Official Title: A Phase IIIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ocrelizumab in Adults with Primary Progressive Multiple Sclerosis

NCT Number: NCT04035005

Document Date: SAP Version 2: 04-Mar-2025

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A PHASE IIIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRELIZUMAB IN ADULTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS**
STUDY NUMBER:	WA40404
STUDY NAME:	O'HAND
VERSION NUMBER:	2
ROCHE COMPOUND(S):	Ocrelizumab/ RO4964913
EUDRACT NUMBER:	2018-001511-73
IND NUMBER:	100,593
NCT NUMBER:	NCT04035005
PLAN PREPARED BY:	[redacted], Ph.D.
	[redacted], Ph.D.

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR: LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document version (v) 3.0.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	16 December 2024	V 6.0, 4 July 2024
2	see electronic date stamp on last page| |day month year	V 6.0, 4 July 2024

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This statistical analysis plan has been updated primarily in response to the U.S. Food and Drug Administration (FDA) information request, ensuring alignment with the content of the response provided:

The Sensitivity Analysis 1 described in Section 4.2.3 will be conducted irrespective of any conditions. A similar tipping point analysis will be conducted for patients who experience censoring because of the following:

- Initiation of another MS DMT or commercial ocrelizumab
- Withdrawal from study.

Moreover, the exploratory endpoint 'Time to 24-week Confirmed Disability Progression' has been included. Additional minor changes have been made to improve clarity and consistency.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
CCOD	clinical cutoff date
CD	cluster of differentiation
CDP	confirmed disability progression
CI	confidence interval
eCOA	Electronic clinical outcome assessments
CRF	Case Report Form
DBT	double-blind treatment
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DMT	disease-modifying therapy
eCRF	electronic Case Report Form
EDSS	expanded disability status scale
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
FSS	Functional System Scores
FU	follow up
Gd	gadolinium
9–HPT	9–hole peg test
HR	hazard ratio
iDMC	Independent Data Monitoring Committee
IRR	infusion-related reaction
IxRS	Interactive Voice/Web-Based Response System
IV	intravenous
LLN	lower limit of normal
MFIS	Modified Fatigue Impact Scale
MS	multiple sclerosis
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSIS	Multiple Sclerosis Impact Scale
Neuro-QoL-UE	Quality of Life in Neurological Disorders-Upper Extremity Function

NfL	neurofilament light chain
OI	opportunistic infections
OLE OCR	open-label extension ocrelizumab
PDP OCR	post-double-progression ocrelizumab
PGIC-F	Patient Global Impression of Change for fatigue
PGIC-UL	Patient Global Impression of Change for upper limb function
PPMS	primary progressive multiple sclerosis
PK	pharmacokinetic
PT	preferred term
RCRM	random coefficient regression model
RMS	relapsing multiple sclerosis
RPM	remote patient monitoring
SAE	serious adverse events
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SDMT	symbol digital modalities test
SMQs	Standardized Medical Dictionary for Regulatory Activities Queries
SOC	System Organ Class

1. INTRODUCTION

Study WA40404 is a Phase IIIb, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ocrelizumab compared with placebo in patients with primary progressive multiple sclerosis (PPMS), including patients later in their disease course.

Ocrelizumab is a recombinant humanized, glycosylated, monoclonal IgG1 antibody that selectively targets and depletes cluster of differentiation (CD) 20-expressing B cells, while preserving the capacity of B-cell reconstitution and preexisting humoral immunity. CD20 is a B-cell surface molecule that is restricted in expression to pre-B cells and mature B cells but is not expressed earlier in the development of B cells (Banchereau and Rousset 1992). Based on the results of ocrelizumab Phase III studies in patient populations with relapsing multiple sclerosis (RMS) and PPMS, ocrelizumab was approved by the United States Food and Drug Administration (FDA) on 28 March 2017 for the treatment of adult patients with RMS and PPMS and by the European Medicines Agency (EMA) on 12 January 2018 for patients with active relapsing forms of multiple sclerosis (MS) defined by clinical or imaging features and for patients with early PPMS in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.

The background for the study can be found in the study protocol.

The analyses described in this Statistical Analysis Plan (SAP) will supersede those specified in Protocol WA40404.

Changes to the protocol-planned analyses are described in Section 4.8.

1.1 TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 1 Primary and Secondary Objectives and Corresponding Estimands

Primary Objective	Estimand Definition
To evaluate the efficacy of ocrelizumab compared with placebo in all randomized patients and in patients with MRI activity (MRI activity is defined as presence of T1 Gd+ lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase).	**Co-primary estimand 1** • **Population**: Patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol), with MRI activity (see Section 2.1.1 of the protocol). • **Endpoint**: Time to onset of composite 12-week CDP, defined as the time from randomization to the first occurrence of at least one of the following progression events:

	– 12-week CDP in 9-HPT, defined as a worsening of 20% from baseline in 9-HPT confirmed for at least 12 weeks. – 12-week CDP in EDSS, defined as an increase of $\geq$ 1.0 point from baseline EDSS score in patients with a baseline EDSS score $\leq$5.5 or an increase of $\geq$ 0.5 point in patients with a baseline EDSS score of > 5.5 that is confirmed for at least 12 weeks. • **Treatment**: – Experimental arm: Ocrelizumab IV 300 mg administered at Day 1 and Day 15, followed by Ocrelizumab IV 600 mg administered every 24 weeks. – Control arm: Matching placebo • **Intercurrent events and handling strategies**: – Withdrawal from treatment and no initiation of another MS DMT or commercial ocrelizumab: Treatment-policy strategy – Withdrawal from treatment and initiation of another MS DMT or commercial ocrelizumab: Hypothetical strategy • **Population-level summary**: HR for time to onset of composite 12-week CDP Co-primary estimand 2 is similar to the co-primary estimand 1 except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol). For more details, see Section 4.2. .
Secondary Objectives	**Estimand Definition**
• To evaluate the efficacy of ocrelizumab compared with placebo in all randomized patients	• **Population**: Patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol). • **Endpoints:** – Time to 12-week CDP in 9-HPT

Secondary Objectives	Estimand Definition
	– Time to 12-week CDP in EDSS – Time to 24-week CDP in 9-HPT – Time to 24-week CDP in EDSS • **Treatment:** as defined above • **Intercurrent events and handling strategies:** as defined above • **Population-level summary:** HR for time to onset of endpoints specified above For more details, see Section 4.3.1
• To evaluate the efficacy of ocrelizumab compared with placebo in all randomized patients	• **Population**: as defined above • **Endpoints:** – Annual rate of change from baseline in radius of total volume of T2 lesions – Annual rate of percent change from Week 24 in total brain volume • **Treatment:** as defined above • **Intercurrent events and handling strategies**: – Withdrawal from treatment and no initiation of another MS DMT or commercial ocrelizumab: Hypothetical strategy – Withdrawal from treatment and initiation of another MS DMT or commercial ocrelizumab: Hypothetical strategy • **Population-level summary**: mean difference in the endpoints specified above between treatment arms For more details, see Section 4.3.2 and Section 4.3.3.

CDP= confirmed disability progression; DMT = disease-modifying therapy; EDSS = expanded disability status scale; Gd = gadolinium; 9–HPT = 9–hole peg test; HR = hazard ratio; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis

Table 2 Exploratory Efficacy Objectives and Endpoints

Exploratory Efficacy Objectives	Endpoints
To evaluate the efficacy of ocrelizumab compared with placebo in the following patient subgroups of all randomized patients (unless otherwise stated): – Age > 55 versus ≤ 55 years – EDSS score ≤ 6.5 versus > 6.5 – MRI-inactive versus MRI-active – Males and females (all randomized patients, MRI-active subgroup and MRI-inactive subgroup) – Region European Union, United Kingdom, and Canada versus other	• Identical to the primary and secondary endpoints
To evaluate the efficacy of ocrelizumab compared with placebo in all randomized patients and the MRI-active subgroup	• Change from baseline to Week 120 in fatigue as measured by MFIS • Annual rate of percent change from baseline and from Week 24 in cervical spinal cord volume on MRI scans • Change from baseline to Week 120 in a measure of manual ability for adults with upper limb impairments (ABILHAND) • Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Neuro-QoL-UE) • PGIC-UL at each scheduled visit until Week 120 • PGIC-F at each scheduled visit until Week 120 • Change from baseline to Week 120 in the MSIS-29 physical domain score • Occurrence of a ≥ 7.5-point increase (worsening) in MSIS-29 physical domain transformed total scores at each scheduled visit until Week 120

Exploratory Efficacy Objectives	Endpoints
	• Time to a ≥ 4-point decrease (worsening) in SDMT sustained for 24 weeks • Time to a ≥ 8-point decrease (worsening) in SDMT sustained for 24 weeks • Time to 24-week CDP • Time to 24-week CDP or a ≥ 4-point decrease (worsening) in SDMT sustained for 24 weeks • Time to 24-week CDP or a ≥ 8-point decrease (worsening) in SDMT sustained for 24 weeks • Change from baseline to Week 120 in the SDMT • Rate of decline in fine motor skills of upper extremities and manual/finger dexterity as measured by smartphone-based digital outcome assessment (Floodlight RPM) • The number of Gd-enhancing T1 lesions and number of new or enlarging T2 hyperintense lesions as detected by mandatory MRI, overall and at each scheduled visit • Annual rate of change from baseline in radius of total non-enhancing T1 lesion volume on MRI scan of the brain

CDP= confirmed disability progression; Gd = gadolinium; MFIS = Modified Fatigue Impact Scale; MRI= magnetic resonance imaging; MSIS = Multiple Sclerosis Impact Scale; Neuro – QoL–UE = Quality of Life in Neurological Disorders-Upper Extremity Function; PGIC–F = Patient Global Impression of Change for fatigue; PGIC-UL = Patient Global Impression of Change for upper limb function; RMP = remote patient monitoring; SDMT = Symbol Digit Modalities Test

Table 3 Other Objectives and Endpoints

Objectives	Endpoints
The main safety objective is to evaluate the safety of ocrelizumab compared with placebo until when patients receive any PDP OCR, OLE OCR, commercial ocrelizumab treatment, or other MS DMT in all patients who receive at least one infusion (partial or complete) of study drug (ocrelizumab or placebo).	• Incidence and severity of adverse events and serious adverse events • Change from baseline in clinical laboratory test results (including hematology, chemistry, and Ig levels) • Change from baseline in vital signs (including systolic and diastolic blood pressure, and pulse rate) following study treatment administration
The PK objective is the characterization of the ocrelizumab PK profile	• Serum concentration of ocrelizumab at specified time points, and derived PK parameters via the population PK approach
The PD objective is the evaluation of ocrelizumab PD	• B-cell levels in blood (including comparing the degree of B-cell depletion between the doses) • Proportion of patients achieving 5 or less B-cells per microliter of blood • Proportion of patients achieving 10 or less B-cells per microliter of blood
The immunogenicity objective is to evaluate the immune response to ocrelizumab.	• Incidence of treatment-emergent ADAs to ocrelizumab relative to the presence of ADAs at baseline. • Relationship between ADA status and pharmacokinetics, PD, and safety

Objectives	Endpoints
The exploratory biomarker objective is to identify biomarkers that are predictive of response to ocrelizumab (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to ocrelizumab, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of ocrelizumab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety:	• NfL levels (actual value and percentage change from baseline) at each visit up to time of clinical cutoff of primary analysis • The prognostic or predictive relationship between baseline NfL and efficacy (including the study primary endpoint, imaging, or key secondary endpoints) • The prognostic relationship between on-treatment NfL (measured at Weeks 24 or 48) and subsequent disability progression on the study primary endpoint and other clinical outcomes • Levels of B or T cell subsets in blood, including but not limited to CD19+ IgD, CD27, CD38, CD4, CD8, CD3, parameters to identify B or T naive, memory and/or B plasmablast/plasma cell subsets • Relationship between biomarkers in blood (plasma and/or serum) and/or CSF (listed in Section 4.5.11 of the protocol) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
The exploratory health status objective is to evaluate health status of patients treated with ocrelizumab	• EQ-5D-5L at each scheduled visit until Week 120 • Change from baseline at each scheduled visit up to and including Week 120 in EQ VAS

ADA = anti-drug antibody; CD = cluster of differentiation; CSF = cerebrospinal fluid; DMT = disease-modifying therapy; DNA = deoxyribonucleic acid; EQ–5D–5L = EuroQol 5–Dimension Questionnaire; EQ VAS = EuroQol Visual Analogue Scale; Ig = immunoglobulin; IL-6 = Interleukin 6; MS = multiple sclerosis; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NfL = neurofilament light chain; OCR = ocrelizumab; OLE open-label extension; PD = pharmacodynamic; PDP = post-double-progression; PK = pharmacokinetic.

