Official Title: A Phase III, Non-Inferiority, Randomized, Open-Label, Parallel Group, Multicenter Study to Investigate the Pharmacokinetics, Pharmacodynamics, Safety and Radiological and Clinical Effects of Subcutaneous Ocrelizumab Versus Intravenous Ocrelizumab in Patients with Multiple Sclerosis

NCT Number: NCT05232825

Document Date: Statistical Analysis Plan Version 3: 22-Dec-2023

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A PHASE III, NON-INFERIORITY, RANDOMIZED, OPEN-LABEL, PARALLEL GROUP, MULTICENTER STUDY TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY AND RADIOLOGICAL AND CLINICAL EFFECTS OF SUBCUTANEOUS OCRELIZUMAB VERSUS INTRAVENOUS OCRELIZUMAB IN PATIENTS WITH MULTIPLE SCLEROSIS**
STUDY NUMBER:	CN42097
STUDY NAME:	OCARINA II
VERSION NUMBER:	3.0
ROCHE COMPOUND(S):	Ocrelizumab (RO4964913)
EUDRACT NUMBER:	2020-005448-48
IND NUMBER:	100,593
NCT NUMBER:	NCT05232825
PLAN PREPARED BY:	[redacted], Ph.D [redacted], Ph.D

STATISTICAL ANALYSIS PLAN AMENDMENT 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 28 February 2022. *The text in italics is taken from protocol v3.*

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
3	See electronic date stamp on the last page of this document	Protocol v3, 13 March 2023
2	28 February 2023	Protocol v2, 24 February 2022
1	7 March 2022	Protocol v1, 21 January 2021

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

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

The changes made after version 2 and prior to 31 May 2023 are described below.

Section	Description of change	Rationale for Change
3.1 Analysis Sets	The definition of the efficacy-evaluable – MRI set was clarified: patients should have at least one brain MRI scan with measurement taken.	To improve clarity.
3.2 Periods and Intercurrent Events Strategies	The definition of the end of the periods was clarified: the CCOD was added as a potential end for all periods; for the controlled period, the end 'Start of 1st SC dose in the SC ocrelizumab treatment period minus 1 day' was changed to 'minus 1 second'; and for the treatment phase, EOS was removed as a potential end and 'withdrawal from treatment (start of SFU)' was added.	To improve clarity.
4.4.2.1.3 Definition of dose 1 completer	The definition of complete dose 1 was added.	To clarify the meaning of '[…] received the full assigned dose of ocrelizumab […]' in the PK-evaluable analysis set definition.
4.5.1.2.1 Main Radiological Estimand	It was clarified that no offset will be used on the main radiological estimand.	To improve clarity.
	It was clarified that no baseline T2 lesion count will be used in the T2 model.	No baseline data had been transferred for T2 lesions by the vendor.

The changes made after 31 May 2023 are described below.

Section	Description of change	Rationale for Change
4.5.1.2.1 Main Radiological Estimand	For the primary analysis, it was clarified that no baseline T2 lesion count will be used in the T2 model. As per version 3, baseline T2 lesion count is included in the T2 model.	At the time of the primary analysis, no baseline T2 lesions data had been transferred. At the time of version 3, baseline T2 lesions data had been transferred by the vendor.
1.1 Objectives and Endpoints	Table 1 was updated.	To be aligned with the global protocol version 3 and to add MRI exploratory endpoints.
1.2 Study Design	Figure 1 was updated.	To be aligned with the global protocol version 3.
3.1 Analysis Sets	For the efficacy-evaluable-MRI analysis set, patients will be grouped according to the treatment they were assigned.	To implement feedback from FDA regarding the grouping received on 1 June 2023.
	The immunogenicity-evaluable-all set definition was changed to include all randomized patients with at least one ADA assessment.	To allow reporting of ADAs at baseline.
	A 'scope' column has been added.	To provide more details.
3.2 Analysis Periods	The heading was changed from 'Periods and Intercurrent Events Strategies' to 'Analysis Periods'. The 'Strategy' and 'Explanation' columns were removed from Table 3. New periods were added, period names and footnotes were updated.	To improve clarity and include additional periods.
4.1 General Considerations	The reported precision was clarified and general imputation rules included.	To be aligned with the method used to produce the results.
4.3.1.2.1 Main Radiological Estimand	The analysis population was described and the summary measure was added.	To improve clarity.

Section	Description of change	Rationale for Change
4.3.2.3 Supplementary Analyses	Variables and intercurrent events handling strategies were added for MRI supplementary analyses.	To improve clarity.
4.3.2.4 Supplementary Analyses –Patients with MRI Assessments in or outside of visit window	A table for time windows for MRI assessments was added.	To provide more details.
4.4.1.4 Partial and Missing Data	Imputation rules were added.	To provide more details.
4.4.2.5 Patient global impression of satisfaction (PGI-SF)	A new section was added.	To be aligned with the global protocol version 3.
4.4.3 Home Administration	A new section was added.	To define analyses for home administration.
4.5.1.2.1 Main Radiological Estimand	Grouping for the main radiological estimand was changed from 'actual treatment received' to 'planned treatment'.	To implement feedback from FDA received on 1 June 2023.
	It was clarified that new or enlarging T2 lesions are relative to the previous available scheduled scan.	The analysis performed by the MRI vendor was based on the number of new or enlarging T2 lesions with respect to the previous available scheduled visit. This reflects medical practice.
	The intercurrent event 'Initiation of treatment for symptoms of multiple sclerosis' was added.	To implement feedback from FDA received on 1 June 2023.
	What is reported when the Poisson model does not converge was clarified: unadjusted rate and two-sided 95% CI will be reported.	To improve clarity.
4.5.1.3 Total Cumulative Dose	It was clarified that the SC dose is not capped.	To provide more details.
4.5.1.4 Dose Modification	It was clarified that modifications of the planned dose prior to the administration of ocrelizumab are not allowed for management of adverse events.	To improve clarity.

Section	Description of change	Rationale for Change
4.5.1.8 Missing data	Imputation rules were detailed.	To provide more details.
4.5.2 Prior/Concomitant medications	Classification on prior, prior/concomitant and concomitant medications was clarified.	To be aligned with the method used to produce the results.
4.5.2.1 Definitions	The name of an MRI visit performed 1 or more days outside the planned visit window was changed from 'delayed' to 'out of window'.	It was only a change in name and did not affect the definition of such a visit.
4.5.2.3 Premedications	Additional details were added.	To provide more details.
4.5.2.5 Missing data	Imputations rules were detailed.	To provide more details.
4.5.3.1.1 Reporting	Additional details were included regarding treatment emergent adverse events.	To provide more details.
4.5.3.1.3 Partial and Missing Data	Imputation rules were described.	To be aligned with the method used to produce the results
	The Table 4 'Definitions of Variables' was removed.	The content was included in the relevant sections in the document and clarified when needed.
4.5.3.2 All Adverse Events Conventions	Added to which dose an AE will be assigned.	To include additional information.
4.5.3.2.1 Adverse Event Duration	The AE duration computation was detailed.	To provide more details.
4.5.3.2.3 Adverse Events Rates per patient Years of Exposure	The computation for the number of AEs per 100 patient-years was added. A typo in the exact upper 95% confidence limit was corrected..	To provide more details and improve clarity.
4.5.3.2.5 Outputs to be generated	It was added that listings of AEs for patients exposed to any other DMT (including commercial ocrelizumab) will be produced.	To provide more details.

Section	Description of change	Rationale for Change
4.5.3.3.2 Duration of Resolved Infections	The derivation of resolved infections duration was clarified.	To be aligned with the method used to produce the results.
4.5.3.4 Infusion-Related Reactions (IRR) and Injection Reactions (IR)	Additional information on IR/IRR was included.	To provide more details.
4.5.3.4.9 Local/Systemic categorization	It was clarified that systemic Injection reactions are those that contain either systemic symptoms only or both local and systemic symptoms.	To improve clarity.
4.5.4.1 Definition and Conventions	The baseline definition was clarified.	To be aligned with the method used to produce the results.
4.6.2 Summaries of Demographics and Baseline Characteristics	References to STREAM default rules were removed.	To improve clarity.
4.6.5 Pharmacodynamics Analyses	Analyses details were added.	To provide more details.
4.6.6 Biomarker Analyses	Additional information on biomarker analyses was included.	To provide more details.
4.6.6.1 Outputs to be generated	Analyses details were added.	To provide more details and to allow more analyses options.

