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STATISTICAL ANALYSIS PLAN

TITLE:	**A SUBSTUDY TO EVALUATE THE SAFETY OF A SHORTER INFUSION OF OCRELIZUMAB IN PATIENTS WITH EARLY STAGE RELAPSING REMITTING MULTIPLE SCLEROSIS ASSOCIATED WITH MA30143 MAIN STUDY**
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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
CCOD	Clinical Cutoff Date
CI	Confidence Interval
Cmax	Maximum concentration
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
DRB	Data Review Board
EC	Ethics Committee
HA	Health Authorities
IA	Interim Analysis
iDCC	Independent Data Coordinating Center
iDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
IRR	Infusion-related Reaction
ITT	Intent-to-Treat
IxRS	Interactive Voice/Web Response System
MS	Multiple Sclerosis
OCR	Ocrelizumab
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
RMS	Relapsing Multiple Sclerosis
ROW	Rest of the World
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
US	United States

1. BACKGROUND

The ENSEMBLE study (MA30143) is a Phase IIIb prospective, single-arm, open-label, multicenter study in patients with early stage relapsing remitting multiple sclerosis (RRMS). ENSEMBLE PLUS is a randomized, double-blinded, parallel-group substudy of ENSEMBLE, initiated after the start of the ENSEMBLE main study to evaluate the safety of a shorter infusion of ocrelizumab versus conventional infusion in a subgroup of eligible patients from the ENSEMBLE main study. There is a single protocol covering the main study, with the substudy featured as an appendix in this protocol.

From here on, the ENSEMBLE main study is referred to as “the main study” and the ENSEMBLE PLUS substudy is referred to as “the substudy”. Approximately 650 to 700 subjects will be enrolled into the substudy.

The scope of this statistical analysis plan (SAP) is to describe the analysis of the substudy, to be conducted after the last randomized patient completes the 24-hour evaluation period after the 1st randomized infusion. All safety data up to the clinical cutoff date (CCOD) will be included to evaluate the safety of the shorter infusion. Database lock and unblinding of the Sponsor will occur several weeks after the CCOD in order to clarify all outstanding data queries.

Version 7.0 of the study protocol was updated to include an interim analysis (IA) for the primary endpoint after approximately 400 patients have been randomized and dosed. The aim of the IA is to evaluate whether an earlier submission of the study results (infusion-related reactions [IRRs]) of the shorter infusion versus the conventional infusion might be possible with a lower number of patients exposed. It is important to note that the currently approved infusion regimen is a barrier to treatment of patients in infusion centers due to the overall duration of ocrelizumab treatment (i.e. at least 5.5 hours). The shorter infusion (i.e. about 3.5 to 4 hours in total) would significantly reduce both the patient burden and the burden of patient management in the infusion center (e.g. scheduling two patients in a day rather than one), provided the safety profile of the shorter infusion is acceptable at the IA stage. It is therefore of the highest importance that the alternative shorter infusion is added as soon as possible to the treatment options for physicians and patients.

Therefore, an IA will be conducted after approximately 400 patients have been randomized and completed the 24-hour evaluation period after the 1st Randomized Dose. This IA is an administrative interim analysis which will not lead to any changes in the substudy protocol or the SAP. Only patients randomized into the substudy at sites where protocol version 7.0 has been approved (EC/IRB and HA, as well as any other required approval as per local regulations) will be included in the IA. The CCOD for this IA will be 27th September 2019. During the several weeks following this CCOD, all outstanding data queries will be resolved, a database snapshot will be taken for this IA,

and the data will be signed off by the Principal Investigator or delegate. Importantly the data used for the primary summary (IRRs at the 1st Randomized Dose) of the IA will be the final data for patients included in the IA. An independent unblinded data coordinating center (iDCC) will be responsible for preparing a subset of key unblinded data summaries from this IA. These unblinded interim results will be reviewed only by the substudy's independent data monitoring committee (iDMC) and the Sponsor's internal substudy data review board (Substudy DRB). A separate Substudy DRB Charter document describes how the Substudy DRB members (or their delegates) will operate and specifies the subset of key unblinded data summaries to be prepared. Following acceptance of the iDMC recommendation to continue the substudy without any change or with minor changes, the Substudy DRB will review this subset of key unblinded data summaries and decide whether to:

a) authorize the unblinding of the substudy for data from the relevant patients included in the IA (approximately 400) and instruct the substudy team to proceed with the IA, which would then be filed with health authorities if the IA results demonstrate the acceptability of the shorter infusion. The substudy team and Substudy DRB would remain blinded to randomized patients not yet eligible for inclusion in the IA at the time of CCOD (approximately 250 to 300). The final analysis of the substudy, once all randomized patients (approximately 650 to 700) have completed the 24-hour evaluation period after the 1st Randomized Dose and all substudy data have then been cleaned and the database locked, will constitute a safety update for the filing package. For the primary summary at the final analysis, in order to eliminate potential bias from any data changes which might arise after the IA, data used for the primary summary (IRRs at the 1st Randomized Dose) in the IA population (approximately 400) locked at the IA CCOD will be combined with those in the post-IA population (approximately 250 to 300) locked at the final CCOD. Final analyses other than the primary summary will be performed on all data up to the final CCOD.

or

b) instruct the substudy team to continue the substudy in a blinded manner until all patients randomized into the substudy (approximately 650 to 700) have completed the 24-hour evaluation period after the 1st Randomized Dose, and all substudy data have then been cleaned and the database locked. This analysis of approximately 650 to 700 patients will then represent the final analysis of the substudy.

The patients, site personnel and the Sponsor's employees outside the Substudy DRB will remain blinded until the Substudy DRB authorizes unblinding (as described above).

The scope of the analysis of the substudy is defined as follows, based on data available at the time of CCOD:

- **Within** the scope of the analysis are all patients randomized into the substudy in countries where protocol version 7.0 has been approved and who have completed the 24-hour evaluation period after the 1st Randomized Dose

- **Outside** the scope of this analysis are i) patients in the main study who were not randomized into the substudy and ii) patients randomized into the substudy who have not yet completed the 24-hour evaluation period after the 1st Randomized Dose and iii) patients randomized into the substudy in countries where protocol version 7.0 has not been approved
- For in-scope patients randomized into the substudy who have completed the 24-hour evaluation period after the 1st Randomized Dose, the following data are **within** the scope of this analysis:
  - all substudy data
  - relevant data captured at the main study screening assessment
  - all data related to adverse events (AEs), including IRRs, captured in the main study prior to randomization into the substudy (but data other than AE/IRR data in this period are **outside** of scope)
  - all AE data captured in the main study after discontinuation from substudy (i.e., all AEs with onset on or after date of randomization are **within** scope, even if AE onset is after the patient discontinues randomized substudy treatment or if AE onset is after the patient discontinues any ocrelizumab treatment)

2. STUDY DESIGN

This is a prospective, multicenter, randomized, double-blind, controlled, parallel arm substudy evaluating the safety of a shorter duration infusion of ocrelizumab in a subgroup of patients with early stage RRMS enrolled in the main study. Please refer to the main study protocol for full details of the design of the ENSEMBLE main study.

Patients randomized into the substudy originate from two sources: i) patients already enrolled into the main study who meet substudy entry criteria and consent to participate, and ii) patients newly enrolled into the main study with a requirement that they will participate in the substudy, subject to meeting substudy entry criteria. A patient is considered to be enrolled in the substudy once written informed consent to participate has been provided (as indicated on the “Informed consent of Ensemble Plus” eCRF page).