1.2 STUDY DESIGN

Study WA40404 is a Phase IIIb, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate efficacy and safety of ocrelizumab administered at a 600 mg intravenous (IV) infusion every 24 weeks in patients with PPMS, including patients later in their disease course. This study will consist of the following phases: screening, double-blind treatment, an optional

post−double-progression ocrelizumab (PDP OCR) treatment, follow-up 1 (FU1), an optional open-label extension (OLE), and follow-up 2 (FU2).

Patients providing informed consent will undergo screening prior to the study drug administration. Eligible patients will be randomized (1:1) in a blinded fashion to either placebo or ocrelizumab. Randomization will be performed through an interactive voice or web-based response system (IxRS).

The expected sample size will be approximately 1000 patients, with at least 350 patients in the magnetic resonance imaging (MRI)-active subgroup. The MRI-active subgroup will consist of patients with T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) as detected by MRI scan during screening. If during the study conduct more than 650 patients have enrolled without MRI activity (referred to as MRI-inactive subgroup thereafter), then subsequently only patients with MRI activity may be enrolled to ensure that at least 350 patients with MRI activity will be randomized.

Patients will be treated for 144 weeks (6 study drug doses, with each dose 24 weeks apart) in the double-blind treatment phase or until the primary analysis, whichever occurs earlier. Patients who experience a double-progression event (DPE; defined as a confirmed 20% increase in 9-HPT time sustained for 24 weeks, and a CDP sustained for 12 weeks) during the double-blind treatment phase will be given the option to switch to PDP OCR after they have completed at least 120 weeks of double-blind treatment and 120-week visit assessments.

Patients will be recruited globally. Patients who prematurely discontinue from study treatment will continue to be followed in the FU1 phase until 144 weeks from randomization for each patient or until the primary analysis, whichever occurs earlier.

The primary analysis will be performed after the last randomized patient reaches the 144 weeks of double-blind treatment (+12 weeks to allow for the confirmation of the latest event) or when at least 340 events are reached, whichever occurs earlier.

1.2.1 Treatment Assignment and Blinding

Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. Eligible patients must be randomized through IxRS prior to receiving any study drug. Patients who discontinue treatment for any reason will not be replaced. Under no circumstances are patients who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study.

The randomization list will not be available to the study centers, monitors, project statisticians, or to the Sponsor project team. All individuals directly involved in the study will remain blinded to the treatment assignment until the primary analysis.

To maintain integrity of the trial results and to prevent potential unblinding of the assigned arm during the double-blind treatment phase as a result of adverse events or changes to laboratory results, the following additional measures will be implemented until the time of the primary analysis:

- To prevent potential unblinding as a result of adverse events or laboratory changes, a "dual assessor" approach will be used to evaluate efficacy and safety. Each site will have two blinded investigators: a principal or Treating Investigator and a rating or Examining Investigator.

  The Treating Investigator will be the safety assessor and should be a neurologist with experience in the care of patients with MS. The Treating Investigator will have access to safety data only and will make all treatment decisions based on the patient's clinical response and laboratory findings.

  The Examining Investigator will be the efficacy assessor and should be a neurologist or other qualified health care practitioner trained and certified in administering and scoring the 9-hole peg test (9-HPT), Functional System Scores (FSS) and expanded disability status scale (EDSS), and System Digital Modalities Test (SDMT). The Examining Investigator (or her/his certified designee) will assess the 9-HPT, EDSS scores (including dysphagia/bladder dysfunction assessments), and SDMT. Until the primary analysis, the Examining Investigator and their qualified designees (if applicable) will not be involved with any aspect of medical management of the patient and will not be allowed access to patient data.

  The Treating Investigator and the Examining Investigator will not be allowed to switch roles. Until the primary analysis, an investigator/site staff at a single site may not be a treating investigator for some patients and an examining investigator for others.

- Patient education: During the double-blind treatment phase, prior to being examined by the Examining Investigator, patients should be instructed not to discuss with the Examining Investigator what (if any) adverse effects they may be experiencing.
- Blinded, central magnetic resonance imaging (MRI) assessments: During the double-blind treatment phase, a blinded, central MRI reader will assess all MRI scans performed during the study. Of note, screening and baseline scans will be used for the assessment of patient eligibility, and therefore they will not be blinded.
- Blinding of laboratory parameters: Selected laboratory parameters that may lead to unblinding of the treatment assignment, such as flow cytometry assessment of cell counts including CD19+ cells, lymphocyte count, and Ig levels will be blinded in all patients until the primary analysis. To ensure patient safety during the study and to allow for assessments of the re-treatment criteria, a central laboratory will provide study investigators and the Medical Monitor(s) with reflex messages triggered by abnormal blinded laboratory results and will be instructed to suspend further

treatment with study drug until the patient becomes eligible for ocrelizumab re-treatment. Investigators will be notified of their patient's abnormal laboratory test results. Consult the laboratory manual for additional information.

- Ocrelizumab and placebo treatment allocation will remain blinded until the primary database lock for the primary analysis.

To facilitate analysis of the biological samples collected in this study, the treatment code will be released to the responsible analytical person when the samples have been received at the analytical site and are ready for assay. The result of the analysis must not be released with individual identification of the patient until after the unblinding for the primary analysis.

Study site personnel and patients will be blinded to treatment assignment until after the primary analysis. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, IxRS service provider, and Independent Data Monitoring Committee (iDMC) members.

While pharmacokinetic (PK) and anti-drug antibody (ADA) samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). ADA samples will be analyzed for all patients treated with active study drug.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code in an emergency situation. However, the Medical Monitor should be informed that the treatment code has been broken.

The investigator will also be able to break the treatment code to determine the suitability of subsequent medical care for a patient. However, approval must be obtained from the Medical Monitor if the investigator wants to break the treatment code to determine patient's eligibility for a subsequent clinical trial testing investigational medicinal products or procedures. The investigator must contact the Medical Monitor prior to breaking the treatment code for any reason other than a medical emergency. The investigator should document and provide a justification for any non-emergency unblinding.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7 of the protocol) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

1.2.2 Independent Review Facility

MRI scans will be read by a centralized reading center for efficacy endpoints. The centralized reading center will be blinded to treatment assignment, and the reading will be performed in the absence of clinical information.

Further details on scanning acquisition sequences, methods, handling and transmission of the scans, certification of site MRI radiologist/technicians, and the procedures for the blinded analysis of the scans at the central reading center are described separately in the MRI Acquisition and Procedures Manual and the Imaging Review Charter.

1.2.3 Data Monitoring

An iDMC is employed to monitor and evaluate patient safety throughout the study, until the primary analysis is performed. Monitoring details are described in the iDMC Charter.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The hypotheses to be tested for the co-primary estimand 1 are:

- H0 (null hypothesis): There is no difference in the time to onset of composite 12–week confirmed disability progression (CDP) between the experimental and control arms in the MRI-active subgroup.
- H1 (alternative hypothesis): There is a difference in the time to onset of composite 12-week CDP between the experimental and control arms in the MRI–active subgroup.

The hypotheses to be tested for the co-primary estimand 2 are:

- H0 (null hypothesis): There is no difference in the time to onset of composite 12-week CDP between the experimental and control arms in all randomized patients.
- H1 (alternative hypothesis): There is a difference in the time to onset of composite 12-week CDP between the experimental and control arms in all randomized patients.

For the secondary endpoints, null and alternative hypothesis are of similar form as for the co-primary estimand 2, i.e., there is no difference (null hypothesis) vs there is a

difference (alternative hypothesis) in endpoint between the experimental and control arms in all randomized patients.

All statistical hypotheses will be tested against two-sided alternatives.

The MRI-active subgroup is defined as patients with any T1 gadolinium (Gd) lesion and/or new and/or enlarging T2 lesion during the screening period or at baseline.

If at least one of the two co-primary estimands is statistically significant, then the trial is positive. Type I error control for the co-primary estimands is detailed in Section 2.1.1.

If only one of the co-primary estimands is positive, the secondary endpoints will be tested for all randomized patients and the MRI-active subgroup but the p-value will not be confirmatory.

If both co-primary estimands are statistically significant, then the secondary endpoints will be tested with $\alpha = 0.05$ in a hierarchical gatekeeping procedure for all randomized patients in the order listed below, and as exploratory in the MRI-active subgroup:

- Time to 12-week CDP in 9-HPT
- Time to 12-week CDP in EDSS
- Time to 24-week CDP in 9-HPT
- Time to 24-week CDP in EDSS
- Annual rate of change from baseline in radius of total volume of T2 lesions
- Annual rate of percent change from Week 24 in total brain volume

2.1.1 Type I Error Control

The type 1 error will be controlled for the co-primary estimands with a fallback and loopback procedure, with an alpha of 0.04 for the MRI-active subgroup. The alpha for the all randomized population will be calculated according to Spiessens-Debois method (2010), based on the final proportion of information in the MRI-active subgroup.

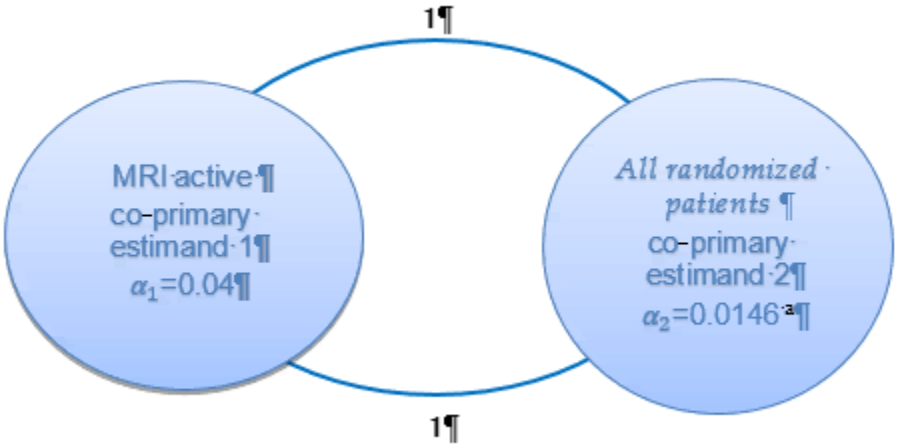
The Spiessens Debois method ensures that type I error control across the all randomized patients population and the MRI-active subgroup is identical to established methods for group-sequential trials. Specifically, under the global null hypothesis of no treatment effect in the all randomized patients population and the MRI-active subgroup, the joint distribution of the log-rank Z-statistics in the all randomized patients population and the MRI-active subgroup has an asymptotic bivariate normal distribution with mean 0 and correlation equal to the square-root of the information fraction in the MRI-active subgroup relative to the all randomized patients population. The critical value for the all randomized patients population can be calculated based on this bivariate normal distribution to ensure that the overall type I error is 0.05. Example R code which uses

the validated R package rpact and a user-defined alpha-spending function which assigns alpha = 0.04 to the MRI-active subgroup is provided below:

```
getDesignGroupSequential(sided = 2, alpha = 0.05,
   informationRates = c(informationFraction,1) ,
   typeOfDesign = "asUser",
   userAlphaSpending = c(0.04,0.05))
```

For example, if 36% (122 of 340) of all events in all randomized patients have occurred in the MRI-active subgroup, the alpha for the all randomized population will be 0.0146 (see Figure 1).

