Official Title: A Phase III Multicenter, Randomized, Double-blind, Double-dummy Study to Evaluate Safety and Efficacy of Ocrelizumab in Comparison with Fingolimod in Children and Adolescents with Relapsing-Remitting Multiple Sclerosis

NCT Number: NCT05123703

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A PHASE III MULTICENTER, RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY STUDY TO EVALUATE SAFETY AND EFFICACY OF OCRELIZUMAB IN COMPARISON WITH FINGOLIMOD IN CHILDREN AND ADOLESCENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS**

STUDY NUMBER: WN42086

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This SAP was developed based on Roche SAP model document V3.0, 1 May 2024.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	9 Nov 2024	6.0, 8 May 2024
2	See electronic date stamp on the last page of this document	6.0, 8 May 2024

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
1.1	Two exploratory endpoints have been added: • Protocol defined ARR by Week 96 • Number of new or enlarging T2 lesions at Weeks 48 and 96	To fulfill the EU PIP key binding elements
2.1	Justification of non-inferiority margin has been added.	For clarity
4.2.3	The condition of more than 5% of patients in ocrelizumab arm withdraw from treatment has been removed. The methodology of tipping point analysis has been added.	The sensitivity will be performed regardless of the rates of treatment discontinuation as suggested by FDA.
4.4.4	Descriptive statistics have been added.	For clarity
4.5.1.3	Treatment duration of ocrelizumab/placebo and fingolimod/placebo have been updated. Both end dates have been updated to treatment withdrawal or CCOD.	For consistency

Additional minor changes have been made throughout to improve clarity and consistency.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AESI	Adverse Event of Special Interest
ALT	alanine transaminase
AST	aspartate transaminase
ARR	annualized relapsed rate
CCOD	clinical cut–off date
CD	cluster differentiation
CDP12	time to onset of 12–week confirmed disability progression in EDSS
CDP24	time to onset of 12–week confirmed disability progression in EDSS
CI	confidence interval
CSDMT4	time to onset of 24–week confirmed 4-point worsening in the Symbol Digit Modalities Test
CSDMT8	time to onset of 24–week confirmed 8-point worsening in Symbol Digit Modalities Test
DBP	double–blind period
DMT	disease-modifying therapy
eCRF	electronic Case Report Form
EDSS	Expanded Disability Status Scale
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level
FDA	Food and Drug Administration
Gd	gadolinium
HR	hazard ratio
iDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRR	infusion related reaction
IxRs	Interactive Voice/Web-Based Response System
IV	intravenous
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
OLE	open-label extension
OI	opportunistic infection
PD	pharmacodynamic

Abbreviation or Term	Description
PK	pharmacokinetic
PO	per oral
POMS	pediatric onset multiple sclerosis
PPMS	primary progressive multiple sclerosis
PRO	Patient-Reported Outcomes
PT	preferred term
QD	once a day
RMS	Relapsing multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
RoW	Rest of World
SAE	serious adverse events
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SFU	safety follow–up
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
T1 Gd	T1 gadolinium
TEAE	treatment emergent adverse event
U.S.	United States

1. INTRODUCTION

The analyses described in this Statistical Analysis Plan (SAP) will supersede those specified in Protocol WN42086 for the purposes of a regulatory filing.

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and degenerative disease of the Central Nervous System that affects approximately one million people in the United States (U.S.) and 2.8 million people worldwide (Wallin et al. 2019; Walton et al. 2020).

Pediatric onset multiple sclerosis (POMS) is rare, with between 3%-5% of patients with MS experiencing their first symptom before reaching the age of 18 years (Chitnis et al. 2012). Its incidence varies according to countries and is estimated around 0.66 to 1.66/100 000 children less than 16 to 18 years old. Most POMS patients are diagnosed during adolescence and are thus "pediatric" for only a few years.

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets and eliminates cluster differentiation (CD)20-expressing B cells, which are believed to play a critical role in MS. Ocrelizumab has been approved for the treatment of both relapsing and primary progressive forms of MS. The clinical studies that were used to support the approval and consisted of two identical Phase III studies in patients with relapsing multiple sclerosis (RMS) (WA21092, OPERA I and WA21093, OPERA II) and one Phase III study in patients with primary progressive multiple sclerosis (PPMS) (WA25046, ORATORIO). These double-blinded control Phase III Studies have been completed. Patients who completed the open–label extension (OLE) of Studies WA21092, WA21093 and WA25046 were allowed to roll over in Study MN43964 (OLERO) to continue treatment with ocrelizumab and for continuation of long-term safety and efficacy data. Phase IIIb and Phase IV studies are planned or ongoing.

The efficacy results from this Phase III program in RMS and in PPMS have generated compelling evidence that in addition to acting on annualized relapse rate (ARR), ocrelizumab has consistent efficacy in slowing disability progression. Regarding safety, in adults, ocrelizumab demonstrates a favorable overall safety profile for over 10 years.

Preventing the accrual of irreversible neurological impairment is a key goal of MS therapy. It is particularly important in pediatric patients where the onset of the disease is much earlier, and patients reach higher Expanded Disability Status Scale (EDSS) milestones at a younger age than in adult-onset MS.

Changes to the protocol-planned analyses are described in Section 4.7.

1.1 TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

This randomised double-blind, double-dummy study will evaluate the safety and efficacy of ocrelizumab compared with fingolimod in children and adolescents with Relapsing

remitting multiple sclerosis (RRMS) aged ≥ 10 to < 18 years over a flexible duration. The double-blind period will last until after the last patient randomised has completed 24–weeks. Primary analysis will comprise of all data up to the date of last patient randomised having completed 24–weeks.

Specific objectives and corresponding endpoints for the study are provided in Table 1. Except where stated, baseline refers to assessments performed at the Day 1 visit.

Table 1 Primary and Secondary Objectives and Corresponding Estimands

Objective	**Estimand Definition**
Key Primary Objectives	Estimand Definition

To demonstrate non-inferiority of ocrelizumab compared with fingolimod	• Population: patients with RRMS aged between ≥ 10 and < 18 years. The analysis population will consist of all randomised patients (approximately 171 patients), with patients grouped according to their assigned treatment
	• Endpoint: the number of protocol-defined relapses during the double-blind treatment period from when patients having initiated study treatment
	• Intercurrent events and handling strategies:
	  • Premature discontinuation from treatment: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, with the exception of subsequent data used to confirm protocol-defined relapse; assuming the future event rate follows the nature behave as observed in the period before withdrawing from treatment hence no imputation will be performed
	  • Initiation of another MS disease-modifying therapy (DMT) medication: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis and no imputation will be performed.
	• Population–level summary: rate ratio of protocol-defined ARR.

Key Secondary Objectives	Estimand Definition
To demonstrate non-inferiority of ocrelizumab compared with fingolimod	• Population: as defined above • Endpoint:

Objective	Estimand Definition
To demonstrate superiority of ocrelizumab compared with fingolimod	• number of new or enlarging T2-hyperintense lesions (T2 lesions) as detected by brain MRI during the double-blind period • Intercurrent events and handling strategies: as defined above • Population-level summary: rate ratio in annualized rate of new or enlarging T2-hyperintense lesions . • Population: as defined above • Endpoints: • Number of new or enlarging T2-hyperintense lesions (T2 lesions) as detected by brain MRI during the double-blind period • Number of T1 Gd lesions at Week 12 • Protocol-defined ARR during the double-blind period • Intercurrent events and handling strategies: as defined above • Population-level summary: • rate ratio of endpoints specified above • Rate ratio of annualized rate of new or newly enlarged T2 lesions • Rate ratio of gadolinium-enhancing T1 lesions per scan • Rate ratio of protocol-defined ARR.

ARR = annualized relapsed rate; DMT = disease-modifying therapy; Gd = gadolinium; MRI = magnetic resonance imaging; MS = multiple sclerosis; RRMS = relapsing remitting multiple sclerosis; T1 Gd = T1 gadolinium.

