults (Blatter, 2009).

Secondary Endpoints

Tetanus Toxoid Immune Response – The proportion of subjects with anti-tetanus toxoid IgG ≥ 0.1 indicative of seroprotection.

Pneumococcal PPSV23- The proportion of subjects with a serologic response and serological protection to PPSV23 will be assessed in this study. Serologic response to PPSV23 is demonstrated by comparing the IgG antibody titers at 4 weeks post vaccination to the pre-vaccination concentration. The antibody titers will be measured by an ELISA method. Of the 23 serotypes contained in PPSV23, there is a subset associated with increased risk of invasive and/or severe

disease, including death: Serotypes 3, 6B, 9N, 11A, 14, 19A, 19F, 22F and 23F (Sjöström, 2006; Weinberger, 2010). These subtypes will be assessed in this study for pneumococcal vaccination immune response. The proportion of subjects with at least a 2-fold increase in post-vaccination anti-pneumococcal polysaccharide IgG titers in at least 5 of these serotypes will constitute the primary analysis for serologic response to PPSV23. Serologic response will also be determined separately for all selected serotypes. Additional secondary endpoints to assess PPSV23 vaccine response are the proportion of subjects with anti-pneumococcal polysaccharide IgG concentration ≥1.3 µg/mL for the selected serotypes indicative of seroprotection. The increase in antibody polysaccharide vaccine criteria (ie, 2-fold increase) is substantiated by studies that show most subjects with a pre-vaccination titer of ≥1.3 mg/mL can mount a 2-fold increase in titer on immunization but only a minority of subjects with high initial titers will be capable of mounting a 4-fold increase in antibody titers after vaccination (Orange, 2012; LaFon, 2018). A normal response to vaccination in unprotected subjects has been defined as conversion to a protected concentration (1.3 µg/mL) with a 2-fold rise in antibody concentration in at least 70% of serotypes tested (Orange, 2012; LaFon, 2018). In addition, in a study comparing anti-pneumococcal vaccine antibody titers from the same specimens tested across multiple reference laboratories, the results for algorithms using a 2-fold cutoff were consistent between laboratories but a 4-fold increase criteria led to disparity across labs with low concordance (Daly, 2015).

Exploratory Endpoints

2021-2022 Seasonal Influenza — The proportion of subjects with a serologic response to the influenza vaccine will be assessed in this study. Serologic response to the influenza vaccine is measured by comparing the anti-influenza IgG and immunoglobulin M (IgM) antibody titers to each strain at 4 weeks post-vaccination to the pre-vaccination concentration. The antibody titers will be measured by hemagglutination inhibition (HI). Subjects with a pre-vaccination IgG antibody titer < 1:10 will have a serologic response if their post-vaccination level is ≥1:40. To demonstrate a serologic response if pre-vaccination titer levels ≥ 1:10, subjects will have at least a 4-fold titer increase in post-vaccination titers. The assessment will be calculated separately for each antigen/strain, and combined, ie, for proportions of subjects who meet responder criteria for at least one antigen. Additional endpoints are HI antibody titers ≥ 1:40 indicative of seroprotection and the Geometric Mean Titer (GMT) ratio of pre- and post-vaccination titers for each strain. These criteria are supported by the Guidance on Harmonization of Requirements for Influenza vaccines, EMA, 1997 and FDA Guidance, 2007. The EMA guidance also recommends for demonstrating overall vaccine immunologic response to determine if a proportion of subjects meet specified criteria based on the endpoints. Successful vaccination is achieved for each treatment arm and for each influenza strain if at least one of the following three criteria is achieved: 1) The number of subjects with serologic response > 40%; 2) The Geometric Mean Concentration (GMC) ratio of post-vaccination antibody titers compared to pre-vaccination is > 2.5; or, 3) The proportion of subjects achieving a hemagglutinin titer ≥1:40 is > 70%. Results of successful vaccination for each treatment group per strain will be reported.

Tetanus Toxoid Immune Response- GMC ratio of pre- and post-vaccination anti-tetanus toxoid IgG and IgM titers will be measured.

Pneumococcal PPSV23- GMC ratio of pre and post anti-pneumococcal IgG and IgM titers to each selected strain.

Diphtheria Toxoid Immune Response - The proportion of subjects with serologic response to the diphtheria toxoid in the Tdap vaccine will be assessed in this study. Serologic response to diphtheria toxoid is measured by comparing the IgG anti-diphtheria antibody titers at 4 weeks post-vaccination to the pre-vaccination titers. The antibody titers will be measured by ELISA. Subjects with a pre-vaccination IgG antibody titer level of ≤ 0.10 IU/mL will have a serologic response if post-vaccination levels are ≥ 0.40 IU/mL. To demonstrate a serologic response if pre-vaccination titer levels are > 0.10 IU/mL and ≤ 2.56 IU/mL, subjects will have at least a 4-fold increase in post-vaccination titers. If subjects have a pre-vaccination titer > 2.56 IU/mL, they will have at least a 2-fold post-vaccination increase in titers to demonstrate a response. This endpoint to assess diphtheria vaccine response is supported by the recommendations to manufacturers of diphtheria vaccines (WHO Technical Report Series, No. 980, Annex 4) which stipulates 0.10 IU/mL as a seroprotective level against diphtheria and established the demonstration of the increased Ab titers needed to demonstrate immune response based on pre-vaccination titer level. The use of an upper baseline level above which a 2-fold increase is required to demonstrate serologic response is supported by the WHO recommendations to establish diphtheria as well vaccine efficacy and by research that demonstrates subjects with higher baseline diphtheria titers are associated with less than a 4-fold increase in titers (Halperin, 2018).

Additional secondary endpoints to assess diphtheria vaccine serologic response are the proportion of subjects with anti-diphtheria toxoid IgG ≥ 0.1 indicative of seroprotection, and the GMC ratio of pre- and post-vaccination anti-diphtheria toxoid IgG and IgM titers.

Pertussis – The proportion of subjects with a serologic response to pertussis toxoid in the Tdap vaccine will be assessed in this study. Serologic response to the pertussis toxoid component of the pertussis vaccine is demonstrated by comparing the IgG antibody titers at 4 weeks post-vaccination to the pre-vaccination concentration. The antibody titers will be measured by ELISA. Pertussis toxin is a key virulence factor that is specific for B. pertussis and responsible for most systemic symptoms associated with pertussis disease (Carbonetti, 2010; Dewan, 2020) and the pertussis toxoid will be assessed for vaccine response in this study. Subjects with a pre-vaccination level of < 5 EL.U./mL will have a serologic response to pertussis toxoid if post-vaccination antibody concentrations are ≥ 20 EL.U./mL. To demonstrate a serologic response if pre-vaccination titer levels ≥ 5 EL.U./mL and < 20 EL.U./mL, subjects will have at least a 4-fold increase in post-vaccination titers. If subjects have a pre-vaccination titer level ≥ 20 EL.U./mL, they will have at least a 2-fold post-vaccination increase in titers to demonstrate a response. The baseline levels and subsequent response have been validated in clinical studies for the assessment of response to pertussis vaccine (Blatter, 2009). Additional secondary endpoints to assess pertussis vaccine serologic response are the proportion of subjects with anti-pertussis toxoid IgG ≥ 5 EL.U./mL indicative of seroprotection, and the GMC ratio of pre- and post-vaccination anti-pertussis toxoid IgG and IgM titers.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic (PK) samples will only be collected in subjects who receive ozanimod as their DMT to characterize the plasma levels of ozanimod and its main major active metabolite (ie, CC112273). Plasma concentrations of ozanimod and metabolites will be determined in plasma using a validated bioanalytical method.

