Multicenter, Phase Ib/IIa Study on the Safety and Efficacy of Autologous Peptide-coupled Red Blood Cells in Patients with Relapsing Remitting Multiple Sclerosis - RED4MS trial

Sponsor Project Code: RED4MS
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STATISTICAL ANALYSIS PLAN

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- AESI definition and corresponding table added (Section 5.5.1)
- Annualized relapse rate was introduced (Section 5.5.2)
- Analysis of lesion volume was introduced (Section 5.5.3)
- The definition of clinically significant change of T25FW was expanded (Section 5.5.6)
- Update as per CTP Version 7.0
- Removed references to Part A and Part B. All analyses for Part B were removed.

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- Added definition of the modified safety analysis set (Section 3.1).
- Clarified that annualized MS relapse rate is calculated based on study participation end until the end of study as opposed to the end of the treatment phase (Section 5.5.2)

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- Added treatment cycle subgroups (Section 3.2) which will be used in disease-related endpoint summaries (Sections 5.5.2-5.5.7)
- Added definitions for treatment cycle 1 and treatment cycle 2 (4.6) which will be used in summaries of adverse events (Section 5.5.1)

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- HLA typing results will not be reported (Section 5.2.1)
- Added rule to consider IMP infusions as not done if the batch number for the IMP bag is "NA" (Section 5.4)
- Added rules for combining the eCRF-based and vendor-provided MRI data (Section 5.5.3)
- Added rules for non-numeric laboratory parameter results (Section 5.5.8)

Version Draft 1.2 (03-FEB-2026): Document updated after the Data Review. Notable changes:
- Vital signs summary now uses the standard definition of baseline (Section 5.5.9)

Version Final 2.0 (03-FEB-2026): Document finalized without further changes.

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LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviation	Description of abbreviation
AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
AP	alkaline phosphatase
ARR	annualized relapse rate
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BDRM	blind data review meeting
CEL	Contrast-Enhancing Lesion
CLS12311	peptide-coupled red blood cells
CSP	clinical study protocol
DSMB	Data Safety Monitoring Board
EDC	1- Ethyl- 3- (3-Dimethylaminoprpyl) – carbodiimide
EDSS	Expanded Disability Status Scale
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EOS	end of study
EOT	end of treatment
GGT	gamma-glutamyl transferase
HLA	Human Leukocyte Antigen
HLGT	high level group term
HLT	high level term
9-HPT	Nine Hole Peg Test
IMP	investigational medicinal product
LLT	lowest level term
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MS	Multiple Sclerosis
MRI	magnetic resonance imaging
PD	protocol deviation
PT	preferred term
RBC	red blood cells
RRMS	relapsing remitting multiple sclerosis
Q1	first quartile
Q3	third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SFU	safety follow up
SOC	system organ class
T cell	T lymphocyte cell
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
T25FW	Timed 25-Foot Walk Test
TLF	tables, listings, figures
WHO-ATC/DDE	World Health Organization-Drug Dictionary

INTRODUCTION

This statistical analysis plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the clinical study protocol (CSP) Version 7.0, 2025-05-09.

The SAP includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data, and it is structured according to different data types. The biomarker analysis and supportive analyses with the goal of estimating the hypothetical effect of different doses of CLS12311 versus a placebo control are outside the scope of this document. The SAP is finalized and signed-off prior to database lock. Any changes from the SAP after the database lock, reason for the changes and additional statistical analyses that may be performed, will be described in an SAP Addendum and discussed in the Clinical Study Report.

All analysis data sets, and statistical output will be produced by the statistics department of Scope International AG using SAS for Windows (SAS Institute Inc., Cary, NC, USA) [1] version 9.4.

1 SCHEDULE OF EVENTS AND TREATMENT

Visit	[redacted]															**UV**
Week																**Unscheduled[12]**
Study Phase	**BL**	**Treatment**												**SFU**		
Informed consent	x															
Eligibility criteria	x	x														
Body weight, height	x															
ECG	x															
Medical history including MS history[1] / Demography/ Smoking history/ Prior medication/ SARS-CoV-2 vaccination status	x															
Physical examination	x					x	x						x		x	x	x
Vital signs	x	x	x	x		x	x		x	x	x		X		x	x	x
Urine pregnancy test[2]	x	x	x	x			x		x	x	x		x		x	x	x
HLA typing[11]	x																
Cranial MRI	x[13]						x[13]						x[13]		x[14]	x[14]	x[14]
Hematology[3]/ Blood biochemistry[4]	x						x						x		x	x	x
Urinalysis[5]	x						x						x		x	x	x
Infectious disease screen[17]	x																
EDSS	x						x						x		x	x	x
9-HPT, T25FW, SDMT	x						x						x		x	x	x
Eligibility for blood donation[6]	[redacted]																
Blood donation																	
CLS12311/ (Placebo)[7]																	

Visit	[redacted]															**UV**
Week																**Unscheduled[12]**
Study Phase	**BL**	**Treatment**												**SFU**		
Concomitant medication/procedures		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MS relapse assessment		x	x	x		x	x		x	x	x		x		x	x
Adverse event assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Telephone-based AE assessment the next day following infusion[18]			x	x						x	x					
Antigen specificity[9]	x						x						x			
Biomarker blood	x						x						x			

MS Multiple Sclerosis; MRI Magnetic Resonance Imaging; EDSS Expanded Disability Status Scale (neurological rating scale); 9-HPT Nine Hole Peg Test (clinical test for hand function); T25FW Timed 25-Foot Walk; SDMT Symbol Digit Modalities Test (cognitive test); ECG electrocardiogram; BL Baseline; EOT End of Treatment; EOS End of Study; ED Early Discontinuation; SFU Safety Follow Up; HLA Human Leukocyte Antigen

[1] MS history means first MS symptoms and diagnosis, prior relapses, prior disease modifying therapies and symptomatic therapies.

[2] Only in female patients of childbearing potential (sexually mature, premenopausal and not surgically sterile). To be performed locally.

[3] Central lab: complete blood count with differential and platelet count, Coombs test, coagulation studies (PT, PTT, INR) and sedimentation rate. Blood group (only at Visit 1).

[4] Central lab: Sodium, potassium, creatinine, eGFR, urea, total bilirubin, GGT, ALT/GPT, AST/GOT, alkaline phosphatase, total protein, albumin, lactate dehydrogenase, fibrinogen, CRP, iron, ferritin, haptoglobin.

[5] Central lab: Specific gravity, pH, glucose, protein, ketones, nitrite, leucocytes and blood.

[6] Establishing the eligibility for the blood donation (blood count, hemoglobin and infectious disease screening) will be performed according to local regulations, with the sample for analysis taken either from the blood donation itself or from a separate blood draw from the patient prior to blood donation, as required locally. The minimum infectious disease panel to be tested is Anti-HIV1/2, HBsAg, Anti-HBc, Anti-HCV and screening for syphilis, and in Switzerland, the blood needs to be additionally tested for HTLV-1/2.

[7] According to dose escalation scheme. A blood compatibility test needs to be carried out prior to each infusion (bedside test or cross-matching according to local regulations).

[8] Dose group 1 will receive placebo only

[9] Cellerys lab: T cell response against one or more of the tolerizing peptides that will be coupled to RBC.

[10] For patients who prematurely discontinue the treatment phase and who have received at least one dose of study drug, the ED visit has to be performed immediately (but not earlier than 2 weeks after the last dosing). For patients who prematurely discontinue the safety follow-up phase the ED visit has to be performed if the last visit has been more than 8 weeks ago.