Once substudy eligibility has been confirmed, patients are randomized into one of the following two groups in a 1:1 ratio, stratified by region (United States [US], Canada, Australia versus Rest of the World [ROW]) and by dose at which the patient is randomized:

- Conventional Infusion Group: patients receive 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over approximately 3.5 hours every 24 weeks for the remainder of the substudy duration (as in the main study)
- Shorter Infusion Group: patients receive a shorter duration infusion of 600 mg ocrelizumab in 500 mL 0.9% sodium chloride infused over 2.0 hours followed by 100 mL 0.9% sodium chloride given as a slow infusion over the remaining 1.5 hours, in

order to mimic the standard-length infusion (3.5 hour) every 24 weeks for the remainder of the substudy duration

The ocrelizumab dose and dosing schedule remain the same in this substudy as in the main study, the only change being the duration of ocrelizumab infusion for the shorter infusion group from the 1st randomized infusion onwards. In this substudy, patient assignment to the randomized treatment group (i.e. actual infusion rate) is kept blinded.

As stated above, patients randomized into the substudy originate from two sources, and further details of these two sources are provided below:

Patients Already Enrolled into the Main Study: when the substudy was first initiated, patients already enrolled into the main study were offered the option to be randomized into the substudy. Subject to providing consent and meeting substudy entry criteria, these patients are to be randomized to either conventional infusion or shorter infusion at the next scheduled dose of ocrelizumab i.e. at Dose 3 or Dose 4 or Dose 5 (at the time the substudy was initiated, it was too late to randomize these patients at Dose 2, and the shorter infusion is never used at Dose 1). Among these patients, the first patient was randomized into the substudy on 1st November 2018. Consequently, for the IA, if the infusion schedule is followed exactly, these patients should have received either 1 or at most 2 randomized doses of ocrelizumab treatment by the time of the IA CCOD. By the time of the analysis of all randomized patients (N=650 to 700 approximately), some of the already enrolled patients will by then have received a 3rd Randomized Dose.

Patients Newly Enrolled into the Main Study for the Substudy: after the substudy was initiated, additional new patients were enrolled into the main study with a requirement that they will participate in the substudy, subject to subsequently meeting substudy entry criteria. These patients then undertook the 4-week main study screening period, and then received Dose 1 of their ocrelizumab treatment. These patients were to be randomized to conventional infusion or shorter infusion at the earliest possible dose of ocrelizumab i.e. at Dose 2 (the shorter infusion is never used at Dose 1). Among these patients, the first patient was randomized into the substudy on 22nd March 2019. Consequently, for the IA, these patients will have received 1 or at most 2 randomized doses of ocrelizumab treatment by the time of IA CCOD. By the time of the analysis of all randomized patients (N=650 to 700 approximately), none of the newly enrolled patients will by then have received a 3rd Randomized Dose.

It is expected that approximately 650 to 700 patients will be enrolled in this substudy, approximately 150 patients already enrolled into the main study plus approximately 550 newly enrolled patients.

To fully clarify the terms “Randomized Dose” and “Dose” (or “OCR Dose”), refer to the Table 1 below which shows several example patients.

Table 1 Dose and Randomized Dose in the ENSEMBLE PLUS Substudy

Example Patient Id	OCR Dose 1, Infusions 1 & 2	OCR Dose 2	OCR Dose 3	OCR Dose 4	OCR Dose 5	OCR Dose 6	OCR Dose 7
Patient [redacted]	Main Study	Main Study	Main Study	Main Study	Main Study	Main Study	Main Study
Patient [redacted]	Main Study	Main Study	RD1	RD2	RD3	RD4	RD5
Patient [redacted]	Main Study	Main Study	Main Study	RD1	RD2	RD3	RD4
Patient [redacted]	Main Study	Main Study	Main Study	Main Study	RD1	RD2	RD3
Patient [redacted]	Main Study	RD1	RD2	RD3	RD4	RD5	RD5

OCR=ocrelizumab; RD=randomized dose

The term "Dose X" (or "OCR Dose X") refers to the number of doses since the initiation of ocrelizumab treatment. "Dose 1" refers to the first dose of ocrelizumab the patient receives and this is in the main study (this dose is split into two equal infusions of 300mg on Days 1 and 15). "Dose 2" refers to the second dose of ocrelizumab (600mg) received at Week 24, "Dose 3" refers to the third dose of ocrelizumab (600mg) received at Week 48 etc. (so generally, for $X \geq 2$, "Dose X" refers to the X^{th} dose of ocrelizumab (600mg) received at Week Y, where $Y = (X-1) \times 24$).

The term "Randomized Dose" refers to the dose at which the patient was randomized into the substudy. For example, if a patient were randomized at Dose 3, then Dose 3 is their 1st Randomized Dose, Dose 4 is their 2nd Randomized Dose, Dose 5 is their 3rd Randomized Dose etc (this is Example Patient [redacted] from the table above).

Example patients from the table above are described as follows:

- Example Patient [redacted]: a main study patient who never entered the substudy
- Example Patient [redacted]: an already enrolled patient, randomized at OCR Dose 3

- Example Patient [redacted]: an already enrolled patient, randomized at OCR Dose 4
- Example Patient [redacted]: an already enrolled patient, randomized at OCR Dose 5
- Example Patient [redacted]: a newly enrolled patient, randomized at OCR Dose 2

Some of the summaries described in the sections below are presented by Randomized Dose and then by Dose within Randomized Dose. For example:

1st Randomized Dose (denoted "RD1" and highlighted in yellow in the table above): presented at Dose 2, at Dose 3, at Dose 4 and at Dose 5

2nd Randomized Dose (denoted "RD2" and highlighted in green in the table above): presented at Dose 3, at Dose 4, at Dose 5 and at Dose 6

3rd Randomized Dose (denoted "RD3" and highlighted in blue in the table above): presented at Dose 4, at Dose 5, at Dose 6 and at Dose 7

Some summaries are also presented "Overall" within each Randomized Dose. For example, for the 1st Randomized Dose, an "Overall" summary consolidates the 1st Randomized Dose at Dose 2, 3, 4 and 5 across all patients (but each patient is included / counted only once in any "Overall" summary, since each patient can of course only receive one 1st Randomized Dose, for example). So in this case, for the 1st Randomized Dose, an "Overall" summary consolidates all the yellow highlighted cells in the table above. Similarly, for the 2nd Randomized Dose, an "Overall" summary consolidates all the green highlighted cells in the table above, etc.

2.1 PROTOCOL SYNOPSIS

The protocol synopsis and the schedule of assessments of the substudy are included in the current version of the protocol.

2.2 OUTCOME MEASURES

2.2.1 Primary Outcome Measure

The primary endpoint in this substudy is the proportion of patients with IRRs occurring during or within 24 hours after the 1st randomized infusion of ocrelizumab.

2.2.2 Secondary Outcome Measures

The following secondary IRR-related variables will be summarized:

- Proportion of patients with IRR overall and by dose at randomization
- Intensity of IRRs
- Proportion of patients with serious IRRs
- Symptoms of IRRs
- IRRs leading to treatment discontinuation
- Subgroup analyses according to IRR history (for example, patients with/without IRR at any previous dose)

2.2.3 Exploratory Outcome Measures

The following exploratory variables will be summarized:

- Proportion of patients with Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 (severe or life-threatening) IRRs
- Number of CTCAE Grade 3 or 4 (severe or life-threatening) IRRs

2.2.4 Pharmacokinetic Analysis: Objectives and Outcome Measures

The pharmacokinetic (PK) analysis will assess any potential relationship between the primary endpoint (described above) and the maximum concentration of ocrelizumab (C_{max}).