One PK sample should be collected early during the Day 1 and Day 28 Visits, and the time of sample collection must be recorded. In addition, the time of the most recent ozanimod dose prior to PK sample collection must be recorded. For subjects who stay at the site for [redacted] hours or more after the first PK sample collection, a second PK sample should be collected immediately prior to visit completion and the time of collection should be recorded. For subjects receiving an ozanimod dose after the first PK sample collection and before visit completion, a second PK sample should be collected immediately prior to visit completion and the time of collection should be recorded. Pharmacodynamic (PD) samples will be collected in all subjects at the Day 1 and Day 28 visits. Pharmacokinetic and PD results may be analyzed for subject medication compliance, concomitant effects, and other analyses related to immune response.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
To evaluate the proportion of subjects meeting serologic response criteria against the tetanus toxoid antigen after vaccination with Tdap in subjects with relapsing forms of MS receiving ozanimod or receiving non-pegylated IFN-β or no DMT
Secondary Objectives
To evaluate the following in subjects with relapsing forms of MS undergoing vaccination and receiving ozanimod or receiving IFN-β or no DMT: • Proportion of subjects meeting tetanus seroprotective criteria • Proportion of subjects meeting pneumococcus serologic response and seroprotective criteria • Safety and tolerability
Exploratory Objectives

Table 1: Study Objectives

To evaluate the following in subjects with relapsing forms of MS undergoing vaccination and receiving ozanimod or receiving non-pegylated IFN-β or no DMT: • Immune response to the seasonal, inactivated influenza vaccine • Proportion of subjects meeting diphtheria serologic response, seroprotective criteria, and the GMC ratio of anti-diphtheria IgG and IgM • Proportion of subjects meeting pertussis serologic response, seroprotective criteria, and the GMC ratio of anti-pertussis IgG and IgM • GMC ratios of IgG and IgM against tetanus antigens • GMC ratios of IgG and IgM against antigens contained in PPSV23 • PK and PD parameters of ozanimod and its active metabolites (ie, CC112273) in subjects who receive ozanimod as their standard of care

Abbreviations: DMT = disease modifying therapy; GMC = geometric mean concentration; IFN = interferon; IgG = immunoglobulin G; IgM = immunoglobulin M; MS = multiple sclerosis; PD = pharmacodynamic; PK = pharmacokinetic; PPSV23 = pneumococcal polysaccharide vaccine; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
Primary	Proportion of subjects with serologic response to tetanus toxoid	Serologic response to tetanus toxoid: If pre-vaccination antibody titer is ≤ 0.10 IU/mL, post-vaccination level ≥ 0.40 IU/mL; if pre-vaccination antibody titer is > 0.10 IU/mL and ≤ 2.7 IU/mL, at least a 4-fold increase in titer; if pre-vaccination antibody titer is > 2.7 IU/mL, at least a 2-fold increase in titer	At the Day 28 post-vaccination visit

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
Secondary	Proportion of subjects with serological protection against tetanus toxoid	Subjects with serological protection have: Anti-tetanus toxoid IgG concentration ≥ 0.1 IU/mL	At the Day 28 post-vaccination visit
	Proportion of subjects with serologic response to at least 5 of the following pneumococcal serotypes: 3, 6B, 9N, 11A, 14, 19A, 19F, 22F and 23F	Serologic response to PPSV23: The proportion of subjects with a ≥ 2-fold increase in anti-pneumococcal polysaccharide vaccine titer in ≥ 5 of the indicated serotypes	At the Day 28 post-vaccination visit
	Proportion of subjects with serological protection against the following pneumococcal serotypes: 3, 6B, 9N, 11A, 14, 19A, 19F, 22F and 23F	Subjects with serological protection have: Anti-pneumococcal polysaccharide IgG concentration ≥ 1.3 µg/mL for indicated serotypes	At the Day 28 post-vaccination visit
	Safety of concomitant vaccine administration in subjects taking ozanimod	(S)AE incidence, severity, causality, type Change from baseline in clinical lab values and incidence of abnormal lab values Listing of subjects with Investigator-confirmed relapses	Over the study

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
Exploratory	Proportion of subjects with serologic response to the seasonal influenza vaccine	Subjects with serologic response have: At least a four-fold titer increase in titer if the pre-vaccination titer ≥ 1:10, or an increase hemagglutination titer ≥ 1:40 in subjects with a pre-vaccination titer < 1:10. To be calculated separately for each antigen/strain, and combined (ie, for proportions of subjects who meet responder criteria for at least one antigen)	At the Day 28 post-vaccination visit
	Proportion of subjects with serological protection against seasonal influenza	Subjects with serological protection have: Hemagglutination inhibition antibody titers ≥ 1:40 To be calculated separately for each antigen/strain, and combined (ie, for the proportion of subjects who have serological protection against at least one influenza strain)	At the Day 28 post-vaccination visit

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
	Geometric Mean Titer (GMT) ratio of anti-influenza antibodies	The ratio of the geometric mean of the post-vaccination anti-hemagglutination inhibition titer (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-hemagglutination inhibition titer To be calculated separately for each antigen/strain.	At the Day 28 post-vaccination visit
	Assessment if at least one of the specified criteria is met for each treatment arm for each influenza strain	For each treatment arm, at least one criterion is met for each strain: Number of subjects with serologic response > 40% The ratio of geometric mean post vaccination antibodies titers compared to pre-vaccination is $\geq$ 2.5 The proportion of subjects achieving a hemagglutinin titer $\geq$ 40 is > 70%	At the Day 28 post-vaccination visit

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
	GMC ratio of anti-tetanus toxoid IgG	The ratio of the geometric mean of the post-vaccination anti-tetanus toxoid IgG concentration (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-tetanus toxoid IgG concentration	At the Day 28 post-vaccination visit
	GMC ratio of anti-tetanus toxoid IgM	The ratio of the geometric mean of the post-vaccination anti-tetanus toxoid IgM concentration (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-tetanus toxoid IgM concentration	At the Day 28 post-vaccination visit
	GMC ratio of anti-pneumococcus IgG for each pneumococcal serotype in PPSV23	The ratio of the geometric mean of the post-vaccination anti-pneumococcus IgG concentration (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-pneumococcus IgG concentration. To be calculated separately for each pneumococcal serotype.	At the Day 28 post-vaccination visit

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
	GMC ratio of anti-pneumococcus IgM for each pneumococcal serotype in PPSV23	The ratio of the geometric mean of the post-vaccination anti-pneumococcus IgM concentration (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-pneumococcus IgM concentration.	At the Day 28 post-vaccination visit
	Proportion of subjects with serologic response to reduced diphtheria toxoid	Serologic response to diphtheria toxoid: If pre-vaccination antibody titer is ≤0.10 IU/mL, post-vaccination level ≥ 0.40 IU/mL; if pre-vaccination antibody titer is > 0.10 IU/mL and ≤ 2.56 IU/mL, at least a four-fold rise in titer; if pre-vaccination IgG concentration is > 2.56 IU/mL, at least a two-fold increase in titer	At the Day 28 post-vaccination visit
	Proportion of subjects with serological protection against reduced diphtheria toxoid	Subjects with serological protection have: Anti-diphtheria toxoid IgG concentration ≥ 0.1 IU/mL	At the Day 28 post-vaccination visit

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
	GMC ratio of anti-diphtheria toxoid IgG	The ratio of the geometric mean of the post-vaccination anti-diphtheria toxoid IgG concentration (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-diphtheria toxoid IgG concentration	At the Day 28 post-vaccination visit
	GMC ratio of anti-diphtheria toxoid IgM	The ratio of the geometric mean of the post-vaccination anti-diphtheria toxoid IgM concentration (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-diphtheria toxoid IgM concentration	At the Day 28 post-vaccination visit

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
	Proportion of subjects with serologic response to pertussis	Serologic response: In initially seronegative subjects (< 5 EL.U/mL), post-vaccination level ≥ 20 EL.U/mL; if pre-vaccination antibody titer ≥ 5 EL.U/mL and < 20 EL.U/mL, at least a 4-fold increase in titer; if pre-vaccination antibody titer ≥ 20 EL.U/mL, at least a 2-fold in titer To be calculated separately for each pertussis antigen	At the Day 28 post-vaccination visit
	Proportion of subjects with serological protection against pertussis	Subjects with serological protection have: Anti-pertussis antigen IgG concentration ≥ 5 EL.U/mL To be calculated separately for each pertussis antigen	At the Day 28 post-vaccination visit

Table 2: Study Endpoints

Endpoint	Name	Description	Time frame
	GMC ratio of anti-pertussis IgG	The ratio of the geometric mean of the post-vaccination anti-pertussis antigen IgG concentration (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-pertussis antigen IgG concentration. To be calculated separately for each pertussis antigen	At the Day 28 post-vaccination visit
	GMC ratio of anti-pertussis IgM	The ratio of the geometric mean of the post-vaccination anti-pertussis antigen IgM concentration (at the post vaccination day 28 visit) divided by the geometric mean of the pre-vaccination anti-pertussis antigen IgM concentration To be calculated separately for each antigen	At the Day 28 post-vaccination visit
	PK	Plasma concentrations of ozanimod and its metabolites (ie, CC112273)	At baseline and end of study
	PD and Plasma biomarker analysis	Cytokines, chemokines, inflammatory markers, and COVID-19 antibodies	At baseline and end of study

3 OVERALL STUDY DESIGN

3.1 Study Design

The proposed study is a Phase 3b, multicenter, open-label, study to evaluate the immunological response to, and the safety of, vaccines in subjects with RMS who receive oral ozanimod 0.92 mg, non-pegylated IFN-β, or no DMT. The overall study design is presented in Figure 1. The schedule of events is presented in Table 3.