[11] Cellerys lab: Test for HLA-[redacted] alleles (no extra blood sample needed; will be taken from blood collected for antigen specificity testing).

[12] In case that symptoms suggest a possible relapse, i.e. new neurological symptoms compatible with MS or worsening of previous symptoms and of at least 24 hours duration, an unscheduled visit will be performed. In case that symptoms are not related to a potential relapse, it is up to the Investigator to decide which of these assessments should be performed during the unscheduled visit.

[13] Brain MRI including Gadolinium enhanced 3D T1 MRI

[14] Brain MRI (without contrast) will be acquired

[15] A telephone interview will be conducted 3-5 days after the second dose of the first treatment cycle has been administered.

[16] The exact time point of Visit 2 is not specified as it is based on central allocation to the dose group and depending on patient recruitment. Other assessments at the study site may be performed on the day before the blood donation

[17] Central labs: At visit 1 serology testing (Anti-HIV-1/2, HBsAg, Anti-HBc, Anti-HCV, screening for syphilis from biochemistry blood to check patient eligibility for blood donation)

[18] is carried out on the following working day. If the phone consultation of the Visit [redacted] coincides with the phone Visit [redacted], the phone consultation of the Visit [redacted] will be skipped.

[19] For Sentinel Patients, no blood donation will be performed at Visi[redacted] Only safety-related assessments will be conducted.

[20] Sentinel Patients are not required to attend Visit [redacted] and Visit [redacted], as no IMP will be administered. Instead, sites will perform telephone-based AE assessments. Optional onsite visits may be arranged upon patient request.

2 OBJECTIVES AND DESIGN

2.1 Study Objectives

2.1.1 Primary Objective

Safety objective:

- To assess the safety and tolerability of peptide-coupled red blood cells (CLS12311) in patients with relapsing remitting multiple sclerosis (RRMS).

2.1.2 Secondary Objectives

Safety objective:

- To assess the safety and tolerability of each dose group of CLS12311

2.1.3 Exploratory Objectives

To understand the mechanism/s of action of tolerance induction with peptide-coupled red blood cells (RBCs) and to identify biomarkers for measuring immune tolerance induction.

2.2 Study Endpoints

2.2.1 Primary Endpoints

Safety Endpoints:

- The number and severity of treatment-emergent adverse events (TEAEs)
- The number and severity of treatment-emergent serious adverse events (TESAEs)
- The number of confirmed relapses
- The number and size of brain lesions

2.2.2 Secondary Endpoints

Safety Endpoints:

- The number and severity of TEAEs in each dose group
- The number and severity of TESAEs in each dose group
- Number of confirmed relapses in the treatment phase in each dose group
- Changes in clinical measures of disease severity: Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk Test (T25FW), Nine Hole Peg Test (9-HPT), Symbol Digit Modalities Test (SDMT) in each dose group.

2.2.3 Exploratory Endpoints

- Percentage of patients in each dose group showing a reduction of antigen-specific T lymphocyte cells (T cells) against the protein(s) they responded to prior to study entry.
- Changes in predefined serum- and cellular biomarkers including autoantigen-specific T cell responses that would indicate proinflammatory activation

The analysis of immunological and biomarker data is outside the scope of this SAP.

2.3 Overall Study Design

Open-label, ascending-dose Phase Ib trial to evaluate the safety and tolerability of three doses of CLS12311 in patients with relapsing-remitting multiple sclerosis (RRMS).

The study will be conducted at approximately 12 sites in Europe.

The total duration will be at least 48 weeks for each participant and will include a total of 16 visits divided into two phases: an open-label treatment phase and a safety follow-up phase. The study phases are described in more detail in the following paragraphs.

Patient eligibility will be assessed during Visit 1 (week 0) at baseline, where general patient and disease characteristics will be recorded. Patients who meet the criteria for enrollment will be sequentially allocated to one of the dose groups. The allocation to the dose group and the timing of treatment administration will be centrally coordinated to ensure appropriate safety assessments between dosing of patients. Hence, the time-period between Visit 1 and Visit 2 might vary between patients.

2.3.1 Open Label Treatment Phase

Single/ first treatment cycle:

The safety and tolerability of a single treatment cycle of CLS12311 will be assessed in an ascending dose study across three dose groups involving a total of 9 patients. Patients will be allocated to a low (total dose [redacted]; n=2), medium (total dose [redacted]; n=3) or high dose (total dose [redacted]; n=4).

Each dose group will start with a sentinel patient, who will inform about the safety of the treatment before dosing additional patients. To ensure the safety of dosing in the subsequent patient, a minimum time interval of four days will be established prior to dosing the next patient. Patients who fail to meet the eligibility criteria during screening will be replaced.

The treatment will start with the lowest dose group (2 patients). Higher dose groups (medium dose in 3 patients, high dose in 4 patients) will only be initiated once safety data from the preceding dose group, based on (S)AEs and relapses, has been confirmed by the sponsor's medical expert(s).

The first patient in each dose group (sentinel patient) will receive a single treatment of CLS12311. Sentinel patients will not receive a second treatment cycle. All sentinel patients will be followed with safety visits until [redacted] according to the schedule of visit (see Section 1). The safety follow-up of sentinel patients will inform about the safety of the treatment prior to second dosing of other patients.

Second treatment cycle:

The safety and tolerability of a second treatment cycle of CLS12311 will be evaluated in a subset of patients (n=6) from the single ascending dose study. Patients who receive a second treatment cycle in Weeks [redacted] of the trial will remain in the same dose group, i.e. low (total dose [redacted]; n=1), medium (total dose [redacted]; n=2) or high dose (total dose [redacted]; n=3). Hence, patients receiving a second treatment cycle will have the following total product exposure during the trial: low dose group [redacted] (n=1), medium dose group [redacted] (n=2) or high dose group [redacted] (n=3).

The second treatment cycle will only be initiated after the safety of the first treatment cycle has been confirmed for the next higher dose group. The cumulative dose given to patients in the second treatment cycle will not exceed the dose of the single treatment cycle, which has already been administered to patients in the next higher dose group.

Twice, after patient 3 and then after patient 6 have completed Visit [redacted], the Sponsor's medical expert(s) will review safety data, including any serious and severe events judged to be related to peptide-coupled RBCs to confirm safety of repeated dosing for patient 2 and for patients 4 and 5, respectively.

[redacted]

2.3.2 Safety Follow-Up Phase

At the completion of the treatment phase, patients will enter a 31-week safety follow up (SFU) period, including three visits: three weeks after the end of the treatment phase (Week 20), at Week 24 and at Week 48.

[redacted]

2.4 Randomization

Randomization is not applicable for this study.

2.5 Treatments

The investigational medicinal product (IMP) CLS12311 consists of autologous RBCs that have been chemically coupled with [redacted] peptides [redacted]) from [redacted] proteins [redacted] expressed in the brain and re-suspended in saline (150 ml). During the manufacturing, the peptides are covalently bound to the surface of RBCs [redacted]

The placebo consists of (uncoupled) autologous RBCs re-suspended in saline (150 ml).

The IMP will be administered by intravenous infusion.