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	antidrug antibody
ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate amino transferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
AUC_{W1-12}	AUC up to Week 12
CCOD	clinical cutoff date
CD19	Cluster of Differentiation 19
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence intervals
C_{max}	maximum concentration
COVID-19	Coronavirus Disease 19
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAP	data analysis plan
DBC	drug basket committee
DMT	Disease modifying therapy
eCRF	Electronic Case Report Form
EDSS	Expanded disability status scale
EOS	end of study
FSS	functional systems scores
GMR	geometric mean ratio
ICF	Informed Consent Form
Ig	Immunoglobulin
IR	injection reactions
IRR	infusion-related reactions
IV	Intravenous
LNRTI	lower and not specified respiratory tract infection
LoPo	list of planned outputs
LRTI	lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis

MSTPQ	MS Treatment Preference Questionnaire
MTS	MedDRA term selection
NfL	neurofilament light
OCR	Ocrelizumab
PD	pharmacodynamic(s)
PGI-SF	Patient global impression of satisfaction
PK	pharmacokinetic(s)
PPMS	primary progressive multiple sclerosis
PPQ	Patient Preference Questionnaire
PT	preferred term
RMS	relapsing-remitting multiple sclerosis
ROW	rest of world
rHuPH20	recombinant human hyaluronidase posterior head protein 20
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDG	Standardized Drug Grouping
SDTM	study data tabulation model
SOC	system organ class
SC	Subcutaneous
SFU	safety follow-up
SMQs	Standardized MedDRA queries
T1Gd+	T1 gadolinium-enhancing
TASQ	treatment administration satisfaction questionnaire
TEAE	treatment emergent adverse events
URTI	upper respiratory tract infection
UTI	urinary tract infection
U.S.	United States of America
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods that will be used to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of ocrelizumab for Study CN42097. The analyses described in this SAP will supersede those specified in the Study CN42097 protocol if there is any inconsistency between the two documents. This SAP is based on Protocol CN42097, version 3.0, dated 13 March 2023.

1.1 OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints

Objectives	**Corresponding Endpoints**
Pharmacokinetic objectives	
Primary Objective	***Corresponding Endpoint***
To demonstrate PK non-inferiority of the SC formulation of ocrelizumab in patients with MS	• *Serum ocrelizumab area under the concentration-time curve (AUC_{W1-12}) after SC administration compared to IV infusion from Day 1 to Week 12*
Secondary Objective	***Corresponding Endpoint***
To determine the maximum serum concentration of ocrelizumab SC in patients with MS	• *Maximum serum concentration (C_{max})*
Radiological and Clinical objectives	
Secondary Radiological Objective	***Corresponding Endpoints***
To evaluate the radiological effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS	• *Total number of T1Gd+ lesions as detected by brain MRI at Weeks 8 and 24* • *Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 12 and 24 relative to the previous scan, respectively*
Exploratory Radiological and Clinical Objective	***Corresponding Endpoints***
To explore the radiological and clinical effects of ocrelizumab SC compared with ocrelizumab IV in patients with MS	• *Total number of T1Gd+ lesions as detected by brain MRI at Week 48 and Week 96* • *Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 8, 48 and 96 relative to the previous scan, respectively* • *The annualized protocol-defined relapse rate by Weeks 24, 48 and 96 in RMS patients*

Objectives	Corresponding Endpoints
	• *Change from baseline in the EDSS at Weeks 48, 72 and 96* • Total number of new or enlarging T2 lesions per MRI scan from Week 8 to Week 96 • Total number of T1Gd+ lesions measured from Week 8 to Week 96 • Total number of T1Gd+ lesions measured from Week 24 to Week 96
Patient-Reported Objective	
Exploratory Objectives	***Corresponding Endpoints***
Patient satisfaction and experience receiving SC administration (at site and at home) and IV route of administration	• *Patient administration satisfaction and experience scores using the TASQ for IV infusion following the first treatment administration in a subset of patients* • *Patient administration satisfaction and experience scores using the TASQ for SC injection*
Patient satisfaction and preference taking ocrelizumab administered SC compared to previous DMTs taken prior to the study	• *Entry treatment experience questions to report overall treatment satisfaction scores from patients who received an MS treatment prior to the study* • *MS treatment preference score to report overall satisfaction taking ocrelizumab* • *MS treatment preference score to report the proportion of patients with a preference for ocrelizumab SC compared to previously taken DMTs*
Patient preference for the SC or IV route of administration, specifically	• *Proportion of patients who prefer the SC or IV route of administration using the PPQ*
Patient global impression of overall satisfaction (PGI-SF) for SC ocrelizumab	• *Proportion of patients who are satisfied or dissatisfied with ocrelizumab SC as a treatment for their MS symptoms*
Safety objective	
Objective	***Corresponding Endpoints***
To evaluate and compare the safety profile after administration of ocrelizumab SC versus ocrelizumab IV and to assess the safety of ocrelizumab SC at the selected dose in patients with MS	• *Incidence and severity of adverse events, with severity determined according to the NCI CTCAE version 5.0* • *Change from baseline in targeted vital signs* • *Change from baseline in targeted clinical laboratory test results*

Immunogenicity objective	
Objective	***Corresponding Endpoints***
To evaluate the immune response to ocrelizumab SC and IV, and rHuPH20	• *Incidence of treatment-emergent anti-drug antibodies (ADAs) to ocrelizumab after SC or IV administration relative to the presence of ADAs at baseline* • *Relationship between ADA status and pharmacokinetics, pharmacodynamics, and safety* • *Incidence of treatment-emergent antibodies to rHuPH20 after SC administration relative to the presence at baseline and relationships between antibodies to rHuPH20 and safety*
Pharmacodynamic objective	
To evaluate the effect of SC ocrelizumab compared with IV ocrelizumab on the PD marker for the mechanism of action of ocrelizumab (i.e., B cell depletion)	• *Proportion of patients achieving CD19+ B cell level ≤ 5 cells /μL at Weeks 12, 24, 48, and/or 96*
Biomarker objective	
To evaluate 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), can provide evidence of ocrelizumab activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology	• *Levels of biomarkers including but not limited to NfL in serum compared between dosing arms at Weeks 12, 24, 48 and/or 96 compared to baseline*

ADA = antidrug antibody; AUC_{W1-12} = AUC up to Week 12; CD19 = Cluster of Differentiation 19; C_{max} = maximum concentration; DMT = disease modifying therapy; EDSS = expanded disability status scale; IV = intravenous; MRI = magnetic resonance imaging; MS = multiple sclerosis; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NfL = neurofilament light; PD = pharmacodynamics; PK = pharmacokinetics; PPQ = Patient Preference Questionnaire; rHuPH20 =recombinant human hyaluronidase posterior head protein 20; RMS = relapsing multiple sclerosis; SC = subcutaneous; T1Gd+ = T1 gadolinium-enhancing; TASQ = Treatment Administration Satisfaction Questionnaire.

Note: The non-Italic format text in the above table has been updated in the SAP and was not present in the protocol.

1.2 STUDY DESIGN

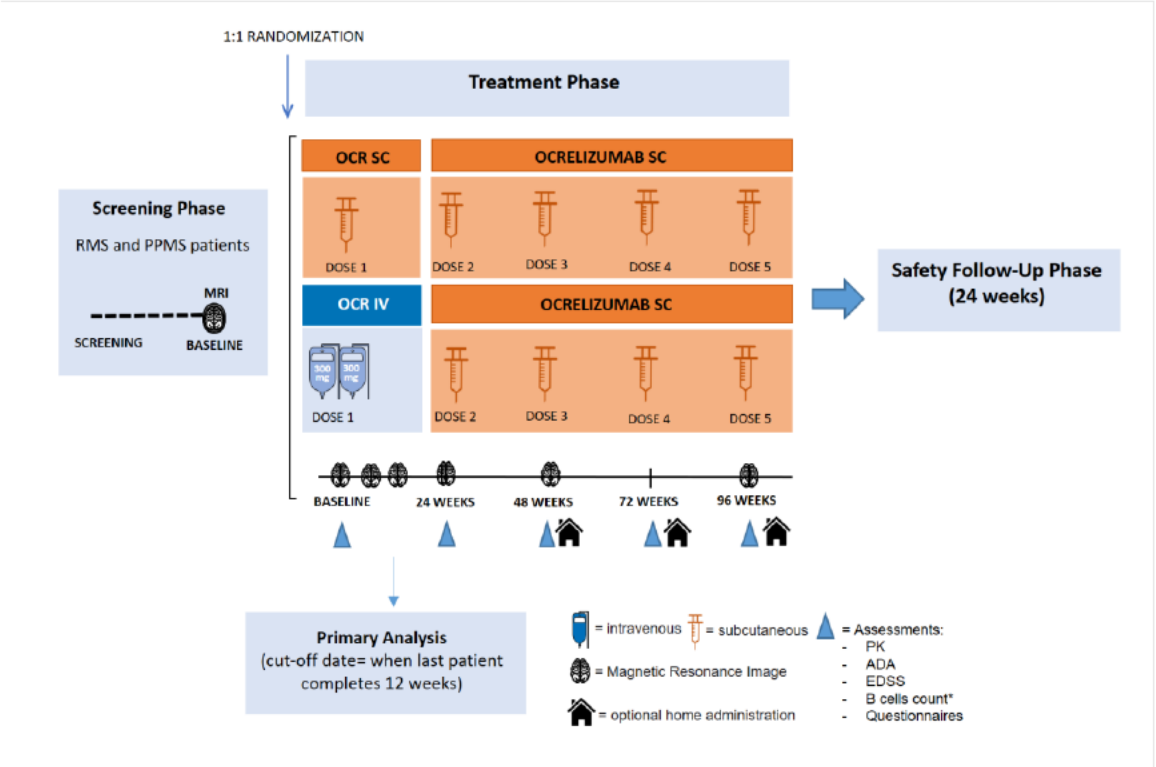
Study CN42097 is a Phase III non-inferiority, randomized, open-label, parallel group, multicenter study to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological, and clinical effects of subcutaneous (SC) administration of ocrelizumab compared with the intravenous (IV) infusion of ocrelizumab in patients with