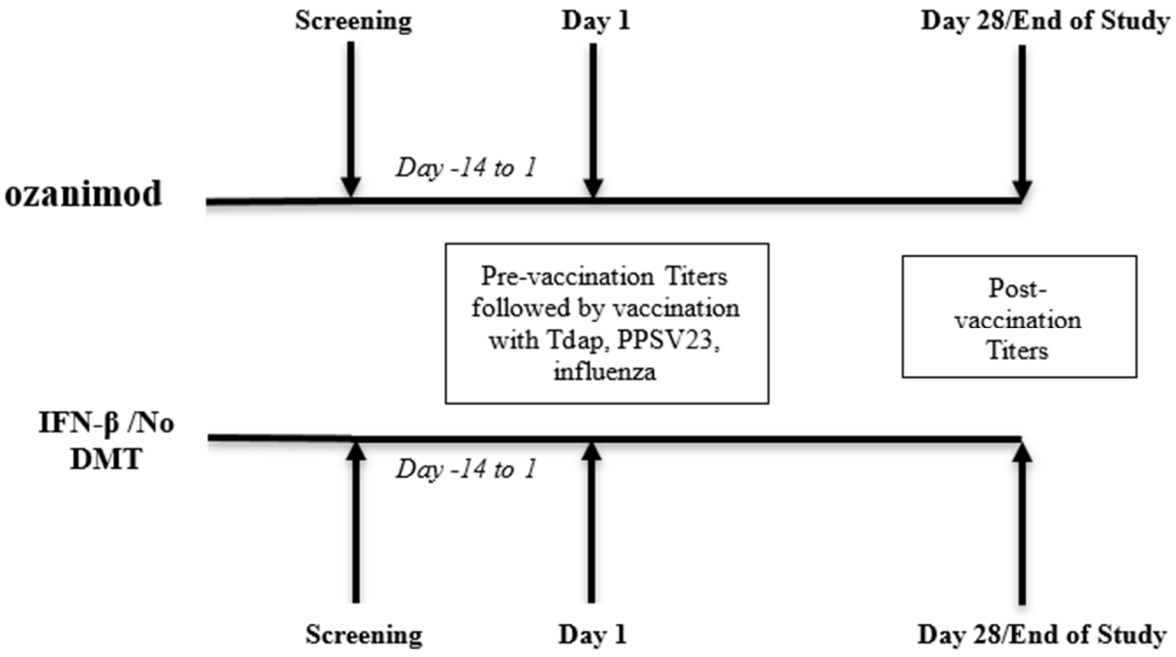
The study will include two cohorts differentiated by the vaccines administered. Cohort 1 comprises subjects who receive Tdap, PPSV23, and the seasonal inactivated influenza vaccine. Cohort 2 comprises subjects who have already received the seasonal influenza vaccine. As a result, Cohort 2 subjects will receive Tdap and PPSV23, only. Initiation of Cohort 2 will be based on the availability of eligible subjects who have not previously been vaccinated with the seasonal inactivated influenza vaccine. Subjects who meet all eligibility criteria but have already received the influenza vaccine as described in Exclusion Criterion #13, will be enrolled in Cohort 2. Subjects who meet all eligibility criteria, including Exclusion Criterion #13, will continue to be enrolled in Cohort 1 throughout the time both cohorts are open for enrollment. Cohort 2 may be opened for enrollment at any time determined by the Sponsor, but is estimated to occur after no less than 60% of subjects of the planned of the planned total enrollment have been recruited into Cohort 1.

No greater than 25% of subjects in either treatment arm who discontinued an S1P modulator due to S1P modulator-associated lymphopenia will be enrolled who have an ALC $<0.5 \times 10^9$/L. This threshold corresponds to approximately the 25th of ALCs mean levels observed in the ozanimod pivotal trials.

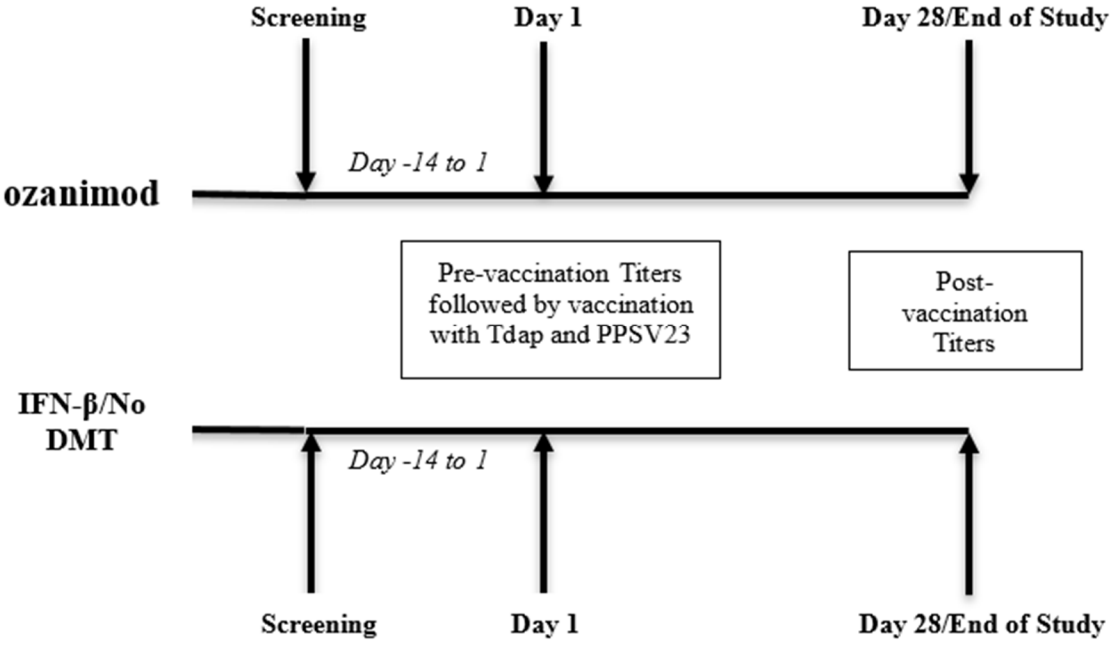
The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Figure 1: Overall Study Design

Cohort 1:



Cohort 2:



Abbreviations: Tdap = Tetanus, diphtheria, and acellular pertussis vaccine; PPSV23 = Pneumococcal polysaccharide vaccine; IFN = Interferon; DMT = Disease modifying therapy.

Screening Period

Subjects who have signed the informed consent form (ICF) will undergo screening evaluations to determine eligibility. The screening period may last from -14 to Day 1 (Baseline). Eligible subjects can enter the active treatment/vaccination period.

The Screening requirements can be performed on the same day as Day 1, provided that all Screening requirements are completed before any Day 1 assessments and vaccine administration is performed. In this case, Day 1 assessments that are also conducted as Screening assessments do not have to be duplicated, including pregnancy screening.

Because the vaccines administered in this study are approved vaccines, they do not require laboratory testing prior to administration and are typically administered on the same day without a prior monitoring period in a broad range of the general population. Conducting Screening and Day 1 assessments on the same day is considered acceptable.

Active Treatment/Vaccination Period

At the Day 1 Visit, eligible subjects in Cohort 1 will have pre-vaccination blood samples collected (for titer determination), followed by administration of the following three vaccines:

- Tdap booster vaccine
- PPSV23
- Seasonal influenza vaccine

At the Day 1 Visit, eligible subjects in Cohort 2 will have pre-vaccination blood samples collected (for titer determination), followed by administration of the following two vaccines:

- Tdap booster vaccine
- PPSV23

The vaccines administered in this study are commercially available and approved in the jurisdictions of the clinical sites, and administration will occur in accordance with the drug label. After Day 1, the post-treatment follow-up period starts.

Post-Treatment Follow Up Period

The post treatment follow-up period spans 28 days, with one visit at post-vaccination Day 28, during which subjects will return to the site to have blood samples collected (for serological determinations) and adverse events (AE) recorded. Upon completion of the Day 28 Visit, subjects have completed the study.