2.2.5 Pharmacodynamic Outcome Measures

There are no pharmacodynamic endpoints in this study.

2.2.6 Safety Outcome Measures

In addition to the assessment of safety via IRRs, safety will also be regularly assessed via reporting of AEs, vital signs and laboratory data (including CD19, CD4 and CD8).

2.3 DETERMINATION OF SAMPLE SIZE

Determination of sample size was described as follows in the protocol (Version 7.0):

Regarding patients already enrolled into the main study, we assume that approximately 40 and 110 will receive the first dose of randomized treatment at Dose 3 or at Dose 4 / subsequent dose, respectively. In addition, since no previously enrolled patients will receive shorter infusion at Dose 2, the Sponsor plans to include approximately 550 new patients, of which approximately 500 are expected to receive the randomized treatment at Dose 2 and be evaluable for the analysis. In total, approximately 650 patients are expected to be randomized into two groups and be evaluable for the final clinical study report (CSR).

The different IRR rates at Dose 2, 3 or 4 or at subsequent dose are considered in the calculation of the pooled IRR rate. In the Opera studies (WA21092 and WA21093), 13.7%, 9.6% and 7.8% of patients had at least one IRR at Dose 2, 3 and 4, respectively, which leads to an expected pooled IRR rate of approximately 12.4% excluding Dose 1 for this substudy. Therefore, we assume an observed IRR rate in the conventional infusion group of 12.4% excluding Dose 1. The 95% confidence intervals (CIs) of the IRR rate difference between shorter and conventional infusion groups as a function of the observed IRR rate in the shorter infusion group are listed in Table 2 (below). The CIs were calculated based on the assumption of Binomial distributed IRR rates, which provide sufficient precision around the IRR rates for this substudy.

Table 2 95% CI of IRR rate difference under different scenarios, based on N=650 (shown as Table 4 in Protocol Version 7.0)

IRR rate in conventional infusion (%)	IRR rate in shorter infusion (%)	Difference in IRR rate (%)	95% CI
12.4	12.4	0	(-5.1, 5.1)
12.4	13.4	1	(-4.2, 6.2)
12.4	14.4	2	(-3.2, 7.2)
12.4	15.4	3	(-2.3, 8.3)
12.4	16.4	4	(-1.4, 9.4)
12.4	17.4	5	(-0.5, 10.5)
12.4	18.4	6	(0.5, 11.5)

CI=confidence interval; IRR=infusion-related reaction

The motivation for undertaking this IA based on approximately 400 patients has been described above in the "Background" section. To demonstrate the impact of fewer patients on the sample size calculation shown in the study protocol (Version 7.0), Table 2 above is repeated below as Table 3, the only difference being that Table 3 is now based on 400 patients rather than 650:

Table 3 95% CI of IRR rate difference under different scenarios, based on N=400

IRR rate in conventional infusion (%)	IRR rate in shorter infusion (%)	Difference in IRR rate (%)	95% CI
12.4	12.4	0	(-6.5, 6.5)
12.4	13.4	1	(-5.6, 7.6)
12.4	14.4	2	(-4.7, 8.7)
12.4	15.4	3	(-3.8, 9.8)
12.4	16.4	4	(-2.9, 10.9)
12.4	17.4	5	(-2.0, 12.0)
12.4	18.4	6	(-1.1, 13.1)

CI=confidence interval; IRR=infusion-related reaction

Comparison of the two tables above shows that using 400 rather than 650 patients increases the expected width of the 95% CI for the between-group difference from around 10 to 11 percentage points to around 13 to 14 percentage points. Depending on the IA results, a sample size of 400 patients could be sufficient to demonstrate the acceptability of the shorter infusion.

2.4 ANALYSIS TIMING

Full details of analysis timing are provided in Section 1, "Background" above.

In summary, the analysis of the substudy will be conducted after the last enrolled patient completes the 24-hour evaluation period after the 1st randomized infusion. An IA will be undertaken by the iDCC with a CCOD of 27th September 2019, including approximately 400 patients. The iDMC and Substudy DRB only will review a subset of key unblinded data summaries from this IA and the Substudy DRB will determine a) whether or not the substudy team should be unblinded, the full IA should be undertaken (all summaries, not just a subset) and this IA should be filed with health authorities or b) to place all further unblinding and preparation of data summaries on hold until all patients randomized into the substudy (approximately 650 to 700) have completed the 24-hour evaluation period after the 1st Randomized Dose, in which case this would represent the final analysis of the substudy.

3. STUDY CONDUCT

3.1 RANDOMIZATION AND BLINDING

Patients were randomized into two groups (Conventional Infusion or Shorter Infusion) in a 1:1 ratio. An independent IxRS provider conducted randomization (with use of blocked randomization) and holds the treatment assignment code. Patients were stratified by region (US / Canada / Australia vs. ROW) and the Dose at which the patient is randomized. For patients previously enrolled into the main study, randomization takes place at the next scheduled infusion visit i.e. at Dose 3, 4 or 5. For newly enrolled patients, randomization takes place at Dose 2.

Blinding of the infusion rates and the actual duration of the infusion is achieved by the following measures:

- The substudy group assignment (randomization) codes are only visible to the pharmacy personnel preparing the drug infusions and to the unblinded personnel operating the infusion pump (from now on, referred to as “infusion nurse”)
- Infusions are pre-loaded and placed into standardized infusion cover bags and placed on an infusion rack, and the actual infusion administration pump is covered and operated by the infusion nurse
- The actual infusion rates and associated activities related to infusion administration are blinded to the site study team (including the study coordinator and the treating investigator), patient and the Sponsor
- The conventional-length infusion is administered as described in the main study protocol. The shorter infusion is administered within 2 hours (500 mL infusion volume at the rates as presented in Table 3 in the substudy protocol), followed immediately by administration of a separate 100mL normal saline (0.9 % NaCl) bag without any additional component over the remaining 1.5h with an approximate infusion rate of 60mL/hr. For patients randomized to the conventional-length infusion, the infusion nurse mimics a switch infusion at approximately 2 hours (timing to be adapted depending on the infusion rate adaptation during the first 2 hours). The infusion nurse checks and adjusts the infusion rates periodically as needed,

both for maintaining the correct rates of the infusion and for maintaining the blinding/masking of the two infusion groups (see Figure 1 and Figure 2 below). Adjustments needed for managing IRRs are allowed at any time and should follow the guidance from the main study protocol. Please refer to substudy protocol Section 4.3.2 Dosage, Administration and Compliance for further details on the infusion preparation and administration.