Table 1 Composition of Drug Product and Placebo

Ingredient	**Investigational medicinal product CLS12311**	**Placebo**
Autologous peptide-coupled RBCs	[redacted] cells (range [redacted]	-
Autologous RBCs (uncoupled)	-	[redacted] cells (range [redacted]
Saline (NaCl 0.9%)	Filled up to the total volume of 150 ml (135 – 165 ml)	Filled up to the total volume of 150 ml (135 – 165 ml)

2.5.1 Dosage

Ascending doses of CLS12311 will be given as follows:

Group 1

- 2 patients (patient 1 and 2): [redacted] peptide-coupled RBCs followed by a single bag placebo at [redacted] and two bags of placebo at [redacted] (from a single blood donation), corresponding to a total dose of [redacted] peptide-coupled RBCs.
- 1 patient (patient 2) will receive a second treatment of [redacted] peptide-coupled RBCs followed by a single bag placebo at [redacted] and two bags of placebo at [redacted] (from a single blood donation), corresponding to a cumulative total dose of [redacted] peptide-coupled RBCs in the trial.

Group 2

- 3 patients (patients 3, 4 and 5): [redacted] peptide-coupled RBCs followed by a single bag placebo at [redacted] (from a single blood donation), corresponding to a total dose of [redacted] peptide-coupled RBCs.
- 2 patients (patients 4 and 5): will receive a second treatment of [redacted] peptide-coupled RBCs followed by a single bag placebo at [redacted] (from a single blood donation), corresponding to a cumulative total dose of [redacted] peptide-coupled RBCs in the trial.

Group 3

- 4 patients (patients 6-9): [redacted] peptide-coupled RBCs (i.e. [redacted] peptide-coupled RBCs) at [redacted] (from a single blood donation), corresponding to a total dose of [redacted] peptide-coupled RBCs.
- 3 patients (patients 7-9): [redacted] peptide-coupled RBCs (i.e. [redacted] peptide-coupled RBCs) at [redacted] (from a single blood donation, corresponding to a cumulative total dose of [redacted] peptide-coupled RBCs in the trial.

A dose of [redacted] peptide-coupled RBCs is equivalent to one blood bag.

Dosing is outlined in Figure 3.

2.6 Sample Size

As this is an exploratory Phase Ib study focusing on safety, no formal sample size calculation has been performed. The number of patients enrolled is considered sufficient to evaluate the safety and tolerability of CLS12311 and to collect preliminary exploratory biomarker data.

2.7 Blinding

Participants of the study will remain unblinded with regard to the dosing regimen.

3 ANALYSIS SETS AND SUBGROUPS

3.1 Analysis Sets

The **enrolled analysis set** (ES) will include all patients who provided informed consent.

The **safety analysis set** (SAF) includes all patients with blood donation (partial/full) for CLS12311 production.

The **modified safety analysis set** (mSAF) includes all patients with an IMP infusion (complete or incomplete).

3.2 Subgroups

The following subgroups will be defined based on their exposure to the IMP:

- **≥ 1 Treatment cycle:** Patients who have initiated at least one treatment cycle (IMP infusion (complete or incomplete)
- **2 Treatment cycles:** Patients who have initiated both treatment cycles (IMP infusions (complete or incomplete)

These subgroups will be analysed in disease-related tables (Sections 5.5.2 to 5.5.7).

4 GENERAL DEFINITIONS AND NAMING CONVENTIONS

In order to avoid ambiguity during the analysis, a number of definitions and conventions for data handling are described here.

4.1 General Methodology and Presentation of the Results

The default summary statistics for quantitative (continuous) variables will be

- the number of patients,
- mean,
- standard deviation (SD),
- median,
- minimum (min) and maximum (max)

Mean, median will be presented to one more decimal place than the raw value. The minimum and maximum values will be presented with the same decimal precision as the raw value. SD will be reported to two decimal places greater than the original value.

For qualitative (categorical) variables, the frequency count and percentage (%) of patients with non-missing data per category will be the default frequency tabulations. Where appropriate and present, the number of missing values will be displayed as "Missing" category.

Percentage values are to be presented to one decimal place, for example, 52.3%.

The denominator used for calculation of the percentages will be specified in a footnote to the tables for clarification.

4.2 Statistical Output Layout

All titles and column headers (consisting of one or several words) will be capitalized; articles, prepositions, and conjunctions, and "To" in infinitives will not be capitalized, except they are at the beginning of titles or headers.

All pages will be numbered according to the table/listing/figure to which the page belongs to. Every table/listing/figure will be numbered from page 1, "Page X of Y" at the bottom of each page.

The definition of baseline and endpoint value will be described in a footnote in every TLF where applicable. Other important definitions will also be presented if necessary.

Dates will be listed in the format: yyyy-mm-dd (e.g. 2003-11-20). Times will be listed in the format: hh:mm (e.g. 13:15) or in the format hh:mm:ss if seconds are collected. When date and time are collected, these are listed in the format: yyyy-mm-ddThh:mm (e.g. 2003-11-20T09:15), yyyy-mm-ddThh, or yyyy-mm-ddThh:mm:ss.

Partial missing dates will be listed in the format yyyy-mm (e.g. 2013-11) if only day is missing or in the format yyyy (e.g. 2013) if month and day are missing.

Missing data including missing dates or times will be displayed in listings as blank fields, unless otherwise specified.

Listings will be sorted by dose group patient number and visit number and parameter where applicable, unless specified otherwise. Sentinel subjects will be flagged in the listings.

4.3 Dose Group Names and Labels

Statistical output will be presented by dose group. The following labels will be used in the outputs:

Table 2: Dose Group Labels

Dose Group	Dose Group Label in TLFs
Group 1 Low Dose	Low Dose
Group 2 Medium Dose	Medium Dose
Group 3 High Dose	High Dose

4.4 Visit Names and Labels

Visits will be presented as "Visit X" (where X is visit number) in the statistical output. Early discontinuation visit will be presented separately from scheduled Visit 13 and will be labelled as "ED Visit" in the statistical output.

Unscheduled visits will be numbered based on the preceding scheduled visit, e.g. "U Visit 4.1" for the first unscheduled visit after the scheduled Visit 4. Multiple unscheduled visits after the same scheduled visit will be numbered and labelled sequentially.

4.5 Study Day Numbering

All assessment days will be related to the first blood donation, which will be referred to as the study Day 1 for the purposes of the statistical analyses. Day –1 is the day that is preceding Day 1 and Day 0 will not be defined.

4.6 Study Periods

Baseline Phase

The baseline phase will be defined as the period from informed consent signature date to the first blood donation date.

Treatment Phase

The treatment phase will be defined as the period from the date of first blood donation until [redacted] ED /EOT.

The treatment phase will be further divided into:

- **Treatment cycle 1:** The period from the date of first blood donation until the day before the second blood donation or the ED visit in case a second blood donation is not performed.
- **Treatment cycle 2:** The period from the date of the second blood donation until [redacted] ED /EOT.

Safety Follow-Up Phase

The follow-up period is a period lasting from the end of the treatment phase until study completion or termination date.

4.7 Definition of Baseline Value

The baseline value for a variable is defined as the last non-missing value collected before the first blood donation.

More details on the definition of baseline can be found in Section 5.

Absolute change from baseline will be calculated as

$$Absolute\ Change\ from\ Baseline\ at\ Visit\ X = Value\ at\ Visit\ X - Baseline\ Value$$

Relative change from baseline (%) will be calculated as

$$Relative\ Change\ from\ Baseline\ at\ Visit\ X = \frac{Value\ at\ Visit\ X - Baseline\ Value}{Baseline\ Value} \times 100$$

Note: Patients with a baseline value of '0' will be excluded from the calculation of relative change.