Relapse Assessments

Subjects who experience worsening neurological symptoms during the study should contact the Investigator and describe their symptoms, ideally within 48 hours of symptom onset. The Investigator will also inquire about worsening neurological symptoms at the Day 28 Visit. If, in the opinion of the Investigator, the worsening neurological symptoms are potentially due to an MS relapse, a relapse visit should be scheduled within 7 days of site contact. The following manifestations are considered consistent with an MS relapse: monophasic clinical episode with

subject-reported neurologic symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or sub acutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection (Thompson, 2018). The relapse visit can take place at the same day as the Day 28 Visit.

3.2 Study Duration for Subjects

This study will include a screening period of up to 14 days. The study period is from Day 1 Vaccination to the 28-day assessment visit. The maximum potential length from screening to end of trial 45 days. Screening and Day 1 may occur on the same day in eligible subjects.

3.3 End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analyses, as prespecified in the protocol, whichever is the later date.

4 STUDY POPULATION

4.1 Number of Subjects

Approximately 60 subjects with relapsing forms of MS will be enrolled; approximately 30 of these subjects will be taking ozanimod for at least [redacted] days prior to the Day 1 Visit, and approximately 30 subjects will be taking non-pegylated IFN-β or not receiving any DMT.

4.2 Inclusion Criteria for All Subjects

Subjects must satisfy the following criteria to be enrolled in the study:

1. Male or female subjects 18 to 65 years of age, inclusive, at the time of signing the ICF.
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject has a diagnosis of MS according to the 2017 revision of the McDonald diagnostic criteria and has RMS: RRMS or secondary progressive MS with active disease based on recent clinical relapse or MRI lesion activity (Thompson, 2018)
5. At Screening, subjects must be on one of the following three treatment options and willing to remain on the same treatment for the duration of the study:
    a. Treatment with ozanimod (0.92 mg maintenance dose). Ozanimod treatment must have been initiated at least [redacted] days prior to the Day 1 Visit. Subjects should be compliant with the ozanimod label. In addition, in the [redacted] days prior to Day 1, ozanimod treatment must not have been interrupted for more than 1 day.
    b. Treatment with a non-pegylated form of IFN-β and compliant with dosing within [redacted] of Day 1 per the manufacturer's label
    c. No treatment with a DMT for RMS
6. Subject is ambulatory (with or without walking aid) at Screening.
7. Subject is relapse-free in the 30 days prior to Day 1; during this period, subjects must have been clinically stable, without systemic corticosteroid or adrenocorticotrophic hormone treatment.
8. Subjects who receive ozanimod or non-pegylated IFN-β as their standard of care medication must do so in accordance with the local drug label.
9. Females of childbearing potential (FCBP) who receive ozanimod as their standard of care medication must agree to use contraception according to the approved local label.

All Subjects:

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

4.3 Exclusion Criteria for Cohort 1

The presence of any of the following will exclude a subject from enrollment:

1. Subject is pregnant, lactating, or has a positive urine β-subunit of human chorionic gonadotropin (β-hCG) measured during screening or on Day 1
2. Subject has any infections, including:
    a. Infection requiring hospitalization or treatment with intravenous (IV) antibiotics, antivirals, antifungal medication, anti-parasite medication within 30 days prior to Day 1
    b. Infection requiring treatment with oral antibiotics, antivirals, antifungal medication, anti-parasite medication within 14 days prior to Day 1
    c. Fever ≥ 40ºC within 14 days of enrollment
    d. SARS-CoV-2 infection with symptoms that have not completely resolved, and based on Investigator assessment in consultation with the Clinical Trial Physician/Medical Monitor, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.
    e. Any ongoing infection at Day 1
3. Subject has history of cancer, including solid tumors and hematological except for basal cell cancer of the skin and carcinoma in situ of the cervix, which are exclusionary if they have not been excised and resolved
4. Subject has a BMI ≥35 kg/m^2
5. Subject has known contraindication against Tdap, PPSV23, or quadrivalent seasonal influenza vaccine (Cohort 1 only), including, but not limited to:
    a. a history of anaphylactic/anaphylactoid or severe allergic reaction to any component of the vaccines, including egg as contained in the influenza vaccine, or a history of an Arthus-type hypersensitivity reaction against tetanus or diphtheria toxoid containing vaccines
    b. Encephalopathy or neurological complication following prior vaccinations containing pertussis antigens
    c. Thrombocytopenia following prior vaccination against tetanus, diphtheria, or pertussis
6. Subject has a history of or currently active primary or secondary immunodeficiency
7. Subjects has a history of Guillain-Barré Syndrome
8. Subject has severely compromised cardiac or pulmonary function for which a systemic hypersensitivity reaction to any of the vaccines would pose a significant risk
9. Subject has any moderate or severe acute illness, as assessed by the investigator
10. Subject has a history of alcohol abuse or drug abuse within 1 year prior to Screening
11. Subject has received any vaccine within 30 days prior to Day 1 including any SARS-CoV-2 (COVID-19) vaccine (first or second dose), or planned vaccines including COVID vaccine throughout the study period.
12. Subject has received any tetanus vaccine within 1 year prior to Screening.
13. Subject has received the seasonal influenza vaccine for the 2021/2022 influenza season prior to Day 1, or history of influenza vaccine for the 2020/2021 influenza season within 6 months prior to Day 1.

14. Subject has received PPSV23 within 5 years prior or PCV13 within 1 year of the Day 1.
15. For subjects receiving ozanimod: known contraindication against receiving ozanimod, according to product label.
16. For subjects on IFN-β: known contraindication against IFN-β or ongoing tolerability issues that might jeopardize compliance during the study (eg, injection site reactions requiring treatment, intolerable influenza-like symptoms, etc).
17. Subject has previous treatment with one of the following medications or interventions within the corresponding timeframe described as follows:
    a. Previous treatment with lymphocyte-depleting therapies (eg, Campath®, anti-CD4, cladribine, cyclophosphamide, mitoxantrone, total body irradiation, bone marrow transplantation, stem cell transplantation, alemtuzumab, or daclizumab)
    b. Previous treatment with teriflunomide within 8 months prior to randomization (unless teriflunomide plasma concentration is less than 0.02 mg/L [20 ng/mL]) or the subject had successfully followed the accelerated elimination procedure as described in the product label.
    c. 180 Days prior to Day 1 or 5 half-lives, whichever is longer: any investigational agent or interventional therapy (excluding life-style interventions)
    d. 180 Days prior to Day 1: azathioprine, methotrexate, cyclosporine, mycophenolate anti-CD20 mAbs (including rituximab, ocrelizumab, ofatumumab), Bruton's tyrosine kinase (BTK) inhibitors. After discontinuation of anti-CD20 mAbs, subjects must have documentation of ALC and gamma globulin levels within the normal range.
    e. 60 Days prior to Day 1: fingolimod, dimethyl fumarate
    f. Subjects who discontinued an S1P modulator due to lymphopenia must have a documented ALC >0.2 X 10^9/L within 6 months prior to baseline and for subjects on ozanimod, documented after a minimum of [redacted] days of treatment with ozanimod.
    g. 30 Days prior to Day 1: Systemic corticosteroids or adrenocorticotropic hormone (ACTH).
    h. 14 Days prior to Day 1: Pegylated IFNβ-1a, glatiramer acetate, siponimod
    i. Planned start of IFN-β or other MS disease modifying therapy after Day 1 throughout the study period.
    j. Use of anti-pyretic treatments, including acetaminophen, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs), for a period of 24 hours prior to administration of the vaccine and for a minimum of 6 hours after.
    k. Any systemic immunosuppressive treatments with potential overlapping effects with the baseline of this study. Corticosteroids that are by non-systemic routes (eg, topical, inhaled, intra-articular) are allowed.
18. History of treatment with IV immunoglobulin (IVIg) or plasmapheresis within 4 weeks prior to Day 1.
19. Any significant medical condition, laboratory abnormality, or psychiatric illness that places the subject at unacceptable risk if he/she were to participate in the study in the opinion of the investigator.
20. Any condition that confounds the ability to interpret data from the study.

4.4 Exclusion Criteria for Cohort 2

All exclusion criteria that applies to Cohort 1 applies to Cohort 2, with the exception of Exclusion Criterion #13.