Figure 1 Graphical Representation of the Control of the Type I Error



MRI = magnetic resonance imaging.

[a] The α level indicated for estimand 2 is an example assuming that 36% (122 of 340) of all events in all randomized patients have occurred in the MRI-active subgroup. The actual alpha level for the primary analysis will be determined based on the actually observed events based on the Spiessens-Debois method.

Calculation of α_1 and α_2 will be as follows:

- α_1 is arbitrarily chosen as 0.04, to maximize the power of the analysis for the MRI-active subgroup.
- α_2: calculated according to the Spiessens-Debois method (Spiessens B and Debois M, 2010). For example, α_2 is calculated assuming 122 events in MRI-active subgroup and 340 events in the all randomized patients , $\alpha_2 = 0.0146$, α_2 will be calculated at the primary analysis, with the proportion of information in the MRI-active subgroup.

Fallback: If the analysis of the co-primary estimand 1 has a p-value < 0.04, then the analysis for the co-primary estimand 2 will be tested with $\alpha = 0.05$.

Loop-back: If the analysis of the co-primary estimand 2 has a p-value < 0.0146, then the co-primary estimand 1 will be tested with $\alpha = 0.05$.

If at least one of the two co-primary estimands is statistically significant, then the trial is positive.

If only one of the co-primary estimands is positive, the secondary endpoints will be tested for all randomized patients and the MRI-active subgroup but the p-value will not be confirmatory.

If both co-primary estimands are statistically significant, then the secondary endpoints will be tested with $\alpha = 0.05$ in a hierarchical gatekeeping procedure for all randomized patients, and as exploratory in the MRI-active subgroup.

2.2 SAMPLE SIZE DETERMINATION

The sample size was estimated on the basis of data from Study WA25046 (ORATORIO).

A two-group test of equal exponential survival is used to determine the sample size for the composite 12-week CDP of EDSS and 9-HPT. With a sample size of 1000 patients (of which at least 350 patients are expected in the MRI-active population), a double-blind treatment phase of 144 weeks, an annual dropout rate of 10%, and a randomization ratio of 1:1, it is expected that approximately 340 events will be observed in all randomized patients (placebo progression rate: 40%), which will provide approximately 80% power to detect a hazard ratio (HR) of 0.70 at a type I error rate of 0.0146 and approximately 75.5% power to detect a HR of 0.75 at a type I error rate of 0.05. Likewise, it is expected that approximately 122 events will be observed in the MRI-active subgroup (placebo progression rate: 44%), which will provide approximately 78% power to detect a HR of 0.60 at a type I error rate of 0.04.

Operating characteristics (power and expected total number of events) for true underlying HR values of 0.60, 0.70, and 0.75 are provided in Table 4 for all randomized patients and the MRI-active subgroup.

Table 4 Operating Characteristics for Possible True Underlying Hazard Ratio Values

	MRI-Active Subgroup	All Patients Randomized	All Patients Randomized
Expected number of events	122	340	340
Expected proportion of placebo patients with composite events at Week 120	44%	40%	40%
2-sided alpha for the log-rank test	0.04	0.0146	0.05
Power	78%	80%	75.5%
Detectable hazard ratio	0.60	0.70	0.75

MRI = magnetic resonance imaging.

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, and patients are followed for 144 weeks.

It should be noted that the type I error rate to be used for the testing in all randomized patients will be adjusted depending on the proportion of events in the MRI-active subgroup at the primary analysis.

3. ANALYSIS SETS

The analysis sets are defined in Table 5 .

Table 5 Participant Analysis Sets

Participant Analysis Set	Description
Full analysis set	All randomized participants; participants will be included in the analyses according to the treatment to which they were assigned.
MRI activity analysis set	All randomized participants with MRI activity, defined as presence of T1 Gd+ lesion[s] and/or new and/or enlarging T2 lesion[s] as detected by MRI scans during the screening phase; participants will be included in the analysis according to the treatment to which they were assigned.
Immunogenicity analysis set	All randomized participants with at least one ADA assessment; participants will be grouped according to treatment received at first exposure or, if no treatment is received prior to study discontinuation, according to treatment assigned.

Participant Analysis Set	Description
Pharmacokinetic analysis set	All randomized participants who have measurable concentrations of ocrelizumab unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred or if data are unavailable, not plausible, or incomplete which may interfere with PK evaluation. Excluded cases will be documented together with the reason for exclusion; participants will be grouped together.
Safety analysis set	All participants who received at least one infusion (partial or complete) of study drug; participants will be included in the analyses according to the treatment that they actually received.
Ocrelizumab exposed analysis set	All randomized participants who received at least one infusion (partial or complete) of ocrelizumab (study drug, PDP OCR, OLE OCR or commercial ocrelizumab); participants will be grouped together.
No major protocol deviation (MRI activity) analysis set	All participants included in the first supplementary analysis as described in Section 4.2.4; participants will be included in the analysis according to the treatment to which they were assigned.
No major protocol deviation analysis set	All participants included in the first supplementary analysis of Section 4.2.7 participants will be included in the analysis according to the treatment to which they were assigned.

ADA = anti-drug antibody; MRI = magnetic resonance imaging; OCR = ocrelizumab; OLE = open-label extension; PDP = post-double-progression; PK = pharmacokinetic.

MRI activity analysis set will be used in the analysis of the co-primary estimand 1.

Full analysis set (FAS) will be used in the analysis of the co-primary estimand 2 and secondary estimands. For exploratory efficacy endpoints, FAS and MRI activity analysis sets will be used. Safety analysis set (SAS) and ocrelizumab exposed analysis set will be used to summarize safety data. No major protocol deviation (MRI activity) analysis set will be used in the first supplementary analysis as described in Section 4.2.4. No major protocol deviation analysis set will be used in a supplementary analysis described in Section 4.2.7 .

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

As per the EMA guideline on multiplicity issues in clinical trials (EMA, 2017) and the FDA guidance for industry on multiple endpoints in clinical trials (FDA, 2022) multiple primary endpoints are designated as co-primary endpoints if study success is defined by a positive outcome in all primary endpoints.

In this SAP, the terminology co-primary endpoint and co-primary estimand is used although study success is defined by a positive outcome in at least one of the two co-primary endpoints, analogous to multiple primary endpoints.

For all continuous variables for which descriptive statistics are reported, the following will be reported: the number of observations, the mean, median, standard deviation, and minimum and maximum. The 25th and 75th percentiles (Q1 and Q3) will also be reported for selected tables. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of patients.

All primary and secondary efficacy endpoints will be stratified by/adjusted for:

- MRI activity, defined as any T1 Gd+ lesion(s) and/or new and/or enlarging T2 lesion(s) during the screening period (yes vs. no)
- Age ($\leq$55. vs. $>$55)
- EDSS score ($\leq$6.5 vs. $>$6.5)
- Region (two regions: European Union, United Kingdom, and Canada vs. other)

The baseline is defined as the most recent value prior to first dose administration (or up to and including the date of randomization for non-treated patients), unless specified otherwise.

The baseline MRI is defined as the most recent MRI prior to randomization.

For EDSS and 9-HPT, baseline is defined as the most recent value prior to randomization.

There will be no imputation of the baseline outcome value, with the consequence that participants missing the baseline outcome measure will not contribute to the analyses which use change from baseline of a given outcome measure as the dependent variable.

For analysis purposes, the time of treatment discontinuation will be defined as 24 weeks after the last dose prior to the date of treatment discontinuation recorded in the electronic Case Report Form (eCRF).

4.2 PRIMARY ENDPOINT ANALYSIS

There are two co-primary analyses:

- In all randomized patients
- In the MRI-active subgroup

Hypothesis test for the co-primary estimand 1 and for the co-primary estimand 2 is described in Section 2.1.

Five attributes of the co-primary estimand 1 and co-primary estimand 2 are provided in Table 1. Further details on the definition of the primary endpoint are provided in Section 4.2.1. Information on primary estimator for co-primary estimand 1 and co-primary estimand 2, intercurrent events and their handling as well as the handling of missing data is described in Section 4.2.2 and Section 4.2.5. Section 4.2.3, Section 4.2.4 and Section 4.2.6, Section 4.2.7 describe sensitivity and supplementary analysis for the co-primary estimand 1 and co-primary estimand 2.

4.2.1 Definition of Primary Endpoint

The primary efficacy endpoint is time to onset of composite 12-week CDP defined as the time from randomization to the first occurrence of at least one of the following progression events:

- **C1**: 12-week CDP in 9-HPT, defined as a 20% worsening from baseline in 9-HPT confirmed for at least 12 weeks
- **C2**: 12-week CDP in EDSS score, defined as an increase of $\geq$ 1.0 point from baseline EDSS score in patients with a baseline EDSS score $\leq$5.5 or an increase of $\geq$0.5 point in patients with a baseline EDSS score of >5.5 that is confirmed for at least 12 weeks

Initial disability progression can occur at any visit, including unscheduled visits. Four conditions must be fulfilled to satisfy the 12-weeks confirmation criteria for disability progression based on C1 and C2:

1. The confirmation (of disability progression) visit must be at least 12 weeks (84 days) after the initial disability progression.
2. The confirmation visit must be either a scheduled or treatment discontinuation visit.
3. Assessments within 30 days after the onset of a protocol-defined relapse cannot be used for confirmation of the progression.
4. All EDSS or 9-HPT assessments between the initial disability progression and the confirmation visit should also fulfill the requirements of disability progression, i.e., $\geq$1.0 point increase in baseline EDSS if baseline EDSS $\leq$5.5 or $\geq$0.5 increase if baseline EDSS $>$5.5, or $\geq$20% increase in 9-HPT from baseline.

If any of the four criteria listed above are not satisfied, then the initial disability progression is not the onset of composite 12-week CDP.

In criteria 3, a protocol-defined relapse is defined as the occurrence of new or worsening neurological symptoms attributable to MS and immediately preceded by a relatively stable or improving neurological state of at least 30 days. Symptoms must persist for at least 24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). The new or worsening neurological symptoms must be accompanied by objective neurological worsening consistent with an increase of at least one of the following:

- Half a step (0.5 point) on the EDSS
- Two points on one of the selected FSS as listed below
- One point on two or more of the selected FSS as listed below

The change must affect the following selected FSS: pyramidal, ambulation, cerebellar, brainstem, sensory, or visual. Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish a relapse. Information related to a protocol-defined relapse will be captured on a clinical relapse event case report form (CRF) page.

If the test results for 9-HPT are not available due to a "physical limitation," the maximum possible value for the scale (16 minutes and 59 seconds) will be imputed. If one of the two trials for the dominant and non-dominant hand is not available and not missing due to a "physical limitation", the result from the other trial will be used to impute the missing value. Very low values will be considered to be outliers. For outliers, the following rules will be applied. Values outside the lower bound will be treated as missing, and the imputation rule will be applied as defined above. For 9-HPT, the lower bound is 10 seconds (Oxford Grice et al. 2003).