4.8 Visit Windows

No visit windowing will be performed. All data will be analyzed using the nominal visit number

4.9 Coding Systems and Conventions

4.9.1 Coding of adverse events and medical history

Adverse event and medical history investigator terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 27 [2].

4.9.2 Coding of medications

Medications are classified according to active drug substance using the World Health Organization-(WHO) drug dictionary WHODrug Global, March 2024 version [3]. The WHO drug code has 11 digits. The generic name is defined by the first 6 of the 11 digits. In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug code. In this study, ATC codes are defined to the 4th level.

4.10 Handling of Missing Data

Handling of missing data, if applicable, is discussed in the relevant sub-sections of Section 5.

5 STATISTICAL ANALYSIS: DEFINITIONS, DERIVATIONS, CALCULATIONS AND METHODOLOGY

5.1 Patient Disposition

5.1.1 Disposition and Withdrawals

The following disposition data will be collected:

- date of informed consent
- re-screening status
- date of study termination
- study completion status
- the primary reason for premature study termination

Screening failures will be all patients who discontinued before blood donation .

A patient may have multiple enrolments if they discontinue before IMP administration. Subjects will be summarized separately for each enrollment. The subject ID used for each enrolment will be provided in listings to identify the subject.

Premature discontinuation will be regarded if a patient meets the qualification criteria but leaves the study prior to having completed all scheduled visits.

Completers will be those patients who completed all visits as scheduled.

The following statistical output will be provided:

Table 15.1.1 Analysis Sets – Enrolled Analysis Set
Number and percentage of patients included in the ES, SAF sets will be provided by dose group and overall. Percentages will be based on the number of patients in the ES.

Table 15.1.2 Screening Failures – Enrolled Analysis Set
Number and percentage of the screening failures will be summarized by reasons associated with the discontinuation. Percentages will be based on the number of patients in the ES.

Table 15.1.4 Patient Disposition – Safety Analysis Set
Number and percentage of patients who completed the study as scheduled, who discontinued prematurely including the reason of discontinuation will be summarized by dose group and overall based on the SAF.

Table 15.1.5 Number of Patients by Country and Site – Safety Analysis Set
Number and percentage of patients in each country and site will be presented by each dose group and overall based on the SAF.

Table 15.1.6 Number of Patients by Visit – Safety Analysis Set
Number and percentage of patients attending each scheduled visit will be presented by each dose group and overall based on the SAF.

Figure 15.1.1 Flow Chart of Patient Disposition – Enrolled Analysis Set
The number of patients with the occurrence of each protocol milestone will be displayed. The number of screening failures and discontinuations as well as their reasons will also be summarized.

Listing 16.2.1.1 Patient Disposition – Safety Analysis Set
The overall disposition listing will include study completion status, termination date as well as the primary reason of premature termination.

Listing 16.2.1.2 Screening Failures – Enrolled Analysis Set
Screening failures will be listed based on the ES, including the reason of discontinuation.

Listing 16.2.1.3 Patient Visits – Enrolled Analysis Set
All visit dates will be listed by patient.

5.1.2 Protocol Deviations

Protocol deviations (PDs) are deviations from the procedures outlined in CSP PDs are classified as follows:

- **Important PDs:** A subset of PDs that may significantly impact the completeness, accuracy, and/or reliability of key study data or critical processes or that may significantly affect a subject's rights, safety, or well-being. For example, important PDs may include enrolling subjects in violation of key eligibility criteria or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.
- **Non-important PDs:** Not meeting the criteria above. Typically, deviations which are not related to collection of primary or key secondary endpoint data or PDs that are not adversely related to subject rights or wellbeing.

The following statistical output will be provided:

Table 15.1.3 Important Protocol Deviations – Safety Analysis Set
The number and percentage of subjects with important protocol deviations, including protocol deviation categories, will be summarized by dose group and overall. Percentages will be based on the number of subjects in the SAF. PDs will be summarized in the overall population as well as within each trial site.

Listing 16.2.1.4 Important Protocol Deviations – Safety Analysis Set
Patients with important protocol deviations will be listed.

5.1.3 Inclusion/Exclusion

The study specific inclusion/ exclusion criteria are presented in Section 8 of the CSP. For each criterion, as appropriate, a response of "Yes/No" is to be obtained at Screening and checked again prior to allocation to treatment, at Visit 2.

The following statistical output will be provided:

Listing 16.2.1.5 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled Analysis Set
Inclusion criteria which were not met and exclusion criteria which were met will be listed.

5.2 Demographic and Other Baseline Characteristics

5.2.1 Demographics and Baseline Characteristics

The following demographic and baseline characteristics were collected:

- Age (years)
- Sex at birth
- Childbearing potential status,
- Race,
- Smoking status,
- Height,
- Weight
- Body mass index (BMI)
- HLA typing [redacted]
- Immunization against Covid-19 status (yes/no)
- History of confirmed Covid-19 infection status (yes/no) and date
- ECG (result: normal/ abnormal and clinical relevance)
- Infectious Disease Screen (Anti-HIV-1/2, HBs-Ag, Anti-HBc, Anti-HCV, Screening for syphilis

HLA typing results will not be reported.

The following statistical output will be presented:

Table 15.1.7.1.1 Demographics – Safety Analysis Set
Table 15.1.7.1.2 Demographics – Modified Safety Analysis Set
Demographic data (age, sex at birth and race) will be summarized by each dose group and overall. The modified safety analysis set summary will be performed by treatment cycle subgroup.

Table 15.1.7.2.1 Baseline Characteristics – Safety Analysis Set
Table 15.1.7.2.2 Baseline Characteristics – Modified Safety Analysis Set
Weight, height, BMI data, HLA typing and smoking status will be summarized by each dose group and overall. The modified safety analysis set summary will be performed by treatment cycle subgroup.

Listing 16.2.1.6.1 Demographics and Baseline Characteristics – Enrolled Analysis Set
Demographic and baseline characteristic data will be listed for patients in the ES.

Listing 16.2.1.6.2 Infectious Disease Screen – Enrolled Analysis Set
Infectious disease screen results will be listed

5.2.2 Multiple Sclerosis History

The following information about MS disease history and status at Visit 1 will be presented:

- Time since first MS symptoms (months)
- Time since first MS diagnosis (months)
- Number of relapses in the last 12 months prior to Visit 1
- Number of relapses in the last 24 months prior to Visit 1
- Number of total relapses in the past 10 years (1-3, 4-6, 7-10, >10)

Time since first MS symptoms and diagnosis in months will be calculated as follows:

$$Time\ (month) = \frac{Date\ of\ Visit\ 1 - Date\ of\ first\ MS\ sympoms/\ diagnosis + 1}{30.4375}$$

Imputations for incomplete first MS diagnosis or symptoms date:

- 15th of the corresponding month, if the month and year are available but the day is missing.
- the 2nd of July of the corresponding year, if the year is available but the day and month are missing.

Imputed date will be used for calculation of the duration in months. Dates as collected will be included in the listings.

The following statistical output will be presented:

Table 15.1.8 MS History – Safety Analysis Set
MS history parameters as defined above will be presented by dose group and overall based on the SAF.

Listing 16.2.1.7 MS History – Enrolled Analysis Set
MS history data will be listed for patients in the ES.