5 TABLE OF EVENTS

Table 3: Table of Events

	Screening	Baseline	Post-Vaccination/ End of study	Relapse
Visit Number	**1**	**2**	**3**	**Unscheduled Relapse visit[a]**
Study Day	**-14 to 1**	**1[a]**	**28 (± 3 days)**	
Informed consent	X			
Inclusion/Exclusion criteria	X	X		
Demographics	X			
Medical history	X			
Vaccination history	X			
MS history	X			
Prior/concomitant medications	X	X	X	X
Ozanimod/IFN-β compliance	X	X	X	X
Clinical and Laboratory Assessments				
Adverse events	X	X	X	X
Pregnancy test[b] and contraception education	X	X	X	X
Vital signs[c]	X	X	X	X
Height[d]	X			
Weight[d]	X		X	X
Physical/neurological examination[e]	X		X	
Symptom-oriented physical examination[e]		X		X
Clinical laboratory evaluations[f]	X[g]	X	X	X
Efficacy Assessment(s)				
Blood draw for antibody concentration or titer determinations[h]		X	X	X
Blood draw for PK/PD, Plasma biomarkers, and COVID-19 antibodies		X[i]	X[i]	
IP				
Administer vaccines[j]		X[k]		

Abbreviations: ALC = absolute lymphocyte count, β-hCG = beta-human chorionic gonadotropin, BMI = body mass index,COVID-19 = SARS-CoV-2, IP = investigational product, IFN = interferon, N-SAID = nonsteroidal anti-inflammatory drug, PD = pharmacodynamic, PK = pharmacokinetic, PPSV23 = pneumococcal polysaccharide vaccine, S1P = sphingosine-1-phosphate, Tdap = tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed.

a. If the assessments for the Screening and Baseline Visits are performed on the same day, assessments do not have to be duplicated. If the assessments of the Relapse visit are performed on the same day as any other visit, assessments do not have to be duplicated.
b. Urine β-hCG test at each visit for women of childbearing potential only. If a urine pregnancy test result is positive, a serum pregnancy test will be performed for confirmation.
c. Vital signs include sitting blood pressure, body temperature and resting pulse. A subject should have rested in sitting position, preferably for at least 5 minutes before measuring blood pressure and pulse. The same arm should be used for blood pressure measurement throughout the study. Body temperature is measured by oral, tympanic, or with temporal thermometer. Manual and digital thermometers are allowed. Resting pulse should be determined by manual palpation according to standard clinical practice. The method for measuring blood pressure, pulse, and temperature should be documented and the same method should be used consistently throughout all visits.
d. Height is measured at the Screening Visit with the subject not wearing shoes. Weight is measured at all Visits with the subject wearing no shoes and light clothing. BMI should be calculated prior to enrollment.
e. Both physical examination and symptom-oriented physical examination will include neurological examination.
f. Day 1 (baseline) and End of Study (Day 28) clinical laboratory tests include serologic antibody testing for COVID-19 (baseline only), chemistry (full panel), hematology, and urinalysis
g. If needed, ALC may be measured for subjects with prior S1P modulator-related lymphopenia if no laboratory data are recorded meeting protocol criteria. Clinical laboratory testing, while not required for screening eligibility except as described in the protocol, may be performed for valid medical concerns after discussion with the medical monitor.
h. Blood draw for titer determinations at relapse visit should occur prior to administration of any steroids.
i. For subjects on ozanimod only. Record the time of PK sample collection and the time of the most recent ozanimod dose administration prior to PK sample collection. If [redacted] hours or more pass between (first) PK sample collection and visit completion, draw a second PK sample immediately prior to visit completion and record time. If an ozanimod dose is administered after the first PK sample collection, record time of administration and collect second PK sample immediately prior to visit completion and record time. For all subjects, plasma sample for biomarker evaluation will be included (eg, inflammatory markers) and COVID-19 antibodies.
j. Cohort 1 will receive Tdap, PPSV23, and influenza vaccine; Cohort 2 will receive Tdap and PPSV23.
k. Subjects should refrain from using anti-pyretic treatments, including acetaminophen, aspirin, and other NSAIDs for a minimum of 6 hours post-vaccination.

6 PROCEDURES

6.1 Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 14 days prior to the Day 1 visit. If screening procedures cannot be completed within 14 days, the Medical Monitor must be contacted to discuss whether any Screening procedures must be repeated prior to enrollment. All screening assessments and procedures are to be performed by the Principal Investigator (PI) or a qualified designee.

Written, signed, and dated informed consent from the subject prior to the performance of any study-related procedures must be obtained by the PI or designee. A copy of the signed informed consent or second original informed consent, signed by both parties (depending on local requirements), must be given to the subject for his/her records.

Safety laboratory analyses and all assessments will be performed centrally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

The following will be performed at screening as specified in Table 3, after informed consent has been obtained:

- Review of eligibility criteria
- Confirmation and source documentation by the PI that subjects have taken ozanimod or IFN-β as prescribed by the manufacturer label and as required in the inclusion criteria
- Demographics (initials, date of birth, sex, race)
- Complete medical history (all relevant medical conditions diagnosed/occurring prior to screening should also be included)
- Vaccination History
- MS History
- Prior and concomitant medication evaluation (including those taken ≤ 30 days before screening, except for those taken for disease)
- Urine pregnancy test confirmed negative and contraception education
- Collection of adverse events
- Vital signs (including blood pressure, temperature, and heart rate)
- Height and weight
- Complete physical examination: including evaluation of heart, lung, head, neck, abdominal, neurological, skin, and extremities
- Blood sampling for ALC evaluation, if needed
- The Screening requirements can be performed on the same day as the Day 1 assessments, provided that all Screening assessments for eligibility are completed before any Day 1 assessments and vaccine administration is performed. In this case, Day 1 assessments that are also conducted as Screening assessments do not have to be duplicated, including urine pregnancy screening.

- A screen failure is defined as a subject who has given informed consent and has failed to meet one or more inclusion criteria and/or has met one or more exclusion criteria.

6.2 Treatment Period - Day 1/Baseline

The following evaluations will be performed at the frequency specified in Table 3. The evaluations should be performed prior to vaccine administration on Day 1, unless otherwise specified.

- Review of subject eligibility
- Confirmation and source documentation by the PI that subjects have taken ozanimod or IFN-β as prescribed by the manufacturer label and as required in the inclusion criteria
- Concomitant medications evaluation
- AE evaluation
- Urine pregnancy test confirmed negative for pregnancy
- Vital signs (including blood pressure, temperature, and heart rate)
- Symptom oriented physical examination
- Urinalysis and blood sampling for the follow laboratory tests:
  - Serologic antibody testing for COVID-19 and other PD parameters
  - Hematology: red blood cell (RBC) count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).
  - Blood Chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, albumin, alkaline phosphatase, creatinine, alanine aminotransferase (ALT) (SGPT), aspartate aminotransferase (AST) (SGOT), gamma-glutamyl transferase (GGT), total bilirubin, and conjugated bilirubin. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy.
- Efficacy assessments, including blood draw for pre-vaccination antibody titer determination, and blood draw for PK (see Section 6.4)
- Administration of Tdap, PPSV23, and influenza vaccine (Cohort 1 only), (intramuscularly or subcutaneously, as described in Table 4)

6.2.1 Post Vaccination/End of Study

An end of study (EOS) evaluation will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in the Table 3:

- Confirmation and source documentation of subject-described compliance with ozanimod and IFN-β dosing as prescribed by the manufacturer label
- Concomitant medications evaluation (including whether any additional vaccines were administered)
- AE evaluation

- Urine pregnancy test
- Vital signs (including blood pressure, temperature, and heart rate)
- Physical/neurological examination and weight
- Urinalysis and blood sampling for the follow laboratory tests:
  - Serologic antibody testing for COVID-19 and other PD parameters
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC.
  - Blood Chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, albumin, alkaline phosphatase, creatinine, ALT (SGPT), AST (SGOT), GGT, total bilirubin, and conjugated bilirubin. Abnormal laboratory parameters inconsistent with clinical presentation of MS or suspicious of underlying medical condition should be repeated for accuracy.
- Efficacy assessments, including blood draw for antibody titer determination, and blood draw for PK

6.2.2 Relapse Assessments

A relapse is defined as a monophasic clinical episode with subject-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or sub acutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection (Thompson, 2018). Subjects who experience worsening neurological symptoms during the study should contact the Investigator site and describe their symptoms, ideally within 48 hours of symptom onset. If, in the opinion of the Investigator, the worsening neurological symptoms are potentially due to a MS relapse, an unscheduled relapse visit should be planned as soon as possible, ideally within 7 days of symptom onset. The unscheduled relapse visit will be conducted if a possible relapse is suspected at any time prior to the Day 28 visit. The Investigator will also inquire about worsening neurological symptoms at the Day 28 Visit. The following evaluations will be performed as specified in Table 3:

- Confirmation and source documentation of subject-described compliance with ozanimod and IFN-β dosing as prescribed by the manufacturer label
- Concomitant medications evaluation (including whether any additional vaccines were administered)
- AE evaluation
- Urine pregnancy test
- Vital signs (including blood pressure, temperature, and heart rate)
- Symptom-oriented physical examination and weight
- Urinalysis and blood sampling for the follow laboratory tests:
  - Hematology: RBC count, total and differential WBC count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, MCV, MCH, and MCHC.