- The infusion nurse (unblinded) or the clinical nurse (blinded) collect vital signs at the time of pre-medication onwards (see Section 4.5.4 of the main study protocol). Vital signs will be reported in the electronic case report form (eCRF). The blinded treating investigator evaluates and confirms all IRRs occurring during or within 24 hours post-infusion.
- The unblinded information related to the infusion is entered into the IxRS system by the unblinded site staff member. The unblinded site staff members must keep confidential any data related to the infusion (group allocation, infusion duration and content, etc.):
  - they must not further communicate these data, neither verbally nor in writing– they must maintain the corresponding files in a locked, access-restricted location
- Additional operational measures are undertaken at local level to ensure the appropriate level of blinding of the personnel involved and the data collected
- The IxRS service provider and iDMC members have access to treatment assignment in order to fulfil their roles during the substudy

Figure 1 Blinding Procedure

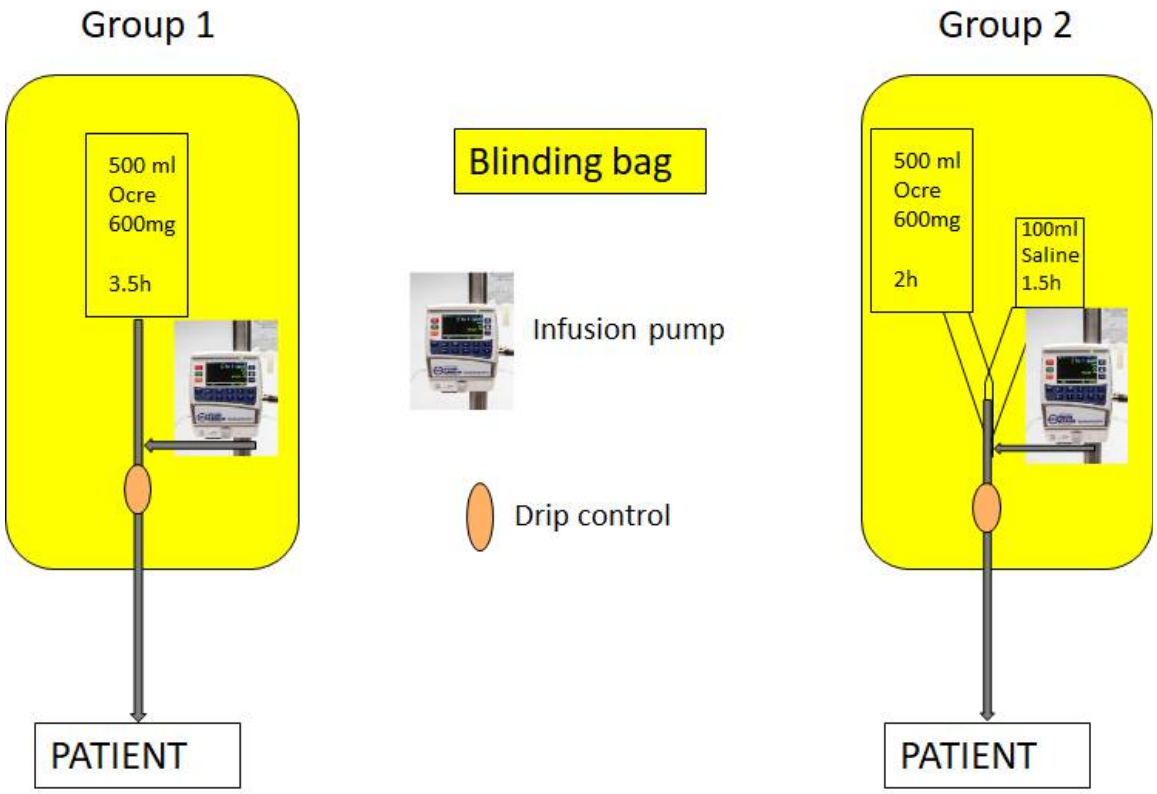
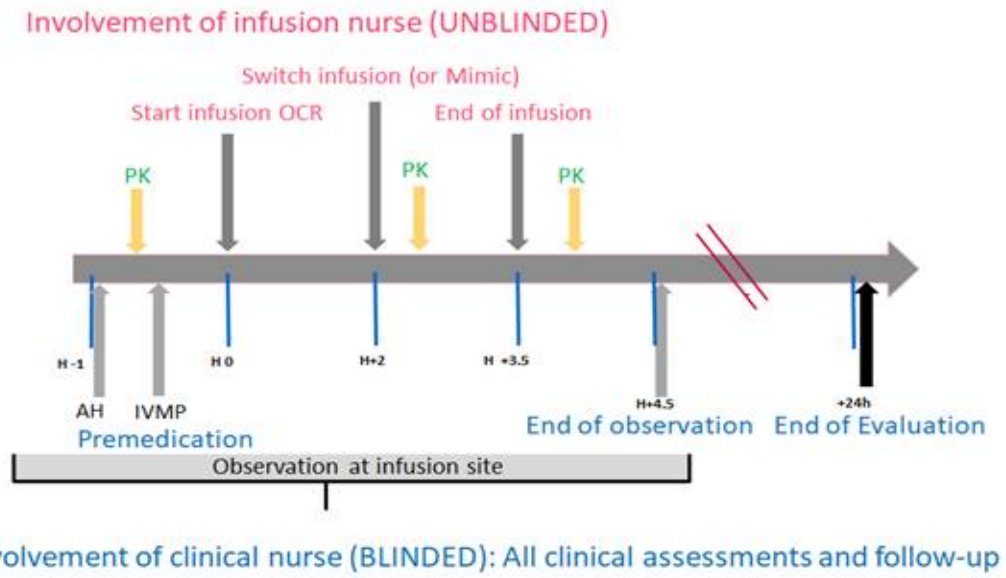


Figure 2 Figure Blinding Procedure



AH=antihistamine; H=hour; IVMP=intravenous methylprednisolone; OCR=ocrelizumab; PK=pharmacokinetic

3.2 INDEPENDENT REVIEW FACILITY

In this substudy, there is no Independent Review Facility or Reading Center to review data for the purpose of making any diagnosis or providing any outcome measure.

3.3 DATA MONITORING

In the interests of patient safety, an iDMC is reviewing cumulative unblinded safety data from the substudy at approximately 3-month intervals, as described in the iDMC Charter. The iDMC will discontinue its activities once the analysis is completed.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

The primary summaries of IRRs will be performed using the Intent-to-Treat (ITT) Population. The Per-Protocol (PP) Population will be used in order to evaluate the influence of major protocol deviations and as a sensitivity check of the primary analyses of IRRs. Other than analyses of IRRs, safety analyses will be based on the Safety Population only. The Safety Population will also be used as a sensitivity check of the primary summaries of IRRs. The Pharmacokinetic (PK) Population will be used for supportive analyses.

All Patients Population

All patients enrolled into the substudy (i.e. written informed consent has been provided) will be included in the All Patients Population, whether or not they were randomized.

ITT Population

All randomized patients will be included in the ITT Population. Patients will be analyzed according to their randomized treatment, regardless of treatment actually received.

PP Population

Patients in the ITT Population with the following major protocol deviations (identified by category and sub-category) will be excluded from the PP Population. Consideration will be given to whether or not the deviation will impact assessment of the primary endpoint (i.e. IRRs):

Category: Main Study Entry Criteria

It is not possible to provide an exhaustive list of sub-categories here. Some examples of this kind of deviation are:

- Informed consent not provided by patient for latest version of protocol ("Protocol Amendment" eCRF page)
- Patient's age at the main study screening visit was not in the range 18-55 years

Category: Substudy Inclusion Criteria

Sub-categories:

- Informed consent not provided by patient ("Informed consent of Ensemble Plus" eCRF page)
- Patient unable to comply with the substudy protocol, in the investigator's judgment

Category: Substudy Exclusion Criterion

Sub-category:

- Patient has previously experienced a serious IRR with ocrelizumab treatment

Category: Medication-Related

It is not possible to provide an exhaustive list of sub-categories here. Examples of this kind of deviation include failure to administer methylprednisolone and/or anti-histaminic drugs in line with protocol requirements, since this may increase the chance of IRRs in those patients.