Composite 12-week CDP in the Presence of Differential Right Censoring

A complicating factor for defining the onset time of the composite 12-week CDP is the presence of differential right censoring in the individual components, i.e., time to 12-week CDP in 9-HPT and time to 12-week CDP in EDSS. In such circumstances, the following algorithm will be used to define the onset time of the composite 12-week CDP:

1. If the onset times of the individual components are all observed, then the onset time of the composite 12-week CDP is the earliest of the observed onset times of the individual components.
2. Otherwise if all onset times of the individual components are right censored, then the onset time of the composite 12-week CDP is right censored at the earliest of the right censored onset times of the individual components.
3. Otherwise if the earliest of the observed onset times occurs prior to or on the same day as the earliest of the right censored onset times of the individual components, then the onset time of the composite 12-week CDP is the earliest of the observed onset times of the individual components.
4. Otherwise if the earliest of the observed onset times occurs after the earliest of the right censored onset times of the individual components, then the onset time of the composite 12-week CDP is set to the earliest of the observed onset times of the individual components.

In scenario 4, the approach to specify the onset time of the composite 12-week CDP as the earliest of the observed onset times of the individual components can in some cases overestimate the true onset time. Nonetheless, the proposed approach is pragmatic and reasonable because it leads to an estimate of the proportion of the composite 12-week

CDP events by the end of the study that is at least as large as the observed proportion, and it has a negligible impact on treatment effect estimation if the independent censoring assumption is plausible for the individual components.

4.2.2 Main Analytical Approach for Co-Primary Estimand 1

The co-primary estimand 1 is the difference in time to onset of composite 12-week CDP, as expressed by the HR, between the experimental and control arms in the MRI-active subgroup of patients with PPMS, including patients later in their disease course, regardless of adherence to the randomized treatment had the patients not initiated another MS disease-modifying therapy (DMT) or commercial ocrelizumab. More specifically, the estimand has the following attributes:

Population: Patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol), with MRI activity (see Section 2.1.1 of the protocol).

Endpoint: Time to onset of composite 12-week CDP.

Treatment:

- Experimental arm: Ocrelizumab IV 300 mg administered at Day 1 and Day 15, followed by Ocrelizumab IV 600 mg administered every 24 weeks
- Control arm: Matching placebo

Population-level summary: HR for time to onset of composite 12-week CDP

The HR will be calculated from a Cox-regression to estimate the treatment-benefit, and the log-rank p-value will be used to test the statistical significance. Both will be stratified by the stratification factors from the randomization.

In order to estimate the co-primary estimand 1, the following intercurrent event handling strategies will be applied:

Withdrawal from treatment and no initiation of another MS DMT or commercial ocrelizumab: All data pre and post treatment discontinuation will be included in the analysis following the treatment-policy strategy.

Withdrawal from treatment and initiation of another MS DMT or commercial ocrelizumab: Future disease progression in the hypothetical scenario as if no other therapy had been initiated is predicted on the basis of previously observed data and the preceding reason for withdrawal from study treatment.

The following strategies will be used:

- If the patient withdraws from study treatment due to lack of efficacy, a disability progression event will be imputed at the time of initiation of another treatment.

- Withdrawal from study treatment due to another reason will be:
  - Imputed as a disability progression event if the patient had an initial disability progression at the date of his or her last EDSS or 9-HPT assessment prior to the initiation of another treatment, whichever is the earliest
  - Censored in all other cases at the date of the last EDSS or 9-HPT assessment prior to the initiation of another treatment, whichever is the earliest

For each component (EDSS and 9-HPT), missing assessments at scheduled visits prior to the last assessment of a patient, i.e. intermediate missing data, will not be imputed. For patients with initial disability progression based on EDSS or $\geq$20% increase in 9-HPT, data collected at the next scheduled visit or treatment discontinuation visit will be used to confirm disability progression.

Every effort is made to keep the patients in the study after they withdraw from treatment, however if patients withdraw their consent to participate in the study their data will be missing after study withdrawal.

Missing data following withdrawal from study with withdrawal from treatment due to lack of efficacy will be imputed as a disability progression event at the time of withdrawal from the study.

Missing data following withdrawal from study with withdrawal from treatment due to another reason will be:

- Imputed as a disability progression event if the patient had an initial disability progression at the date of his or her last EDSS or 9-HPT assessment, whichever is the earliest
- Censored in all other cases at the date of the last EDSS or 9-HPT assessment, whichever is the earliest

Patients without any disability progression events (including imputed events) during the double-blind treatment period will be censored at the date of the last EDSS or 9-HPT assessment during the double-blind treatment period, whichever is the earliest.

4.2.3 Sensitivity Analyses for Co-Primary Estimand 1

A sensitivity analysis that adjusts for sex and duration since the onset of MS symptoms will be performed to assess the impact of these prognostic factors.

Additionally, the following sensitivity analyses will be conducted.

1. The primary analysis is performed under the assumption that patients who withdraw from study treatment due to a reason other than lack of efficacy and had an initial progression at the date of their last EDSS or 9-HPT assessment prior to initiation of another MS DMT or commercial ocrelizumab, or withdrawal from study, would have had that progression confirmed had they not initiated another MS DMT or

commercial ocrelizumab or withdrawn from the study. As this assumption could be implausible, the robustness of the estimated treatment effect to violations of this assumption will be investigated by repeating the primary analysis with the following imputation rules: For patients who withdraw from study treatment due to a reason other than lack of efficacy and had an initial progression at the date of their last EDSS or 9-HPT assessment prior to initiation of another MS DMT or commercial ocrelizumab, or withdrawal from study, multiple imputation will be used to either impute a progression event or to censor the time to onset of confirmed progression. The presence or absence of a progression event will be imputed from a Bernoulli distribution with success probability ranging from 0-1 in increments of 0.33. This procedure will be applied within arms followed by treatment effect estimation in 100 imputed data sets. An overall estimate of the treatment effect and associated standard error for computing 95% Wald intervals will be obtained by applying Rubin's rules on the log HR scale and then back transforming to the original scale:

$$log(HR) = 1/100 \sum_{m=1}^{100} \log(HR_m) \text{ and } SE(log(HR)) = \sqrt{V_w + \left(1 + \frac{1}{100}\right) V_B}$$

where HR_m is the HR estimated in the mth imputed data set, V_w is the sample mean of the estimated variance of $log(HR_m)$, and V_B is the sample variance of $\log(HR_m)$. The scenarios that result in non-significant treatment effect estimates will be identified for a tipping point analysis.

2. The primary analysis is performed under the independent censoring assumption. However, this assumption may not be plausible. A similar tipping point analysis as the one described in 1. will be conducted for patients who experience censoring because of the following:
    - Initiation of another MS DMT or commercial ocrelizumab
    - Withdrawal from study (missing data)

    Additionally, if at least 10% of the patients randomized to the ocrelizumab arm experience censoring because of the above, a sensitivity analysis may be performed, where it will be attempted to predict the onset of composite 12-week CDP event times for these patients using the observed profile of patients randomized to the placebo arm. The proposed approach appears conservative yet plausible for the study drug. It assumes no treatment effect after the censoring. In the placebo arm, this is compatible with a missing at random (MAR) assumption whereas in the active drug arm, the imputation is under a missing not at random (MNAR) assumption. The proposed sensitivity analysis is based on the multiple imputation approach in Atkinson et al. 2019. Specifically, the following steps will be applied:

    a) Fit a Weibull model with hazard function $\alpha \cdot time^{\alpha-1} \exp\{\beta_0 + \beta_1 X_i\}$ to time to onset of composite 12-week CDP in patients randomized to the placebo arm. Here, α, β_0, β_1 are unconstrained parameters to be estimated, time is time from randomization, X_i is a vector containing the baseline EDSS and 9-HPT values for patient i.

b) Simulate 100 sets of $\{\alpha, \beta_0, \beta_1\}$, from the estimated asymptotic normal distribution of the maximum likelihood estimator of these parameters.

c) Let W_i be the time from randomization for patient i at the time of withdrawal from the study or initiation of another MS DMT or commercial ocrelizumab. Let F_i be the time from randomization for patient i at the clinical cut-off date or at week 144, whichever is earlier. For each set of simulated parameter values, generate onset of composite 12-week CDP event times for patients who have not had composite 12-week CDP up to and including W_i, and where $W_i < F_i$. This will result in 100 complete analysis data sets, i.e., where composite 12-week CDP events times are either available or are censored at F_i. In order to simulate composite 12-week CDP events time O_i for patient i, the following formula will be used:

$$O_i = \{W_i^{\alpha} - \log(U_i)\exp(-\beta_0 - \beta_1 X_i)^{\alpha}\}^{\frac{1}{\alpha}}$$

Here, U_i is generated from a standard uniform distribution. If $O_i > F_i$, the onset time of composite 12-week CDP is recorded as censored at F_i in the analysis data set, otherwise it is set to O_i.

d) For each of the 100 complete analysis data sets, estimate the log HR and its associated standard error with the Cox model used for the primary analysis. Then, use Rubin's rules to combine the estimates from the 100 complete data sets, as described in sensitivity analysis 1, to obtain an overall estimate of the treatment effect on the HR scale and associated 95% Wald interval.

4.2.4 Supplementary Analyses for Co-Primary Estimand 1

1. The primary analysis will be repeated after excluding patients who meet the exclusion criteria/do not meet the inclusion criteria listed below at baseline.

   Inclusion criteria:

   - Diagnosis of PPMS in accordance with the McDonald criteria (Thompson et al. 2017)
   - Age 18−65 years at time of signing Informed Consent Form
   - EDSS score at screening and baseline $\geq$ 3.0 to 8.0, inclusive
   - Disease duration from the onset of MS symptoms relative to randomization date:
     - Less than 20 years in patients with an EDSS score at screening 7.0−8.0
     - Less than 15 years in patients with an EDSS score at screening 5.5−6.5
     - Less than 10 years in patients with an EDSS score at screening $\leq$5.0
   - Documented history or presence at screening of at least one of the following laboratory findings in a CSF specimen (source documentation of laboratory results and method must be verified)
     - Elevated IgG index

    - One or more IgG oligoclonal bands detected by isoelectric focusing
- Screening and baseline 9-HPT completed in $>$ 25 seconds (average of the two hands)
- Ability to complete the 9-HPT within 240 seconds with each hand at screening and baseline
- Neurological stability for $\geq$ 30 days prior to baseline

Exclusion criteria:

- History of relapsing-remitting or secondary progressive MS at screening
- Patients requiring symptomatic treatment of MS (e.g., fampridine) and/or physiotherapy who are not on a stable regimen. Patients must not initiate symptomatic treatment of MS or physiotherapy within 4 weeks of randomization
- Known presence of other neurologic disorders that could interfere with the diagnosis of MS or assessments of efficacy and/or safety during the study
- Any concomitant disease that may require chronic treatment with systemic corticosteroids or immunosuppressants during the course of the study
- Pregnant or breastfeeding
- Treatment with any investigational agent within 24 weeks prior to screening (Visit 1) or 5 half-lives of the investigational drug (whichever is longer), or treatment with any experimental procedure for MS (e.g., treatment for chronic cerebrospinal venous insufficiency)
- Previous treatment with B cell−targeting therapies (e.g., rituximab, ocrelizumab, atacicept, belimumab, ofatumumab, and alemtuzumab)
- Any previous treatment with bone marrow transplantation and hematopoietic stem cell transplantation
- Any previous history of transplantation or anti-rejection therapy
- Treatment with IV Ig or plasmapheresis within 12 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to screening

In addition, the hypothetical strategy will be used to handle the following intercurrent events:

- Received no study drug
- Received study drug that had been mishandled (e.g., incorrect storage temperature) and was not approved for subsequent use
- Received study drug but was not randomized
- Received prohibited disease-modifying therapy for MS
- Misadministration of study drug (e.g. overdosage, incorrect study medication, patient received study drug other than the one the patient was randomized to)

- Missed two or more consecutive as per protocol 9HPT/EDSS assessments in either double-blind treatment (DBT) or FU1
- Unintended unblinding

Under this strategy, data after these intercurrent events will be treated as missing and the time to onset of composite 12-week CDP will be censored at the last assessments prior to the intercurrent event times. However, observed data after the intercurrent events will still contribute to the confirmation period for determining if an initial progression can be confirmed. This analysis estimates the treatment effect of ocrelizumab in a population who always receives the study treatment as planned and with no major protocol deviations.

