STUDY PROTOCOL

ClinicalTrials.gov Submission Cover Page

Protocol ID	MSB-IG-H-2101
Official Title	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
NCT Number	NCT06430671
EU CT Number	2023-510127-30-00
Protocol Version	Version 7.0
Document Date	May 9, 2025
Sponsor	Cellerys AG Wagistrasse 21, 8952 Schlieren, Switzerland

CLINICAL STUDY PROTOCOL

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

CLS12311

EU-CT No.: 2023-510127-30-00

CELLERYS AG

Wagistrasse 21, 8952 Schlieren, Switzerland

Version 7.0	2025-05-09

This clinical trial will be conducted in compliance with the protocol, the Clinical Trial Regulation (EU) No. 536/2014, applicable national legislations, and the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

EXECUTIVE SUMMARY - CHANGE IN STUDY DESIGN IN PROTOCOL VERSION 7.0

Protocol version 7 reflects a change in the study design. Prior versions of the protocol included a Phase Ib (Part A) - a dose-escalation phase to assess safety, tolerability and preliminary biological effects of CLS12311, followed by a Phase II (Part B), aiming to extend the safety dataset and gather proof-of-concept for efficacy of the treatment. The Sponsor has decided not to initiate the Phase II (Part B) study. This decision is not based on a change in the risk-benefit assessment.

The current protocol version has therefore been amended to indicate that the study will conclude after completion of Phase Ib (Part A) only.

1 RESPONSIBILITIES AND ADDRESSES

Coordinating Investigator

[redacted]

Sponsor

Cellerys AG
Wagistrasse 21
8952 Schlieren, Switzerland

EU legal representative
SCOPE International
Konrad-Zuse-Ring 18
68163 Mannheim, Germany

Chief Medical Officer

[redacted]

Statistician

[redacted]

CRO

SCOPE International
Konrad-Zuse-Ring 18, 68163 Mannheim
Phone: +49 621 429 390
E-Mail: contact@scope-international.com

SAE hotline: SAE reporting to SCOPE International by fax or email within 24 hours after obtaining knowledge of the event:

Fax: +370 523 27903
E-mail: safety@scope-international.com

Emergency phone number (24/7): +370-5-2327902

All institutions, participants and their contact details will be given in a separate document.

2 ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
APC	Antigen-Presenting Cell
AR	Adverse Reaction
AST	Aspartate Aminotransferase
BL	Baseline visit
BMI	Body Mass Index
BP	Blood Pressure
CD	Cluster of Differentiation
CEL	Contrast-Enhancing Lesion
CK	Creatin Kinase
ClinO	Ordinance on Clinical Trials in Human Research
CNS	Central Nervous System
eCRF	electronic Case Report Form
CRO	Clinical Research Organization
CRP	C-reactive Protein
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria of Adverse Events
CTR	Clinical Trials Regulation (EU) No. 536/2014
DMT	Disease Modifying Therapy
DSMB	Data Safety Monitoring Board
DTH	Delayed Type Hypersensitivity
EAE	Experimental Autoimmune Encephalomyelitis
EBV	Epstein Barr Virus
ECG	Electrocardiogram
EDC	1- Ethyl- 3- (3-Dimethylaminoprpyl) – carbodiimide
EDSS	Expanded Disability Status Scale
EDTA	Ethylene Diamine Tetra-Acetate
ED	Early Discontinuation
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOT	End of Treatment
EOS	End of Study

ETIMS	Establish Tolerance in MS
FS	Functional System
GBCA	Gadolinium-based contrast agent
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyltransferase
GMP	Good Manufacturing Practice
GOT	Glutamat-Oxalacetat-Transaminase
GPT	Glutamat-Pyruvat-Transaminase
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLA-DR	Human Leukocyte Antigen Class II
9-HPT	Nine Hole Peg Test (clinical test for hand function)
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	(Patient) Identification
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRTS	Interactive Response Technology System
ISF	Investigator Site File
ITT	Intent-To-Treat
i.v.	Intravenous
MBP	Myelin Basic Protein
MOG	Myelin Oligodendrocyte Glycoprotein
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multple Sclerosis Functional Composite
NA	Not Applicable
NFL	Neurofilament Light Chain
p-value	Probability value
PBMC	Peripheral Blood Mononuclear Cells