either relapsing-remitting multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS). The study will consist of the following study phases:

- *Screening*
- *Treatment (controlled period and SC ocrelizumab treatment period)*
- *Safety follow-up (SFU)*

For further details, please refer Study Protocol Section 3. The study design is shown in Figure 1.

Figure 1 Study Schema



ADA = anti-drug antibody; EDSS = expanded disability status scale; IV = intravenous; MRI = Magnetic Resonance Image; OCR = ocrelizumab; PK = pharmacokinetics; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis; SC = subcutaneous.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESIS

Rules for declaring non-inferiority are described in Section 4.4 .

2.2 SAMPLE SIZE DETERMINATION

Sample size determination details are provided in Study Protocol Section 6.1.

3. ANALYSIS SETS AND PERIODS

3.1 ANALYSIS SETS

The analysis sets are defined in Table 2.

Table 2 Analysis Sets

Analysis set	Definition	Scope
PK-evaluable	All patients who have received the full assigned dose of ocrelizumab and have measurable serum concentrations of ocrelizumab unless major protocol deviations or unavailability of information (e.g., exact blood sampling time, exact dosing information or incomplete dose administration, missing concentration data) occurred, or if data are unavailable, not plausible, or incomplete, that may interfere with the PK evaluation. Patients will be grouped according to the actual dose and actual route of administration.	All analyses of PK parameters will be based on this analysis set.
Safety-evaluable - All	All randomized patients who received at least one infusion (partial or complete) or injection (partial or complete) of study drug (ocrelizumab IV or ocrelizumab SC). Patients will be grouped according to treatment received at first exposure	Analyses of exposure and safety parameters will be based on this analysis set.
Safety-evaluable - SC	All randomized patients who received at least one injection (partial or complete) of ocrelizumab SC. Patients will be grouped together.	Analyses of exposure and safety parameters will be based on this analysis set.

Efficacy-evaluable - MRI	All randomized patients who received, during the controlled period (i.e., time until the Week 24 dose of ocrelizumab SC), at least one infusion (partial or complete) or injection (partial or complete) of study drug (ocrelizumab IV or ocrelizumab SC) and having at least one brain MRI scan with measurement taken. Patients will be grouped according to the treatment they were assigned.	All analyses of MRI parameters will be based on this analysis set.
Full Analysis	All randomized patients. Patients will be grouped according to treatment they were assigned.	The following analyses will be based on this analysis set: - Patient Disposition - Stratification factors - Major Protocol Deviations - EDSS Score - Annualized Protocol-Defined Relapse Rate
Immunogenicity -evaluable - All	All randomized patients with at least one ADA assessment. Patients will be grouped according to treatment received at first exposure or, if no treatment is received prior to study discontinuation, according to the treatment they were assigned.	Analyses of immunogenicity parameters will be based on this analysis set.
Pharmacodynamics-evaluable	All randomized patients who received at least one infusion (partial or complete) or injection (partial or complete) of study drug (ocrelizumab IV or ocrelizumab SC). Patients will be grouped according to treatment they received at the first exposure.	All analyses of pharmacodynamics parameters will be based on this analysis set.
Other endpoints - evaluable	All patients in the RMS and PPMS populations and in the overall population who received at least one infusion (partial or complete) or injection (partial or complete) of study drug (ocrelizumab IV or ocrelizumab SC). Patients will be grouped according to treatment they received at first exposure	All analyses of PRO parameters will be based on this analysis set.

ADA = antidrug antibody; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetics; PPMS = Primary progressive multiple sclerosis; RMS = Relapsing-remitting multiple sclerosis; SC = subcutaneous

3.2 ANALYSIS PERIODS

The analysis periods are defined in Table 3.

Table 3 Analysis Periods

Period Definition	Start	End
Controlled period	1st dose	End date is defined as the earliest between – Start of other disease modifying therapies, or commercial ocrelizumab – Start of 1st SC dose in the SC ocrelizumab treatment period-1 second – Withdrawal from study/death – Withdrawal from treatment* – Clinical cutoff date (CCOD)
Controlled period – irrespective of DMT start	1st dose	End date is defined as the earliest between – Start of 1st SC dose in the SC ocrelizumab treatment period-1 second – Withdrawal from study/death – Withdrawal from treatment* – CCOD
Treatment phase or SFU- irrespective of DMT start or treatment withdrawal	1st dose	End date is defined as the earliest between – EOS – Withdrawal from study/death – CCOD
Treatment phase or SFU – irrespective of treatment withdrawal	1st dose	End date is defined as the earliest between – Start of other disease modifying therapies, or commercial ocrelizumab – EOS – Withdrawal from study/death – CCOD
Treatment phase	1st dose	End date is defined as the earliest between – Start of other disease modifying therapies, or commercial ocrelizumab – Start of SFU** – Withdrawal from study/death – Withdrawal from treatment* – CCOD
Treatment phase – irrespective of DMT start	1st dose	End date is defined as the earliest between – Start of SFU** – Withdrawal from study/death – Withdrawal from treatment* – CCOD
Ocrelizumab SC treatment period-	2nd dose	End date is defined as the earliest between

irrespective of DMT start		– Start of SFU** – Withdrawal from study/death – Withdrawal from treatment* – CCOD
OCR SC all exposure	1st dose SC ocrelizumab	End date is defined as the earliest between – Start of other disease modifying therapies, or commercial ocrelizumab – Start of SFU** – Withdrawal from study/death – Withdrawal from treatment* – CCOD
OCR SC all exposure – irrespective of treatment withdrawal	1st dose SC ocrelizumab	End date is defined as the earliest between – Start of other disease modifying therapies, or commercial ocrelizumab – EOS – Withdrawal from study/death – CCOD
SFU	Start of SFU**	End date is defined as the earliest between – EOS – Withdrawal from study/death – CCOD

DMT = disease modifying therapy: EOS = end of study; OCR = ocrelizumab; PD = pharmacodynamics; SC = subcutaneous; SFU = safety follow up.

The cutoff date is the clinical cutoff date (CCOD) associated to production of outputs for study required deliveries (e.g., the CCOD for an independent Data Monitoring Committee (iDMC) delivery, for answering to regulators).

* the withdrawal from treatment date is defined as the last exposure date for patients with 'Reason for completion/discontinuation' field not marked as 'Completed' on the Study Drug Completion/Early Discontinuation eCRF page.

** the start of SFU is defined as the day after the date 'Date subject completed or discontinued from study period' (from the Subject Disposition eCRF page) if 'Study period' is selected as 'Treatment Period' and 'Specify the period of the study the subject will continue into' is selected as 'Safety Follow up'.

4. STATISTICAL ANALYSES

All computations and generation of tables, listings and data for figures will be performed using Statistical Analysis Software (SAS)® Version 9.4 or later (SAS Institute, Cary, NC, USA). If necessary, other appropriate statistical software, including R, version 3.6 or later may be used.

4.1 GENERAL CONSIDERATIONS

Within each section, significance and confidence level (if applicable) will be specified.

Unless otherwise specified, baseline is defined as the latest assessment before the start of the period under consideration.