  - Blood Chemistry: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, albumin, alkaline phosphatase, creatinine, ALT (SGPT), AST (SGOT), GGT, total bilirubin, and conjugated bilirubin.
- Blood draw for antibody titer determination prior to the administration of any steroid treatment

The relapse visit can take place at the same day as the Day 28 Visit. If relapse occurs at Day 28 visit, assessments do not have to be duplicated.

Subjects who experience a relapse may receive treatment with IV corticosteroids, if judged to be clinically appropriate by the Investigator. The following standardized treatment regimen should be used: as warranted, up to 1.0 g IV methylprednisolone per day for a maximum of 5 consecutive days. No deviation from the standardized treatment regimen is allowed unless approved by the Medical Monitor. The Investigator is asked to draw antibody titers prior to steroid administration during an unscheduled relapse visit, regardless of its proximity to the Day 28 Visit. Blood draw for antibody titers will also occur at the Day 28 Visit.

The analysis of any relapses captured during the study will be descriptive.

6.3 Follow-up Period

Not applicable.

6.4 Efficacy Assessment

The immunological response is measured by comparing post- to pre-vaccination titers or concentrations of and IgG and IgM antibodies against vaccine antigens as described in detail in Table 2.

Serological response to vaccines is generally characterized as a 2 or 4-fold increase in titers if subjects are above levels of seroprotection at baseline. If subjects are below levels of seroprotection at baseline, serologic response is generally measured by demonstrating a response above seroprotection criteria. The specific levels are based on vaccine guidelines and are consistent with other studies of immune response with concomitant immunomodulatory treatments. Additional assessments would include evaluation of the GMT ratio post- to pre-vaccination antibody titers.

For vaccines utilized in the study containing a single component, the response of that component will be measured. For PPSV23 and pertussis vaccines, important subcomponents will be assessed in the primary analysis of these vaccines for immune response. All antigens contained within the seasonal influenza vaccine will be assessed for immune responses.

6.5 Pharmacokinetics

PK samples will only be collected in subjects who receive ozanimod as their standard of care treatment, to characterize the plasma levels of ozanimod and its main metabolites (ie, CC112273). Plasma concentrations of ozanimod and metabolites will be determined in plasma using a validated bioanalytical method.

One PK sample should be collected early during the Day 1 and Day 28 Visits, and the time of sample collection must be recorded. In addition, the time of the most recent ozanimod dose prior

to PK sample collection must be recorded. For subjects who stay at the site for [redacted] hours or more after the first PK sample collection, a second PK sample should be collected immediately prior to visit completion and the time of collection should be recorded. For subjects receiving an ozanimod dose after the first PK sample collection and before visit completion, a second PK sample should be collected immediately prior to visit completion and the time of collection should be recorded.

6.6 Biomarkers, Pharmacodynamics, Pharmacogenomics

Blood samples will be analyzed by the central laboratory upon receipt, subject to national and local requirements. PD blood biomarkers include but are not limited to markers of inflammation and possible measurements of SARS-CoV-2 serologic status.

One PD sample should be collected early during the Day 1 and Day 28 Visits, and the time of sample collection must be recorded. The total amount of blood collected for biomarker and safety evaluations will be specified in the Informed Consent Form. In addition to the required biomarker analyses described above, if the subject has granted consent where allowed by the regulatory authorities and local ethics committee, residual samples will be stored for up to 15 years and may be used for additional analyses.

6.7 Additional and Optional Research

Additional and optional research as described below may be performed using left-over samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

6.7.1 Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.7.2 Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact their ability to participate in the main study.

7 DESCRIPTION OF STUDY TREATMENTS

7.1 Description of Investigational Products

Tdap, PPSV23, and Seasonal Influenza Vaccines

All vaccines used in this study will be provided to the clinical sites. The commercial names of the Tdap and pneumococcal vaccines are BOOSTRIX® and PNEUMOVAX®. The seasonal inactivated influenza vaccine will be determined based on supply for the 2021/2022 influenza season. For all vaccines, the pre-filled syringe (0.5 ml) dosage form must be used. Vaccines must be stored in a secure location at the site at 2ºC to 8ºC (36ºF to 46ºF) and protected from light until

used for vaccine administration. Prior to the administration of vaccines, sites should check the vaccine expiration date and vigorously shake the pre-filled syringes. The contents of the syringe should appear as a homogeneous solution without particulate matters or discoloration. Vaccine batch and lot number must be documented.

7.2 Treatment Administration and Schedule

At the Day 1 Visit, eligible subjects will have pre-vaccination blood samples collected (for serological determinations), followed by parenteral administration of Tdap, PPSV23, and seasonal inactivated influenza vaccine (Cohort 1), or Tdap and PPSV23 (Cohort 2).

The vaccines administered in this study are commercially available and approved in the jurisdictions of the clinical sites, and administration will occur in accordance with the product labels. After Day 1 the post-treatment follow-up period starts.

Post-vaccination

After vaccination, subjects should be observed for approximately 15 minutes, or as per recommended local guidelines, whichever is longer, for development of hypersensitivity reactions. Should hypersensitivity reactions occur, the Investigator should record the event as an AE and should monitor pulse and blood pressure. The Investigator must determine if treatment with steroid, antihistamines, epinephrine/adrenaline, or hospital admission is warranted and act accordingly. If no hypersensitivity reactions develop or a mild to moderate hypersensitivity reaction has stabilized, subjects can leave the site. Subjects should be informed that over the counter ibuprofen or acetaminophen (paracetamol) can be used to treat post-vaccination pain or fever, but subjects should refrain from using anti-pyretic treatments, including acetaminophen, aspirin, and other NSAIDs for a minimum of 6 hours post-vaccination (Scheifele, 2018; Doedee, 2014).

Vaccine administration must conform with the label requirements and must be performed by someone who is experienced in intramuscular and subcutaneous administration of medicinal products. Sites must have epinephrine or adrenaline medication available that can be administered in case of anaphylactic reactions. Subjects should be stably seated or reclined before and during vaccine administration to avoid injuries from falls or in case of syncopal reactions. Standard hygiene practices should be applied during vaccine administration, including skin disinfection with alcohol swaps at the site of vaccine administration and hand cleaning or wearing gloves by the person administering the vaccine. The seasonal influenza vaccine and Tdap must be administered intramuscularly, and PPSV23 should be administered subcutaneously. The recommended anatomical site of administration for each vaccine is listed in Table 4 . Only one vaccine must be administered per anatomical site. On the day that the vaccine is administered, subjects who receive IFN-β injections must not have IFN-β administered at a site of vaccine administration.

Table 4: Route and Anatomical Site of Vaccine Administration

Vaccine	Route of Administration	Recommended Anatomical Site of Administration
BOOSTRIX®	Intramuscular	Left deltoid muscle
PNEUMOVAX®	Intramuscular or Subcutaneous	Lateral mid-thigh (either cohort) or right deltoid muscle (Cohort 2 only)
Cohort 1 Only: Seasonal inactivated influenza vaccine	Intramuscular	Right deltoid muscle

Intramuscular administration

A sterile needle for intramuscular injection (28 to 25 gauge) of appropriate length should be attached to the prefilled syringe and a separate needle must be used for each vaccine. The needle should enter the skin at a 90-degree angle and the vaccine should be administered at approximately the center of the deltoid muscle. Deeper administration in the muscle mass is generally associated with fewer adverse reactions compared with injections close to the subcutaneous tissue. Table 5 lists the needle length for adults based on weight, which is based on CDC recommendations (https://www.immunize.org/catg.d/p3084.pdf). Once the needle is inserted to the muscle tissue, the vaccine is injected, followed by withdrawal of the needle. A simple band aid can be used to cover the injection site.

Subcutaneous administration

A sterile needle for subcutaneous injection (23 to 25 gauge; 16 mm [5/8 inch] length) should be attached to the prefilled syringe and a separate needle must be used for each vaccine. The skin at the injection site should be elevated between thumb and index finger of the vaccinator and the needle should enter the skin at approximately a 45-degree angle. Once the needle is inserted in the subcutaneous tissue, the vaccine is injected, followed by withdrawal of the needle. A simple band aid can be used to cover the injection site.