2. Supplementary estimand applying treatment-policy strategy to withdrawal from study treatment and to initiation of other treatments:

   This supplementary estimand will use a treatment-policy strategy to estimate the treatment effect of ocrelizumab versus placebo on disability progression, on the basis of initial treatment, regardless whether patients adhered to randomized treatment or initiated other treatments (e.g., discontinued treatment or switched to another MS DMT or commercial ocrelizumab).

3. Supplementary estimands to estimate the treatment effect had the patient not withdrawn from study treatment:

   The supplementary estimands will use a hypothetical strategy to estimate the treatment effect of ocrelizumab versus placebo on disability progression had the patient not withdrawn from study treatment as follows:

   - The same estimand as the primary analysis for the Oratorio study (WA25046): If the patient withdraws from treatment without any prior events, an event is imputed as if the patient had an initial disability progression at the date of his or her last EDSS or 9-HPT assessment prior to withdrawal from treatment, whichever is the earliest, and no follow-up data are available, otherwise the patient is censored in all other cases at the date of the last EDSS or 9-HPT assessment prior to withdrawal from treatment, whichever is the earliest.
   - Estimand counting withdrawal due to lack of efficacy as treatment failure: This estimand will estimate the treatment effect measured as time to disease progression or discontinuation from the randomized treatment due to lack of efficacy (composite endpoint). Same as the estimand above (Study WA25046); however, patients who withdrew from treatment due to lack of efficacy will also have an imputed event.
   - Estimand counting withdrawal due to lack of efficacy or due to adverse events as treatment failure: This estimand will estimate the treatment effect measured as time to disease progression or discontinuation from the randomized treatment due to lack of efficacy or due to an adverse event (composite

endpoint). Same as the estimand above (Study WA25046); however, patients who withdrew from treatment due to lack of efficacy or due to an adverse event will also have an imputed event.

4.2.5 Main Analytical Approach for Co-Primary Estimand 2

The co-primary estimand 2 will be similar to the co-primary estimand 1 except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol).

4.2.6 Sensitivity Analyses for Co-Primary Estimand 2

The sensitivity analysis for co-primary estimand 2 will be similar to the sensitivity analysis for co-primary estimand 1 except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol).

4.2.7 Supplementary Analyses for Co-Primary Estimand 2

The supplementary analyses for co-primary estimand 2 will be similar to the supplementary analyses for co-primary estimand 1 except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol).

4.2.8 Subgroup Analyses for Primary Endpoint

Refer to Section 4.4 and Section 4.6.8 for the subgroup analyses for the primary endpoint.

4.3 SECONDARY ENDPOINTS ANALYSES

Hypothesis tests for the secondary estimands are described in Section 2.1 .

If only one of the co-primary estimands is positive, the secondary endpoints will be tested for all randomized patients and the MRI-active subgroup but the p-value will not be confirmatory.

If both co-primary estimands are statistically significant, then the secondary endpoints will be tested with $\alpha = 0.05$ in a hierarchical gatekeeping procedure for all randomized patients in the order listed below, and as exploratory in the MRI-active subgroup:

- Time to 12-week CDP in 9-HPT
- Time to 12-week CDP in EDSS
- Time to 24-week CDP in 9-HPT
- Time to 24-week CDP in EDSS
- Annual rate of change from baseline in radius of total volume of T2 lesions

- Annual rate of percent change from Week 24 in total brain volume

All attributes for the secondary estimands are provided in Table 1. Further details on the estimands attributes and estimation methods (i.e., estimators) are provided below.

4.3.1 Estimands for Time to Event Endpoints

All secondary estimands which focus on the analysis of time to event endpoints have the same estimand attributes (except for Endpoint attribute) and estimation method as for the co-primary estimand 2 (Section 4.2.5).

The time to 12-week CDP in 9-HPT and time to 12-week CDP in EDSS are the individual components of the composite 12-week CDP as defined in Section 4.2.1.

The time to 24-week CDP in 9-HPT and time to 24-week CDP in EDSS will be defined over a 24-week confirmation window (≥161 days) for the disability progression.

4.3.2 Estimand for Annual Rate of Change from baseline in radius of total volume of T2 lesions

Estimand: The estimand is the mean difference in annual rate of change from baseline in radius of total volume of T2 lesions between the experimental and control arms in patients with PPMS, including patients later in their disease course, where no treatment discontinuation nor initiation of another MS DMT or commercial ocrelizumab can occur.

Estimator: A random coefficient regression model (RCRM) will be used to quantify the mean difference in annual rate of change from baseline in radius of total volume of T2 lesions between the experimental and control arms. The mean structure of the model is as follows:

$$E\left[Y_{ij}\middle|time_{ij},T_i,X_i\right] = time_{ij}(\beta_0 + \alpha X_i + \beta_1 T_i + u_i),$$

where Y_{ij} represents change in the cube root of total volume of T2 lesions from baseline at visit j for patient i, $time_{ij}$ is the time from baseline in years at visit j for patient i, T_i is an indicator such that $T_i = 1$ if patient i was randomized to the ocrelizumab arm and $T_i = 0$ otherwise, X_i is a vector containing the cube root of the baseline total volume of T2 lesions and randomization stratification factors for patient i, α is a vector of regression coefficients for X_i, β_0 is the adjusted mean of the annualized rate of change in radius of total volume of T2 lesions for the placebo arm, β_1 is the adjusted mean difference in the annualized rate of change in radius of total volume of T2 lesions between the experimental and control arms, and u_i is a subject-specific random effect that follows a mean zero normal distribution with unknown common variance for all patients. Only scheduled visits will be included in the analysis. The statistical significance of the estimated mean difference will be calculated by using the Wald test, where the standard error is estimated using the robust sandwich variance estimator.

In order to estimate the aforementioned estimand, the following intercurrent event handling strategies will be applied:

Withdrawal from treatment and no initiation of another MS DMT or commercial ocrelizumab: All data after treatment discontinuation will be treated as missing following the hypothetical strategy.

Withdrawal from treatment and initiation of another MS DMT or commercial ocrelizumab: All data after treatment discontinuation will be treated as missing following the hypothetical strategy.

Sample Statistical Analysis System code can be found below (Statistical Analysis System code is regarded as “draft” until fully validated at the analysis stage):

```
PROC MIXED DATA=dataset empirical;
CLASS USUBJID ARMCD StratificationFactors;
MODEL AVAL_N= ARMCD Baseline StratificationFactors / solution cl;
RANDOM intercept / subject=USUBJID type=un;
run;
```

where AVAL_N is the change from baseline in the cube root of the total volume of T2 lesions divided by time at each scheduled visit, and Baseline is the cube root of the total volume of T2 lesions at baseline.

4.3.3 Estimand for Annual Rate of Percent Change from Week 24 in Total Brain Volume

Estimand: The estimand is the mean difference in annual rate of percent change from Week 24 in total brain volume between the experimental and control arms in patients with PPMS, including patients later in their disease course, where no treatment discontinuation nor initiation of another MS DMT or commercial ocrelizumab can occur.

Estimator: An RCRM will be used to quantify the mean difference in annual rate of percent change from Week 24 in total brain volume between the experimental and control arms. The mean structure of the model is as follows:

$$E\left[Y_{ij}\middle|time_{ij},T_i,X_i\right]=time_{ij}(\beta_0+\alpha X_i+\beta_1 T_i+u_i),$$

where Y_{ij} represents percentage change in total brain volume from Week 24 at visit j for patient i, $time_{ij}$ is the time from Week 24 in years at visit j for patient i, T_i is an indicator such that $T_i=1$ if patient i was randomized to the ocrelizumab arm and $T_i=0$ otherwise, X_i is a vector containing the cube root of the Week 24 total brain volume and randomization stratification factors for patient i, α is a vector of regression coefficients for X_i, β_0 is the adjusted mean of the annualized rate of percentage change in total brain volume for the placebo arm, β_1 is the adjusted mean difference in the annualized rate of

percentage change in total brain volume between the experimental and control arms, and u_i is a subject-specific random effect that follows a mean zero normal distribution with unknown common variance for all patients. Only scheduled visits will be included in the analysis.

The statistical significance of the estimated mean difference will be calculated by using the Wald test, where the standard error is estimated using the robust sandwich variance estimator.

In order to estimate the aforementioned estimand, the following intercurrent event handling strategies will be applied:

Withdrawal from treatment and no initiation of another MS DMT or commercial ocrelizumab: All data after treatment discontinuation will be treated as missing following the hypothetical strategy.

Withdrawal from treatment and initiation of another MS DMT or commercial ocrelizumab: All data after treatment discontinuation will be treated as missing following the hypothetical strategy.

Sample Statistical Analysis System code can be found below (Statistical Analysis System code is regarded as “draft” until fully validated at the analysis stage):

```
PROC MIXED DATA= dataset empirical;
CLASS USUBJID ARMCD StratificationFactors;
MODEL AVAL_N = ARMCD Week24 StratificationFactors / solution cl;
RANDOM intercept / subject=USUBJID type=un;
run;
```

where AVAL_N is the percent change from Week 24 in total brain volume divided by time at each scheduled visit, and Week24 is the cube root of the Week 24 total brain volume.

4.4 EXPLORATORY ANALYSIS

The secondary efficacy endpoints will be evaluated as exploratory analyses for the MRI-active subgroup.

The primary and secondary endpoints will also be evaluated in the following patient subgroups of all randomized patients unless otherwise stated, as exploratory analyses:

- Age $\leq$ 55 versus $>$55 years
- EDSS score $\leq$6.5 versus $>$ 6.5
- MRI-inactive versus MRI-active

- Males and females (all randomized patients, MRI-active subgroup and MRI-inactive subgroup)
- Region European Union, United Kingdom, and Canada versus other

All results will be summarized in a forest plot.

The estimands will have the same attributes (except for the Population attribute) and estimation method as for the corresponding primary or secondary endpoints (Section 4.2.2 Section 4.3.1).