Descriptive statistics on continuous data will include the following with the listed precision (unless specified otherwise): number of observations, mean (D + 1), standard deviation (D + 1), median (D + 1), 25th percentile (D + 1), 75th percentile (D + 1), minimum (D), maximum (D), with D the number of decimals in the collected value.

Descriptive statistics on categorical data will include the following: number of observations, frequency and percentage of each category under consideration. One decimal will be displayed for percentages.

Unless otherwise specified, summaries will be produced using the allocation described in the Analysis sets.

In general, missing outcome data will not be replaced or imputed unless specified otherwise.

The following imputation rules will be applied when imputing the date/time of any assessments, events and exposure start and end, unless specified otherwise:

- For analysis (start) date/time: missing month and/or day will be imputed with '01' and each of missing hours, minutes, seconds with '00'.
- In case of multiple time points possible per visit: date/time will be imputed as above on pre-dose time points. On post-dose time points, time will be imputed as: missing hours with '23' and each of missing minutes and seconds with '59'.
- For analysis end date/time: missing month will be imputed with '12', day with the last day of the month, missing hours with '23' and each of missing minutes and seconds with '59'.

4.1.1 Reporting

There will be at least two reporting transactions:

- Study CN42097 Primary Clinical Study Report (CSR): the clinical cutoff date (CCOD) is set to 12 weeks after the last patient has been randomized. All available data will be included. This means that, for some patients, there may be data beyond Week 12 (e.g., Week 24 data).
- Study CN42097 Final CSR: the CCOD is set to the end of study (EOS) (see Protocol Section 3.2 "End of Study and Length of Study").

4.1.2 Participant Disposition

The number of patients who enroll, discontinue treatment or study, or complete the study will be summarized. Reasons for premature treatment and study discontinuation will be listed and summarized.

4.2 PRIMARY PHARMACOKINETIC (PK) ENDPOINT ANALYSIS

The primary objective for this study is to establish the non-inferiority of ocrelizumab SC compared with ocrelizumab IV on the basis of serum ocrelizumab area under the curve (AUC) up to Week 12 (AUC_{W1-12}).

The geometric mean ratio (GMR) of AUC SC versus AUC IV will be presented, together with the two-sided 90% confidence interval (CI).

The non-inferiority will be established if the lower end of the two-sided 90% CI of the GMR of AUCs is > 0.8. The non-inferiority limit of 0.8 corresponds to a maximal 20% loss in AUC for the SC administration compared with IV. All available results for pharmacokinetics (PK) samples obtained during the first 12 weeks will be included in the PK analysis (with the exceptions as defined in Table 2).

The primary comparison between SC and IV administered ocrelizumab will be based on the AUC_{W1-12} (i.e., over the first 3 months of the 6 monthly dosing interval after first dose), as absorption is expected to be complete by Week 12.

4.2.1 Definition of Primary Endpoint

The primary endpoint is serum ocrelizumab area under the concentration-time curve (AUC_{W1-12}) after SC administration compared to IV infusion from Day 1 to Week 12.

4.2.2 Main Analytical Approach for Primary Endpoint

4.2.2.1 Estimands for Primary Analysis

The estimand for the primary analysis is based on the following attributes:

a) *Treatment: Ocrelizumab IV administered at Day 1 and Day 14, 300 mg each visit (Reference), versus ocrelizumab SC at the determined dose at Day 1 (Experimental).*

b) *Population: RMS and PPMS patients defined through the in/exclusion criteria reflecting the target population. The analysis population will consist of all randomized patients who have received the full assigned dose of ocrelizumab and have available PK data (and all necessary supporting information, i.e., exact dosing administration information, exact blood sampling times), with patients grouped according to their actual treatment. The number of randomized patients excluded from the analysis is expected to be small, falling under the following categories:*

   – *Withdrawal after randomization and prior to dosing. Every effort will be made to ensure all randomized patients will receive the treatment on Day 1. Treatment will start within 24 hours of randomization.*

   – *Withdrawal from treatment between Day 1 and Day 14 dosing for patients randomized to IV arm. These patients would have received 300 mg only from the Day 1 infusion. Their PK data cannot be compared with the patients who receive the full 600 mg dose. In the three Phase III Studies,* (OPERA I WA21092, OPERA II WA21093 and ORATORIO WA25046) *< 3% patients did*

not receive the Day 14 dosing in each study. Reasons for treatment discontinuation will be documented.

- *Incomplete dosing. A small number of patients may receive incomplete dosing. In the three Phase III Studies* (OPERA I WA21092, OPERA II WA21093 and ORATORIO WA25046)*, 0.6%-2% of the patients received < 80% of the planned volume at the Day 1 infusion. No reliable PK comparison can be performed if the received dose is less than the full dose.*
- *Missing all PK data due to other reasons. Every effort will be made to ensure all PK samples with all supporting information are collected. Among these patients excluded from the analysis, systematic bias in potential exposure levels is not expected compared to all patients. All PK data from all patients in this study will be inspected visually. Samples and/or patients excluded from the analysis will be documented, together with the reason for exclusion.*

c) *Variable: estimated AUC_{W1-12}, using all available ocrelizumab serum concentrations from the PK samples.*

d) *Intercurrent events: they are handled within the population specification. Among the patients in the analysis population, there could be some missing individual PK samples due to missed visits, early withdrawal or other reasons. Every effort will be made to collect PK samples on schedule. The non-linear mixed effect model can estimate the AUC with limited PK data, assuming the data are missing at random.*

e) *Summary measure: GMR and two-sided 90% CI of SC versus IV of AUC between Week 1 and Week 12. Non-inferiority would be established if the lower end of the two-sided 90% CI is > 0.8.*

The primary analysis will occur once the last patient enrolled has completed the Week 12 visit, to ensure all PK samples in the first 12 weeks are included. A sensitivity analysis will be done using AUC from Week 1 to Week 24, using all available samples collected until CCOD (12 weeks after the last patient enrolled).

4.2.2.1.1 Statistical Analysis and Sample SAS Code of the Main Estimand

Descriptive statistics will be used to summarize the estimand variable on the PK-evaluable set.

To estimate the geometric mean ratio of AUC_{W1-12} SC versus AUC_{W1-12} IV, the natural logarithm of the estimated AUC_{W1-12}, will be modeled by a linear regression that includes the treatment variable and is adjusted for the stratification factors. A sample unvalidated SAS code is provided in Appendix 2 where,

- Log(PKVAR) is the natural logarithm of the estimated AUC_{W1-12}
- TRT is the variable associated to treatment (Reference: Ocrelizumab IV)
- STRAT1 STRAT2 STRAT3 are the variables associated to the stratification factors. These are:

- Baseline body weight (<70 kg vs. ≥70 kg)
- Disease subtype (RMS vs. PPMS)
- Region (U.S. vs. rest of the world [ROW])

- In case of randomization errors, the electronic Case Report Form (eCRF) data and not the randomization data will be used (Yelland et al. 2015)

4.2.2.1.2 Sensitivity Analysis

The primary analysis will be repeated with the following variable: AUC from Week 1 to Week 24.

4.2.2.1.3 Definition of Complete Dose 1

For subjects receiving IV, a subject has a complete Dose 1 if they received both Day 1 and Day 14 infusions, and the deviation from the planned dose is not more than +/- 10% of the planned total dose (sum of Day 1 and Day 14 infusions). For example, if a subject receives 260 mg on Day 1 and 300 mg on Day 14, this is considered a complete Dose 1.

For subjects receiving SC, a subject has a complete Dose 1 if the subject received the first SC dose, and the deviation from the planned dose is not more than +/- 10%.

4.3 SECONDARY ENDPOINTS ANALYSES

4.3.1 Secondary Pharmacokinetic Endpoints

The secondary PK objective of this study is to determine maximum concentration observed (C_{max}) of ocrelizumab SC in patients with multiple sclerosis (MS).

Descriptive statistics will be used to summarize such parameter on the PK-evaluable set.

4.3.2 Secondary Efficacy Endpoints

4.3.2.1 Main Radiological Estimand

The secondary efficacy analysis will be done separately for each MS subtype (RMS or PPMS), for specific visits, and each variable (T1 gadolinium-enhancing [T1Gd+] lesions or new or enlarging T2 lesions).