5.2.3 Medical History

All medical conditions within the last 30 days prior to Visit 1 as well as all relevant conditions of more than 30 days prior to Visit 1 except for diagnosis of MS will be collected in the electronic case report form (eCRF).

Medical history is classified as:

- **Prior medical conditions** are the conditions which started and ended prior to Visit 1.
- **Ongoing medical conditions** are the conditions which are marked as ongoing at Visit 1 or with a stop date at or after Visit 1

If the stop date of a medical history condition is incomplete or missing, it will be assumed to be ongoing except if the incomplete stop date indicates that the condition stopped prior to the Visit 1.

The following statistical output will be provided:

Table 15.1.9.1 Prior Medical Conditions – Safety Analysis Set
Table 15.1.9.2 Ongoing Medical Conditions – Safety Analysis Set
Medical history will be summarized displaying counts and percentages of patients having at least one medical condition and will be presented by SOC and by PT within SOC. SOCs and PT within SOC are to be sorted by descending order of overall incidence. Percentages will be based on the number of patients in the SAF.

Listing 16.2.1.8 Medical History – Enrolled Analysis Set
Medical history conditions will be listed for patients in the ES.

5.3 Prior and Concomitant Medications

All concomitant and prior medications including symptomatic therapies for MS administered within 30 days prior to Visit 1 as well as MS disease modifying therapies used within 10 years prior to Visit 1 or during the safety follow-up period will be documented in the eCRF.

Plasmapheresis and non-pharmacological therapies used for medical history or adverse event will be documented as well.

Medications and therapies will be classified as 'prior', 'concomitant' or 'post-treatment' based on start/stop dates:

- **Prior medications/therapies** are defined as those medications/therapies starting and ending prior to Visit 1.
- **Concomitant medications/therapies** are defined as medications/therapies started at or after Visit 1 and include medications/therapies started prior to the Visit 1 but continued after the visit.
- **Post-treatment medications/therapies** are defined as medications/therapies which started during the safety follow-up phase.

If the start or stop date of a medication/therapy is incomplete or missing, it will be assumed to be concomitant except if the incomplete start or stop date indicates that the medication/therapy stopped prior to the Visit 1 or started after the treatment phase.

The following statistical output will be provided:

Table 15.1.10.1 Prior Medications and Therapies – Safety Analysis Set
Table 15.1.10.2 Concomitant Medications and Therapies – Safety Analysis Set
The number and percentage of patients with at least one medication within each ATC 2nd level subgroup and substance name (or combination of substances) will be presented by dose group and overall based on the SAF. The ATC 2nd level subgroups and substance names within ATC 2nd level subgroup will be ordered by descending overall incidence.

Listing 16.2.1.9 Medications and Therapies – Enrolled Analysis Set
All medications, prior, concomitant and post-treatment, will be listed for patients in the ES.

5.4 Exposure to IMP

Patients of all three dose groups will receive treatment with CLS12311 within 13 weeks from enrolment in the study. CLS12311 will be administered at [redacted] for sentinel patients and [redacted] for all other patients. CLS12311 will be manufactured from blood donations taken at [redacted]

The following blood donation and IMP exposure data will be collected in the eCRF:

- Eligibility for blood donation
- Date of blood donation
- Donated blood volume (mL)
- Status of blood production release

- Blood group compatibility
- Date of IMP application
- Application start and end time
- Completion status (complete/incomplete/not done)
- Discomfort following medication infusion
- Date and time of discharge

IMP application will be considered as incomplete if at least one bag is applied incompletely. If the batch number for a bag is collected as "NA", the infusion completion status will be considered as "Not Done".

The following statistical output will be provided:

Table 15.1.11 Exposure to IMP– Safety Analysis Set
Number and percentage of patients by number of blood donations, IMP application status by visit as well as number and percentage of patients who completed one IMP cycle and who completed both IMP therapy cycles will be provided by dose group and overall based on the SAF. Number and percentages of patients who received at least one infusion of IMP and who received at least one infusion of IMP in the second treatment cycle will be provided as well.

Listing 16.2.2.1 Blood Donation – Safety Analysis Set
Listing 16.2.2.2 Application of IMP – Safety Analysis Se
Blood donation and IMP application data will be displayed for each patient based on the SAF.

5.5 Safety Analysis

5.5.1 Adverse Events

All medical conditions that started after the informed consent including clinically relevant worsening of previous medical conditions will be documented as adverse events (AEs) in the eCRF. AEs might either be observed by the Investigator during scheduled clinical examinations (e.g. physical examination, AE assessment, see below) or during unscheduled clinical examinations or reported by the patient.

Adverse event data includes:

- adverse event term
- start/stop dates or ongoing
- intensity (Grade 1 - mild, Grade 2 - moderate, Grade 3 - severe, Grade 4 - life-threatening, Grade 5 - death)
- relationship to study treatment (related, not related)
- relationship to blood donation (related, not related)
- action taken with study treatment (dose not fully applied, dose delayed, dose not applied, treatment permanently discontinued, patient other – specified)
- other actions (blood donation delayed, blood donation with reduced volume, no further blood donations, patient withdrawn from the trial, other – specified)
- outcome of event (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown)
- seriousness (yes/no)
- AE of special interest (AESI)

All AEs will be presented in listings.

Summaries of adverse events will include AEs defined as **treatment-emergent adverse events (TEAEs)**, defined as AEs with the first onset or worsening after the blood donation for CLS12311 production.

If the start date of an AE is incomplete or missing, it will be assumed to be treatment-emergent except if the incomplete start date or the stop date indicates that the event started prior to the blood donation for CLS12311.

Adverse events will also be assigned to study periods (see Section 4.6) based on their onset dates. If the date of an AE is incomplete or missing, it will be assumed to have occurred in each period which could be covered by the incomplete dates.

Adverse events will be further assigned to the following categories:

- **Serious Adverse Events (SAEs):** defined as AEs considered by the investigator as serious, including AEs with a missing seriousness assessment.
- **Related TEAEs**: AEs assessed as "Related" to study treatment or blood donation, including events with missing IP relationship assessment.
- **TEAEs leading to discontinuation:**
    - AEs for which "Action taken with study treatment" is indicated as "Treatment permanently discontinued"
    - AEs for which "Other action taken" is documented as "No further blood donations" or "Patient withdrawn from the trial"
- **TEAEs leading to death:** AEs documented as having a "fatal" outcome.

The intensity or severity of an adverse event is defined according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0, 2017) and provided in Table 3.

Table 3 Adverse Event Intensity Classification

Intensity	Explanation
Mild (Grade 1)	• Asymptomatic or mild symptoms • Clinical or diagnostic observations only • Intervention not indicated
Moderate (Grade 2)	• Moderate, minimal, local or non-invasive intervention indicated limiting age-appropriate instrumental activities of daily living (ADL)
Severe (Grade 3)	• Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling symptoms limiting self-care activities of daily living
Life-threatening (Grade 4)	• Life-threatening consequences: urgent intervention indicated
Death (Grade 5)	• Death related to AE or to multiple sclerosis

AEs of special interest are defined as severe AEs (Grade of >=3) which are related to the IMP and occurring within one day following infusion of CLS12311/placebo: dyspnea, tachycardia, fever, chills, malaise, shock, infection, allergic reaction, renal or liver failure. Adverse events of special interest will be assessed by the investigator.