pH	Value potential Hydrogenium-Value
PLP	Proteolipid Protein
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PV	Pharmacovigilance
PVE	Polypropylene/Vinyl Ethylene Acetate
RAB	Relapse Assessment Board
RASGRP	RAS Guanyl Releasing Protein
RBC	Red Blood Cells
RR	Relative Risk
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analyses Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test (cognitive test)
SJL mice	Swiss James Lambert mice
SFU	Safety Follow Up
SOP	Standard Operating Procedure
SP	Secondary Progressive
SUSAR	Suspected Unexpected Serious Adverse Reaction
T cell	T lymphocyte cell
TCC	T Cell Clone/s
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
T25-FW	Timed 25-Foot Walk Test
TMF	Trial Master File
TSTA3	Tissue Specific Transplantation Antigen 3, also known as GDP L-fucose synthase
WCS	Worst Case Scenario

3 PROTOCOL SUMMARY / SYNOPSIS

Study title	Multicenter, Phase Ib/IIa Study on the Safety and Efficacy of Autologous Peptide-coupled Red Blood Cells in Patients with Relapsing Remitting Multiple Sclerosis
Brief study title	Peptide-coupled Red Blood Cells for the Treatment of Multiple Sclerosis
Acronym	RED4MS
Version Number	7.0
Version Date	2025-05-09
Development phase	Phase Ib
Study No.	MSB-IG-H-2101
EU-CT No.	2023-510127-30-00
Study drug	Peptide-coupled red blood cells (CLS12311)
Coordinating Investigator	[redacted]
Sponsor	Cellerys AG Wagistrasse 21 8952 Schlieren, Switzerland EU legal representative: SCOPE International Konrad-Zuse-Ring 18, 68163 Mannheim, Germany
CRO	SCOPE International Konrad-Zuse-Ring 18, 68163 Mannheim Phone: +49 621 429 390 E-Mail: contact@scope-international.com
Study design	**Phase Ib** open-label trial evaluating ascending-doses of CLS12311 *Note: Originally, the study was designed to include a Phase IIa part (Part B). The Phase IIa (Part B) will not be conducted. This amendment reflects the adjustment to a Phase Ib only design.*
Study objectives	**Safety Objective** Primary safety objective: • To assess the safety and tolerability of CLS12311 in patients with relapsing remitting multiple sclerosis (RRMS) Secondary safety objective: • To assess the safety and tolerability of each dose group of CLS12311 **Exploratory objective** • To understand the mechanism/s of action of tolerance induction with peptide-coupled RBCs and to identify biomarkers for measuring immune tolerance induction

Primary endpoint	**Safety endpoint** • Safety and tolerability of CLS12311 measured by the number and severity of treatment-emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) and/or worsening of disease by clinical (relapses) and imaging (number and size of brain MRI lesions) MRIs will be assessed centrally by independent readers.
Secondary endpoints	**Safety endpoints** • Number and severity of TEAEs and TESAEs in each dose group • Number of confirmed relapses in the treatment phase in each dose group • Changes in clinical measures of disease severity (EDSS, 9-HPT, T25-FW, SDMT) following CLS12311 administration in each dose group
Exploratory endpoints	**Exploratory immunological and biomarker measures** • Percentage of patients in each dose group showing a reduction of antigen-specific T cells against the protein(s) they responded to at the study entry • Changes in predefined serum- and cellular biomarkers including autoantigen-specific T cell responses that would indicate proinflammatory activation
Study plan	Multicenter, open-label, dose-escalation Phase Ib trial evaluating the safety and tolerability of intravenous CLS12311 in subjects with RRMS. Eligibility will be assessed during baseline (week 0), when 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 timing of treatment administration will be coordinated centrally. All enrolled patients will be followed for at least 48 weeks, with visits as outlined in the Schedule of Events -Table 4.1. **Open Label Treatment Phase:** at least 17 weeks *Single treatment cycle* The safety and tolerability of a single treatment cycle of CLS12311 will be assessed in an open label, ascending dose study over three dose groups in 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. The treatment will start with the lowest dose group. Further dosing in the higher dose groups will only be initiated if, in the preceding dose group, safety based on (S)AEs and relapses until visit 5 has been confirmed by Sponsor's medical expert(s). 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. The DSMB will evaluate all safety data of the ascending dose study after the last patient in Part A has completed the [redacted] *Second treatment cycle* The safety and tolerability of a second treatment cycle of CLS12311 will be investigated in a subgroup of patients (n=6) from the initial ascending dose study of the first treatment cycle. The sentinel patients will not receive a second treatment cycle. All other patients will remain in the same dose group and receive a second treatment cycle of [redacted](n=1), [redacted](n=2) or [redacted](n=3) at [redacted] of the study. Thus, patients receiving a second treatment cycle will have the following total product exposure: low dose group $6x10^{11}$ (n=1), medium dose group [redacted] (n=2) or high dose group [redacted] (n=3).