Table 5: Recommended Needle Lengths for Intramuscular Vaccination in the Deltoid Muscle (Adults)

Weight Range	Recommended Needle Length
Men and Women < 60 kg (<130 lbs)	5/8 to 1-inch (16 to 25 mm) – when using 5/8-inch (16 mm) length, stretch skin over deltoid muscle (do not bunch muscle)
Men and Women 60 to 70 kg (130 to 152 lbs)	1 inch (25 mm)
Men 70 to 118 kg (152 to 260 lbs)	1 to 1.5 inches (25 to 38 mm)
Women 70 to 90 kg (152 to 200 lbs)	
Men > 118 kg (260 lbs)	1.5 inches (38 mm)
Women > 90 kg (200 lbs)	

Ozanimod and Non-pegylated IFN-β

Ozanimod and non-pegylated IFN-β are provided as standard of care medication by the Investigator. They are not provided as part of this study, and the Sponsor will not reimburse sites or subjects for the cost of the standard of care medication. During the study, subjects should continue their standard of care medication according to their regular schedule. Drug compliance will be based on subject report and recorded in source documents.

7.3 Method of Treatment Assignment

All subjects who meet all eligibility criteria, including Exclusion Criterion #13, will be enrolled into Cohort 1. All Cohort 1 subjects will receive the following vaccines:

- Tdap
- PPSV23
- Seasonal Influenza Vaccine

Cohort 2 may be opened for enrollment at any time determined by the Sponsor. Subjects who meet all eligibility criteria, with the exception of Exclusion Criterion #13 will be enrolled in Cohort 2. Subjects who meet all eligibility criteria, including Exclusion Criterion #13, will continue to be enrolled in Cohort 1 throughout the time both cohorts are open for enrollment. All Cohort 2 subjects will receive the following vaccines:

- Tdap
- PPSV23

7.4 Packaging and Labeling

Not applicable

7.5 Investigational Product Accountability and Disposal

All vaccine supply will be accounted for in accordance with GCP. If errors or damages in the vaccine supply shipments occur, the Investigator should contact the Clinical Monitor immediately. Each Investigator will provide copies of the vaccine accountability records for inclusion in the Trial Master File after database lock. The Clinical Monitor will periodically check the supplies of vaccine held by the Investigator or pharmacist to verify accountability of all supply used.

The Investigator will provide the vaccines only to the identified subjects of this study, according to the procedures described in this study protocol. After the end of the study, the Clinical Monitor will perform final accountability.

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6 Investigational Product Compliance

It is the Investigator's responsibility to ensure subjects are fully compliant with their DMT. Drug compliance will be based on subject report and recorded in source documents.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

All concomitant treatments, including blood and blood products, used from 30 days prior to Day 1 until Day 28, must be reported on the CRF along with dosage information, dates of administration, and reasons for use. For medications with a single active ingredient, generic names for concomitant medication should be used, if possible. For combination products, brand names should be used. The total daily dose should be filled in whenever possible.

Treatment for symptoms related to MS (eg, spasticity, incontinence, pain, fatigue, and depression) is not restricted, but Investigators should attempt to keep therapies or treatments reasonably constant throughout the study period. Changes may be made if appropriate for a subject's well-being in the clinical judgment of the Investigator.

8.1 Prohibited Concomitant Medications and Procedures

The following medications cannot be used during the trial through the End of Treatment Visit:

- Any medications prohibited by the product labels of country for ozanimod and IFN-β compounds
- Any approved and unapproved disease-modifying MS agents, excluding ozanimod and IFN-β
- Treatment with Class Ia or Class III anti-arrhythmics (examples of prohibited systemic cardiac medications are provided in Table 6) or treatment with a combination of 2 or more agents known to prolong PR interval (eg, combination of a beta blocker and verapamil) are prohibited during the study unless approved by the Sponsor's representative. Note that Table 6 does not provide a comprehensive list. The Medical Monitor should be contacted for further guidance if needed.
- Systemic corticosteroid therapy or ACTH, except for treatment of protocol-defined treatment of relapses. Corticosteroids that are by non-systemic routes (eg, topical, inhaled, intra-articular) are allowed.
- Any vaccine, including first or second dose of COVID-19 vaccine
- Intravenous immunoglobulin (IVIg) or plasmapheresis
- Immunosuppressive agents known to deplete lymphocytes
- Breast cancer resistance protein inhibitors (eg, cyclosporine, eltrombopag)
- Monoamine oxidase inhibitors (eg, selegiline, phenelzine)
- CYP2C8 inhibitors (eg, gemfibrozil and clopidogrel) or inducers (eg, rifampicin)

Table 6: Examples of Prohibited Cardiac Medications (Systemic Use)

Pharmaceutical Class	Example Medications
Class Ia or Class III Antiarrhythmic drugs	amiodarone, bepridil hydrochloride, disopyramide, dofetilide, dronedarone, flecainide, sotalol, ibutilide, lidocaine, procainamide, propafenone, quinidine, tocainide

8.2 Required Concomitant Medications and Procedures

Not applicable

9 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the Sponsor.

9.1 Overview

This is a non-randomized, open-label study in which all subjects remain on their pre-study (baseline) treatment per protocol. Subjects will be recruited by investigators from MS clinical practice patients and prospectively assessed for immune response to vaccination. The statistical analyses will focus on estimating immune response rates, adjusting for baseline subject-level characteristics. No formal statistical hypothesis is evaluated. To mitigate for potential differences in the recruited subject population in the ozanimod and non-ozanimod arms that potentially could affect immune response, response rates will be estimated based on a logistic regression model adjusting for several factors, eg, age, sex, body mass index (BMI), and baseline absolute lymphocyte count (ALC). The results of the statistical analyses for immune response endpoints will be summarized for subjects receiving ozanimod (ozanimod arm) and subjects not receiving ozanimod (non-ozanimod arm) as their standard of care disease modifying therapy for MS. Analyses of safety will be summarized by descriptive statistics separately for the ozanimod and non-ozanimod arms.

9.2 Study Population Definitions

The study will include two cohorts differentiated by the vaccines administered. Cohort 1 comprises subjects who receive Tdap, PPSV23, and the seasonal inactivated influenza vaccine. Cohort 2 comprises subjects who receive Tdap and PPSV23 only. Initiation of Cohort 2 will be based on the availability of eligible subjects who have not previously been vaccinated with the seasonal inactivated influenza vaccine.

The modified intent-to-treat (mITT) population consists of all subjects who received at least one vaccination and summarized according to their initial treatment status (ozanimod vs. non-ozanimod) regardless of systemic use of corticosteroids.

The per-protocol (PP) population consists of all subjects who received the correctly assigned vaccinations, had no steroid use, and did not receive any other vaccines throughout the study.

9.3 Sample Size and Power Considerations

The sample size of the study is 60 subjects with an estimated 30 subjects expected to have received ozanimod and 30 subjects expected to not have received ozanimod as standard of care DMT. It is expected that approximately 60% of the subjects not receiving ozanimod as standard of care therapy will have a serologic response to vaccination with Tdap (Kappos, 2015).

With a sample size of 30 subjects for the ozanimod arm, assuming the response rate is 45%, the expected half width of the 95% confidence interval (based on normal approximation) is approximately 0.175. We note that in simulations (assuming a true response rate of 0.45), the estimated response rate falls within 0.267 and 0.633 among 95% of the simulated trials (across 100,000 simulations).

9.4 Background and Demographic Characteristics

The following summaries will be provided by treatment status (ozanimod vs non-ozanimod) based on the mITT population:

Subject's age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

9.5 Subject Disposition

The following summaries will be provided by treatment status (ozanimod vs non-ozanimod) based on the mITT population.

The number and percentage of subjects will be summarized. Subject disposition, including the number of subjects who enrolled, completed the trial, and discontinued the trial with reasons for discontinuation. Subject demographics include age, sex, race, ethnicity, height, weight, and body mass index.

Baseline characteristics include age at MS symptom onset, age at MS diagnosis, years since MS symptom onset, years since MS diagnosis, number of relapses within the last 12 months, number of relapses within the last 24 months, and number of GdE lesions.

9.6 Immune Response Analysis

The primary endpoint analysis and all analyses for immune-response to vaccination will be performed in the per-protocol population, ie, in subjects who received the correctly assigned vaccinations and had no major protocol violations. Sensitivity analyses will be conducted within the mITT population consisting of all subjects who received at least one vaccination and summarized according to their initial treatment status (ozanimod vs non-ozanimod) regardless of protocol violations

If Cohort 2 is initiated, then not all subjects will receive the seasonal inactivated influenza vaccine. For the purposes of summarizing the Tdap and PPSV23 vaccines, all subjects in Cohorts 1 and 2 will be combined, since they generally would have had the opportunity to receive all three vaccines. For evaluating the seasonal inactivated influenza vaccine, the analyses will be based on Cohort 1 subjects.