Table 2 Exploratory Objectives and Endpoints

Exploratory Objectives	Endpoints
To evaluate the efficacy of ocrelizumab compared with fingolimod	• Time to the first relapse (Kaplan-Meier proportion of relapse-free patients) • Time to the first new or enlarging T2 lesions (Kaplan-Meier proportion of patients free of new or enlarging T2 lesions) • Protocol defined ARR by Week 96

Exploratory Objectives	Endpoints
	• Number of new or enlarging T2 lesions at Weeks 48 and 96 • Change in total T2 lesion volume from baseline to Weeks 24, 48 and 96 • Change in total T1-hypointense lesion (T1 lesion) volume from baseline to Weeks 24, 48, and 96 • Change in the Symbol Digit Modalities Test (SDMT) from baseline to Weeks 48 and 96 • Time to 24–week confirmed 4-point worsening in the SDMT • Time to onset of 24–week confirmed 8-point worsening in SDMT • Change from baseline in the EDSS at each scheduled visit during the double-blind period • Time to confirmed disability progression over the treatment period, defined as an increase of $\geq$ 1.0 point from baseline EDSS (when the baseline score is $\leq$ 5.5). Expanded Disability Status Scale will be confirmed at a regular scheduled visit at least 12–weeks and/or 24–weeks after the initial documentation of neurological worsening • Change in patient- and caregiver-reported Pediatric Quality of Life Inventory™ (PedsQL™) Generic Core Scale, Version 4.0, from baseline to Weeks 48 and 96 • Change in patient-reported fatigue, as measured by the PedsQL Multidimensional Fatigue Scale (domain scores and total score) from baseline to Weeks 48 and 96 • Change in EQ-5D-5L from baseline to Weeks 48 and 96 • Patient Global Impression of Change (PGIC) for fatigue, cognition, and overall MS symptoms at Weeks 48 and 96 • Caregiver Global Impression of Change (CaGI-C) for fatigue, cognition, and overall MS symptoms at Weeks 48 and 96 • Change in MS symptom severity and impact assessed by patient and caregiver interviews at Weeks 48 and 96

Exploratory Objectives	Endpoints
To measure disease activity	Severity of protocol-defined relapse Change in EDSS categories from baseline to at each scheduled visit (improvement/ stable/ deterioration) over the course of the study.

ARR = Annualized relapse rate; CaGI-C = Caregiver Global Impression of Change; EDSS = Expanded Disability Status Scale; EQ–5D–5L = European Quality of Life 5 Dimensions 5 Level Version; MS = multiple sclerosis; PGIC = Patient Global Impression of Change; PedsQL = Pediatric Quality of Life Inventory; SDMT = Symbol Digit Modalities Test.

Table 3 Other Objectives and Endpoints

Objectives	Endpoints
Safety Objectives and Endpoints	
The safety objective to evaluate the safety of of ocrelizumab compared with fingolimod	• Incidence and severity of adverse events • Change from baseline in vital signs and clinical significant abnormalities in ECG following study treatment administration • Change from baseline in clinical laboratory test results.
Pharmacokinetic and Pharmacodyamic Objectives and Endpoints	
The PK objective is to assess the pharmacokinetics of ocrelizumab in all children/adolescents enrolled in this study	Serum concentration of ocrelizumab at specified time points, and derived PK parameters via the population PK approach.
The PD objective is to characterize the ocrelizumab PD profile	B-cell levels in blood.
Immunogenicity Objectives and Endpoints	
The immunogenicity objective is to evaluate the immune response to ocrelizumab	Prevalence of ADAs at baseline and incidence of ADAs during the study.

ADA = anti–drug antibody; PK = pharmacokinetic.

1.2 STUDY DESIGN

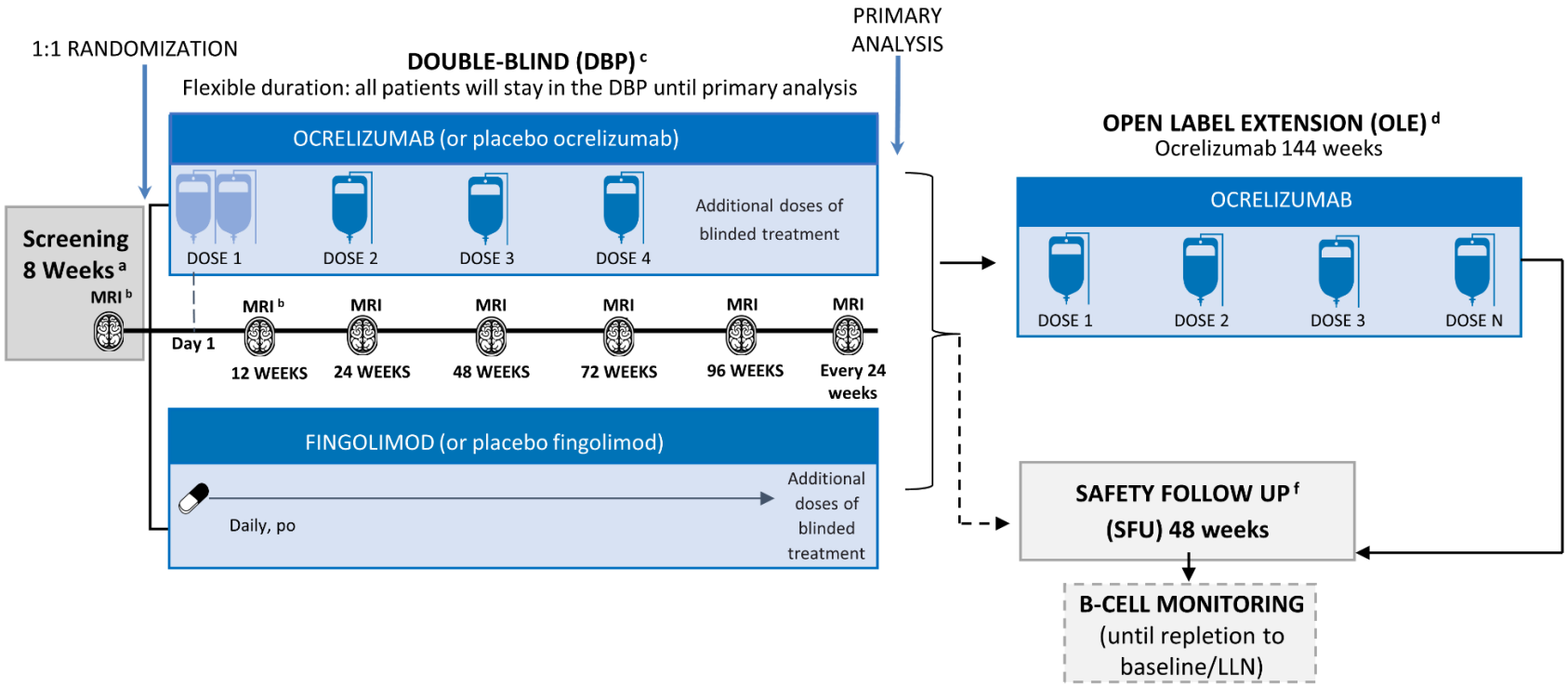
This Phase III randomised, double-blind, double-dummy, multicenter study will evaluate the safety and efficacy of ocrelizumab administered by IV infusion every 24–weeks compared with fingolimod taken per oral (PO) once a day (QD), in children and adolescents with RRMS aged ≥ 10 and < 18 years.

This study consists of the following study periods: a screening period, a double-blind period, an optional OLE period, and a safety follow–up (SFU) period. The study duration will vary for each patient, as described in Figure 1 and Table 4.

Figure 1 presents an overview of the study design. "The schedule of activities is available in the protocol Appendix 1". Table 4 provides an overview of the treatment assignment.

The clinical cutoff date (CCOD) will be approximately when the last randomised patient completes 24–weeks since first ocrelizumab/ocrelizumab placebo infusion. The total length of the study per patient, from screening to the end of the SFU, will vary from patient to patient because of the flexible duration of the double-blind treatment period, which depends on each patient's time point of inclusion during the enrollment period.

Figure 1 Study Schema



DBP = double-blind period; Gd = gadolinium; LLN = lower limit of normal; MRI = magnetic resonance imaging; OLE = open-label extension; SFU = safety follow-up.

[a] The screening period may be extended for relevant clinical, administrative, or operational reasons, but cannot exceed 10 weeks.

[b] Brain MRI with and without a Gd-contrast agent should be performed at Baseline and Week 12. Subsequent brain MRIs should be performed without Gd-contrast agent only.

[c] The double-blind period will continue for all patients until primary analysis (see Protocol Section 3.1.2). The primary analysis will be conducted after the last patient randomised has completed 24–weeks since first blinded ocrelizumab/ocrelizumab placebo infusion.