Category: Procedural: Infusion-Related

It is not possible to provide an exhaustive list of sub-categories here. Some examples of this kind of deviation are:

- Patients who received any randomized treatment other than that to which they were randomized (excluded from the PP Population from the time of this deviation onwards)
- Blinded site staff becoming unintentionally unblinded to a patient's blinded randomized treatment assignment
- Patients who were mis-stratified for randomization. Since the randomization is stratified by region and 1st Randomized Dose, an example of this would be a patient who started randomized treatment at Dose 2, but was incorrectly randomized from the Dose 3 randomization list in the IxRS system (and in this situation, it is impossible to know whether the patient would have received the same treatment if the stratification had been performed correctly).

Category: Procedural: Other

It is not possible to provide an exhaustive list of sub-categories here. An example of this kind of deviation is non-adherence to schedule of assessments.

Category: Other

It is not possible to provide an exhaustive list of sub-categories here. This will include any major protocol deviations detected during the study conduct not classified in one of the above categories/sub-categories.

The data sources of major protocol deviations in the clinical trial database will be Roche's Protocol Deviation Management System (PDMS), plus filenotes created to

document randomization/stratification issues encountered with the IxRS system. Entries in the PDMS system are made and maintained by study medical monitors, and will be provided in the form of an Excel file to substudy statistical programmers for incorporation into the substudy datasets. Similarly, an Excel file will be prepared to summarize all filenotes relating to IxRS technical issues, and again provided to substudy statistical programmers for incorporation into the substudy datasets.

The following programmatic data checks will be undertaken:

- Check that all patients met all main study entry criteria, based on the question "Did subject meet all eligibility criteria?" on the "Subject Eligibility" eCRF page
- Check that the patient's age at the main study screening visit was in the range 18-55 years
- Check that no patient with a serious IRR on ocrelizumab treatment prior to randomization was then randomized
- Check that each patient provided informed consent for the substudy (based on the "Informed Consent of Ensemble Plus" eCRF page)
- Check that each patient actually received the correct randomized treatment (the actual treatment is collected in the IxRS system)

Safety Population

The Safety Population will include all randomized patients who received any dose or part of a dose of ocrelizumab treatment. Patients who received any randomized treatment other than that to which they were randomized will be analyzed according to the treatment actually received. Any patient receiving at least one shorter infusion (whether or not this is their randomized treatment) at any time during the substudy will be assigned to the shorter infusion group at all randomized doses, regardless of the randomized dose at which the patient actually first received the shorter infusion.

Pharmacokinetic (PK) Population

The PK Population will include all randomized patients receiving any ocrelizumab treatment who had at least one measurable concentration value unless major protocol deviations or unavailability of information occurred that may interfere with the PK evaluation.

4.2 ANALYSIS OF STUDY CONDUCT

All relevant data up to the point of the CCOD will be included to evaluate substudy conduct. The following summaries will be prepared to evaluate the substudy conduct (number of patients and percentage):

- List of randomization failures – these are patients who consented to participate in the substudy but were not randomized. A listing of these patients will be provided, which will include whether the patient was already or newly enrolled,

date of first ocrelizumab treatment, date of informed consent and the reason for non-randomization.

- Enrollment by country and center. A summary of randomized treatment assignments will be presented. A summary of the numbers of patients enrolled but not randomized will also be presented.
- Randomization assignment by stratification factors: region (US, Canada, Australia versus ROW) and 1st Randomized Dose. Listings will be prepared to show a) these stratification factors and b) any discrepancies in these stratification factors when the clinical trial database and IxRS databases are compared.
- Summaries of patient disposition (tabular and graphical), including the number of randomized doses received and numbers of patients ongoing in and discontinued from the substudy. This will be presented for all patients, for patients already enrolled in the main study, and for patients newly enrolled.
- Summary of reasons for early discontinuation from the substudy, for all patients, for patients already enrolled in the main study, and for patients newly enrolled.
- Summary of reasons for early discontinuation from ocrelizumab treatment, for all patients, for patients already enrolled in the main study, and for patients newly enrolled.
- Summary of reasons for early discontinuation from the main study, for all patients, for patients already enrolled in the main study, and for patients newly enrolled.
- Summaries of ITT, PP, Safety and PK Populations, showing numbers of patients in each population
- Summary and listing of major protocol deviations, leading to exclusion from the PP Population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

To assess treatment group comparability, summaries of baseline characteristics will be presented by randomized treatment group. These will be for the ITT Population only.

For continuous variables, the mean, median, SD, minimum, and maximum will be calculated. For categorical variables, the number and percentage in each category will be displayed. The units/categories to be used are indicated within the brackets and separated by commas.

4.3.1 Demography

In addition to summary statistics and frequency counts for all patients in the ITT Population, demographic characteristics will also be summarized separately for patients already enrolled in the main study, and for patients newly enrolled. The following characteristics will be summarized:

- Age at Randomization (years): summary statistics displayed will include mean, median, SD, minimum, and maximum, percentage and number in each category (<40, ≥40). Note that the main study required patients to be aged 18-55 inclusive, but there are no specific age requirements for the substudy.
- Sex at Screening Visit of Main Study: the number and percentage of male and female patients will be displayed.
- Race at Screening Visit of Main Study: the number and percentage of the following categories will be displayed: White; Black or African American; Asian (Indian Subcontinent, Other than Indian subcontinent), American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; Multiple and Unknown
- Ethnicity at Screening Visit of Main Study: the number and percentage of the following categories will be displayed: Hispanic or Latino, not Hispanic or Latino, Not Reported and Unknown
- Weight (kg) at Screening Visit of Main Study: summary statistics will be displayed, as described for age at randomization.
- Body Mass Index (BMI) at Screening Visit of Main Study: summary statistics will be displayed, as described for age at randomization.
- Details of demographic characteristics will be listed.

4.3.2 MS Disease History at Randomization

- Duration since MS symptom onset at randomization (years): summary statistics calculated will include mean, median, SD, minimum, and maximum (calculated in years, i.e., divide by 365.25). Frequency counts will also be presented.
- Duration since MS diagnosis at randomization (years): summary statistics calculated will include mean, median, SD, minimum and maximum (calculated in years, i.e., divide by 365.25). Frequency counts will also be presented.

Duration since MS symptom/diagnosis onset will be calculated up to the randomization date. If month of symptom/diagnosis onset date is missing, the month of January will be used. If symptom/diagnosis onset date is missing, the first (1st) of the month will be used.

Details of MS disease history will be listed.

4.3.3 Pre-Randomization IRRs and Serious IRRs

The number of patients with an ocrelizumab infusion, the number and percentage with any pre-randomization IRR and the number and percentage with any pre-randomization

serious IRR will be presented. For newly enrolled patients randomized at Dose 2, these numbers will be presented at Dose 1 Infusion 1, Dose 1 Infusion 2 and overall. For previously enrolled patients randomized at Dose 3, 4 or 5, these numbers will be presented at Dose 1 Infusion 1, Dose 1 Infusion 2, Dose 2, Dose 3, Dose 4 and overall. An overall summary of these numbers for all patients in the ITT Population will also be presented.

4.3.4 Previous Diseases (Other Than MS) Prior to Randomization

Diseases reported on the “General Medical History and Baseline Conditions Log” eCRF page are summarized as previous diseases if disease status was recorded as a) "Resolved" or as b) "Ongoing" (with or without treatment) and disease end date was known to be before date of substudy randomization or if c) the “End Date Unknown” box was checked (which indicates the disease had ended but the end date was unknown).