The following endpoints will be evaluated in all randomized patients and the MRI-active subgroup as exploratory analyses:

- Change from baseline to Week 120 in fatigue as measured by Modified Fatigue Impact Scale (MFIS)
- Annual rate of percent change from baseline and from Week 24 in cervical spinal cord volume on MRI scans
- Change from baseline to Week 120 in a measure of manual ability for adults with upper limb impairments (ABILHAND)
- Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Quality of Life in Neurological Disorders-Upper Extremity Function [Neuro-QoL-UE])
- Patient Global Impression of Change for upper limb function (PGIC-UL) at each scheduled visit until Week 120
- Patient Global Impression of Change for fatigue (PGIC-F) at each scheduled visit until Week 120
- Change from baseline to Week 120 in the Multiple Sclerosis Impact Scale (MSIS)29 physical domain score
- Occurrence of a $\geq$ 7.5-point increase (worsening) in MSIS-29 physical domain transformed total scores at each scheduled visit until Week 120
- Time to a $\geq$ 4-point decrease (worsening) in SDMT sustained for 24 weeks
- Time to a $\geq$8-point decrease (worsening) in SDMT sustained for 24 weeks
- Time to 24-week CDP
- Time to 24-week CDP or a $\geq$4-point decrease (worsening) in SDMT sustained for 24 weeks
- Time to 24-week CDP or a $\geq$8-point decrease (worsening) in SDMT sustained for 24 weeks
- Change from baseline to Week 120 in the SDMT
- Rate of decline in fine motor skills of upper extremities and manual/finger dexterity as measured by smartphone-based digital outcome assessment (Floodlight remote patient monitoring [RPM])

- The number of Gd-enhancing T1 lesions and number of new or enlarging T2 hyperintense lesions as detected by mandatory MRI, overall and at each scheduled visit
- Annual rate of change from baseline in radius of total non-enhancing T1 lesion volume on MRI scan of the brain

MFIS

- **Physical Subscale:** Assesses the impact of fatigue on physical functioning (e.g., difficulty walking or performing physical tasks). This will be calculated as the sum of the individual items from questions 04, 06, 07, 10, 13, 14, 17, 20 and 21.

- **Cognitive Subscale:** Evaluates how fatigue affects cognitive abilities, such as concentration, thinking, and memory. This will be calculated as the sum of the individual items from questions 01, 02, 03, 05, 11, 12, 15, 16, 18 and 19.

- **Psychosocial Subscale:** Measures the effect of fatigue on emotional well-being and social activities. This will be calculated as the sum of the individual items from questions 08 and 09.

The total score will be derived as the sum of all 21 individual items.

Neuro-QoL-UE

The Quality of Life in Neurological Disorders-Upper Extremity Function (Neuro-QoL-UE) is a 20 item questionnaire that assesses upper limb function. Items include assessments of dressing, cooking, eating, cleaning, and writing from which the patient uses a 5-point Likert scale to rate his or her performance ranging from “Without Any Difficulty” (5) to “Unable To Do” (1). The Neuro-QoL-UE total score will be calculated as the sum of the scores for each item. The Neuro-QoL-UE total score will be derived as missing if the patient completes less than 10 items. Otherwise, it will be derived as the sum of all completed items, and if any of the items are missing, the total score from all completed items will be divided by the number of questions answered and then multipled by 20. The total score will range from 0 to 100, with a higher score indicating a worse upper extremity function (National Institute of Neurological Disorders and Stroke, 2015).

PGIC-UL

The PGIC-UL is a single item questionnaire completed by the patient to assess upper limb function compared with the function over the last 6 months. The patient will be asked to rate their upper limb function using a 7-point Likert scale ranging from “very much better” (1) to “very much worse” (7).

PGIC-F

The PGIC-F is a single item completed by the patient to assess changes in fatigue over the last 6 months. Patients will be asked to respond on a 7-point Likert scale from "very much better" (1) to "very much worse" (7).

MSIS-29

The MSIS-29, v2 is a 29-item patient-reported measure of the physical and psychological impacts of MS. Patients are asked to rate how much their functioning and well-being has been impacted over the past 14 days on a 4-point scale, from "Not at all" (1) to "Extremely" (4).

MSIS-29 physical impact and MSIS-29 psychological impact scores will be derived as per the MSIS-29v2 scoring manual (appendix - MSISv1 and v2 scoring instructions).

The MSIS-physical impact observed score is the sum of items 1-20. The MSIS-physical impact score will be transformed onto a 0 to 100 scale using the following formula:

$$\frac{100 \times (\text{'Physical scale} - \text{raw}' - min\ possible\ score)}{\max possible\ score - \min possible\ score} = \frac{100 \times (observed\ score - 20)}{80 - 20}$$

The MSIS-psychological impact observed score is the sum of items 21-29. The MSIS-psychological impact score will be transformed onto a 0 to 100 scale using the following formula:

$$\frac{100 \times (\text{'Psychological scale} - \text{raw}' - min\ possible\ score)}{\max possible\ score - \min possible\ score} = \frac{100 \times (observed\ score - 9)}{36 - 9}$$

A higher score indicates a greater impact of MS.

For respondents with missing data, but where at least 50% of the items in a scale have been completed, a respondent–specific mean score computed from the completed items can be computed as described below.

For example, if a respondent has completed 15 items in the physical scale, the respondent–specific mean score is obtained as the sum of the completed items divided by 15. This value is then used as the score for each of the missing 5 items. The total score is then obtained as usual by summing the values of the 15 completed items and the 5 imputed items. Note: respondents must have completed a minimum of 10 items in the physical scale, or 5 items in the psychological scale to use this imputing process.

SDMT

The SDMT is a brief and easy to administer performance test that involves a simple substitution task. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses will be collected orally. The SDMT total score is calculated as the number of correct responses. A higher score indicates greater cognitive functioning.

4.4.1 Estimands for Continuous eCOA Endpoints

Estimand: The estimand is the mean difference in the endpoint between the experimental and control arms in patients with PPMS, including patients later in their disease course, and regardless of adherence to the randomized treatment or use of another MS DMT or commercial ocrelizumab.

Endpoints:

- Change from baseline to Week 120 in fatigue as measured by MFIS
- Change from baseline to Week 120 in a measure of manual ability for adults with upper limb impairments (ABILHAND)
- Change from baseline to Week 120 in the upper limb domain of a life quality measure for patients with neurological disorders (Neuro-QoL-UE)
- Change from baseline to Week 120 in the MSIS-29 physical domain score
- Change from baseline to Week 120 in the SDMT

Summary Measure and Primary Estimator: MMRM will be used to quantify mean difference in the endpoints between the experimental and control arms. The fixed effects in the model will include independent variables of randomized treatment, visit, baseline outcome, treatment-by-visit interaction, baseline outcome by visit interaction, along with the randomization stratification factors. An unstructured variance-covariance structure will be applied to model the within-subject errors across visits. The restricted maximum likelihood (REML) method will be used for estimation of variance components. In the case of non-convergence, compound symmetry will be used, together with a robust estimator of standard error (“sandwich” estimator).

The statistical significance of the estimated mean difference will be calculated by using the Wald test.

In order to estimate the estimand of interest, the following intercurrent event handling strategies will be applied:

Withdrawal from treatment and no initiation of another MS DMT or commercial ocrelizumab: All data available will be included in the analysis following the treatment-policy strategy.

Withdrawal from treatment and initiation of another MS DMT or commercial ocrelizumab: All data available will be included in the analysis following the treatment-policy strategy.

The estimand for continuous electronic Clinical Outcome Assessments (eCOA) endpoints in the MRI-active subgroup will be similar except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol), with MRI activity (see Section 2.1.1 of the protocol).

4.4.2 Estimands for Categorical eCOA Endpoints

Estimand: The estimand is the proportion of patients in each category at each scheduled visit until Week 120, in the experimental and control arms in patients with PPMS, including patients later in their disease course, and regardless of adherence to the randomized treatment or use of another MS DMT or commercial ocrelizumab.

Endpoints:

- PGIC-UL at each scheduled visit until Week 120
- PGIC-F at each scheduled visit until Week 120

Summary Measure and Primary Estimator: The number and proportion of patients in each category will be summarized at each scheduled visit until Week 120.

The same intercurrent event handling strategies as for the estimands for continuous eCOA endpoints (Section 4.4.1) will be applied.

The estimand for categorical eCOA endpoints in the MRI-active subgroup will be similar except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol), with MRI activity (see Section 2.1.1 of the protocol).

4.4.3 Estimand for Proportion of Responders

Estimand: The estimand is the proportion of patients with a $\geq$7.5-point increase (worsening) in MSIS-29 physical domain transformed total scores at each scheduled visit until Week 120 in the experimental and control arms in patients with PPMS, including patients later in their disease course, and regardless of adherence to the randomized treatment or use of another MS DMT or commercial ocrelizumab.

Endpoint:

- Occurrence of a $\geq$7.5-point increase (worsening) in MSIS-29 physical domain transformed total scores at each scheduled visit until Week 120

Summary Measure and Primary Estimator: The number and proportion of patients with a ≥7.5-point increase (worsening) in MSIS-29 physical domain transformed total scores will be summarized at each scheduled visit until Week 120.

The same intercurrent event handling strategies as for the estimands for continuous eCOA endpoints (Section 4.4.1) will be applied.

The estimand for proportion of responders in the MRI-active subgroup will be similar except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol), with MRI activity (see Section 2.1.1 of the protocol).

4.4.4 Estimands for Time to Event Endpoints

Estimand: The estimand is the difference in time to the event, as expressed by the HR, between the experimental and control arms in patients with PPMS, including patients later in their disease course, regardless of adherence to the randomized treatment had the patients not initiated another MS DMT medication or commercial ocrelizumab

Endpoints:

- Time to a≥4-point decrease (worsening) in SDMT sustained for 24 weeks
- Time to a≥8-point decrease (worsening) in SDMT sustained for 24 weeks
- Time to 24-week CDP
- Time to 24-week CDP or a≥4-point decrease (worsening) in SDMT sustained for 24 weeks
- Time to 24-week CDP or a≥8-point decrease (worsening) in SDMT sustained for 24 weeks

All other estimand attributes and the estimation method will be identical as for the co-primary estimand 2 in Section 4.2.5 .

Missing assessments at scheduled visits prior to the last assessment of a patient, i.e. intermediate missing data, will not be imputed. For patients with an initial worsening, data collected at the next scheduled visit or treatment discontinuation visit will be used to confirm the worsening.

Missing data and patients without any events (including imputed events) during the double-blind treatment period will be handled similarly as for the co-primary estimand 1 in Section 4.2.2

The estimand for time to event endpoints in the MRI-active subgroup will be similar except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol), with MRI activity (see Section 2.1.1 of the protocol).

4.4.5 Estimands for Rate of Change of Continuous MRI Endpoints

Estimand: The estimand is the mean difference in the endpoint between the experimental and control arms in patients with PPMS, including patients later in their disease course, where no treatment discontinuation nor initiation of another MS DMT or commercial ocrelizumab can occur.

Endpoints:

- Annual rate of percent change from baseline and from Week 24 in cervical spinal cord volume on MRI scans
- Annual rate of change from baseline in radius of total non-enhancing T1 lesion volume on MRI scan of the brain

The same population definition, intercurrent events handling strategies and estimator will apply as for the annual rate of change from baseline in radius of total volume of T2 lesions (Section 4.3.2).

The estimand for rate of change of continuous MRI endpoints in the MRI-active subgroup will be similar except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2 of the protocol), with MRI activity (see Section 2.1.1 of the protocol).

4.4.6 Estimands for Expected Counts at each Scheduled Visit

Estimand: The estimand is the ratio of the mean endpoint between the experimental and control arms in patients with PPMS, including patients later in their disease course, where no treatment discontinuation nor initiation of another MS DMT or commercial ocrelizumab can occur.

Endpoints:

- The number of Gd-enhancing T1 lesions as detected by mandatory MRI, overall and at each scheduled visit
- The number of new or enlarging T2 hyperintense lesions as detected by mandatory MRI, overall and at each scheduled visit

Summary Measure and Primary Estimator: Separate negative binomial models will be fitted to the data on the endpoints at each scheduled visit and overall for the total count. The mean function of the model will be parameterized using the log link function and the linear predictor will include as an offset either the log number of MRI scans for Gd-enhancing T1 lesions or log time in years of scan relative to baseline for new or enlarging T2 hyperintense lesions, an indicator variable for the assigned treatment and the randomization stratification factors as independent variables. The statistical significance of the estimated ratio of means will be calculated by using the Wald test.

In order to estimate the aforementioned estimand, the same intercurrent event handling strategies as those for brain volume in Section 4.3.2 Section 4.3.3 will be applied.