[d] Following database lock of the DBP, patients should continue to receive blinded treatment, as per Schedule of Assessments (see Table 1 in the Protocol), until the primary analysis is completed and the decision to start the OLE phase is communicated by the Sponsor. The OLE period will

last for at least 144 weeks and may be extended until the patient turns 18 years old (or as required per local regulation) or until commercial ocrelizumab is approved for children and available in the country for these patients, whichever occurs first (see Protocol Section 3.1.3).

[e] Patients in Group B switching from fingolimod to ocrelizumab must meet the eligibility criteria as per Protocol Section 4.1.3. The first dose of ocrelizumab will be administered as two half-dose IV infusions 14 days apart, and subsequent IV doses will be administered as single infusions every 24–weeks.

[f] Safety follow-up period will start after the double-blind period or the OLE period and last for at least 48 weeks, counting from the final ocrelizumab dose received (see Protocol Section 3.1.4).

Table 4 Overview of Treatment Assignment

Group	Double-Blind Period [a]						OLE Period [b]			SFU [c]
	Flexible Duration						At Least 144 weeks			48 weeks
	1st Dose		2nd Dose	3rd Dose	4th Dose	Additional Treatment Dose N (Every 24–weeks)	Open-Label Treatment Dose 1, 2, N (Every 24–weeks)			
	Day 1 Infusion	Day 15 Infusion	Week 24 Infusion	Week 48 Infusion	Week 72 Infusion	Week 96+ Infusions	Day 1 Infusion	Day 15 Infusion	Week 24+Infusion	
A Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	-	Ocrelizumab	-
	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily				
B Fingolimod	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily		Ocrelizumab		
	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab				

N = number of patients; OLE = open-label extension; SFU = safety follow-up.

Group	Double-Blind Period [a]						OLE Period [b]			SFU [c]
	Flexible Duration						At Least 144 weeks			48 weeks
	1st Dose		2nd Dose	3rd Dose	4th Dose	Additional Treatment Dose N (Every 24–weeks)	Open-Label Treatment Dose 1, 2, N (Every 24–weeks)			
	Day 1 Infusion	Day 15 Infusion	Week 24 Infusion	Week 48 Infusion	Week 72 Infusion	Week 96+ Infusions	Day 1 Infusion	Day 15 Infusion	Week 24+Infusion	
A Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	Ocrelizumab	-	Ocrelizumab	-
	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily	Placebo Fingolimod Daily				
B Fingolimod	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily	Fingolimod Daily		Ocrelizumab		
	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab	Placebo Ocrelizumab				

[a] The double-blind period will continue for all patients until primary analysis (see Protocol Section 3.1.2).

[b] Patients in Group B switching from fingolimod to ocrelizumab must meet the eligibility criteria as per Protocol Section 4.1.3. The first dose of ocrelizumab will be administered as two half-dose IV infusions 14 days apart, and subsequent IV doses will be administered as single infusions every 24–weeks. The OLE period will last for at least 144–weeks, or may be extended until the patient turns 18 years old (or as required per local regulation) or until commercial ocrelizumab is approved for children and available in the country for these patients, whichever occurs first (see Protocol Section 3.1.3).

[c] SFU period will start after the double-blind period or the OLE period and last for at least 48 weeks, counting from the final ocrelizumab dose received (see Protocol Section 3.1.4).

1.2.1 Treatment Assignment

This is a randomised, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been confirmed for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS). Eligible patients must be randomised through IxRS prior to receiving any study medication. Patients who discontinue treatment for any reason will not be replaced. Patients will be randomly assigned to one of two treatment arms: ocrelizumab plus fingolimod placebo (Group A) or fingolimod plus ocrelizumab placebo (Group B) (see Protocol Section 3.1.2). Randomization will occur in a 1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

Randomization will be stratified according to the following factors:

- Region (U.S. or Rest of World [RoW])
- Pre-pubertal status (yes vs. no)
- T1 gadolinium (Gd) lesions at baseline (yes or no); the baseline T1 Gd lesion is defined as screening magnetic resonance imaging (MRI).

Note: Pre-pubertal status is defined as a Tanner stage score <2.

1.2.2 Blinding

This study will be performed in a double-blind, double-dummy fashion. Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. The randomization list will be blinded and will remain blinded until the end of the double-blind period, i.e., until the time of the primary analysis (as defined in the SAP).

Patients, parents/legal guardians, investigators, and the sponsor will remain blinded to the original (randomised) treatment allocation of all patients until the primary analysis is completed and the primary results are available and communicated by the Sponsor. See Protocol Sections 4.2.3, 4.6.5, and 4.6.18 for additional measures.

To maintain integrity of the trial results and to prevent potential unblinding of the assigned arm during the double-blind period as a result of adverse events (AEs) or changes to laboratory results, several additional measures will be implemented until the time of the primary analysis, including a "dual assessor approach" (i.e., two blinded investigators per site: a treating investigator and an examining investigator) and an independent physician for the supervision of the first administration of study treatments; see Protocol Section 4.2.3 for details and definitions. 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,

IxRS service provider, independent Data Monitoring Committee (iDMC) members and sample handling staff at the external analytical laboratory facilities (not at sites).

Note: While PK and ADA samples will 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. Therefore, PK and ADA samples from patients assigned to the comparator arm will not be analyzed except on request (e.g., to evaluate a possible error in dosing).

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; however, the treatment code should not be broken except in emergency situations.

Prior to provision of treatment allocation information after the primary analysis, if the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly prior to unblinding. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

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 Protocol Section 5.7) 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, parent/legal guardian, 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.

1.2.3 Independent Pediatric Multiple Sclerosis Review

An independent review to confirm the diagnosis of pediatric RRMS will be performed by independent experts prior to any patient enrollment. The details of this review process will be described in a charter.

1.2.4 Data Monitoring

An external iDMC will be instituted to further protect the well-being of patients in the study. The iDMC will review safety data throughout the study until completion of the primary analysis. After the Sponsor is unblinded for the primary analysis, iDMC involvement in safety monitoring throughout the OLE period is no longer needed. The conduct of the iDMC will be detailed in the iDMC Charter.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The null hypothesis for the primary analysis will be tested at the $\alpha = 0.025$ level (one-sided test) with a non-inferiority margin of 3:

- H0 (null hypothesis): Protocol-defined ARR is higher in patients treated with ocrelizumab compared to patients treated with fingolimod, i.e., ocrelizumab is inferior to fingolimod in protocol-defined ARR

- H1 (alternative hypothesis): Protocol-defined ARR is not higher in patients treated with ocrelizumab compared to patients treated with fingolimod.

The non-inferiority margin of 3 can be justified using the lower bound of a 95% confidence interval from the PARADIGMS study. In a non-inferiority trial, a larger non-inferiority margin allows for a reduced sample size. Given the low incidence of pediatric MS and as a rare disease, this would increase the feasibility of this study (Chitnis et al. 2018).

If the upper bound of the 95% confidence interval (CI) of the rate ratio of ARR is smaller than the non–inferiority margin of 3, non-inferiority will be concluded.

The following secondary efficacy estimands will be tested according to the hierarchical order listed below, if the primary estimand and each preceding estimand have reached the significance level of 0.05:

1. Non-interiority of ocrelizumab compare with fingolimod based on the number of new or enlarging T2-hyperintense lesions as detected by brain MRI during the double–blind period with a non-inferiority margin of 1.27. A margin of 1.27 represents that ocrelizumab preserves 50% of the treatment effect. If the upper bound of the 95% CI of the rate ratio of annualized rate of new or enlarging T2 lesions is smaller than the non-inferiority margin of 1.27, non–inferiority will be concluded.

Superiority of ocrelizumab vs fingolimod will be tested in the hierarchical order listed below, if all preceding estimands have reached the significance level of 0.05:

1. Number of new or enlarging T2 lesions during the double-blind period
2. Number of T1 Gd lesions at Week 12
3. Protocol-defined ARR during the double-blind period.

All comparisons (non-inferiority and superiority tests) will be made in the hypothetical situation that patients neither withdraw from the study treatment nor start another MS disease-modifying therapy (DMT).

2.2 SAMPLE SIZE DETERMINATION

The sample size for this study was estimated based on data from ocrelizumab Phase III studies in adults with RMS (WA21092 OPERA I [NCT01247324] and WA21093 OPERA II [NCT01412333]) and from a fingolimod Phase III study in pediatric patients with MS (PARADIGMS [NCT01892722]).