Diseases reported on the “Adverse Event/IRR/MS Relapse” eCRF page are summarized as previous diseases if a) AE onset date was on or after date of first ocrelizumab treatment in the main study, and AE end date was before the date of substudy randomization or b) if AE onset date was before date of first ocrelizumab treatment in the main study, and AE intensity worsened after initiation of ocrelizumab treatment but before date of substudy randomization, and AE end date was before the date of substudy randomization.

Previous diseases reported via the “General Medical History and Baseline Conditions Log” eCRF are summarized separately from those reported via the “Adverse Event/IRR/MS Relapse” eCRF page. In each of these two separate summaries, the total number of patients with at least one previous disease and the total number of previous diseases will be presented. The number and percentage of patients reporting previous diseases will be presented by system organ class (SOC) and preferred term (PT) (for further details of how AEs are coded and reported, please refer to the “Common Adverse Events” section later in this document).

4.3.5 Current Diseases (Other Than MS)

Diseases reported on the “General Medical History and Baseline Conditions Log” eCRF page are summarized as current diseases if disease status was recorded as "Ongoing" (with or without treatment) and disease end date was missing and the “End Date Unknown” box was not checked.

Diseases reported on the “Adverse Event/IRR/MS Relapse” eCRF page are summarized as current diseases a) AE onset date was on / after date of first ocrelizumab treatment in the main study and AE end date was either missing or on / after date of substudy randomization or b) if AE onset date was before date of substudy randomization, and AE intensity worsened after substudy randomization, and AE end date was unknown or on / after the date of substudy randomization.

Current diseases reported via the "General Medical History and Baseline Conditions Log" eCRF are summarized separately from those reported via the "Adverse Event/IRR/MS Relapse" eCRF page. In each of these two separate summaries, the total number of patients with at least one current disease and the total number of current diseases will be presented. The number and percentage of patients reporting current diseases will be presented by SOC and PT.

4.3.6 Previous Treatments (Other Than For MS) Prior to Randomization

- Did patient receive any prior treatments, other than for MS? (defined as treatments with a stop date before date of randomization): number and percentage of patients (yes or no)
- Each previous non-MS treatment: number and percentage of patients receiving each treatment

4.3.7 Concomitant Treatments (Other Than For MS)

- Did patient receive any concomitant treatments, other than for MS? (defined as treatments with a start date on or after date of randomization, or with a start date before date of randomization but continuing into the substudy on/after date of randomization): number and percentage of patients (yes or no)
- Each previous non-MS treatment: number and percentage of patients receiving each treatment

4.4 EFFICACY ANALYSIS

No analyses of efficacy data are planned for this substudy.

4.5 SAFETY ANALYSES

This is a descriptive study and no formal inferential statistical analyses will be performed.

Summaries of the primary endpoint (proportion of patients with IRRs occurring during or within 24 hours after the 1st randomized infusion of ocrelizumab, as described below in Section 4.5.2.1) will provide point estimates of the between-treatment difference and associated symmetric two-sided 95% CIs. These summaries will be presented both unstratified and stratified for the stratification factors of 1st Randomized Dose and region (US / Canada / Australia vs. ROW).

Safety data include but are not restricted to AE data, laboratory data, previous and concomitant treatment data, infusion information including IRR data, withdrawal data, fatalities, vital signs and dosing information.

All summaries of IRRs will be based on the ITT Population (with the exception of additional sensitivity analyses for the primary endpoint only, based on PP and Safety Populations). All other safety summaries will be based on the Safety Population.

The term “Pre-Randomization” will be used refer to the period of time before the patient is randomized into the substudy. The term “Randomized Period” will be used to refer to the period of time during which a patient receives randomized treatment in the substudy. If a randomized patient discontinues from randomized treatment, they effectively discontinue from the substudy, and after this they will either:

a) continue to receive ocrelizumab in the main study according to conventional infusion guidelines – this period of time will be referred to as “Post Substudy, On Treatment”

b) discontinue ocrelizumab treatment entirely and enter a safety follow-up period, as described in the main study protocol – this period of time will be referred to as “Post Substudy, Off Treatment”

4.5.1 Exposure to Study Medication

Within the substudy, in both randomized groups ocrelizumab is given as single infusions of 600mg at 24-week intervals. The only difference between the randomized groups is the duration of the infusion.

Patients will be considered to have received a dose of treatment if at least part of that infusion was given. If a dose is completely missed instead of delayed, the next dose number will be based on the number of previous doses received.

For each patient, the length of exposure to randomized treatment is from the date on which the patient first received randomized treatment (Substudy Day 1) until the last known alive date or CCOD, whichever is earlier. For patients who withdrew early from randomized treatment, the exposure is until the last known alive date (i.e., duration of exposure is equivalent to duration of observation period, and these terms are used interchangeably in this SAP). To summarize, the duration of exposure for a patient will be calculated as:

(Date of last contact* – date of 1st Randomized Dose) + 1

* Earlier of 1) date of CCOD 2) last known alive date

The following aspects of exposure to ocrelizumab will be summarized by randomized group:

- Treatment duration (weeks): frequency counts (number of patients and percentage) for 0-23 weeks, 24-47 weeks and 48-71 weeks will be presented
- Number of doses received: frequency counts (number of patients and percentage) and summary statistics (mean, SD and median) will be presented
- Total cumulative dose (derived to mg): summary statistics (mean, SD, median, lower and upper quartiles, minimum and maximum) will be presented

- Ocrelizumab infusion duration (minutes): summary statistics (mean, SD, median, lower and upper quartiles, minimum and maximum) will be presented by Randomized Dose and overall (all randomized doses).
- The number and percentage of infused patients with $< 80\%$ and $\geq 80\%$ of the planned infusion volume will be presented, along with the number and percentage of infused patients who were pre-treated with methylprednisolone (or equivalent) only, with antihistamine only and with both methylprednisolone (or equivalent) and antihistamine. These summaries will be presented by Randomized Dose and then by Dose within Randomized Dose (and overall within Randomized Dose i.e. across all Doses).
- The number and percentage of patients in either randomized group with any IRR receiving <80% or ≥80% of the planned ocrelizumab volume will be presented, along with the number and percentage of infused patients in the shorter infusion group with any IRR receiving <80% or ≥80% of the planned saline volume. These summaries will be presented by Randomized Dose and then by Dose within Randomized Dose (and overall within Randomized Dose i.e. across all Doses).

4.5.2 Adverse Events

4.5.2.1 Infusion-Related Reactions

IRRs are collected on the "Adverse event/IRR/MS relapse" and "Infusion Related Reaction" eCRF pages. The symptom(s) of an IRR and the IRR itself may be of different intensities. IRR symptoms (collected on the "Infusion Related Reaction" eCRF page) will be coded in MedDRA and summarized by SOC and PT. IRRs (in fact all AEs) are categorized on the "Adverse Event/IRR/MS Relapse" eCRF page as occurring 1) during infusion or 2) within 24 hours after end of infusion.

Summaries of pre-randomization IRRs and serious IRRs are described above in Section 4.3.3. In all other summaries of IRRs, only IRRs occurring during the substudy will be included. IRRs occurring after withdrawal from the substudy will not be included in these IRR summaries (but will be included in AE summaries, which will include all AEs with an onset date after the date of randomization, even if the onset is after the patient discontinues randomized treatment).