Patients will be grouped according to their planned *treatment and included if receiving, during the controlled period, at least one full or partial dose of either reference or experimental treatment.*

T1Gd+ lesions will be performed and analyzed on Week 8 and 24 visits while new and/or enlarging T2 lesions will be analyzed on Week 12 (relative to the previous available scheduled scan*) and Week 24 (relative to* the previous available scheduled scan*).*

The estimand for the secondary efficacy analysis follows a combination of while on study and treatment-policy and estimates the treatment effect on the considered magnetic

resonance imaging (MRI) variable, regardless of adherence, on the basis of the following attributes:

a) *Treatment: Ocrelizumab IV (Reference) versus ocrelizumab SC (Experimental).* Refer to the protocol for the dose and dosing schedule.

b) *Population: RMS or PPMS patients defined through the in/exclusion criteria reflecting the target population. The analysis population* is *the* efficacy-evaluable MRI Analysis set.

c) Variable: total number of T1Gd+ lesions (Week 8 or 24) or new and/or enlarging T2 lesions from all subjects at Week 12 or 24. New and/or enlarging T2 lesions are relative to the previous available scheduled *scan.*

d) Intercurrent events will be handled as follows:

- *Withdrawal from treatment or incomplete dosing:* these intercurrent events will be ignored (a treatment policy strategy will be applied) *and MRI assessment will be collected in all patients.*
- Initiation of treatment for symptoms of multiple sclerosis: the intercurrent event will be ignored (a treatment policy strategy will be applied).

e) Summary measure and *Population-level-summary estimator*

The summary measure is the variable rate in the experimental and reference arm.

- *The estimand variable will be modeled by a negative binomial regression that includes the treatment variable and is adjusted for covariates. Covariates for variable total number of T1Gd+ lesions are: baseline T1Gd+ lesion (present or not), and geographical region (United States of America [U.S.] vs. ROW). Covariates for variable new and/or enlarging T2 lesions are baseline T2 lesion count and geographical region (U.S. vs. ROW). The adjusted incidence rates (for each treatment arm) estimated from such models will be reported along with the two sided 95% CIs.*
- *If the negative binomial model fails to converge due to an extremely low number of patients with lesions, unadjusted rate and Poisson two sided 95% CI will be reported instead.* If even the Poisson model does not converge, unadjusted rate and two sided 95% CI will be reported.
- *No formal statistical testing will be done. The estimated rates (adjusted or unadjusted) and two sided 95% CI will be evaluated to confirm that SC and IV treatment result in similarly low rates of lesions.*

- In line with the estimand definition, all data pre and post the intercurrent events ‘Withdrawal from treatment’, 'Incomplete dosing' and ‘Initiation of treatment for symptoms of multiple sclerosis’ will be included in the analysis following the treatment-policy strategy.
- In case of delayed 14-day infusion (on patients on IV arm) no ad hoc handling will be performed.

f) Handling of missing data

- *MRI performed but not possible to read the number of lesions:* No data will be imputed.
- *MRI not performed: No data will be imputed.*
- *Withdrawal from study (missing data): No data will be imputed.*

– In case of missing or partially missing MRI date, the target study date will be used (see Table 4 in Section 4.3.2.4).

4.3.2.2 SAS Code for the Main Radiological Estimand

A sample unvalidated SAS code is provided in Appendix 3, where,

- COUNT is the estimand variable under consideration
- TRT is the variable associated to treatment
- COVX are the covariates in the model

As no offset will be included, the data step and the offset option should not be included in the main radiological estimand

4.3.2.3 Supplementary Analyses

Week 24 assessments should be performed during the controlled treatment period (i.e., before Week 24 SC dosing). It is not ruled out that some MRI assessments are collected after the Week 24 SC dosing has been given (i.e., during the ocrelizumab SC treatment period) or as potential unscheduled visits if a subject discontinued treatment. This supplementary estimand will apply a hypothetical-policy strategy on such assessments. Hence, this supplementary estimand will be performed as the main estimand excluding assessments performed during the ocrelizumab SC treatment period or SFU.

For this supplementary analysis, the main radiological estimand analysis will be repeated using the following variables and intercurrent events handling strategies:

Variable

- Number of T1Gd+ lesions as detected by brain MRI at Week 8, prior to the second dose
- Number of T1Gd+ lesions as detected by brain MRI at Week 24, prior to the second dose
- Number of new or enlarging T2 lesions as detected by brain MRI at Week 12, prior to the second dose, relative to the previous available scheduled scan
- Number of new or enlarging T2 lesions as detected by brain MRI at Week 24, prior to the second dose, relative to the previous available scheduled scan

Intercurrent events

- Withdrawal from treatment: all data after this event will be treated as missing (an hypothetical strategy will be applied)

- Incomplete dosing: a treatment-policy strategy will be applied
- Initiation of treatment for symptoms of multiple sclerosis: a treatment-policy strategy will be applied

All data after withdrawal from treatment will be treated as missing following the hypothetical strategy. All data pre and post the intercurrent events 'Incomplete dosing' and 'Initiation of treatment for symptoms of multiple sclerosis' will be included in the analysis following the treatment-policy strategy. For analysis purposes, the time of withdrawal from treatment is defined in the footnote of Table 3.

4.3.2.4 Supplementary Analyses –Patients with MRI Assessments in or outside of visit Window

An MRI visit is considered out of window if it is performed 1 or more study days outside the planned visit window (windows are visit specific, see Table 4). Study days are defined based on days on study since the date of the first study drug exposure, with the day of the first exposure being Study Day 1.

The main radiological estimand analysis will be repeated with the following constraints:

- The assessment is included if the associated MRI visit is in window
- The assessment is included if the associated MRI visit is out of window

Table 4 Time Windows for MRI assessments

Analysis Visit	Target Study Day	Time Window (in Study Days)
BASELINE	< 0 (Approximately, -10)	Not defined
DAY 1	1	1-1
WEEK 8	56	43-70
WEEK 12	84	71-98
WEEK 24	168	155-182
WEEK 48	336	309-364
WEEK 96	672	645-700

4.3.2.5 Output to be Generated

In addition to the main and supplementary estimand analyses, the secondary MRI parameters will be summarized using descriptive statistics. A listing of MRI assessments will also be provided.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.4 EXPLORATORY ENDPOINTS ANALYSIS

4.4.1 Exploratory Radiological and Clinical Endpoints

The parameters defined in protocol Section 2.2.2 will be summarized by descriptive statistics by treatment in the RMS and PPMS patient populations and in the overall population.

4.4.1.1 Expanded Disability Status Scale

The expanded disability status scale (EDSS) is based on a standard neurological examination, incorporating functional systems (visual, brainstem, pyramidal, cerebellar < sensory, bowel and bladder, and cerebral [or mental]) that are rated and then scored as functional systems scores (FSS), and ambulation, which is scored as ambulation score. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6 and an ambulation score that is rated from 0 to 16. These ratings are then used in conjunction with observations, as well as information, concerning ambulation and use of assistive devices to determine the total EDSS score. All FSS, ambulation score, and total EDSS scores will be captured electronically and completed in real-time. Note that the following items do not need to be scored for this study: sexual dysfunction and fatigue. In this study, eurostatus-eEDSS definitions and calculating algorithms will be used (D'Souza et al. 2017).

Baseline is defined as the latest assessment before the start of the exposure period under consideration.

Expanded disability status scale computation is provided by Signant Health.

4.4.1.2 MRI Parameter Total Number of New or Enlarging T2 Lesions as Detected by Brain MRI at Week 8

The main radiological estimand analysis will be repeated with the following variable:
Total number of new or enlarging T2 lesions as detected by brain MRI at Week 8 relative to the previous scan (i.e., relative to Baseline).

4.4.1.3 Other MRI Parameters and Protocol Defined Relapse Rate

These parameters, including

- *Total number of T1Gd+ lesions as detected by brain MRI at Week 96*
- *Total number of new or enlarging T2 lesions as detected by brain MRI at Weeks 48 and 96 relative to the previous scan, respectively*

will be summarized with descriptive statistics.

4.4.1.4 Partial and Missing Data

For protocol defined relapse rate, the event onset date/time imputation will be based on the rules mentioned under Section 4.1. However, additional imputations will be

performed in this case taking into consideration the relapse resolution date/time and exposure date/time corresponding to the relapse.

4.4.1.5 MRI Parameters – Sums of Number of Lesions Over Time

The variables

- total number of T1Gd+ lesions measured from Week 24 to Week 96 (computed as the sum of T1Gd+ lesions at Week 24, Week 48 and Week 96)
- total number of T1Gd+lesions measured from Week 8 to Week 96 (computed as the sum of T1Gd+ lesions at Week 8, Week 24, Week 48 and Week 96)
- total number of new or enlarging T2 lesions per MRI scan from Week 8 to Week 96 (computed as the sum of new or enlarging T2 lesions compared to previous available scheduled scan at Week 8, Week 12, Week 24, Week 48 and Week 96)

will be analyzed with a negative binomial model.