The protocol-defined ARR in pediatric patients with MS treated with fingolimod is 0.12 (Chitnis et al. 2018). Assuming patients treated with ocrelizumab have the same ARR of 0.12 and a dispersion parameter of 1, a sample size of 171 patients in total (1:1 randomization allocation) is required for a non-inferiority margin of 3 at a power of 80% and a one-sided type I error rate of 2.5%, given a recruitment period of around 30 months, flexible duration of minimum follow up of 24–weeks and a drop-out rate of 3% per year.

3. ANALYSIS SETS

All efficacy endpoints will be analyzed using the full analysis set, which is described in Table 5. Table 5 also covers analysis sets relevant to the PK, immunogenicity, biomarker and safety objectives of this study.

Table 5 Analysis set

Analysis Set	Description
Full analysis set	All randomised patients, with patients grouped according to their randomised (assigned) treatment.
Immunogenicity analysis set*	All patients with at least one ADA assessment; participants will be grouped according to treatment received.
Pharmacokinetic analysis set*	All patients 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.
Safety analysis set	All randomised patients who receive at least one dose (partial or complete) of study drug (ocrelizumab or fingolimod), with patients grouped according to their actual treatment received.

ADA = Antidrug antibody; PK = pharmacokinetic.

* PK and ADA samples from patients assigned to the comparator arm will not be analyzed except on request (e.g., to evaluate a possible error in dosing) (Protocol Section 4.2.2).

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

For continuous variables, descriptive statistics (e.g., number of patients [n], mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, maximum) will be

calculated and summarized. For categorical variables, the number and percentage in each category will be displayed.

Full analysis set is used to estimate the primary estimand and the secondary estimand. Patients will be analyzed according to the treatment to which they were assigned.

Safety analysis set is used to present safety data. Patients will be analyzed according to the treatment to which they were assigned. Patients that received erroneously a mixture of treatments from both planned treatment arms will be excluded from their original randomized treatment and summarize separately.

Baseline refers to assessments performed at the Day 1 visit (within 48 hours of randomization), unless stated otherwise. Expanded Disability Status Scale will be performed prior to the ocrelizumab/ocrelizumab placebo infusion. Day 1 EDSS assessment on or prior to the date of the first study treatment will be considered as baseline. If Day 1 EDSS is missing, the screening EDSS will be considered as baseline. Magnetic resonance imaging performed during screening will be considered as baseline. Laboratory samples collected at the Day 1 visit prior to the time of the first study treatment will be considered as baseline. If missing, the latest laboratory data during screening period will be considered as baseline.

4.2 PRIMARY ESTIMAND ANALYSIS

Hypothesis test for the primary estimand is described in Section 2.1.

The definition of the primary endpoint is provided in Section 4.2.1. Five attributes of the primary estimand are provided in Section 4.2.2. Information on primary estimator, intercurrent events and their handling strategies as well as the handling of missing data are described in Section 4.2.2. Section 4.2.3 describe sensitivity and for the Primary Estimand. Section 4.2.4 describe the supplementary estimands.

4.2.1 Definition of Primary Endpoint

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 for at least 30 days. Symptoms must persist for $>$24 hours and should not be attributable to confounding clinical factors (e.g., fever, infection, injury, or 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 half a step on the EDSS score, or 2 points on one of the appropriate FS scores, or 1 point on two or more of the appropriate FS scores. The change must affect the selected FS (i.e., 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 the diagnosis of a relapse.

Protocol defined relapse will be derived programmatically based on the following steps:

1. Clinical relapse is reported on Adverse Event electronic Case Report Form (eCRF), and then once the box for "Is the event and MS Relapse" is ticked, the MS Relapse eCRF form will be activated
2. Check box for “Did the symptoms persist for >24 hours and were not attributable to confounding clinical factors (e.g. fever, infection, injury, adverse reactions to concomitant medications)” is checked ‘Yes’ on Clinical MS relapse event eCRF
3. Check if the first EDSS assessment at a visit (unscheduled or scheduled) on or after the onset date of the relapse is increased by $\geq$ half a step from the previous EDSS; OR selected FSS domains relevant to the relapse event (pyramidal, ambulation, cerebellar, brainstem, sensory, or converted visual) are increased by ≥ 2 points on one domain or ≥ 1 point on two or more domains. When deriving point 3 above do the following:
    - For EDSS/FSS, take the last EDSS/FSS score before each clinical relapse onset date
    - Then take the first EDSS/FSS score on or after each clinical relapse onset date.
4. If two adjacent protocol defined relapses are within 30 days (i.e., the onset dates are ≤ 30 days apart) then the later relapse is not a protocol defined relapse (even if criteria 1 to 3 are satisfied).

4.2.2 Main Analytical Approach for Primary Estimand

The primary efficacy objective is to demonstrate non-inferiority of ocrelizumab vs fingolimod in protocol-defined ARR, as measured through the rate ratio in counts during the double-blind treatment period, in the hypothetical situation that patients neither withdraw from the study treatment nor take any another MS DMT based on the following attributes:

a) Treatment: ocrelizumab administered by IV infusion every 24−weeks vs fingolimod taken PO QD.

b) Population: patients with RRMS aged between ≥ 10 and < 18 years. The analysis population will consist of all randomised patients (approximately 171 patients), with patients grouped according to their assigned treatment.

c) Variable: the number of protocol-defined relapses during the double-blind treatment period from when patients having initiated study treatment.

d) Intercurrent events will be handled as follows:
    - Premature discontinuation from treatment: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, with the exception of subsequent data used to confirm protocol-defined relapse; assuming the future event rate follows the nature behave as observed in the period before withdrawing from treatment hence no imputation will be performed.

- Initiation of another MS DMT medication: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis and no imputation will be performed.

e) Summary measure: rate ratio of protocol-defined ARR.

The treatment effect and ARR on each treatment arm will be estimated based on a negative binomial regression model with randomised treatment as the main effect and adjusted for the stratification factors (region [U.S. vs. RoW], pre-pubertal status (yes vs. no), and presence of T1 Gd lesions at baseline [yes vs. no]). The stratification factors are collected via electronic data capture system. Pre-pubertal is defined as Tanner stage score <2 collected in the eCRF. Presence of T1 Gd lesions at baseline [yes vs. no] recorded in NeuroRX will be used for analysis. The response variable is the number of protocol-defined relapses during the double-blind period for each patient. The log-transformed exposure for each patient will be included in the model as an offset variable in order to adjust for varying duration of follow-up. For patients who discontinue the study treatment early, only data collected before the early treatment discontinuation will be included in this analysis (with the exception of subsequent data used to confirm protocol defined relapse); no imputation of missing data will be performed.

The ratio of the protocol-defined ARR between ocrelizumab and fingolimod will be presented, together with the 95% confidence interval (CI) of rate ratio. The non-inferiority will be established if the upper bound of the 95% CI of the ARR ratio is smaller than 3.

4.2.3 Sensitivity Analyses

To assess the robustness of the estimated treatment effect to the proposed missing data handling strategy for missing data due to early treatment discontinuation, a tipping point analysis will be performed. Missing data from each treatment arm will be imputed based on the "missing at random" assumption, and then a penalty will be added to the imputed data in the respective arm in the following steps.

1. Predict the event rate for each patient based on their treatment arm and stratification factors using the negative binomial model.

2. Apply a penalty by multiplying the event rate by a parameter ranging from 1.33 to 1.99 in increments of 0.33.

3. Simulate the number of relapses patients would have experienced during the unobserved period (from the time of treatment withdrawal until CCOD) for patients who withdrew treatment early using the penalized event rate and a Poisson process for each simulation.