	The second treatment cycle will only be administered after verifying the safety of the first treatment cycle given to the first patient in the next higher dose group, has been confirmed in [redacted]. Only after confirmation of the tolerability and safety of the treatment in **patient 3** (single dose of [redacted]) in [redacted], the second treatment cycle of patient 2 (total cumulative dose of [redacted]) will be permitted. Patients 4 and 5 will receive second treatment (total cumulative dose of [redacted]) only if the week 7 safety data of **patient 6** (single dose of [redacted]) will support a second dosing of CLS12311. Information on the safety of the second treatment cycle in patient 2 will be available prior to administration of the second treatment in patients 4 and 5, as the information of the safety of the second treatment cycle in patient 4 or 5 will be available prior to dosing of the second treatment cycle in patients 7 - 9. In patients who received at least one dose of study drug and prematurely discontinue treatment period and/or choose not to stay in the study until the [redacted], a study visit according to the early discontinuation (ED) will be performed. After the last patient in the high dose group has completed [redacted] the safety data (including MRI data, relapses and EDSS) from all patients will be evaluated by the DSMB. **Safety Follow Up**: approximately 31 weeks At the completion of the treatment phase at [redacted], patients will enter a safety follow up (SFU) of 31 weeks. During the safety follow up period patients will be assessed as per Schedule of Events - Table 4.1. Patients who discontinue the safety follow-up phase and their last visit has been more than 8 weeks ago, shall perform a study visit according to early discontinuation (ED) visit. **Withdrawal Criteria** Patients must be withdrawn from the study under the following circumstances: • Pregnancy detected at any time during the study. Pregnancy in patients who become pregnant after the first study dose will be followed until delivery. Patients may volunteer further information regarding child health at 12 months after birth • A positive result in the infectious disease screen analyzed according to local regulations during eligibility testing and/or release of autologous RBC donation. • The patient withdraws consent • Patient takes any of the drugs mentioned under exclusion criterion No. 2 (except for relapse treatment as outlined in section 11.2 of the study protocol) • The patient is unable or unwilling to comply with the protocol • Any other disease or condition which could interfere with the participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures • Any medical condition, which the physicians and Investigators deem severe or compromising regarding the safety of the patient and/or the study results, e.g. disease progression requiring the use of effective MS treatment (DMT)
Number of planned patients	In total 9 patients will be enrolled to receive a first treatment cycle in an ascending dose study of CLS12311. 6 of these patients will receive a second treatment cycle once safety of the first treatment cycle has been confirmed.