TEAEs will be summarized using crude and exposure-adjusted incidence rates. A crude incidence rate will be calculated as number of patients with a TEAE divided by number of patients at risk (at the beginning of the study). An exposure-adjusted TEAE incidence rate per 1 patient-year will be defined as number of patients who experienced a TEAE divided by the total time from the blood donation until occurrence of the event for those who experienced an event, or the end of the safety follow-up for those who did not, multiplied by 365.25, among patients at risk at the beginning of the study:

$$I_{AE} = \frac{n}{\sum_i t_i} \times 365.25 = \frac{n}{T} \times 365.25$$

where n is the total number of patients with the corresponding AE, t_i is equal to the study day of the first corresponding AE for each patient or end of the safety follow-up, T is total time from blood donation until the first event or safety follow-up.

The following statistical output will be provided:

Table 15.2.1.1 Overall Summary of TEAEs – Safety Analysis Set
An overview of TEAEs:

- TEAEs
- Non-serious TEAEs
- Serious TEAEs
- TEAEs related to study treatment or blood donation
- Serious TEAEs related to study treatment or blood donation
- ≥ Grade 3 TEAEs
- TEAEs leading to discontinuation
- TEAEs related to study treatment or blood donation leading to discontinuation
- TEAEs leading to death
- TEAEs of special interest

will be displayed by the dose group and overall, for the patients in the SAF.

Table 15.2.1.2.1 Incidence of TEAEs – Safety Analysis Set
Table 15.2.1.2.2 Exposure Adjusted Incidence of TEAEs – Safety Analysis Set
Table 15.2.1.3.1 Incidence of Non-Serious TEAEs – Safety Analysis Set
Table 15.2.1.3.2 Exposure Adjusted Incidence of Non-Serious TEAEs – Safety Analysis Set
Table 15.2.1.4.1 Incidence of Serious TEAEs – Safety Analysis Set
Table 15.2.1.4.2 Exposure Adjusted Incidence of Serious TEAEs – Safety Analysis Set
Table 15.2.1.5.1 Incidence of TEAEs Related to Study Treatment or Blood Donation – Safety Analysis Set
Table 15.2.1.5.2 Exposure Adjusted Incidence of TEAEs Related to Study Treatment or Blood Donation – Safety Analysis Set
Table 15.2.1.6.1 Incidence of Serious TEAEs Related to Study Treatment or Blood Donation – Safety Analysis Set
Table 15.2.1.6.2 Exposure Adjusted Incidence of Serious TEAEs Related to Study Treatment or Blood Donation – Safety Analysis Set
Table 15.2.1.7 Incidence of TEAEs Leading to Discontinuation – Safety Analysis Set
Table 15.2.1.8 Incidence of TEAEs Leading to Death – Safety Analysis Set
Table 15.2.1.9 Incidence of Adverse Events of Special Interest – Safety Analysis Set
Crude and exposure-adjusted incidence rates of TEAEs will be summarized by dose group, SOC and PT. SOCs and PTs within each SOC will be ordered by descending number of adverse events in the total column. Tables showing crude incidence rates will be summarized by study period and overall.

Table 15.2.1.10.1 Incidence of TEAEs by Intensity – Safety Analysis Set
Table 15.2.1.10.2 Incidence of TEAEs by Intensity – Modified Safety Analysis Set
TEAEs will be summarized as above within each severity category. The modified safety analysis set summary will be performed by treatment cycle subgroup.

All AE data will be listed as follows:

Listing 16.2.3.1 Adverse Events: MedDRA Coding
MedDRA system organ class and preferred terms assigned to each reported AE name will be displayed.

Listing 16.2.3.2 Adverse Events: General – Enrolled Analysis Set
Listing 16.2.3.3 Non-Serious Adverse Events – Safety Analysis Set
Listing 16.2.3.4 Serious Adverse Events – Safety Analysis Set
Listing 16.2.3.5 Adverse Events of Special Interest – Safety Analysis Set
Listing 16.2.3.6 Adverse Events Leading to Discontinuation – Safety Analysis Set
Listing 16.2.3.7 Adverse Events Leading to Death – Safety Analysis Set
All AEs will be displayed by patient including the PT of an AE, start and stop dates, duration and other characteristics of AEs.

5.5.2 Multiple Sclerosis Relapse

MS relapse is defined as an appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical relapse-qualifying event. The abnormality must be present for at least 24 hours and occurred in the absence of fever (< 37.5°C) or known infection.

Severe relapses involve 1) at least one of the following functional systems: motor, cerebellar, brainstem, spinal cord and 2) lead to an increase in EDSS of at least 1 point.

MS relapse assessment will be documented in the eCRF. The following parameters will be collected:

- MS relapse status (resolved/ ongoing)
- Start date
- New neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical relapse-qualifying event (yes – new/worsening, no)
- Did the symptoms last for at least 24 hours (yes/no)
- Did the symptoms occur in absence of fever or known infection (yes/no)
- Hospitalization status and the reason of hospitalization (patient disability status, routine process for high dose corticosteroid treatment, other therapies as consequence of relapse)
- Plasmapheresis for their MS relapse (yes/no)
- End of symptoms (date (or ongoing), outcome (death, no recovery, complete recovery, partial recovery))
- Short description
- Confirmed relapse by neurological experts (yes/no)
- Meeting criteria for severity as assessed by neurological experts (yes/no)

The following MS relapse parameters will be summarized:

- Patients experiencing an MS relapse according to the investigator
- Patients with centrally confirmed MS relapses
- Patients with severe centrally confirmed MS relapse
- Annualized Relapse Rate (ARR), defined as total number confirmed MS relapses divided by the number of subject-years of post-treatment study participation duration (including the treatment phase and safety follow-up phase):

$$ARR = \frac{number\ of\ relapses}{post-treatment\ study\ participation\ duration\ (days)} \times 365.25$$

The following statistical output will be presented:

Table 15.2.2 Summary of MS Relapse – Modified Safety Analysis Set
The number and percentages of patients having experienced a relapse will be presented by visit, dose group and overall. The total number of patients with confirmed relapse and the ARR will be presented by dose group and overall. This summary will be performed by treatment cycle subgroup.

Listing 16.2.4 MS Relapse – Enrolled Analysis Set
MS relapse assessment data will be listed.

5.5.3 Magnetic Resonance Imaging

Cranial MRI will be performed as follows; the data will be collected in the eCRF as described below:

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of contrasts enhancing lesions (CEL)	x	x	x		
Number of new/enlarging T2 lesions*		x	x	x	x
Total number of T2 lesions	x				

* New/enlarging T2 lesions are calculated in reference to the previous MRI

Cranial MRI scans without contrast agent can also be performed during unscheduled visits. The number of new/ enlarging T2 lesions observed during unscheduled visit will be documented in the eCRF.

The number of CELs, total or new/ enlarged T2 lesions collected during the scheduled visits will be summarized. All collected data will be listed.

Baseline will be defined as the number of CELs at Visit 1.

Lesion size data will be available from MRI images and will be summarized by visit, dose group, and overall.

When combining the eCRF-based MRI data and the MRI data provided by Jung Diagnostics GmbH (JungD), the following rules will be applied:

- Data collected during an unscheduled visit after a scheduled visit with planned MRI assessments where MRI was not performed will be assigned to that scheduled visit.
- Gad+ lesion data available in the JungD data set will not be used if it is collected during a visit where contrast enhancing lesion (CEL) data collection is not planned.
- Gad+ lesion data available in the JungD data set where CEL data collection was planned and is not available in the eCRF due to data collection issues will be used.