4. Repeat the simulation 100 times to account for variability.

5. Combine results using Rubin's rules to estimate the treatment effect and the corresponding standard error.

4.2.4 Supplementary Analyses

The following supplementary analyses will be conducted:

1) The primary estimand as described in Section 4.2.2 will be repeated but using a treatment policy strategy for the intercurrent event of treatment discontinuation to estimate the treatment effect of ocrelizumab versus fingolimod regardless of adherence to the randomised treatment. All data collected during the double-blind period will be included in the analysis. For premature study discontinuation, multiple imputation of missing data based on trajectories from patients within the same treatment arm who withdraw from treatment but remain in the study will be performed. The supplementary analysis will be performed only if more than 5% patients within the same treatment arm who withdraw from treatment but remain in the study for valid imputation

2) The primary estimand as described in Section 4.2.2 will be repeated with treatment effect being estimated and adjusted for pre specified stratification factors and neurological stability for $\geq$ 30 days [yes vs no]. Patients not neurologic stable is defined as patients experiencing relapse between 30 days prior to screening and the date of randomization. Relapse occurred prior to screening is collected in eCRF-MS History page. Patients will be considered as not neurologic stable if the end date of most recent relapse is between 30 days prior to screening and the date of randomization. If the end date is missing, the patient would be considered as not neurological stable

3) The primary estimand will be repeated after excluding patients who meet the following exclusion criteria/do not meet the following eligibility criteria at baseline:

- Age $<$ 10 or $\geq$ 18 years at randomization
- Unconfirmed diagnosis of Pediatric RRMS by the Independent Pediatric MS review Committee including:
  - Known presence or suspicion (based on clinical or laboratory parameters) of other neurologic disorders that may mimic MS
  - In case of an acute disseminated encephalomyelitis (ADEM) like appearance of the first MS relapse, a second relapse with clear MS like features is required
  - Clinical or laboratory findings at first presentation not typically for MS, such as signs of infection; signs of encephalopathy such as confusion, convulsion, reduced state of consciousness
  - Abnormal findings in the cerebrospinal fluid (CSF) at first MS presentation: Protein $>$ 100 mg/dL. Pleocytosis $>$ 50 cells/mm^3. Presence of neutrophils

or eosinophils above the normal reference range per local laboratory, or atypical cells

  - Atypical MRI findings: ADEM-like presentation of lesions; lesions in atypical location for MS; bilateral optic neuritis; extensive spinal cord lesions ($\geq$3 spinal segments)

- EDSS $>$ 5.5
- Patients without disease activity defined as follow: At least one relapse during the year prior to screening or two relapses in the previous two years prior to screening or evidence of at least one Gd-enhancing lesion on MRI within 6 months prior to randomization (criteria more stringent for patients from Germany)
- Pregnant or lactating patients, including positive serum beta-human chorionic growth hormone (b-hCG) measured at screening, or positive pregnancy test prior to the first infusion of ocrelizumab
- Patients that are aquaporin-4 positive and/or myelin oligodendrocyte glycoprotein antibody positive
- Patients with significant uncontrolled somatic diseases or any other significant condition that may preclude patient from participating in the study
- Patients having received prior treatment with any investigational agent within 24−weeks of screening or 5 half−lives, whichever is longer
- Patients having received prior treatment with B-cell−targeted therapies (i.e., rituximab, ocrelizumab, obinutuzumab, atacicept, belimumab, or ofatumumab)
- Patients having received prior treatment with alemtuzumab, anti-CD4, cladribine, mitoxantrone, daclizumab, laquinimod, total body irradiation, or bone marrow transplantation
- Patients having received prior treatment with any other immunomodulatory or immunosuppressive medication not already listed above without appropriate washout as described in the applicable local label
- Patients having received treatment with natalizumab within 12 months prior to randomization
- Patients having received treatment with teriflunomide within 24−weeks prior to treatment allocation (4 weeks if patients performed the accelerated elimination procedure after confirmation of plasma level $<$ 0.02mg/L)
- Patients having received prior treatment with fingolimod
- Patients having received treatment with any other S1P receptor modulator (e.g., BAF312/siponimod) within 24−weeks prior to treatment allocation
- Patients having received treatment with dimethyl fumarate within 4−weeks prior to treatment allocation and lymphocyte count $<$ LLN for age- and sex-specific reference range
- Patients having received treatment with intravenous immunoglobulin within 12−weeks prior to treatment allocation

- Patients having received treatment with plasmapheresis within 4 weeks prior to treatment allocation
- Patients who did not complete systemic corticosteroid therapy within 7 days prior to treatment allocation.

4.2.4.1 Subgroup Analyses for Primary Estimand

The primary and key secondary efficacy estimands will be presented for the following subgroups:

- Stratification factor: region (U.S. vs. RoW)
- Stratification factor: pre-pubertal status (yes vs. no)
- Stratification factor: presence of T1 Gd lesions at baseline (yes vs. no)
- Demography: baseline weight ($\geq$35 kg vs. $<$35 kg)
- Demography: baseline age ($\geq$14 years old vs. $<$14 years old)
- Time of enrollment: enrollment time (early vs. late) randomised 1 year prior to CCOD vs within a year of CCOD
- Wash out period of prior corticosteroids use: $>$30 days prior to randomization vs $\leq$30 days prior to randomization.

Summaries of the primary and secondary estimand by these subgroups and associated 95% CIs will be presented in forest plots.

4.3 SECONDARY ESTIMANDS ANALYSIS

Hypothesis tests for the secondary estimands will be conducted in a hierarchical order predefined in Section 2.1. Each test will be at a significant level of 0.05 without adjustment. Only all the preceding estimands have reached the significant level of 0.5, will the next test on the hierarchical sequence be performed. For the non-inferiority test, the 95% CI will be reported. The non-inferiority will be established if the upper bound of the 95% CI is less than the margin. For superiority test, the p-value of 0.05 or less is interpreted as confirmatory, otherwise it is reported as non-confirmatory. Further details on the estimands attributes and estimation methods (i.e., estimators) are provided below.

4.3.1 Secondary Estimands

All secondary estimands which focus on the analysis of rate ratio have the same estimand attributes as provided below.

Endpoints:

- Number of new or enlarging T2 lesions during the double-blind period: including data at each scheduled visit as well as withdraw treatment visit (if applicable)
- Number of T1 Gd lesions at Week 12: patient withdraw before Week 12 will be treated as missing T1 at Week 12 and no imputation will be performed

- Protocol-defined ARR during the double-blind period.

The secondary estimand follows a hypothetical strategy that patients neither withdraw from the study treatment nor take another MS DMT based on the following attributes:

a) Treatment: ocrelizumab administered by IV infusion every 24–weeks vs fingolimod taken PO QD

b) Population: patients with RRMS aged between ≥ 10 and < 18 years. The analysis population will consist of all randomised patients (approximately 171 patients), with patients grouped according to their assigned treatment

c) Variable: total count of endpoints specified above during the double-blind treatment period from when patients having initiated study treatment

d) Intercurrent events will be handled as follows:

   - Premature discontinuation from treatment: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, with the exception of subsequent data used to confirm protocol-defined relapse; assuming the future event rate follows the nature behave as observed in the period before withdrawing from treatment hence no imputation will be performed
   - Initiation of an MS DMT medication: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis and no imputation will be performed.

e) Summary measure and primary estimator: The rate ratio will be used to quantify the difference in counts. A negative binomial model will be fitted to the total count during the double-blind treatment period. The mean function of the model will be parameterized using the log link function and the linear predictor will include log–transformed exposure for each patient as an offset (except the endpoint of T1 Gd lesions at Week 12), and 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.

4.4 EXPLORATORY ANALYSIS

This section defines estimands for exploratory efficacy endpoints listed in Table 2.

4.4.1 Definition of Confirmed Disability Progression

Time to onset of 24–week confirmed 4-point worsening in the Symbol Digit Modalities Test (CSDMT4) is defined as 24–week confirmed decrease of 4–points on SDMT from baseline.

Time to onset of 24–week confirmed 8-point worsening in SDMT(CSDMT8) is defined as 24–week confirmed decrease of 8–points on SDMT from baseline.

Time to onset of 12–week confirmed disability progression in EDSS (CDP12) is defined as a 12-week confirmed increase of one step on EDSS from baseline in patients with a

baseline EDSS score of $\leq$5.5 or a 12−week confirmed increase of half a step in patients with a baseline EDSS score of $>$5.5.

Time to onset of 24−week confirmed disability progression in EDSS (CDP24) is defined as a 24-week confirmed increase of one step on EDSS from baseline in patients with a baseline EDSS score of $\leq$5.5 or a 24−week confirmed increase of half a step in patients with a baseline EDSS score of $>$5.5.

4.4.2 Estimand for Time-to-Event Endpoints

Estimand: The estimand is the difference in endpoint, as expressed by the hazard ratio (HR), between ocrelizumab administered by IV infusion every 24−weeks vs fingolimod taken PO QD, and only data collected before withdraw from treatment will be included in the analysis.

Endpoints:

- Time to the first protocol defined relapse (Kaplan-Meier proportion of relapse-free patients)
- Time to the first new or enlarging T2 lesions (Kaplan-Meier proportion of patients free of new or enlarging T2 lesions)
- Time to onset of 24−week confirmed 4-point worsening in the Symbol Digit Modalities Test (CSDMT4).
- Time to onset of 24−week confirmed 8-point worsening in SDMT(CSDMT8).
- Time to onset of 12−week confirmed disability progression in EDSS (CDP12).
- Time to onset of 24−week confirmed disability progression in EDSS (CDP24).