The estimand for expected counts at each scheduled visit in the MRI-active subgroup will be similar except the population will be patients with PPMS, including patients later in their disease course, as defined by the study inclusion and exclusion criteria (See Sections 4.1.1 and 4.1.2 of the protocol), with MRI activity (see Section 2.1.1 of the protocol).

4.5 SAFETY ANALYSES

The SAS and the ocrelizumab exposed analysis set are described in Section 3. All safety parameters will be summarized and presented in tables on the basis of these analysis sets.

The baseline is defined as the last available assessment prior to the first study drug administration for the safety analysis set and as the last available assessment prior to the first ocrelizumab administration [study drug, post-double-progression ocrelizumab (PDP OCR), or commercial ocrelizumab] for the ocrelizumab exposed analysis set.

For the safety analysis set, the safety data will be summarized from the first study drug administration until when patients receive any PDP OCR, open-label extension ocrelizumab (OLE OCR), commercial ocrelizumab treatment, or other MS DMT. In addition, the adverse event (AE) profile will be summarized in the following subgroups:

- Age >55 versus ≤ 55
- EDSS score ≤ 6.5 versus >6.5
- MRI-inactive versus MRI-active
- Males and females
- Treated prior to randomization with another DMT for MS

For the ocrelizumab exposed analysis set, the safety data will be summarized from the first ocrelizumab administration (study drug, PDP OCR, OLE OCR or commercial ocrelizumab) until when patients receive any other MS DMT.

In an exploratory analysis, the AE profile will be summarized using data collected from the first ocrelizumab administration until the end of the study. Every effort will be made to collect the safety data until the end of the study.

Safety will be assessed through summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs. All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to National Cancer Institute Common

Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. All AEs, serious adverse events (SAEs), AEs leading to death, AEs of special interest, and AEs leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent AEs) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized. Relevant laboratory and vital sign (pulse rate and blood pressure) data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post baseline severity grade. Changes in vital signs will be summarized.

4.5.1 Extent of Exposure

Study treatment exposure such as treatment duration, total dose received, and number of doses and infusion modifications will be summarized with descriptive statistics.

4.5.1.1 Details in Defining the Number of Doses and Total Dose Received

The first dose is given as two infusions administered 2 weeks apart. If a patient receives any infusion at Dose 1, the patient is counted as having received the first dose.

If a dose is completely missed instead of delayed, the next dose number will be consecutive to the previous dose received.

4.5.1.2 Treatment Duration and Duration under Observation Definitions

Treatment duration during the DBT and FU1 phases will be calculated as follows:

(Date of the last recorded treatment observation during the DBT and FU1 phases*−Date of first dose of the DBT phase)+1

*The date of the last recorded treatment observation during the DBT and FU1 phases is defined as the earliest between:

- date of last dose received during the DBT phase + 24 weeks
- last day prior to entering in FU2 as per the subject disposition eCRF page
- last day prior to the first OLE dose
- last day prior to the first PDP OCR dose
- last day prior to start of commercial ocrelizumab treatment or other MS DMT
- clinical cutoff date (CCOD) for the primary analysis reporting
- date of discontinuation from the study as indicated on the subject disposition eCRF page
- date of death

Treatment duration for all ocrelizumab exposed patients will be calculated as follows:

(Date of the last recorded treatment observation for all ocrelizumab exposed patients*−Date of the first dose of ocrelizumab (study drug, PDP OCR, OLE OCR or commercial ocrelizumab))+ 1

*The date of the last recorded treatment observation for all ocrelizumab exposed patients is defined as the earliest between:

- date of last dose of ocrelizumab (study drug, PDP OCR, OLE OCR or commercial ocrelizumab)+24 weeks
- last day prior to start of other MS DMT (not including commercial ocrelizumab)
- date of discontinuation from the study as indicated on the subject disposition eCRF page
- CCOD for the primary analysis reporting
- date of death

The duration under observation during the DBT and FU1 phases for a patient will be calculated as follows:

(Date of last observation during the DBT and FU1 phases*−Date of first infusion in the first dose)+1

*Date of last observation during the DBT and FU1 phases is defined as the earliest between:

- the latest recorded date in all CRF and non CRF data prior to CCOD
- last day prior to entering in FU2 as per the subject disposition eCRF page
- last day prior to the first OLE dose
- last day prior to the first PDP OCR dose
- last day prior to start of commercial ocrelizumab treatment or other MS DMT
- date of discontinuation from the study as indicated on the subject disposition eCRF page
- date of death

The duration under observation for all ocrelizumab exposed patients will be calculated as follows:

(Date of last observation for all ocrelizumab exposed patients* −Date of first infusion in the first dose of ocrelizumab)+1

*Date of last observation for all ocrelizumab exposed patients is defined as the earliest between:

- the latest recorded date in all CRF and non CRF data prior to CCOD

- last day prior to start of other MS DMT (not including commercial ocrelizumab)
- date of discontinuation from the study as indicated on the subject disposition eCRF page
- date of death

The duration of observation, within a dose, is defined in a similar manner as follows:

(Day prior to first infusion in the n+1th dose*−Date of first infusion in the nth dose)+1

*With the exception of the last dose received by the patient where the date of last observation during the DBT and FU1 phases or for all ocrelizumab exposed patients is used as defined above.

4.5.2 Adverse Events

AEs will be defined as all AEs including infusion-related reaction (IRRs) and serious MS relapses, but excluding non-serious MS relapses. Therefore, those AEs recorded on the AE and IRR CRF pages will be included.

For each recorded AE, the term entered by the investigator describing the event (the "reported term") will be assigned to a standardized term (the "Preferred Term" [PT]) and assigned to a superclass term on the basis of the MedDRA World Health Organization (WHO) dictionary of terms. All analyses of AE data will be performed using the PTs unless otherwise specified.

For all summary tables, the AEs will be sorted by System Organ Class ([SOC]; in decreasing order of overall incidence) and then by PT (in decreasing order of overall incidence). Summaries of AEs will be generated to summarize the incidence of treatment-emergent AEs only. Treatment-emergent events are defined as those AEs with an observed or imputed date of onset on or after the start date of trial treatment or with CRF flag "Event occurred prior to first study drug administration" equals "no". If the onset date of the AE is prior to the day of first dose, the AE will be considered treatment-emergent only if the most extreme intensity is greater than the initial intensity (i.e., the intensity for a given AE increases and its end date is on or after the date of the first dose). An AE with a completely missing, non-imputed start date will be assumed to be treatment emergent unless the AE has a complete, non-imputed end date that is prior to the date of the first dose.

AEs will be assigned to a dose if the AE onset date is on or after the date of the first infusion of that dose but before the first infusion of the next treatment dose. AEs that are reported during non-dosing phases (Follow-up 1, Follow-up 2) will be assigned to the last dose received. AEs that start prior to the first dose and worsen during treatment (i.e., treatment-emergent) will be assigned to the first treatment dose.

The number of patients who experienced a related AE will be summarized by SOC and PT. AEs will be summarized by SOC and PT by intensity grade. Multiple occurrences of the same event within a patient will be counted once at the greatest intensity/highest grade for this PT. For AEs leading to death, the most extreme intensity will be overwritten by Grade 5 (death). Any AEs and the SOC overall rows of the summary table will count patients according to AEs by intensity (grade).

All patient deaths will be listed.

SAEs will be defined as all SAEs including serious MS relapses and serious IRRs. The number of patients who experienced an SAE will be summarized by SOC and PT. Related SAEs will be summarized by SOC and PT. Additionally, the most frequent SAEs (≥1%) will be presented by SOC and PT.

Clinical relapse will be considered an SAE when the relapse results in hospitalization for any reason other than routine treatment of the relapse (e.g., for a treatment course beyond the standard treatment described or when hospitalization is prolonged). These events will be listed and summarized.

A patient may experience an AE that leads to withdrawal from study treatment. Withdrawal from study treatment for an AE may not necessarily lead to withdrawal from the study. Only AEs that led to study treatment withdrawal are of interest. Patients who withdraw early from the study because of AEs will be summarized under disposition. The number of patients who experienced an AE that led to study treatment withdrawal as well as the number of patients who experienced an AE that led to modification or interruption of study drug will be summarized by SOC and PT. The number of patients previously treated with an another DMT for MS who experienced an AE will be summarized by SOC and PT.

For each treatment group, the incidence count for each AE PT will be defined as the number of patients reporting at least one treatment-emergent occurrence of the event. The incidence rate will be calculated as the incidence count divided by the total number of patients in the population. Each table will also present the overall number of patients experiencing at least one AE and the total number of AEs reported.

The rate per 100 patient-years by treatment group (along with the 95% CI) will be calculated for specific events of interest such as all AEs, SAEs, infections and serious infections (see Section 4.5.4), opportunistic infections ([OIs]; see Section 4.5.5), and malignancies (see Section 4.5.6).

- The number of AEs per 100 patient-years is calculated as:

  (Total number of AEs ÷Total number of patient-years) × 100

- The 95% confidence interval (CI) for the number of AEs per 100 patient-years will be calculated using the exact method based on the Poisson distribution (Sahai and Khurshid 1993):

  Exact lower 95% confidence limit = chisq (p = 0.025, df = 2 Y) / (2T)

  Exact upper 95% confidence limit = chisq [p = 0.975, df = 2(Y + 1)] / (2T)

  where Y is the total number of AEs, T is total number of patient-years at risk and chisq (p, df) is the quantile of the upper tail probability of the Chi-squared distribution with df degrees of freedom. This approach has the advantage of providing an estimate for the upper 95% confidence limit even when the total number of AEs is zero.

The rates per 100 patient-years will be summarized by treatment and dose and by treatment (including all doses).

4.5.3 Infusion Related Reactions

The occurrence of an IRR and its corresponding symptoms are collected on the dedicated eCRF page. Symptoms will be coded in the MedDRA and summarized by PTs.

For IRRs, the number and percentage of patients with at least one infusion reaction will be presented per infusion (patients with multiple events within an infusion will count only once). In addition, the total number of IRRs will be summarized (multiple events will be counted). The total and percentage of events (based on the total number of patients with at least one IRR) by most extreme intensity will be summarized per infusion and per dose. The number of serious IRRs will also be presented. For multiple events in a given patient, the most extreme intensity will be used and the total number of events of each intensity will be equal to the total number of patients with at least one IRR if there are no missing extreme intensities. The total number of IRRs experienced by each subject will be summarized across the treatment doses.

Onset times of IRRs, if known, are recorded on the CRF. The number of patients with at least one IRR, the total number of IRRs, and the intensity of the IRR will be presented by the time of event (i.e., During infusion, Event occurred within 24 hours after end of IMP infusion, time not available) as well as by dose.

Additionally, similar tables will be presented by the pre-medication subgroup (methylprednisolone plus antihistaminics, or methylprednisolone plus antihistaminics and analgesic/antipyretic).

Symptoms of IRRs and symptoms of serious IRRs will be presented by infusion. Symptoms of IRRs that led to interruption of study drug or symptoms of IRR that led to discontinuation of study drug will also be presented. Symptoms of IRR experienced by

patients during an infusion and symptoms of IRR experienced within 24 hours after end of IMP infusion will also be presented.

In addition, concomitant treatments for IRRs by class and PT will be presented by infusion.

4.5.4 Infections

Infections will be defined from the AE data using the MedDRA SOC of “Infections and infestations”. Infections will be classified according to the pathogen type (e.g., bacterial, fungal, viral, parasitical, unknown, or other).

An infection will be defined as serious if the event is an SAE as defined in Section 4.5.2. A listing will be presented of non-serious infections treated with an IV anti-infective.