4.4.1.6 Output to be Generated

Analyses methods are described within Section 4.4.1 and sub sections.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.4.2 Exploratory PRO Endpoints

The parameters defined in Protocol Section 2.3 will be summarized by descriptive statistics by treatment in the RMS and PPMS patient populations where needed, and in the overall population.

4.4.2.1 Entry Treatment Experience

The Entry Treatment Experience Questionnaire is administered at baseline to understand whether patients had taken any MS treatment prior to starting the study and if so, the reason for stopping it and their level of satisfaction when they were taking it. For individuals who took an MS treatment prior to starting the study, the measure contains 4-items and for individuals who were not on a prior MS treatment it contains 1-item. Items are rated on a 2- , 3- , 4- or 8- point scale and are evaluated individually. It will be completed prior to the patient's first ocrelizumab treatment and will take approximately 30 seconds-1 minute to complete. No derivation is required.

4.4.2.2 Treatment Administration Satisfaction Questionnaires (TASQ)

The Treatment Administration Satisfaction Questionnaires (TASQ) measures contain 13 items rated on a 3- or 5-point Likert scale (from 1-3 or 1-5), for which a higher score corresponds to higher satisfaction and a more positive experience. This is except for item 7, which should be interpreted descriptively. Items will be evaluated individually.

The TASQ will be completed by the patient 30-60 minutes after completion of their ocrelizumab treatment. Patients whose first ocrelizumab treatment was SC injection will

complete the TASQ SC at Baseline visit, whereas patients whose first ocrelizumab treatment was IV infusion will complete the TASQ IV at the Baseline* visit. All patients complete the TASQ SC at Weeks 24 and 48. It will take between 2-4 minutes to complete.*

*Note: Baseline refers here to the Baseline visit rather than to the Baseline assessment defined in Section 4.1.

4.4.2.3 Patient Preference Questionnaire (PPQ)

The Patient Preference Questionnaire (PPQ) is administered to understand patients' preference of ocrelizumab administration via IV infusion versus SC injection. Patients are asked to respond on either 3- or 5- point scale, from which each item will be evaluated individually.

This measure will only be completed by the subset of patients whose first ocrelizumab treatment was administered as an IV infusion. It will be completed prior to the patient's ocrelizumab SC injection at Week 48, and will take approximately 30 seconds-1 minute to complete. No derivation is required.

4.4.2.4 MS Treatment Preference Questionnaire (MSTPQ)

The MS Treatment Preference Questionnaire (MSTPQ) is used to understand patients' preference for ocrelizumab compared to any treatment they were taking before starting the study. It consists of three items and is rated on a 4- or 6- point scale, from which each item can be evaluated individually. The MSTPQ will be administered at Week 48 prior to ocrelizumab treatment and will take approximately 30 seconds-1 minute to complete. No derivation is required.

4.4.2.5 Patient global impression of satisfaction (PGI-SF)

The patient global impression is one item used to assess patient's overall satisfaction (PGI-SF) of ocrelizumab SC as a treatment for their MS symptoms. The PGI-SF is rated on a four point Likert scale ranging from Very satisfied (1) to Very dissatisfied (4). It is scored descriptively and takes approximately 30 seconds – 1 minute to complete. The PGI-SF will be administered at Week 96 prior to the patient's ocrelizumab treatment.

4.4.2.6 Output to be Generated

Data will be summarized using descriptive statistics.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.4.3 Home Administration

To allow for the possibility of home administration at participating sites, from the third ocrelizumab dose onwards (i.e., Week 48 onwards) the ocrelizumab dose can be

administered by a healthcare professional at the patient's home or another suitable location.

Such setting will be compared descriptively versus the clinical setting on selected outputs targeting demographics and baseline characteristics, safety (including Injection reactions), exposure, protocol deviations and selected questionnaires. Such analysis will be performed if at least one subject will undergo home administration.

4.4.3.1 Output to be Generated

Data will be summarized using descriptive statistics and listings will be provided.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5 SAFETY ANALYSES

Safety will be assessed through summaries of exposure to study treatment, adverse events (AEs), changes in laboratory test results, and changes in vital signs.

4.5.1 Extent of Exposure

4.5.1.1 Exposure Duration (Months)

Exposure summaries will be provided based on the various definition provided in Section 3.2: Analysis Periods.

4.5.1.2 Definition of Dose

The first dose of ocrelizumab IV is given as two infusions administered 2 weeks apart. If a patient receives any infusion at Dose 1 or receives any SC dose during the study, the patient is counted as having received at least one dose.

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

4.5.1.3 Total Cumulative Dose

As per the eCRF design, total cumulative dose is capped at 100% for IV, so the actual dosage for each infusion does not exceed 600 mg. The SC dose is not capped.

4.5.1.4 Dose Modification

Modifications of the planned dose prior to the administration of ocrelizumab are not allowed for management of adverse events. The number of unintended modifications of the administered dose due to e.g. adverse events, medication error of equipment malfunction, will be reported.

4.5.1.5 Dose Interruption

An injection is interrupted if ‘Was the injection interrupted or withdrawn?’ (SC) question in the eCRF is set to yes. For IV, an infusion is interrupted, if there are intermediate

infusion start/ends and at least one intermediate infusion end is not coincident with the subsequent intermediate infusion start.

4.5.1.6 Dose Delayed

A dose is delayed if 'Was the dose delayed?' question in the eCRF is set to yes.

4.5.1.7 Output to be Generated

Study treatment exposure (such as treatment duration, total dose received, and number of cycle) and other data *will be summarized with descriptive statistics*. Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5.1.8 Missing data

No imputation of partial or missing date components of exposure start and end is allowed. Nevertheless, the time component will be imputed following the rules in Section 4.1.

In case the actual exposure end is after the clinical cutoff date, the latter will be used as the exposure end with time imputed with '23' for hours, '59' for minutes and '59' for seconds.

4.5.2 Prior/Concomitant Medications

Prior/concomitant medication will be summarized with descriptive statistics.

Coronavirus Disease (COVID-19) vaccines will be listed.

The prior/ concomitant medications will be classified by therapeutic-level indication (2nd level designation) using the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization [WHO], ATC/DD Index, 2020). The ATC coding system has fourteen main anatomical or pharmacological groups (1st level), followed by the therapeutic or pharmacological subgroups characterized in the 2nd level.

Classification on prior, prior/concomitant and concomitant will be based on the start and end of the medication administration relative to the start of the first study drug exposure.

4.5.2.1 Prior Medication (Any) for MS

Medication for MS will be classified based on a flag in the eCRF. A prior medication for MS, which includes disease modifying therapy (DMT), is defined as any previous medications taken for the treatment of MS at any time since disease onset and medications taken for the symptoms of MS in the 3-month period prior to the baseline visit. Such prior medication for MS as well as the corresponding start and end dates will be recorded at the baseline visit in the eCRF.

DMT will be classified based on Disease Modifying Therapies for Multiple Sclerosis Custom Drug Basket prepared by the Drug Basket Committee (DBC).

4.5.2.2 COVID-19 vaccine

COVID-19 vaccines are selected based on Roche customized drug grouping for vaccinations for COVID-19.

4.5.2.3 Premedications

Data about premedications (medication name, dose, route of administration, and dose form) and whether premedications are taken as per protocol is recorded in the premedications eCRF form.

Premedications are taken as per protocol if there are at least two premedications taken belonging to corticosteroids and antihistaminic. Antihistamines will be identified using the Standardized Drug Grouping (SDG) 'Antihistamines (SDG)' while corticosteroids will be identified using the 'Corticosteroids (SDG) - narrow scope'.

4.5.2.4 Output to be Generated

Data will be summarized using descriptive statistics.

Details of the outputs as well as Analysis Periods (Section 3.2) will be described elsewhere.

4.5.2.5 Missing data

No imputation is performed in case the year component of administration start and end is missing or if the recorded administration start/end date/time is completely missing.

4.5.3 Adverse Events

All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

All AEs, serious adverse events (SAEs), AEs leading to death, adverse event 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.

4.5.3.1 General Considerations

4.5.3.1.1 Reporting

Adverse event reporting will focus on treatment emergent adverse events (TEAEs). An AE is included if the event start date is between the start and end of the period as

defined in Table 3. Treatment emergent adverse events with a start date prior to the first study drug administration are considered belonging to the period for periods starting with the first study drug administration.