Summary Measure and Primary Estimator: The Kaplan-Meier estimates will be used to quality the difference in time to first event between study treatments. The HR estimated from a Cox proportional hazards model, stratified by the for the stratification factors (region [U.S. vs. RoW], pre-pubertal status (yes vs. no), and presence of T1 Gd lesions at baseline [yes vs. no]), will be used to quantify the difference in time to onset of CSDMT24 / CDP12/ CDP24 between study treatments. For all endpoints, the statistical significance between study treatments will be tested using the log rank test.

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

- **Early discontinuation from study treatment**: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, with the exception of subsequent data used to confirm protocol-defined relapse, no imputation will be performed
- **Initiation of an MS DMT medication**: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, no imputation will be performed.

4.4.3 Estimand for Continuous Endpoints at Scheduled Visits

Estimand: The estimand is the mean difference in the endpoint between ocrelizumab administered by intravenous infusion every 24−weeks vs fingolimod taken PO QD, and only data collected before withdrawing from treatment will be included in the analysis.

Endpoints:

- Change in the SDMT from baseline to Weeks 48 and 96
- Change from baseline in the EDSS at each scheduled visit during the double-blind period

Summary Measure and Primary Estimator: Mixed model for repeated measures will be used to quantify mean difference in the endpoints between the ocrelizumab and fingolimod arms. The fixed effects in the model will include independent variables of randomised treatment, visit (nominal post-baseline visits as per the Schedule of Assessments), 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-patient errors, if non-convergence, a compound symmetry covariance structure can be used. The restricted maximum likelihood method will be used for estimation of variance components. 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:

Early discontinuation from study treatment: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, no imputation will be performed.

Initiation of MS DMT medication: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, no imputation will be performed.

Change from baseline to each scheduled visit will be summarized. Mixed model for repeated measures will be applied to visits. Missing data resulting from patients that withdraw their consent to participate in the study and/or a serious Good Clinical Practice will not be imputed (including following death).

4.4.4 Estimand for Annual Rate of Change from baseline in radius of total lesion volume

Estimand: The estimand is the mean difference in annual rate of change from baseline in radius of total lesion volume between patient with ocrelizumab administered by intravenous infusion every 24−weeks vs fingolimod taken PO QD, in the hypothetical

situation that patients neither withdraw from the study treatment nor take any another MS DMT.

Endpoints:

- Change in total T2 lesion volume from baseline to Weeks 24, 48 and 96
- Change in total T1-hypointense lesion (T1 lesion) volume from baseline to Weeks 24, 48, and 96.

Estimator: A random coefficient regression model will be used to quantify the mean difference in annual rate of change from baseline in radius of total lesion volume between the ocrelizumab and fingolimod arms. The mean structure of the model is as follows

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

where Y_{ij}represents change in the cube root of total lesion volume 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 lesion 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 change in radius of total lesion volume for the fingolimod arm,β_1 is the adjusted mean difference in the annualized rate of change in radius of total lesion volume between the ocrelizumab and fingolimod arms, and μ_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. The mean, median, SD, and minimum and maximum values of the change in total T2 lesion volume from baseline to Weeks 24, 48, and 96 as well as of change in T1-hypointense lesion volume from baseline to Weeks 24, 48, and 96 will be presented.

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

Early discontinuation from study treatment: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, no imputation will be performed.

Initiation of MS DMT medication: Hypothetical strategy, only data collected before this intercurrent event will be included in the analysis, no imputation will be performed.

4.4.5 Analysis for PRO Endpoints at Scheduled Visits

The analysis population will consist of all patients with at least PRO assessment. Patients will be grouped according to treatment received, if no treatment is received prior

to study discontinuation, according to treatment assigned. Summary statistics at baseline and Weeks 48, and 96 as well as difference from baseline to Week 48, difference from baseline to Week 96 for each treatment group will be provided; no formal statistical testing will be performed.

- Change in patient- and caregiver-reported Pediatric Quality of Life Inventory™ (PedsQL™) Generic Core Scale, Version 4.0, from baseline to Weeks 48 and 96
- Change in patient-reported fatigue, as measured by the PedsQL Multidimensional Fatigue Scale (domain scores and total score) from baseline to Week 48 and 96
- Change in EQ-5D-5L from baseline to Weeks 48 and 96
- Patient Global Impression of Change for fatigue, cognition, and overall MS symptoms at Weeks 48 and 96
- Caregiver Global Impression of Change for fatigue, cognition, and overall MS symptoms at Weeks 48 and 96
- Change in MS symptom severity and impact assessed by patient and caregiver interviews at Weeks 48 and 96.

4.4.6 Disease Activity

The analysis population will consist of all randomised patients (approximately 171 patients), with patients grouped according to their assigned treatment. The disease characteristics will be summarized and listed, unless otherwise stated.

Change in EDSS categories from baseline to at each scheduled visit will be summarized at patient level.

- EDSS change categories (improvement/ Stable/ Deterioration). The definition is as follows:
  - Improvement: decrease from baseline ≥ 1.0.
  - Stable: change from baseline between (inclusive) -0.5 to 0.5.
  - Deterioration: increase from baseline ≥ 1.0.

The following measures of protocol defined-relapse characteristics will be summarized at relapse level using descriptive statistics.

- Severity (Mild/Moderate/Severe), the severity of protocol defined relapses will be derived according to the criteria below.

Mild relapse	**Moderate relapse**	**Severe relapse**
EDSS increase of 0.5 point	EDSS increase of 1 to 2 points	Exceeding Moderate criteria
Or	Or	Or
2-points on one FS scales	2-points on two to three FS scales	Exceeding Moderate criteria
Or	Or	

Mild relapse	Moderate relapse	Severe relapse
1-point on two or three FS scales	1-point change in four or more FS scales	

EDSS = Expanded Disability Status Scale; FS = functional system.
(Panitch et al. 2002)

- Grading as per CTCAE
- Steroid used (yes/no),
- Hospitalization (yes/no),
- Outcome (Fatal, Not Recovered/Not Resolved, Recovered/Resolved, Recovered/Resolved with Sequelae, Recovering/Resolving, Unknown)
- Duration of relapse (days).

4.5 SAFETY ANALYSES

The Safety analysis set will consist of all patients (approximately 171 patients) who receive at least one dose (partial or complete) of study drug (ocrelizumab or fingolimod) and is described in Section 3. All safety parameters will be summarized and presented in tables based on this analysis set. Randomised patients who receive incorrect therapy will be excluded from their original randomized treatment and summarized separately.

Safety data will be summarized by treatment arm regardless of premature study treatment discontinuation but until switch to another DMT (including ocrelizumab or commercial fingolimod) during the double-blind period.

Safety will be assessed through summaries of exposure to study treatment, the incidence and nature of all AEs, changes in laboratory test results, changes in vital signs, changes in ECG. Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics. 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, adverse events of special interest (AESI), 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.

Note that, due to the nature of the study drugs potentially leading to related AEs, safety monitoring of the first dose (and re–initiation of fingolimod/placebo after interruption) is performed by an Independent Physician and his/her independent team at site. Corresponding safety data (Adverse events, Concomitant Medication or Procedures) will be recorded in a separate database in which potentially unblinded information will be collected. Should AEs not resolve by the time the Independent team hands over the patient to the Blinded team, then this safety data will be reported as Not Recovered/Not Resolved in the database, and AEs and Concomitant Medication will be transferred to the Blinded database for the Treating physician (PI) to continue monitoring the safety of the patient (see Appendix 1: WN42086 Handover Form_Version 2.0). This may lead to duplicate data entries since it will be reported in both databases. As a result, the total number of AE might be over reported. However, based on the safety profiles of both study drugs, the expectation is that majority, if not all, of the AEs will resolve prior to the date when the patient is handed over to the blinded team. The total number of handed over AEs will be summarized and indicated in the AE listing.

4.5.1 Extent of Exposure

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

4.5.1.1 Definition of the Number of Doses and Total Dose Received

The first dose of ocrelizumab or ocrelizumab placebo 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 an infusion is completely missed instead of delayed, the next dose number will be consecutive to the previous dose. Split infusions of one delayed dosing will be counted as one dose. All ocrelizumab or ocrelizumab placebo will be administered at the study site.