The number of patients who experienced an infection will be summarized by SOC and PT and by intensity.

The number of infections experienced by more than 5% of patients will be summarized by SOC and PT.

The number of patients who experienced a serious infection will be summarized by SOC and PT.

Identified pathogen codes will not be summarized but will only be listed within the listings of infections and serious infections. Infections and serious infections will be summarized by pathogen types.

The rate per 100 patient-years by treatment group (along with the 95% CI) will be calculated for infections and serious infections overall and by dose based on the number of patient-years observation for the specific dose.

For infections and serious infections, the incidence rate ratio will be calculated. For these analyses, the incidence rate ratio with 95% CI based on the Poisson distribution exact method will be presented.

4.5.5 Opportunistic Infections

Potential OIs will be retrieved using the "Opportunistic infections (narrow) (Standardised MedDRA Queries [SMQs])" basket.

The number of patients who experienced an OI and serious OI will be summarized by SOC and PT.

The rate per 100 patient-years by treatment group (along with the 95% CI) will be calculated for OIs overall and by dose.

4.5.6 Malignancies

Malignancy and pre-malignancy AEs will be identified using the SMQ of “Malignant tumours (narrow)” and “Pre-malignant disorders,” respectively.

The number of patients with a malignancy and serious malignancy will be summarized by SOC and PT. The pre-malignancy AEs will be listed.

The rate per 100 patient-years by treatment group (along with the 95% CI) will be calculated for malignancies.

4.5.7 Multiple Sclerosis Relapses

For clinically reported relapses, the number and percentage of patients experiencing an event will be summarized.

4.5.8 Pregnancies

Pregnancy information will be summarized in individual patient listings.

4.5.9 Magnetic Resonance Imaging Data

Non-MS pathology reported by the local safety radiologist on the CRF will be listed by treatment arm.

4.5.10 Laboratory Data

Abnormal laboratory outcomes will be reported. A summary of the number and percentage of patients with abnormal laboratory outcomes, along with each grade by laboratory parameter, will be summarized by treatment group for all laboratory assessments.

The absolute values and changes from baseline at each visit will be summarized for all laboratory assessments, including those for hematology, chemistry, immunoglobulins (IgA, IgM, IgG) and T-cell subtype (CD3, CD4, CD8).

For the liver laboratory parameters, the number and percentage of patients with an elevated post-baseline Aspartate aminotransferase (AST) or Alanine Transaminase (ALT) level will be summarized by treatment.

The association of decrease in each immunoglobulin (IgA, IgM, IgG) and serious infections will be investigated by reporting the incidence rate of serious infections per 100 patient year during the episodes of confirmed drop of immunoglobulin levels below lower limit of normal (LLN) versus the incidence rate of serious infections per 100 patient year in the remaining exposure (before or after a confirmed drop, and during the overall exposure for the patients without any confirmed drop of immunoglobulin) for each treatment arm. The exposure of a confirmed episode is counted from the day the immunoglobulin first decreased below LLN until the day it is normalized above LLN, and

the serious infections with onset date in between are counted. The 95% CI will be calculated using Poisson distribution methods.

The association of decrease in each T-cell subtype (CD3, CD4, CD8) and serious infections will also be investigated.

Immunoglobulins

The median immunoglobulin levels (IgA, IgG, IgM, and total Ig) will be displayed graphically over time from the first infusion of study drug. Absolute values, changes from baseline, and percent changes from baseline will be summarized over time. At each time point, the number and percentage of patients with immunoglobulin levels lower than the lower limit of normal will be presented.

HBV DNA

Hepatitis B virus (HBV) DNA (polymerase chain reaction [PCR]) in patients who enrolled with negative hepatitis B surface antigen (HBsAg) and positive total hepatitis B core antibody (HBcAb) will be listed.

4.5.11 Vital Signs

Changes from study baseline in vital signs including systolic and diastolic blood pressure, and pulse rate will be summarized by visit and group.

Changes from pre-infusion baseline to post-infusion time points will also be summarized for each infusion.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

The number of patients who enroll, discontinue treatment or study, or complete the study will be summarized. Reasons for premature treatment and study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

Intercurrent events will be summarized and listed.

4.6.2 Summaries of Demographics and Baseline Characteristics

Demographic and baseline characteristics (including age, sex, history of MS, stratification factors, MRI and Lab data) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group, for the MRI-active subgroup and all randomized patients as allocated.

A summary of discrepancies in the age, region, EDSS values and MRI activity (stratification factors) between the IxRS and the eCRF will be provided.

4.6.3 Pharmacokinetic Analyses

The pharmacokinetic analysis set (PAS) is described in Section 3. All PK parameters will be summarized and presented in tables on the basis of this analysis set.

PK analysis of ocrelizumab serum concentration versus time data will be conducted using a population PK approach. Nonlinear mixed effects modeling (with software NONMEM) will be used to analyze the sparse sampling dose-concentration-time data of ocrelizumab. Patients who have measurable concentrations of ocrelizumab will be included in the PK analysis, unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occur, or if data are unavailable, not plausible, or incomplete, that would interfere with the PK evaluation. The PK data of this study may be pooled with data from other studies. Exposure (area under the concentration-time curve) to ocrelizumab will be estimated. Additional PK analyses will be conducted as appropriate.

4.6.4 Pharmacodynamic Analyses

B-cell levels in blood will be evaluated for the safety analysis set described in Section 3. The characterization of the ocrelizumab PD profile will be based on the following endpoints:

- B-cell levels in blood (including comparing the degree of B-cell depletion between the doses).
- Proportion of patients achieving 5 or less B-cells per microliter of blood
- Proportion of patients achieving 10 or less B-cells per microliter of blood

The median CD19 cell count will be displayed graphically over time. Absolute CD19 counts and percent changes from baseline in the CD19 count will be summarized over time.

4.6.5 Immunogenicity Analyses

The immunogenicity analysis set (IAS) set is described in Section 3. All immunogenicity parameters will be summarized and presented in tables on the basis of this analysis set.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post baseline incidence) will be summarized by treatment group. When determining post baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post baseline samples is at least 0.60 titer unit greater than the titer of

the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post baseline samples are negative, or if they are ADA positive at baseline but do not have any post baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported via descriptive statistics.

4.6.6 Biomarker Analyses

The safety analysis set is described in Section 3. All biomarker parameters will be summarized and presented in tables on the basis of this analysis set.

Biomarkers will be assessed at baseline and subsequent timepoints. Pharmacodynamic biomarkers will be presented as absolute value over time and/or percent change relative to baseline over time and/or proportion of participants with biomarker levels within a defined threshold over time. Biomarker levels at baseline or over time may be compared with efficacy or safety measurements to assess prognostic or predictive properties. Descriptive or summary statistics will be used to describe biomarker assessments.

Neurofilament light chain (NfL) treatment response will be presented as absolute values over time, percent change relative to baseline over time, and/or proportion of participants with NfL levels below a pre-defined threshold over time.

Baseline NfL levels or NfL levels on treatment determined by the appropriate assay and to be determined pre-defined cutoffs will be used to assess the relationship of baseline or on-treatment NfL to future efficacy, imaging, or other outcomes.

Analysis will include, but is not limited to, the determination of the B-cell number (CD19+), B-cell subsets (e.g., CD19, CD27, IgD, CD38 markers to assess naive, memory, plasmablasts, and/or other populations), and T-cell counts (CD3+, CD4+, CD8+).

A Biomarker Analysis Plan that describes planned analyses of Biomarker data will be prepared and finalized prior to the database lock for the primary analysis reporting .

4.6.7 Health Status Analyses

The EQ-5D-5L is a validated instrument to describe and value health (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item descriptive system questionnaire (EQ-5D-5L) that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and a visual analog scale (EQ VAS) that rates the overall health. The frequency of EQ-5D-5L item responses by dimension and severity level will be reported at baseline and each scheduled visit up to and including Week 120 by

treatment arm. EQ VAS will be reported as level and change from baseline at each scheduled visit up to and including Week 120 by treatment arm. Further exploratory analyses of EQ-5D-5L may include the calculation of the EQ-5D-5L utility index score to inform pharmacoeconomic modeling. Note these exploratory analyses will not be included in the Clinical Study Report (CSR).

4.6.8 Analyses of Subgroups of Interest

For the endpoints:

– Time to composite 12-week CDP

– Time to 12-week CDP in 9-HPT

– Time to 12-week CDP in EDSS

The following subgroup analyses of all randomized patients will be performed:

- ORATORIO like patients EDSS at screening $\leq$ 6.5 & Age at screening $\leq$55 & Disease duration from the onset of MS symptoms ($<$15 years in patients with an EDSS at screening$>$5.0,$<$ 10 years in patients with an EDSS at screening $\leq$5.0) vs other patients

All results will be summarized in a forest plot.

4.7 INTERIM ANALYSES

4.7.1 Planned Interim Analysis

There is no planned interim analysis.

4.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

The endpoint Annual rate of percent change from baseline in total volume of T2 lesions was changed to the endpoint Annual rate of change from baseline in radius of total volume of T2 lesions.

The endpoint Annual rate of percent change from baseline in total non-enhancing T1 lesion volume on MRI scan of the brain was changed to the endpoint Annual rate of change from baseline in radius of total non-enhancing T1 lesion volume on MRI scan of the brain.

The rationale for not considering the percent change from baseline is that certain patients might have zero lesions at baseline, in which case the percent change from baseline would be non-estimable. Moreover, the percent change from baseline in lesion could be highly skewed due to very small baseline values and hence would not follow a normal distribution. The radius transformation is applied as the RCRM model for the analysis relies on a normality assumption.

5. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

6. REFERENCES

Atkinson A, Kenward MG, Clayton T et al. Reference-based sensitivity analysis for time-to-event data, Pharmaceutical Statistics, 2019;18:645–58.

Banchereau J, Rousset F. Human B lymphocytes: phenotype, proliferation, and differentiation. Advances in Immunology, 1992;52:125−262

Brooks R, on behalf of the EuroQol Group. EuroQol: the current state of play. Health Policy. 1996;37:53–72.

EuroQol Group (1990). EuroQol--a new facility for the measurement of health-related quality of life. Health policy (Amsterdam, Netherlands), 16(3), 199–208.

Guideline on Multiplicity Issues in Clinical Trials. European Medicines Agency, 2017 https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-multiplicity-issues-clinical-trials_en.pdf

Guidance for Industry: Multiple Endpoints in Clinical Trials. U.S. Food and Drug Administration, 2022 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials

Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research. 2011 Dec;20:1727-36.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-1727.

National Institute of Neurological Disorders and Stroke (NINDS). User Manual for the Quality of Life in Neurological Disorders (Neuro-QoL) Measures, Version 2.0, 2015.
https://www.healthmeasures.net/administrator/components/com_instruments/uploads/Neuro-QOL_User%20Manual%20v2_24Mar2015.pdf

Oxford Grice KA, Vogel KA, Le V, et al. Adult Norms for a Commercially Available Nine Hole Peg Test for Finger Dexterity. The American Journal of Occupational Therapy, 2003; 57: 570-73.

Sahai H and Khurshid A. Confidence intervals for the mean of a Poisson distribution: A review. Biometrical Journal, 1993;35:857-67

Spiessens B and Debois M. Adjusted significance levels for subgroup analyses in clinical trials. Contemporary Clinical Trials, 2010;31:647–656. https://pubmed.ncbi.nlm.nih.gov/20832503/

Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurology, 2018;17:162–73

Signature Page for Statistical Analysis Plan- Study WA40404 v2 - Published
System identifier: RIM-CLIN-1000265

Approval Task	[redacted] Company Signatory 04-Mar-2025 08:24:38 GMT+0000