The following statistical output will be presented:

Table 15.2.3 Summary of MRI Data – Modified Safety Analysis Set
The default summary statistics of number of CELs, new/ enlarging T2 and total number of T2 lesions and lesion size as well as change from baseline will be presented by dose group and overall. This summary will be performed by treatment cycle subgroup.

Listing 16.2.5 MRI Data – Enrolled Analysis Set
MRI results will be listed.

5.5.4 Expanded Disability Status Scale

The EDSS is an ordinal scale used for assessing neurological impairment in MS based on a neurological examination. It consists of scores in each of seven functional systems (FSs), as well as ambulation score that are then combined to determine the EDSS steps (ranging from 0 (normal) to 10 (death due to MS).

EDSS assessment data from eCRF include:

- Visual function score (0 - 6)
- Brainstem functions score (0 - 5)
- Pyramidal functions score (0 - 6)
- Cerebellar functions score (0 - 5)
- Sensory functions score (0 - 6)
- Bowel and bladder functions score (0 - 6)
- Cerebral functions score (0 - 5)
- Ambulation score (0 - 12)
- EDSS score (0 - 10)

The following statistical output will be presented:

Table 15.2.4 Summary of EDSS Score – Modified Safety Analysis Set
EDSS score including change from baseline (last value before first blood donation) at each visit will be summarized by dose group and overall. This summary will be performed by treatment cycle subgroup.

Listing 16.2.6 Expanded Disability Status Scale – Enrolled Analysis Set
EDSS, ambulation score and FS assessment data will be listed.

5.5.5 Nine Hole Peg Test

The 9HPT is a quantitative measure of upper extremity (arm and hand) function. It is composed of a square board with nine pegs. At one end of the board there are holes for the pegs to fit into, and at the other end is a dish to store the pegs. The patient has to pick up each of the nine pegs one at a time and

place them as quickly as possible in the nine holes. Once all pegs are placed in the holes, the patient has to remove them again one at a time as quickly as possible and replace them into the container. The total time to complete the task is recorded. Both the dominant and non-dominant hands are tested twice (two successfully completed trials of the dominant hand, followed immediately by two successfully completed trials of the non-dominant hand). The best result will be recorded in the eCRF.

An increase of 20% in the timing of the 9HPT in any of arms is defined as an indicator for an increase of disease severity. The number and percentage of subjects with a clinically significant change in the timing of 9HPT will be summarized for each (dominant and non-dominant) arm and overall, when the increase is observed in any of arms. If the task was completed at baseline but not completed due to physical limitations at post-baseline assessments, this will also be considered as an increase of disease severity.

The following statistical output will be presented:

Table 15.2.5.1 Summary of 9HPT – Modified Safety Analysis Set
The default summary statistics of 9HPT test score in seconds and relative change from baseline (last value before first blood donation) of 9HPT test results will be presented by dose group and overall. This summary will be performed by treatment cycle subgroup.

Table 15.2.5.2 Summary of Clinically Significant Change in 9HPT – Modified Safety Analysis Set
Number and percentages of patients with a clinically significant change in the time of 9HPT will be presented for dominant, non-dominant arm and overall (for any of arms) by dose group and overall. This summary will be performed by treatment cycle subgroup.

Listing 16.2.7 Nine Hole Peg Test – Enrolled Analysis Set
9HPT assessments and relative change from baseline together with reason of non-completion will be listed.

5.5.6 Timed 25-Foot Walk

The T25FW is a quantitative measure of walking function. The examining investigator will time the patient from the start of the walk to the end of the 25 feet. The task will be immediately administered again by having the patient walk back the same distance. The score for the T25FW will be the average (in seconds) of the two complete trials. In case only one trial is available the score will be equal to the time of available trial.

An increase of 20% in walking time of the T25FW is defined as an indicator for an increase of disease severity. If an assistive device was introduced or the test was failed to complete as compared to the baseline it will be considered as a clinically significant change.

The following statistical output will be presented:

Table 15.2.6.1 Summary of T25FW – Modified Safety Analysis Set
The default summary statistics of T25FW test score in seconds and relative change from baseline of T25FW test results will be presented by dose group and overall. This summary will be performed by treatment cycle subgroup.

Table 15.2.6.2 Summary Clinically Significant Change in T25FW – Modified Safety Analysis Set
Number and percentages of patients with a clinically significant change as defined above will be presented by dose group and overall. In addition, the number and percentage of patients with clinically significant increase in walking time of the T25FW as well as number and percentage of patients for whom assistive device was introduced or who failed to complete the test as compared to the baseline

will be presented by dose group and overall. This summary will be performed by treatment cycle subgroup.

Listing 16.2.8 Timed 25-Foot Walk – Enrolled Analysis Set
T25FW assessments and relative change from baseline (Visit 1) will be listed.

5.5.7 Symbol Digit Modalities Test

The SDMT assesses processing speed, which is considered an important measure of cognitive dysfunction in MS patients. The SDMT is a test where using the reference key, the patient has 90 seconds to pair specific numbers with given geometric figures. The number of correct responses in 90 seconds will be considered the SDMT score. A decrease by 4 points on the SDMT score from baseline (last value before blood donation) represents a clinically significant change in cognitive processing.

The following statistical output will be presented:

Table 15.2.7.1 Summary of SDMT Score – Modified Safety Analysis Set
SDMT score will be summarized including change from baseline by dose group and overall. This summary will be performed by treatment cycle subgroup.

Table 15.2.7.2 Summary Clinically Significant Change in SDMT Score – Modified Safety Analysis Set
Number and percentages of patients with a clinically significant change in SDMT score will be presented by dose group and overall. This summary will be performed by treatment cycle subgroup.

Listing 16.2.9 SDMT Score – Enrolled Analysis Set
SDMT assessment data will be listed.

5.5.8 Clinical Laboratory Evaluation

Clinical laboratory values (hematology, biochemistry and urinalysis) are collected at Visit 1, Visit 7, Visit 13, Visit 15, Visit 16 and unscheduled visits.

The following parameters are collected:

Hematology: complete blood count with differential and platelet count, Coombs test, coagulation studies (PT, PTT, INR) and sedimentation rate. Blood group is assessed only on Visit 1.

Biochemistry: Sodium, potassium, creatinine, eGFR (only at Visit 1), urea, total bilirubin, GGT, ALT/GPT, AST/GOT, alkaline phosphatase, total protein, albumin, lactate dehydrogenase, fibrinogen, CRP, iron, ferritin, haptoglobin.

Urinalysis: specific gravity, pH, glucose, protein, ketones, nitrite, leukocytes and blood. Microscopic analysis for leukocytes, erythrocytes, casts, bacteria in case of positive dipstick result for leukocytes, nitrite, protein or blood.

Urine pregnancy tests will be performed locally at all visits except Visit 6 and telephone interviews only in female patients of childbearing potential.

Hematology and biochemistry test results will be flagged to show whether it is a value below (low), above (high) or within (normal) the reference range. Clinical significance of laboratory values is evaluated by the investigator and in the case of a clinically significant finding, the finding will be recorded as an adverse event.

The following rules will be used in order to include results for numeric parameters with non-numeric results in analysis:

- **C Reactive Protein:** The "<0.6 mg/L" results will be set to 0.59 mg/L (reported value) and 5.6 nmol (standardized value).
- **Glomerular Filtration Rate, Estimated:** Will be categorized into "<60.0", "60-90", and ">90.0" [mL/min/1.73m2v] and analyzed as a categorical variable.
- **Bilirubin:** The "<0.1 mg/dL" results will be set to 0.1 mg/dL (reported value) and 1.7 umol (standardized value).