The following AEs are defined as treatment emergent events:

- AEs with an observed or imputed date of onset: on or after the start date of first dose or with eCRF flag 'Event occurred prior to first study drug administration' equals 'no';
- AEs such that:
  - the onset date is prior to the day of first dose
  - the end date is on or after the date of the first dose or with a completely missing end date
  - the most extreme intensity is greater than the initial intensity;
- AEs with a completely missing, non-imputed start date unless the AE has a complete, non-imputed end date that is prior to the date of the first dose.

For each recorded AE, 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 on the basis of the MedDRA 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).

4.5.3.1.2 Relapses

Serious MS relapses are considered SAEs, but non-serious MS relapses are not considered AE.

4.5.3.1.3 Partial and Missing Data

Adverse Event Onset Date and Time

For adverse events and symptoms of IR and IRR, the event onset date/time imputation will be based on the rules mentioned under Section 4.1. However, additional imputations will be performed in this case taking into consideration the event resolution date/time and exposure date/time corresponding to the event.

4.5.3.2 All Adverse Events Conventions

Adverse events will be assigned to a dose if the AE onset date is on or after the date of the first infusion/injection of that dose and before the date of infusion/injection of the next treatment dose. Adverse events that are reported during the SFU period will be assigned to the last dose received. Hence, the last dose for a patient may be of a

variable length. Adverse events that start prior to the first dose and worsen during treatment (i.e., treatment-emergent) will be assigned to the first treatment dose.

4.5.3.2.1 Adverse Event Duration

The AE duration is computed as (resolution date minus onset date) plus 1 day. No duration is computed in case of imputed onset/resolution dates.

4.5.3.2.2 Summaries by SOC and PT

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of adverse events' rows, multiple occurrences of the same AE in an individual are counted separately.

4.5.3.2.3 Adverse Events Rates per Patient Years of Exposure

Multiple occurrences of the same AE in one patient are counted multiple times.

The number of AEs per 100 patient-years is calculated as total number of AEs divided by total number of patient-years multiplied by 100.The 95% CI for the number of AEs per 100 patient-years is calculated as follows (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 X^2 distribution on 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. However, the potential within subject correlation due to recurrent events is ignored.

4.5.3.2.4 Adverse Events by Highest CTCAE Severity

Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient (most extreme).

To SOC 'Overall' or 'Any adverse event' row counts, a patient contributes only with the AE occurring with the highest grade within the SOC or overall, respectively.

If, within a patient, there is a mixture of missing and non-missing assessment, the highest non missing will be reported.

If, within a patient, all severities are reported missing, then at patient level the severity is reported as missing.

4.5.3.2.5 Outputs to be Generated

Data will be summarized using descriptive statistics. Listings, including listings of AEs for patients exposed to any other DMT (including commercial ocrelizumab), will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5.3.3 Infections

4.5.3.3.1 Definition

Infections are identified either by MedDRA SOC or by infections type.

MedDRA SOC definition: Infections are identified using AEs falling into the MedDRA Infections SOC "Infections and Infestations".

Type definition: Infection types are identified using adverse events falling into the ocrelizumab specific Adverse Events Glossary of Terms for each type. The preferred term can be classified in more than one type. Below terms report such types via ocrelizumab specific MedDRA term selection (MTS) basket of terms.

- Sepsis narrow
- Sepsis broad (including systemic injection reactions [SIRS], septicemia, etc.)
- Herpes virus infections
- Central nervous system infections
- Gastrointestinal infection
- All Respiratory tract infections (combination of lower respiratory tract infection [LRTI] plus upper respiratory tract infection [URTI])
- Lower respiratory tract infection (LRTI)
- Lower and not-specified respiratory tract infections (LNRTI)
- Skin infections Skin infections
- Upper respiratory tract infection (URTI)
- Urinary tract infection (UTI)
- Infectious pneumonia
- Melanoma skin malignancies

4.5.3.3.2 Duration of Resolved Infections

The derivation of resolved infections duration is identical to the one implemented for general AEs (see Section 4.5.3.1.3).

4.5.3.3.3 Outputs to be Generated

Data will be summarized using descriptive statistics. Listings will be produced.

Details of the outputs as well as Analysis Periods (Section 3.2) will be described elsewhere.

4.5.3.4 Infusion-Related Reactions (IRR) and Injection Reactions (IR)

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion or injection should be captured as a diagnosis (e.g., 'infusion-related reaction', 'injection reaction' [which is applicable for local or systemic injection reactions] or 'anaphylactic reaction') on the adverse event eCRF.

4.5.3.4.1 IRR Definition

Infusion-related reactions (IRRs) are adverse events for which at least one infusion relation reaction symptom is reported in the corresponding eCRF form.

4.5.3.4.2 IR Definition

Injection reactions (IRs) can be either local or systemic. These are adverse events for which at least one injection reaction symptom is reported in the corresponding eCRF form.

4.5.3.4.3 IRs by Severity

Multiple occurrences of the same IR in one individual are counted once at the highest grade for this patient (most extreme) either overall or by dose.

4.5.3.4.4 IR/IRR Symptoms

The derivations of onset, resolution and duration for IR/IRR symptoms are identical to the ones implemented for AEs Section 4.5.3.1.3.

4.5.3.4.5 Onset Date time of IRs/IRRs

The onset date time of an IR/IRR is defined as the onset date/time (with missing components imputed) of the first (i.e., earliest) symptom. If no symptoms are collected, the IR/IRR onset is defined as the parent AE onset date time.

4.5.3.4.6 End Date time of IRs/IRRs

The end date time of an IR/IRR is defined as the latest end date/time (with missing components imputed) among all its symptom resolution date/times. If no symptoms are collected, the IR/IRR end date/time is defined as the parent AE resolution date/time.

4.5.3.4.7 IR Duration – Time component of the Event Ignored

The IR onset and end dates (imputed if needed) will be used for the derivation of 'IR duration (days) - Time component of the event ignored' for all the reactions where both onset and end are not completely missing. The IR duration is calculated only when the outcome is recovered/resolved or recovered/resolved with sequelae.

4.5.3.4.8 IR Duration – Time Component of the Event Mandatory

The IR onset and end date/time will be used for the derivation of 'IR duration (days) - Time component of the event mandatory' for all the reactions where both IR onset and end date/time- are fully collected (up to minutes). The IR duration is calculated only when the outcome is recovered/resolved or recovered/resolved with sequelae.

4.5.3.4.9 Local/Systemic Categorization

Local or systemic injection reaction categorization will be done via the injection reaction symptoms eCRF when the site enters a 'Local' or 'Systemic' symptom. Please note such categorization applies to IRs only.

Local IRs are those that have either local symptoms only or both local and systemic symptoms.

Systemic IRs are those that have either systemic symptoms only or both local and systemic symptoms.

4.5.3.4.10 Counting of Local/Systemic IRs

In summaries by local and systemic IRs, an IR can belong to both categories. Hence the sum of local plus systemic IRs can be greater than the overall.

4.5.3.4.11 Outputs to be Generated

Data will be summarized using descriptive statistics. Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5.3.5 Adverse Events at the Injection Site that do not Meet the IR Definition

4.5.3.5.1 Definition

Adverse events that belong to the high-level term: 'Injection site reactions' with onset after 24 hours or those that are not considered IRs as defined in the study protocol.

4.5.3.5.2 Outputs to be Generated

Data will be summarized using descriptive statistics.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5.3.6 COVID-19

COVID-19 events are identified via the Standardized MedDRA Query (SMQ) (Narrow) for COVID-19 related events (SMQ ID 20000237). At the time of analysis, the latest revision of the SMQ will be used.

4.5.3.6.1 Outputs to be Generated

Data will be summarized using descriptive statistics. Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5.3.7 Death

4.5.3.7.1 Outputs to be Generated

Listings will be produced.

4.5.3.8 Adverse Events of Special Interests (AESI)

4.5.3.8.1 Definition

Adverse events of special interest for this study are as follows:

- Grade 3 or higher injection site reactions
- Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate amino transferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see protocol Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when contamination of the study drug is suspected.

4.5.3.8.2 Outputs to be Generated

Listings will be produced.

4.5.3.9 Non-Treatment Emergent Adverse Events (TEAE)

4.5.3.9.1 Outputs to be Generated

Data will be summarized using descriptive statistics.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5.3.10 Onset after 24 Weeks from Last Dose (among Patients Who Withdrew from Treatment)

4.5.3.10.1 Outputs to be Generated

Listings will be produced.

4.5.3.11 Adverse Events with Partial Onset Dates

Adverse events with partial onset dates may not be attributed to any period. Hence the listing will help to ascertain the AEs that may not be attributed to any period.