The ozanimod and non-ozanimod treatment group immune response rates and differences will be estimated based on a model adjusting for baseline demographics (eg, age, gender, BMI, baseline ALC, etc). We note the estimates of treatment differences should be interpreted with caution, since, in addition to the limited sample size, the ozanimod and non-ozanimod arms are not randomized. Some or all of the aforementioned factors may not be feasible to include in the analysis model. Analysis details will be provided in the statistical analysis plan such as the required number of subjects within each factor stratum (eg, if within a factor stratum level there are less than 10 subjects, then that factor will be excluded from the model).

9.7 Safety Analysis

All subjects who receive at least 1 vaccine, the mITT population, will be included in the safety analyses. Adverse events will be summarized by worst severity grade. Adverse events, with particular focus on treatment-emergent AEs, will be summarized by MedDRA system organ class, and preferred term. This will include vaccine-related adverse events, adverse events leading to death or to discontinuation from treatment, serious adverse events, and events of interest.

Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from baseline will be produced. The change from baseline for blood pressure monitoring, each of the vital signs and physical examination parameters will be summarized. The incidence of abnormal vital signs parameters and outlier physical examination results will be tabulated.

By-subject listings will be provided for all relevant safety data. Graphical displays and figures will be provided where useful to assist in the interpretation of results.

9.8 Interim Analysis

Not applicable

10 ADVERSE EVENTS

10.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the vaccine administration, as well as those serious adverse events (SAEs) made known to the Investigator at any time thereafter that are suspected of being related to IP. All AEs (serious/non-serious) will be recorded on the CRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Drug Safety.

All AEs related to SARS-CoV-2 must be collected continuously during the study including at the safety follow visit(s). After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs, including SARS-COV-2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up. COVID-19 related AEs/SAEs will be captured in specific clinical safety program CRF pages

10.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

10.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or

require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- a procedure for protocol/disease-related investigations (eg, sampling for laboratory tests) However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2 Severity/Intensity

For each AE, the Investigator must assess the severity/ intensity of the event.

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily life (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

Moderate

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with ADLs but able to carry out daily social and functional activities.
- Drug therapy may be required

Severe (could be non-serious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention

- Interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3 Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for each AE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4 Duration

For each AE, the Investigator will provide a record of the start and stop dates of the event.

10.2.5 Action Taken

The Investigator will report the action taken with IP as a result of each AE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6 Outcome

The Investigator will report the outcome of the event for each AE.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as the AE. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

If any of the following results are observed during the treatment period, the Investigator will be notified and asked to repeat the laboratory tests with approximately 7 days:

- Absolute lymphocyte count (ALC) <200 cells/µL
- Absolute neutrophil count (ANC) <1000 cells/µL
- Total WBC >20,000 cells/µL

If the repeat values also exceed these limits, the Investigator will be informed that the subject's results for the abnormal parameter have fallen outside the acceptable thresholds.

If ANC or total WBC counts are confirmed outside the acceptable limits, the Medical Monitor will contact the treatment investigator to request close monitoring for risk of infection and appropriate follow-up, at the discretion of the investigator.

If ALC results are confirmed on repeat as below 200 cells/µL, the investigator will be instructed temporarily discontinue ozanimod and repeat ALC laboratory testing every week until ALC level is >500 cells/µL. The investigator may resume ozanimod at that point per the product label.

Liver Function Tests

If a subject is found to have elevations in ALT and/or AST ≥ 3x the upper limit of normal (ULN) from baseline labs or during the study, a retest should be performed within 7 days after the original test. If the abnormality is confirmed, weekly testing should continue, and the Medical Monitor should be consulted. The Investigator should establish causality.

At any time, if any of the following occur and there are no apparent alternative causes for the finding, the investigational drug must be permanently discontinued, and an AE reported:

- ALT or AST > 8x ULN or
- ALT or AST > 5x ULN with confirmation, within 2 weeks or
- ALT or AST > 3x ULN and (total bilirubin > 2x ULN or INR > 1.5) or

- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

The Investigator should establish causality further and liver function evaluation should be performed (for example, coagulation panel and alkaline phosphatase) in consultation with the Medical Monitor.

10.4 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events. Any subject with a suspected or confirmed pregnancy should discontinue ozanimod and consult the medical monitor.

10.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is enrolled in the study are considered immediately reportable events. A pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as an SAE. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the IP should also be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.4.2 Male Subjects

If a female partner of a male subject enrolled in the study becomes pregnant, the male subject should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5 Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after vaccine administration) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the CRF, but do not require reporting to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

The SAE is recorded within the CRF, and the data is transmitted electronically to Celgene Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the CRF as well.

10.6 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to ozanimod based on the Investigator Brochure.

In the United States, expedited reports sent to the FDA by the sponsor based on the reasonable possibility threshold are known as 'IND safety reports' and will be reported in accordance with 21 CFR 312.32.

For reporting to the FDA, events that are not suspected to be causally related to IP by the sponsor will not be considered adverse reactions.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to BOOSTRIX®, PNEUMOVAX23®, and the seasonal inactivated influenza vaccine based on the US Prescribing Information (USPI) or EU Summary of Product Characteristics (SmPC).

Serious adverse reactions and nonserious adverse reactions will be reported to the Regulatory Authorities, in accordance with Regulation (EC) No. 726/2004 and/or Directive 2001/83/EC as amended, and also in accordance with country-specific requirements for countries within the EEA.

Celgene or its authorized representative shall notify the Investigator of the following information

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with the IRB/EC. (See Section 13.3 for record retention information).

11 DISCONTINUATIONS

11.1 Study Discontinuation

The following events are considered acceptable reasons for discontinuing a subject from the study:

- Screen Failure
- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the CRF)
- Physician Decision
- Site terminated by Sponsor: An indication that a clinical study was stopped at a particular site by its Sponsor.
- Study terminated by Sponsor: An indication that a clinical study was stopped by its Sponsor.
- The details concerning the reason for study discontinuation should be recorded in the CRF and in the source documents.
- The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number listed on the Emergency Contact Information page of the protocol.

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol. This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician or Medical Monitor or designee for emergency calls.

11.3 Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

12 REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

12.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

12.3 Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

12.4 Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12.5 Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

12.6 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations, and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

12.7 Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

12.8 Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc.).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

13 DATA HANDLING AND RECORDKEEPING

13.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

13.2 Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

13.3 Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records.

If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

14 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

14.1 Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

14.2 Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

14.3 Product Quality Complaint

Issues that call into question IP safety, purity, potency, quality, and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to the study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all sponsor supplied IP suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging, and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labelling, and IP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps).

When reporting, provide as much product information as possible. Suspected IP quality issues will be investigated, and a response will be provided back to the investigational site.

15 PUBLICATIONS

As described in Section 12.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.
Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

16 REFERENCES

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APPENDIX A TABLE OF ABBREVIATIONS

Table 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AAN	American Academy of Neurology
ACTH	Adrenocorticotropic hormone
ADL	Activities of daily life
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ARR	Annualized relapse rate
AST	Aspartate aminotransferase (SGOT)
β-hCG	β-subunit of human chorionic gonadotropin
BMI	Body mass index
BTK	Bruton's tyrosine kinase
CDC	Centers for Disease Control
CI	Confidence interval
CNS	Central nervous system
COVID-19	SARS-CoV-2
CRF	Case report form
DMT	Disease modifying therapy
EC	Ethics committee
EEA	European economic area
EMA	European Medicines Agency
EOS	End of study
EU	European Union
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GA	Glatiramer acetate
GCP	Good Clinical Practice
GdE	Gadolinium-enhancing
GGT	Gamma-glutamyltransferase
GMC	Geometric mean concentration
GMT	Geometric mean titer

Table 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
HI	Hemagglutination
ICF	Informed consent form
ICH	International Council on Harmonisation
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IND	Investigational new Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IVIg	Intravenous immunoglobulin
IV	Intravenous
LAM	Lactational amenorrhea method
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MS	Multiple sclerosis
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per protocol
PPSV23	Pneumococcal polysaccharide vaccine
RBC	Red blood cell
RMS	Relapsing multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event
SC	Subcutaneous

Table 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
STIKO	Standing Committee on Vaccination at the Robert Koch Institute
SUSAR	Suspected unexpected serious adverse reaction
Tdap	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed
ULN	Upper limit of normal
US	United States of America
USPI	US Prescribing Information
WBC	White blood cell
WHO	World Health Organization