The first dose of fingolimod will be administered at the study site. The subsequent fingolimod in bottles/blisters will be either be dispensed at the study site or delivered to the patient at their home address. At the Dispense fingolimod/placebo and compliance check visit, fingolimod will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. Patient compliance of daily administration of fingolimod will be monitored via reconciliation of medications returned to site at each visit (i.e., every 12–weeks). At each visit, the total number of capsules taken, and total number of capsules returned between two study visits will be entered to eCRF by site. If the exact number of capsules taken is not known, a best estimate will be recorded based on the number of days in dosing period and the number of reported missed dose.

4.5.1.2 Definition of the Fingolimod compliance

Fingolimod compliance at scheduled visit is defined as number of capsules taken counted by site at schedule visit divided by duration of dispense kits to be used $\times$ 100%. Example., the first dose of fingolimod/placebo was administered on 11 September 2023.

The Week 12 visit occurred on 6 December 2023. The patient took fingolimod/placebo on the date of scheduled visit. At the visit of Week 12, the start date administered and end date administered in the Administration of Fingolimod/Placebo eCRF were recorded as 11 September 2023 and 6 December 2023, respectively.

- Number of days between the Baseline and Week 24 visits: 11 September 2023 to 6 December 2023 = 85 days
- Number of capsules taken between visits: 81 capsules taken.

Compliance (%) at Week 12 = (Capsules taken / Number of days) × 100% = 81 / 85 × 100% = 95%

Overall fingolimod compliance is defined as the sum of number of total capsules taken divided by the days of (Date of the withdraw from treatment during the Data Blind Period (DBP) or CCOD, whichever earlier, − Date of first fingolimod dose in DBP + 1)/7.

4.5.1.3 Definition of the Treatment Duration and Exposure

Ocrelizumab/placebo

Treatment duration for ocrelizumab/placebo will be calculated as date of treatment withdrawal or CCOD, whichever is earlier, minus the date of the first infusion plus one day.

The following measures of ocrelizumab/placebo exposure will be summarized using descriptive statistics:

- Treatment duration in weeks as continuous and categorical (0–24, 24-48, 48-72, 72-96…)
- Treatment duration in years as categorical (0–1, 1-2, …)
- Number of doses
- Total cumulative dose (mg) as continuous.

Fingolimod/placebo

Treatment duration for fingolimod/placebo will be calculated as date of treatment withdrawal or CCOD, whichever is earlier, minus the date of the first dose plus one day.

The following measures of fingolimod/placebo exposure will be summarized using descriptive statistics:

- Treatment duration in weeks as continuous and categorical (0–12, 12–24, 24–36…)
- Treatment duration in years as categorical (0–1, 1-2, …)
- Compliance (≥80%, <80%) every 12–weeks as well as during DBP
- Total cumulative dose (mg) as continuous

- Number of dose interruptions as continuous.

Exposure

The exposure (time at risk) in years will be calculated as [(Date of last known alive−Date of first exposure to the study treatment)+1] / 365.25.

The date of the last known alive is defined as (1) last date of treatment administration where patient received a valid dose (2) last complete date of lab assessment with a valid test result (3) last complete onset date of AEs (4) last complete end date of AEs (5) death date (6) date of last contact, whichever the latest.

The exposure (time at risk) will be applied to each safety endpoint. All safety data until CCOD will be reported.

4.5.2 Adverse Events

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 (the "System Organ Class" [SOC]) on the basis of the MedDRA dictionary of terms version 27.0.

Definitions

Treatment-emergent adverse event (TEAE): Adverse Events with an observed or imputed date of onset on or after the start date of trial treatment. 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.

Imputation of incomplete date: in order to evaluate if an AE is treatment-emergent, incomplete dates will be imputed as follows:

- If the start date is incomplete:
  - If the day is missing, impute to 1, or to the day of first dose of ocrelizumab if the month and year is the same as the dosing date.
  - If the month is missing, impute to January, or to the month of first dose of ocrelizumab if the year is the same as the year of dosing.
  - If the date is completely missing, then the date will remain missing
- If the end date is incomplete:
  - If the day is missing, impute to the last day of the month
  - If the month is missing, impute to December

– If the date is completely missing, then the date will be missing.

If the imputed start date of an AE is post first dose, it is considered treatment emergent. If the imputed stop date of an AE is prior first dose, it is considered non-treatment emergent.

Serious Adverse Events: Serious Adverse Event is defined using 'Is the event non–serious or serious' from the Adverse events CRF page.

Adverse Events of Special Interest:

- Cases of potential medicine-induced liver injury that include an elevated alanine transaminase (ALT) or aspartate transaminase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law and in the protocol
- Suspected transmission of an infectious agent by the study medicine, as defined in the protocol.

Output Conventions

All AE summaries will be based on TEAEs only. For all summary tables, the AEs will be sorted by SOC (in decreasing order of overall incidence) and then by PT (in decreasing order of overall incidence). Within each level of SOC and PT, patients reporting more than one AE will be counted only once. For AEs by grade (intensity), the highest grade of the same AE in an individual will be reported. Additionally, the most frequent AEs (≥1%) will be presented by SOC and PT.

For SAEs, 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.

AESIs will be listed.

A patient may experience an AE that leads to the discontinuation of his/her study treatment. Note that relapse leads to discontinuation is reported as lack of efficacy. Patients who withdraw early from the study treatment because of AEs will be summarized under disposition. The number of patients who experienced an AE that led to discontinuation of study treatment 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 (multiple occurrences of the same AE in 1 patient will be counted only once).

The rate per 100 patient-years by treatment group (along with the 95% CI using the exact method based on the Poisson distribution) will be calculated for 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).

All patient deaths will be listed.

4.5.3 Infusion Related Reactions

The occurrence of an infusion related reaction (IRR) is collected in the AE eCRF and its corresponding symptoms are collected on the dedicated eCRF.

The symptom(s) of an IRR may be of different intensities. Symptoms will be coded in the MedDRA and summarized by PTs. The intensity of an IRR is defined as the most extreme intensity among the symptoms.

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 patient will be summarized across the treatment doses.

Onset times of IRRs, if known, are recorded on the eCRF. 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 investigational medicinal product [IMP] infusion, Time not available).

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

Symptoms of IRRs and symptoms of serious IRRs will be presented by infusion. IRRs that led to interruption of study drug or 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, the number of patients who experienced an IRR will be summarized by symptoms.

AEs other than IRRs experienced by the patient within 24 hours of an infusion will be presented by infusion (may include the day of the infusion and the following day). The

onset date of the AE will be matched to the date of an infusion; onset dates will not be imputed.

The treatments for IRRs will be summarized.

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.

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.

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.

4.5.5 Opportunistic Infections

Opportunistic infections (OIs) will be defined using the MedDRA standardized MedDRA query (SMQ) “Opportunistic infections (narrow).”

The number of patients who experienced an OI will be summarized by SOC and PT and displayed according to their actual treatment received.

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

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 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. This analysis will be conducted for final analysis.

4.5.7 Pregnancies

Pregnancy information will be listed.

4.5.8 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 and Ig levels).

For the liver laboratory parameters, the number and percentage of patients with an elevated post-baseline AST or ALT or gamma-glutamyl transferase or alkaline phosphatase level will be summarized by treatment.

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.

Antibody Titers

If data are available, antibody titers for mumps, rubella, varicella, Streptococcus and pneumoniae will be summarized for the number and percentages of patients with a positive level by visit.

HBV DNA

Hepatitis B virus (HBV) DNA (polymerase chain reaction) in patients who enrolled with negative HBsAg and positive total HBcAb will be listed.

4.5.9 Vital Signs

Vital sign and physical examination results data will be included in individual patient listings.

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.

4.5.10 ECGs

ECG data will be included in individual patient listings. Change from baseline of ECG abnormalities during the DBP will be summarized. Baseline ECG is the last ECG assessment before treatment. For a patient with multiple ECG assessments during treatment, the worst assessment will be used.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

The following analyses will be conducted to evaluate the study conduct:

- Summary and list of major protocol deviations
- Summaries of full analysis set and safety populations, including numbers of patients in each analysis set
- Summary of patient disposition, including the number of patient randomised, number of patients enter DBP/ OLE/ SFU, number of patients discontinue from treatment, discontinue from study, reasons for withdrawal from study treatment and withdrawal from study at each study phases
- Consort diagram of the study disposition including intercurrent events
- Table of the number of patients switching to other disease modifying therapies
- Figure of cumulative enrollment over time
- Summary and listing of intercurrent events
- Summary and Kaplan-Meier plots of:
  - Time to discontinuation of study treatment during the blinded treatment period. (All other patients will be censored at date of their last known alive during the blinded treatment period)
  - Time to discontinuation from the study. (All other patients will be censored at their last assessment during the study)
- Observation time will be summarised as continuous and categorical (<1, $1-2$, ≥ 2). Observation time is defined as exposure (see Section 4.5.1.2).