The primary endpoint of this substudy is the proportion of patients with IRRs occurring during or within 24 hours after the 1st randomized infusion of ocrelizumab. A stratified method will be applied, to take account of the two stratification factors, region and 1st Randomized Dose. The weighted average of the proportion difference across strata based on Cochran-Mantel-Haenszel weights is estimated. This approach will result in a stratified estimated difference between the proportions in the two randomized groups, which will be presented along with an associated 95% CI. This method is described by (Zhao et al. 2001) and its practical implementation is further described by (Zhang 2016). The (unstratified) estimated difference between the proportions in the two randomized

groups will also be presented along with an associated 95% CI. This summary will be presented for all patients, for patients with at least one pre-randomization IRR and for patients with no pre-randomization IRRs. The primary endpoint will be summarized for the ITT Population, and also for the PP and Safety Populations additionally, as sensitivity analyses. The primary endpoint will be further described in graphical bar-chart format (ITT Population only).

If the IA leads to an early unblinding of the substudy team to patients included in the IA, in order to eliminate potential bias from any data changes which might arise after the IA, data used for the primary summary (IRRs at 1st Randomized Dose) in the IA population (N=400 approximately) locked at the IA CCOD will be combined with those in the post-IA population (N=250 to 300 approximately) locked at the final CCOD to perform the primary summary at the final analysis. Final analyses other than the primary summary will be performed on all data up to the final CCOD.

An IRR overview summary will be presented, showing the number and percentage of infused patients with any IRR and any serious IRR. This summary will be presented by Randomized Dose and then by Dose within Randomized Dose (and overall within Randomized Dose i.e. across all Doses), and overall (all randomized doses). This summary will be presented for all patients, for patients with at least one pre-randomization IRR and for patients with no pre-randomization IRRs.

Further summaries of IRRs will be presented by Randomized Dose and then by Dose within Randomized Dose as follows:

- The number and percentage of patients with IRR symptoms will be presented by SOC (in decreasing order of overall incidence) and PT (in decreasing order of overall incidence).
- The number and percentage of patients with IRRs by most extreme intensity will be presented (Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening, grade 5 = fatal). Multiple IRRs in one patient are counted only once at the most extreme (highest) intensity observed.
- The number and percentage of patients with IRRs, grouped by most extreme intensity into not severe (Grade 1 or 2) and severe (Grade 3 to 5) will be presented. Again, multiple IRRs in one patient are counted only once at the most extreme (highest) intensity observed.
- The number and percentage of patients with IRRs leading to intervention in ocrelizumab infusion, with intervention defined as infusion slowed down, or infusion interrupted or infusion discontinued
- The number and percentage of patients with IRR symptoms leading to discontinuation of ocrelizumab infusion will be presented by SOC (in decreasing order of overall incidence) and PT (in decreasing order of overall incidence).

- The number and percentage of patients with IRR symptoms leading to interruption of ocrelizumab infusion will be presented by SOC (in decreasing order of overall incidence) and PT (in decreasing order of overall incidence).
- The number and percentage of patients with IRR symptoms leading to slowing down of ocrelizumab infusion will be presented by SOC (in decreasing order of overall incidence) and PT (in decreasing order of overall incidence).
- The number and percentage of patients with IRRs who received pre-medications (methylprednisolone (or equivalent) only, antihistamine only, methylprednisolone (or equivalent) plus antihistamine)
- The number and percentage of patients with IRR symptoms will be presented by SOC (in decreasing order of overall incidence) and PT (in decreasing order of overall incidence), shown separately for the following two time periods: a) during ocrelizumab/saline infusion and b) within 24 hours after the end of ocrelizumab/saline infusion
- The number and percentage of patients with IRR symptoms will be presented by SOC (in decreasing order of overall incidence) and PT (in decreasing order of overall incidence), shown separately for the following two time periods: a) from the start of ocrelizumab infusion to switch/dummy switch to saline infusion and b) from switch/dummy switch to saline infusion to end of infusion.
- The number and percentage of patients with IRRs by outcome (recovered / resolved, recovered / resolved with sequelae, recovering / resolving, not recovered / not resolved, fatal and unknown)
- The number and percentage of patients with IRRs who received symptomatic treatments for any IRR

All IRRs and symptoms occurring before and during the substudy will be listed, with separate listings created for IRRs occurring prior to randomization and for IRRs occurring post-randomization during the substudy.

4.5.2.2 Overview of Adverse Events

To provide an overview of patient safety results, an AE profile summary table will be presented. For each randomized group, this will show the following:

Total number of patients (and percentage) with at least one AE

Total number of AEs

Total number of deaths (and percentage)

Total number of patients (and percentage) with at least one of:

- AE with fatal outcome
- Serious AE (SAE)
- Serious infection (defined using AEs falling into the MedDRA “Infections and Infestations” SOC and “serious” responses to the question “Is the event non-serious or serious?” from the “Adverse Event/IRR/MS Relapse” eCRF page)

- SAE leading to withdrawal from ocrelizumab treatment (withdrawal from ocrelizumab treatment defined as “drug withdrawn” in response to the SAE, taken from the “Adverse Event/IRR/MS Relapse” eCRF page)
- SAE leading to ocrelizumab dose modification/interruption (modification/interruption defined as “dose delayed”, “dose reduced” or “drug temporarily interrupted” in response to the SAE, taken from the “Adverse Event/IRR/MS Relapse” eCRF page)
- AE leading to withdrawal from ocrelizumab treatment (withdrawal from ocrelizumab treatment defined as “drug withdrawn” in response to the AE, taken from the “Adverse Event/IRR/MS Relapse” eCRF page)
- AE leading to ocrelizumab dose modification/interruption (modification/interruption defined as “dose delayed”, “dose reduced” or “drug temporarily interrupted” in response to the AE, taken from the “Adverse Event/IRR/MS Relapse” eCRF page)
- IRRs leading to withdrawal from ocrelizumab treatment at the 1st Randomized Dose
- Malignancies (defined using AEs falling into the Standard MedDRA Query “'Malignant tumours (narrow)” from the “Adverse Event/IRR/MS Relapse” eCRF page)
- Infections (defined using AEs falling into the MedDRA “Infections and Infestations” SOC from the “Adverse Event/IRR/MS Relapse” eCRF page)

The AE profile summary described above will be repeated per 100 patient-years (100PY) exposure, in order to adjust for any differences between randomized groups in the duration of observation period. Estimates of incidence rates per 100PY will be provided, along with associated 95% CIs. For further details, please refer to the “Common Adverse Events” section later in this document.

4.5.2.3 Common Adverse Events

AEs will be defined as all AEs including IRRs and serious MS relapses, but excluding non-serious MS relapses. Therefore, those AEs recorded on the “Adverse event/IRR/MS relapse” eCRF page will be included.

AEs reported from randomization onwards at all randomized doses will be included in summary tables. These summary tables will show all AEs combined, and will not show any separate summaries by Randomized Dose nor Dose.

All AEs with an onset date after the date of randomization will be included, even if the onset is after the patient discontinues randomized treatment. AEs will be flagged by substudy period based on time of onset, as described at the end of Section 2 (periods are “Randomized Period”, “Post Substudy, On Treatment” and “Post Substudy, Off Treatment”).

For each AE recorded, the term entered by the investigator describing the event (the "reported term") will be assigned a standardized term (the "preferred term" (PT)) based on the Medical Dictionary for Regulatory Activities (MedDRA) World Health Organization (WHO) dictionary of terms. All analyses of AE data will be performed using the PTs unless otherwise specified. All AEs will be mapped to PTs and system organ classes (SOCs).