Numeric laboratory parameters will be summarized using standard units.

The following statistical output will be provided:

Table 15.2.8.1.1 Summary of Clinical Laboratory Tests: Hematology – Safety Analysis Set
Table 15.2.8.1.2 Summary of Clinical Laboratory Tests: Biochemistry – Safety Analysis Set
The default summary statistics of clinical laboratory test results will be presented by visit, dose group and overall. The absolute change from baseline (last value before first blood donation) will be presented as well.

Table 15.2.8.1.3 Summary of Clinical Laboratory Tests: Urinalysis – Safety Analysis Set
For categorical test results the number and percentage of patients by categorical test results will be presented by dose group and overall. The percentage will be based on number of patients with non-missing results at each visit. For continued test results the default summary statistics of clinical laboratory test results will be presented by visit, dose group and overall. The absolute change from baseline will be presented as well.

Table 15.2.8.2.1 Clinical Laboratory Tests: Incidence of Hematology Abnormalities – Safety Analysis Set
Table 15.2.8.2.2 Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety Analysis Set
The number and percentage of patients with Low, Normal, High categories of each laboratory parameter will be presented by treatment and overall. The percentages will be based on the number of patients at the specified visit.

Table 15.2.8.2.3 Clinical Laboratory Tests: Incidence of Urinalysis Abnormalities – Safety Analysis Set
The number and percentage of patients with abnormal values of urinalysis parameters will be displayed in normal/abnormal categories. The percentages will be based on the number of patients at the specified visit.

Table 15.2.8.3.1 Clinical Laboratory Tests: Shift Table of Hematology Results – Safety Analysis Set
Table 15.2.8.3.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results – Safety Analysis Set
Shift tables showing changes in the number and frequency of patients with respect to the normal range between baseline (last value before first blood donation) and Visit 7 and Visit 13 will be provided by the dose group.

Listing 16.2.10.1 Laboratory Data – Hematology – Enrolled Analysis Set
Listing 16.2.10.2 Laboratory Data – Biochemistry – Enrolled Analysis Set
Safety laboratory test results will be listed.

Listing 16.2.10.3 Laboratory Data – Urinalysis – Enrolled Analysis Set
All urinalysis test results will be listed.

Listing 16.2.10.4 Urine Pregnancy Test – Enrolled Analysis Set
Urine pregnancy test results will be listed.

5.5.9 Vital Signs

Vital signs will be assessed at all scheduled and unscheduled visits except telephone interviews. Vital sign measurements will include blood pressure (systolic and diastolic, mmHg), heart rate (beats/minute) and body temperature (ºC). Patients must remain in the same body position for 5 minutes prior to having their heart rate and blood pressure taken.

At Visit 3, Visit 4, Visit 10, and Visit 11 vital signs will be recorded in different time points:

- Within 15 min prior to infusion of 1st bag
- 15 min after infusion start of 1st bag
- End of infusion of 2nd bag
- 1 hour after end of infusion of 2nd bag
- 2 hours after end of infusion of 2nd bag

The following statistical output will be provided:

Table 15.2.9 Summary of Vital Signs – Safety Analysis Set
Vital signs will be summarized including change from baseline at each visit and timepoint by dose groups and overall.

Listing 16.2.11 Vital Signs – Enrolled Analysis Set
Vital signs data will be listed.

5.5.10 Physical Examination Findings

Physical examinations will be performed at scheduled and unscheduled visits as described in Section 1, on relevant body systems (eyes, ears, nose and throat, head and neck, lungs/chest, heart/cardiovascular system, abdomen, skin and mucosae, lymph nodes, musculoskeletal system, nervous system (other findings that are not reflected in the EDSS or not related to MS), other-specified).

Any abnormal physical examination findings will be assessed clinically relevant/not relevant by the investigator in the eCRF.

The following statistical output will be presented:

Table 15.2.10 Summary of Physical Examination Findings – Safety Analysis Set
Number and percentage of patients with normal, abnormal, Not CR abnormal, CR abnormal physical examinations findings will be displayed by visit, dose group and overall. The percentages will be based on the number of patients at the specified visit.

Listing 16.2.12 Physical Examinations – Enrolled Analysis Set
Physical examination findings will be listed.

6 DATA MONITORING

An independent Data Safety Monitoring Board will be established to monitor safety data and the performance of the RED4MS trial.

Details and timing of the DSMB are provided in separate document DSMB Charter.

7 CHANGES TO THE ANALYSIS AS LAID DOWN IN THE PROTOCOL AND MODIFICATIONS

No changes to the analysis as laid down in the CSP, Final 7.0.

8 REFERENCES

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4. L. Kappos, J. Antel, G. Comi, X. Montalban, P. O'Connor, C.H. Polman, T. Haas, A.A. Korn, G. Karlsson, E.W. Radue, and F.D.S. Group, Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med 355 (2006) 1124-40.
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9 LIST OF STATISTICAL OUTPUTS

Shells for tables, listings, and figures are available in the following appendices:

- Table Shells, Appendix No. 1 to SAP Version Final 2.0
- Listing Shells, Appendix No. 2 to SAP Version Final 2.0
- Figure Shells, Appendix No. 3 to SAP Version Final 2.0

9.1 List of Tables

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Table 15.1.5 Number of Patients by Country and Site – Safety Analysis Set	RED4MS-T-1501050000-countrysite-saf.rtf
Table 15.1.6 Number of Patients by Visit – Safety Analysis Set	RED4MS-T-1501060000-visit-saf.rtf
Table 15.1.7.1.1 Demographics – Safety Analysis Set	RED4MS-T-1501070101-demo-saf.rtf
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Table 15.1.7.2.1 Baseline Characteristics – Safety Analysis Set	RED4MS-T-1501070201-basechar-saf.rtf
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Table 15.1.10.2 Concomitant Medications and Therapies – Safety Analysis Set	RED4MS-T-1501100200-conmed-saf.rtf
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9.2 List of Listings

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Listing 16.2.1.3 Patient Visits – Enrolled Analysis Set	RED4MS-L-1602010300-visits-enr.rtf
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Listing 16.2.1.5 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled Analysis Set	RED4MS-L-1602010500-ie-enr.rtf
Listing 16.2.1.6.1 Demographics and Baseline Characteristics – Enrolled Analysis Set	RED4MS-L-1602010601-demo-enr.rtf
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Listing Identifier, Title	Output file
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Listing 16.2.3.3 Non-Serious Adverse Events – Safety Analysis Set	RED4MS-L-1602030300-ae-nonser-saf.rtf
Listing 16.2.3.4 Serious Adverse Events – Safety Analysis Set	RED4MS-L-1602030400-sae-saf.rtf
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Listing 16.2.10.4 Urine Pregnancy Test – Enrolled Analysis Set	RED4MS-L-1602100400-preg-enr.rtf
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Listing 16.2.12 Physical Examinations – Enrolled Analysis Set	RED4MS-L-1602120000-pe-enr.rtf

9.3 List of Figures

Figure Identifier, Title	Output file
Figure 15.1.1 Flow Chart of Patient Disposition – Enrolled Analysis Set	RED4MS-F-150101-disp-enr.rtf

10 SIGNATURES

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