4.6.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics

For continuous variables, the mean, median, SD, and minimum and maximum values will be calculated. For categorical variables, the number and percentage in each category will be displayed. For each item in the following lists, the units and categories to be used are indicated in parentheses and separated by commas. All durations are calculated with respect to the date of randomization, if not stated otherwise.

The following demographic, MS history, baseline disease characteristics will be summarized and listed in the full analysis set, unless otherwise stated:

Demographic and stratification factors based on available eCRF data and Baseline disease characteristics:

- Age at randomization (years) as continuous and categorical (<12, $12-14$, >14)
- Sex (Male/ Female), if female (Childbearing Potential, Premenarchal)
- Self-reported race and ethnicity
- Height (cm), weight (kg), and Body Mass Index (kg/m²)
- Region (U.S., RoW)
- Tanner stage (<2, ≥ 2)
- EDSS score as continuous
- SDMT as continuous
- Presence of T1 Gd lesions at baseline (Y/N)
- Number of Gd-enhancing T1 lesions
- Number of hyperintense T2 lesions.

Note that race cannot be collected in in some countries (e.g. France), and date of birth cannot be collected in some countries. For incomplete date of birth, if the day is missing, impute to 1. If the month is missing, impute to January. One year is defined as 356.25 days.

MS disease history

- Duration (years) since onset of MS symptoms and its category (≤ 1 year, >1 to ≤ 3 years, >3 to ≤ 5 years, >5 years)
- Duration (years) since MS diagnosis and its category (≤ 1 years, >1 to ≤ 3 years, >3 to ≤ 5 years, >5 years)
- Treatment with any MS disease-modifying therapy prior to the baseline visit (Yes [treatment-experienced patients], No [naive patients])
- Type of DMT used prior to enrollment
- Prior treatment with any steroids as MS therapy prior to baseline (Y/N)
- Number of relapses in the last 1 year prior to screening and its category (0, 1, 2, 3 and ≥ 4)
- Number of relapses in the last 2 years prior to screening and its category (0, 1, 2, 3 and ≥ 4)
- Time since last relapse from randomization.

Medical History

Medical history will be summarized by SOC and PT. For each previous and concurrent medical history recorded medical history (MH), the term entered by the investigator

describing the event (the “reported term”) will be assigned a standardized term (the “Preferred Term” [PT]) and assigned to a superclass term (the “System Organ Class” [SOC]) on the basis of the MedDRA 27.0.

Vaccination History

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination and non-SARS-CoV-2 vaccination history will be summarized and listed, as well as SARS-CoV-2 vaccination during the study.

Other vaccination history (vaccines other than SARS-CoV-2) will also be summarized and listed.

4.6.3 Pharmacokinetic Analyses

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

Nonlinear mixed-effects modeling will be used to analyze the sparse concentration-time data of ocrelizumab via the population PK approach. 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) occurred which may interfere with PK evaluation. The PK data of this study may be pooled with data from other studies. The PK analysis may be reported separately from the main study Clinical Study Report.

4.6.4 Immunogenicity Analyses

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline 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 postbaseline 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 postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline 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 may be analyzed and reported via descriptive statistics if there is sufficient data.

4.6.5 Biomarker Analyses

Biomarkers will be assessed at baseline and subsequent timepoints following administration of study treatment. Descriptive or summary statistics will be used to describe biomarker assessments.

The PD biomarker, the median CD19+B–cell count, will be displayed graphically over time from the first infusion of study drug. Absolute CD19+B-cell counts and percent changes from baseline in the CD19+B-cell count will be summarized over time. The number and percentage of patients whose CD19+B-cell counts have repleted will be summarized over time. Repletion is defined as the CD19+ B-cell count having returned to their baseline value or LLN. Reference LLN values were derived from Garcia-Prat et. al. 2019 for patients under 18 years of age (age 9–13 years, LLN=170 cells/μL; age 14-17 years, LLN=140 cells/μL). For patients who are 18 years and older at time of analysis, 80 cells/μL would be used as the LLN, to be consistent with previous adult ocrelizumab analyses (Opera I and II).

Levels of B-cell subsets or T-cell subsets in blood, including but not limited to CD19, IgD, CD27, CD38, CD4, CD8, CD3 parameters, may be presented as absolute value over time and/or change relative to baseline over time.

4.7 INTERIM ANALYSES

Interim analysis is not planned.

4.8 CHANGES TO PROTOCOL-PLANNED ANALYSES

New exploratory objectives on disease activity are added (Section 4.4.6).

5. SUPPORTING DOCUMENTATION

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

6. REFERENCES

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Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Mult Scler. 2020;26:1816-21.

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Appendix 1: WN42086 Handover Form_Version 2.0

HANDOVER FORM FOR ONGOING AEs, Infusion Related Reactions and Concomitant Medications between independent and treating study team

(Please note that use of this form is suggested but not mandatory)

*Please complete this form **ONLY** in case subject has ongoing AE(s) at the moment of handover*:*

1) ***AEs with no potential to reveal treatment assignment,*** *that are ongoing after the 24-hour telephone call following initial fingolimod/placebo dosing or re-start of treatment in case it was interrupted more than 14 days, should be handed over to the treating study team **after 24-hour telephone call***
2) ***AEs with a potential to reveal treatment assignments,*** *that are ongoing for 15 days following initial fingolimod/placebo dosing or re-start of treatment in case it was interrupted more than 14 days, should be handed over to the treating study team **on day 15 of the study or 15 days from treatment re-start***

In case subject has both type of AEs (option 1 and 2) handover form to be completed **on day 15*

(PLEASE COMPLETE IN CAPITALS)

Client: F. Hoffmann-La Roche Ltd	**Protocol ID:** WN42086	**Country:**	**Site #**
Treating physician name:		**Independent physician name:**	
A. Subject Information			
1. Site-Subject Number:	**2. Randomization Date:** (DD/MMM/YYYY)	**3. Sex:** ☐ Male ☐ Female	

B. Adverse Event (AE)	**Event1**	**Event2**	**Event**
1. AE term			
2. Onset date: (DD/MMM/YYYY)			
3. Ongoing: (If NO don´t enter in this form)	☐Yes	☐Yes	☐Yes

4. Severity	Grade_____ according to: ☐CTCAE ☐Table 3, protocol	Grade_____ according to: ☐CTCAE ☐Table 3, protocol	Grade_____ according to: ☐CTCAE ☐Table 3, protocol
5. Suspect study drug relationship	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No

C. AE information (PLEASE COMPLETE IN CAPITALS)

Description of the AE(s) (include signs/symptoms, diagnostics and treatment given):

_____

_____

_____

_____

_____

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_____

_____

_____

D. Infusion Related Reaction (IRR)	**IRR1**	**IRR2**	**IRR3**
1. IRR term			
2. Onset date: (DD/MMM/YYYY)			
3. Ongoing: (If NO don´t enter in this form)	☐Yes	☐Yes	☐Yes

E. Treatment given (PLEASE COMPLETE IN CAPITALS)

Adverse event	**Drug**	**Dose, unit, frequency**	**Route**	**Drug start date**	**Drug end date or ongoing**

F. Prepared By:	
Name:	**Title:** ☐Physician ☐Nurse ☐Other, specify:
Telephone #:	
Fax #:	
Independent physician signature:	**Date (DD/MMM/YYYY):**

IMPORTANT Please note:
These AEs, IRRs and Concomitant Medications must also be entered into the Blinded database by the Treating Study Team so that subsequent data, including resolution details can be captured in the Blinded database.

To do this, the Independent Dosing Team that should attach print outs from the Unblinded database of the ongoing AEs, IRRs and Concomitant Medications documented on this form.

This may be done by going into an individual AE, IRR or ConMed and using the print function of the internet browser. Please do not use the 'View PDF' function.

Signature Page for Statistical Analysis Plan - WN42086 - Published
System identifier: RIM-CLIN-989077

Approval Task	[redacted] Company Signatory 20-Feb-2025 10:14:52 GMT+0000