Summaries of AEs will be generated summarizing the incidence of treatment-emergent AEs only. These are defined as either: a) AEs with an observed or imputed date of AE onset which is on or after the date of 1st Randomized Dose or b) AEs with an observed or imputed date of AE onset which is before the date of 1st Randomized Dose and which worsens in intensity. An AE with a completely missing non-imputed start date will be assumed to be treatment emergent unless the AE event has a complete non-imputed end date which is prior to the date of the 1st Randomized Dose. In this substudy, the term "treatment-emergent" will always be used to mean "randomization-emergent" (it does not refer to the first dose of ocrelizumab treatment in the main study).

For each randomized 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. In some summaries, AEs will also be evaluated by exposure time (incidence rate per 100 patient-years (100PY) exposure), in order to adjust for any differences between randomized groups in the duration of observation period. Estimates of incidence rates per 100PY will be provided, along with associated 95% CIs calculated using an exact method based on the Poisson distribution. 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 the same patient will be counted only once at the greatest intensity/highest grade for this PT. For AEs leading to death, the most extreme intensity will be overwritten by Grade 5 (death).

SAEs are defined as all serious AEs, including serious MS relapses and serious IRRs.

The number and percentage of patients experiencing adverse events will be presented by SOC and PT. This summary will be repeated per 100PY to account for the duration of patient exposure.

The most frequent AEs ($\geq$5% in either randomized group) will be presented by PT.

The number and percentage of patients experiencing AEs suspected to be caused by ocrelizumab will be presented by SOC and PT.

All AEs occurring post-randomization will be listed.

4.5.2.4 Adverse Events by Intensity

The number and percentage of patients experiencing AEs will be presented by most extreme intensity by SOC and PT. This summary will be repeated showing only AEs with maximum intensity of Grade 3, 4 or 5.

4.5.2.5 Deaths

All patient deaths occurring post-randomization will be listed.

4.5.2.6 Serious Adverse Events

The number and percentage of patients experiencing an SAE will be summarized by SOC and PT. This summary will be repeated per 100PY to account for the duration of patient exposure.

The number and percentage of patients experiencing SAEs suspected to be caused by ocrelizumab will be presented by SOC and PT.

The number and percentage of patients experiencing SAEs will be presented by most extreme intensity by SOC and PT.

All SAEs occurring post-randomization will be listed.

4.5.2.7 Adverse Events Which Led to Early Discontinuation from Ocrelizumab Treatment

The number of patients experiencing an AE which led to early discontinuation from ocrelizumab treatment will be summarized by SOC and PT.

All AEs which led to early discontinuation from ocrelizumab treatment will be listed.

4.5.2.8 Adverse Events Which Led to Modification or Interruption of Ocrelizumab Treatment

The number of patients experiencing an AE which led to modification or interruption of ocrelizumab treatment will be summarized by SOC and PT.

4.5.2.9 Pregnancies

Information on pregnancy tests and pregnancy outcomes post-randomization will be listed.

4.5.3 Laboratory Data

4.5.3.1 Hematology and Biochemistry

All available laboratory assessments (hematology and biochemistry separately) will be summarized in the IA (N=400 approximately) and in the analysis of all randomized patients (N=650 to 700 approximately).

To summarize laboratory data, all assessments, both scheduled and unscheduled, will be included. Visit windows will be applied as follows:

- Randomization: most recent available assessment prior to substudy randomization (Substudy Day 1)
- 24 weeks after 1st Randomized Dose: include all assessments after substudy randomization (Substudy Day 2) up to 36 weeks after 1st Randomized Dose (Substudy Day 253)
- 48 weeks after 1st Randomized Dose: include all assessments from the day after 36 weeks after 1st Randomized Dose (Substudy Day 254) to 60 weeks after 1st Randomized Dose (Substudy Day 421)
- 72 weeks after 1st Randomized Dose: include all assessments from the day after 60 weeks after 1st Randomized Dose (Substudy Day 422) to 84 weeks after 1st Randomized Dose (Substudy Day 589)
- 96, 120, 144 etc weeks after 1st Randomized Dose: continue to define windows in the same way as described above

If multiple values of the same laboratory parameter occur within the same time window, the worst value for that parameter will be presented in the summary table.

Absolute value and change from randomization values at each visit (24 weeks after 1st Randomized Dose, 48 weeks after 1st Randomized Dose etc.) will be summarized (mean, SD, median, minimum and maximum).

A summary of the number and percentage of patients with single and replicated laboratory abnormalities will presented for each laboratory parameter.

4.5.3.2 CD4, CD8 and CD19

All available CD4, CD8 and CD19 assessments will be summarized in the IA (N=400 approximately) and in the analysis of all randomized patients (N=650 to 700 approximately).

Visit windows will be applied to CD4, CD8 and CD19 assessments in the same way as described above for hematology and biochemistry.

Summary statistics will be presented for CD19 values, separately for patients experiencing IRRs during/post-infusion versus patients not experiencing IRRs. Additionally, box plots of CD19 values versus IRR maximum intensity will be presented (by Randomized Dose). These are considered exploratory summaries.

Absolute value and change from randomization values at each visit (24 weeks after 1st Randomized Dose, 48 weeks after 1st Randomized Dose etc.) will be summarized (mean, SD, median, minimum and maximum).

4.5.4 Vital Signs

Vital signs parameters are systolic blood pressure, diastolic blood pressure and pulse rate (body temperature is not included -- measurement of body temperature after the main study screening visit was required in earlier versions of the protocol, but in later versions this was only required at screening, but at any time sites could record body temperature for specific reasons e.g. temperature increase).

Vital signs parameters prior to start of each ocrelizumab infusion (baseline) and at 15, 30, 45 minutes, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5 hours post start of ocrelizumab infusion and 1 hour post end of ocrelizumab/saline infusion will be summarized (mean, SD, median, minimum and maximum). The change from baseline will also be summarized (mean, SD, median, minimum and maximum). Additionally, box plots of each vital signs parameter during the time of the infusion will be presented (by Randomized Dose).

Vital signs abnormalities are defined as follows:

- Systolic blood pressure <90mmHg or >140mmHg
- Diastolic blood pressure <50mmHg or >90mmHg
- Pulse rate <60pm or >100bpm

The number and percentage of patients with any vital signs abnormalities and with each abnormality described above will be presented, for all patients, for patients experiencing IRRs during/post-infusion and for patients not experiencing IRRs. These summaries will be presented by Randomized Dose and then by Dose within Randomized Dose (and overall within Randomized Dose i.e., across all Doses).

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

4.6.1 Pharmacokinetic Analyses

All summaries involving PK data will be based on the PK Population.

For all patients combined (both randomized groups), a box plot will be prepared to show the maximum ocrelizumab serum concentration plotted versus IRR maximum intensity (none, mild, moderate, severe, life-threatening and fatal) for each randomized dose. This plot will be repeated for conventional infusion patients only, then for shorter infusion patients only.

4.6.2 Pharmacodynamic Analyses

There are no pharmacodynamic endpoints in this study.

4.7 MISSING DATA

All methods for handling missing data are described above, section by section, for each endpoint. These relate mostly to imputation of missing or incomplete dates.

4.8 INTERIM ANALYSES

An interim analysis will be undertaken, as described fully in Section 1, “Background”, and in subsequent sections. This is an administrative IA which will not lead to any changes in the substudy protocol nor the substudy SAP. Since this is a descriptive analysis and no inferential analyses will be undertaken, considerations of alpha spending are not relevant.

5. REFERENCES

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