4.5.3.11.1 Outputs to be Generated

Listings will be produced.

4.5.3.12 Cases of Accidental Overdose and Medication Errors

4.5.3.12.1 Definition

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- *Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose*
- *Medication error: accidental deviation in the administration of a drug. In some cases, a medication error may be intercepted prior to administration of the drug.*

Special situations are not in themselves adverse events but may result in adverse events.

As an example, an accidental overdose that resulted in a headache would require two entries on the adverse event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

4.5.3.12.2 Outputs to be Generated

Data will be summarized using descriptive statistics. Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5.3.13 Malignancies, Anaphylactic reactions and Hypersensitivity

4.5.3.13.1 Definition

Malignancies are identified using the "Malignant tumors (SMQ)" narrow.

Anaphylactic reactions are identified using the "Anaphylactic reactions (SMQ)".

Hypersensitivity events are identified using the "Hypersensitivity (SMQ)".

4.5.4 Laboratory Data

4.5.4.1 Definition and Conventions

Baseline is defined as the latest assessment prior to the period start as defined in Section 3.2.

For calculation of summary statistics, values reported as < X (where X is the lower limit of measurement range) are set to 0.5*X and values reported as > Y (where Y is the upper limit of measurement range) are set to missing.

For changes from baseline summaries, a window approach will be used: the latest assessment within a 7-days window will be taken.

4.5.4.2 Outputs to be Generated

Relevant laboratory 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.

Data will be summarized using descriptive statistics. Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

For immunoglobulin, the mean levels (IgA, IgG, IgM, and total Ig) will be displayed graphically over time from the first infusion of study medication. The absolute values and 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.

4.5.5 Vital Signs

4.5.5.1 Definition and Conventions

Per each visit, for parameters 'Systolic Blood Pressure, Sitting (mmHg)', 'Diastolic Blood Pressure, Sitting (mmHg)' and 'Pulse Rate, Sitting (beats/min)', Baseline is defined as the last assessment taken among 'PRIOR TO PREMEDICATION' and "PRIOR TO OCRELIZUMAB INFUSION" on IV arm in the eCRF Vital Signs IV page and "PRIOR TO THE OCRELIZUMAB INJECTION" on SC arm in the Vital Signs SC page associated to that visit.

No per-visit Baseline is defined on a given visit if such assessments are missing.

For changes from Baseline summaries, a window approach will be used: the latest assessment within a 7-day window will be taken.

4.5.5.2 Outputs to be Generated

Relevant vital sign (pulse rate, blood pressure, pulse oximetry) data will be displayed by time, with grades identified where appropriate. Changes in vital signs will be summarized using descriptive statistics.

Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.5.6 Pregnancies

4.5.6.1 Outputs to be Generated

Listings will be produced.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Patient disposition is described in Section 4.3.

Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

No imputation for missing or partial data will be performed.

4.6.1.1 Protocol Deviations

The protocol deviations and their classification will be described on a separate plan. A subset of protocol deviations due to COVID-19 will be produced.

4.6.1.2 Outputs to be Generated

Data will be summarized using descriptive statistics. Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.6.2 Summaries of Demographics and Baseline Characteristics

4.6.2.1 MS and Non-MS Disease History

For each recorded non-MS disease, the term entered by the investigator describing the disease (the “reported term”) will be assigned a standardized term (PT) and assigned to a superclass term on the basis of the MedDRA WHO dictionary of terms.

An event will be considered a medical history or an adverse event based on the following:

- Onset before informed consent form (ICF): medical history event.
- Onset between ICF and randomization: SAE if the event was caused by protocol mandated intervention or medical history if the event was not caused by protocol mandated intervention.
- Onset between randomization and first dose: AE/SAE which are non TEAE /TEAE (see the definition of TEAE in Section 4.5.3.1.1)
- Onset at and after first dose: treatment emergent AE/SAE

4.6.2.2 MRI Assessments

If during the screening phase, a MRI scan is required for MS diagnosis then it can serve as a baseline scan.

4.6.2.3 Outputs to be Generated

Demographic and baseline characteristics (including age, sex, and stratification factors) will be summarized using mean, standard deviation, median, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

MS disease history will be described summarizing disease type (RMS vs PPMS), duration since MS symptom onset (years), duration since diagnosis (years), duration from last relapse (years) and proportion of patients with prior relapses.

Non-MS disease history will be summarized by SOC and PT.

MRI, vital signs and laboratory baseline data will be summarized using descriptive statistics. Listings will be produced. Details of the outputs will be described elsewhere.

4.6.3 Pharmacokinetic Parameters Derivation and Analyses

In order to estimate the PK parameters, nonlinear mixed effects modeling or other appropriate methods will be used to analyze the concentration versus time data of ocrelizumab derived from this study.

The influence of covariates such as body weight, sex, and B-cell count will be taken into account. Additional PK analyses may be conducted as appropriate.

Exposure (AUC up to Week 12, and AUC up to Week 24) to ocrelizumab and C_{max} will be estimated for each patient.

Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

4.6.4 Immunogenicity Analyses

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).

In addition, the incidence of treatment-emergent antibodies to human recombinant DNA-derived hyaluronidase enzyme (rHuPH20) after SC administration relative to the presence at baseline will be determined in the same manner as described above for ADAs to ocrelizumab.

4.6.4.1 Outputs to be Generated

The numbers and proportions of ocrelizumab ADA-positive patients and ADA negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. The relationship between ADA to ocrelizumab and antibodies to rHuPH20 status and safety, efficacy, pharmacokinetics, and biomarker endpoints will be analyzed and reported via descriptive statistics as appropriate as data allow. Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.6.5 Pharmacodynamics Analyses

Cluster of Differentiation 19 (CD19+) B-cell count in blood will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. Baseline is defined as the latest assessment before first ocrelizumab exposure.

4.6.5.1 Outputs to be Generated

The data will be presented as absolute value over time and/or percent change relative to baseline and/or proportion of patients achieving 5 or less B cells/µL in blood over time, and/or proportion of patients achieving less than 10 cells/µL. Data will be summarized using descriptive statistics. Listings will be produced.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.6.6 Biomarker Analyses

Levels of biomarkers including but not limited to neurofilament light (NfL) in serum will be assessed at baseline and subsequent timepoints following administration of ocrelizumab. The following endpoints may be included in the biomarker analysis:

- 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 naïve, memory and/or B plasma blast/plasma cell subsets.

4.6.6.1 Outputs to be Generated

The data will be presented over times and/or changes relative to baseline. Data will be summarized using descriptive statistics including the geometric mean. 95% Confidence intervals may be reported. Listings will be produced.

A mixed model for repeated measurements (MMRM) may be used to estimate the mean change from baseline in the log transformed value of biomarker (including but not limited to Serum Nfl), at each scheduled visit for each treatment arm.

Details of the outputs as well as analysis periods (Section 3.2) will be described elsewhere.

4.7 INTERIM ANALYSES

No interim analyses are planned.

5. SUPPORTING DOCUMENTATION

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

Appendix 1 Changes to Protocol-Planned Analyses

Apart from the PD endpoint for the proportion of patients achieving equal and less than 5 cells/μL overtime as per protocol, the data on proportion of patients achieving less than 10 cells/μL have been added. This addition aims to align with the optimal interpretation of B cell count data, considering the newly established lower limit of quantification set at 10 cells/μL using the TBNK assay in conventional flow cytometry (Looney et al. 2023) (see Section 4.6.5). Exploratory MRI endpoints have been added.

Appendix 2 SAS code on Main PK Estimand

Unvalidated code

```
Proc GLM data=data method=XXX;
   Class TRT STRAT1 STRAT2 STRAT3;
   Model Log(PKVAR) = TRT STRAT1 STRAT2 STRAT3;
   Lsmeans TRT;
   Estimate "SC-IV" TRT -1 1/cl alpha=0.10;
Run;
```

Appendix 3 SAS code on Main Radiological Estimand

Unvalidated code

```
DATA LOGTRAN:
     SET XXXXX;
     LOGEXP = LOG(EXPOSURE);
RUN;

PROC GENMOD DATA=LOGTRAN;
   CLASS TRT(PARAM=REF REF=OCR IV);

     MODEL COUNT = TRT COV1 COV2 / TYPE3 DIST=NEGBIN
               OFFSET=LOGEXP LINK=LOG;
     LSMEANS TRT / EXP CL;
     ODS OUTPUT LSMEANS=lsm ;
     ODS OUTPUT ParameterEstimates=est;
where paramcd ="EstimandPARAMCD";

RUN;
```

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