Timelines	The total duration of study participation in Part A for each subject will be at least 48 weeks. Subject eligibility will be determined at Baseline (visit 1, week 0), followed by a 17-week treatment phase and a 31-week safety follow up phase. The duration of the study is expected to be approx. 20 months. The end of this study is defined as the date when the last patient, last visit (LPLV) occurs.
Patient population	The study population will consist of patients with a diagnosis of RRMS in accordance with the revised 2017 McDonald Criteria. Patients previously treated with MS drugs will be allowed to participate in this study provided that they did not take certain medications within the timeframes defined in the exclusion criteria. Given MS's gender and age distribution, with females affected up to three times more than males, the study population is expected to have a higher proportion of females.
Study location	The study will be performed at approximately 12 sites in Europe.
Main inclusion criteria	<u>General inclusion criteria (to be assessed at the beginning of the baseline period based on patient interview and medical history):</u> 1. RRMS according to the 2017 McDonald criteria 2. Male or female patients (assigned at birth) aged 18-55 years inclusive 3. Disease duration (since diagnosis) <10 years 4. EDSS at baseline 0-5.5 5. Untreated patients or patients being off therapy for the time periods listed under exclusion criterion No. 2. Patients are either not eligible to receive approved therapies or have explicitly chosen not to receive such therapies after being adequately informed by the investigators 6. Only for sexually active female patients of childbearing potential (sexually mature, pre-menopausal and not surgically sterile): the patient is willing to use a highly effective method of contraception (defined in the study protocol) throughout the complete treatment phase or at least for 4 weeks after the last dose of CLS12311 7. Male patients willing to use contraception (condoms) throughout the complete treatment phase or at least for 4 weeks after the last dose of CLS12311, unless surgically sterile 8. Basic immunization against SARS-CoV-2, i.e. both doses of two-dose vaccines (or one dose of a vaccine and a SARS-CoV-2 infection before or after vaccination) OR a dose of a single-dose vaccine
Main exclusion criteria	<u>General exclusion criteria (to be assessed at the beginning of the baseline period based on patient interview and medical history):</u> 1. Patients with an active chronic disease (or stable but treated with immunomodulatory/-suppressive therapy) of the immune system other than MS (e.g. rheumatoid arthritis, scleroderma, Crohn's disease, ulcerative colitis, etc.) or with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug-induced immune deficiency) 2. Prior treatment with any of the medications below within the specified time-frame: a. glatiramer acetate, interferon-beta within 4 weeks prior to screening visit 1 b. dimethylfumarate, diroximel-fumarate within 4 weeks prior to screening visit 1

	c. teriflunomide within 4 weeks prior to screening visit 1, provided accelerated elimination procedure (eg. cholestyramine) was performed and teriflunomide plasma level are below 0.02 mg/L before randomization d. fingolimod, ozanimod within 12 weeks prior to screening visit 1, provided normal lymphocyte counts (see exclusion criterion No. 18) e. siponimod, ponesimod within 8 weeks prior to screening visit 1, provided normal lymphocyte counts (see exclusion criterion No. 18) f. natalizumab within 12 weeks prior to screening visit 1 g. ocrelizumab, ofatumumab, rituximab, alemtuzumab, cladribine, mitoxantrone within 52 weeks prior to screening visit 1 h. plasma exchange, intravenous immunoglobulin within 8 weeks prior to screening visit 1 i. azathioprine, methotrexate, cyclophosphamide or any other continuous immunosuppressive therapy within 24 weeks prior to screening visit 1 j. any other immunosuppressive monoclonal antibody treatment within 24 weeks prior to screening visit 1 k. Prior autologous hematopoietic stem cell transplantation l. Corticosteroid treatment for MS relapse within 4 weeks prior to screening visit 1 m. Patients who participated in the ETIMSred trial 3. History of HIV, chronic or active Hepatitis C, chronic or active Hepatitis B or prior Syphilis, which has not been sufficiently treated 4. Long-Covid19 syndrome 5. History of splenectomy or chronic liver disease 6. History of coronary artery disease, chronic heart failure, aortic stenosis 7. Current anticoagulation therapy 8. Uncontrolled grade II hypertension (≥160 systolic and/or ≥100 diastolic blood pressure; according to ISH global practice guidelines) despite treatment or without treatment 9. History of stroke 10. Pregnant female confirmed by a positive pregnancy test or breast-feeding 11. History of alcohol or drug abuse within the 1 year prior to screening visit 1 12. History of or existing malignancy within the last 5 years prior to enrollment except history of basal cell carcinoma and melanoma in situ 13. History of or existing relevant central nervous system disorder (other than MS) 14. Allergy to gadolinium-based contrast agents 15. Any other disease or condition, which could interfere with the participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures <u>Specific exclusion criteria (to be assessed during the baseline period):</u> 16. Anemia, defined as hemoglobin levels ≤12.5 g/dl (7.25 mmol/l) for female and ≤13.5 g/dl (8.37 mmol/l) for male participants (may be repeated if 11.5 -12.5 g/dl in females and 12.5 - 13.5 g/dl in males)

	17. Erythrocyte count <4.0 E12/L in female and <4.5 E12/L in male patients (may be repeated if >3.8 E12/L in female and >4.3 E12/L in male) 18. Lymphopenia with total lymphocyte counts ≤1000/µl (may be repeated if >800/µl) 19. Positive HIV testing 20. Positive results of baseline period testing for serological markers for hepatitis B, C, and Syphilis indicating acute or chronic infection 21. Patient is not eligible for blood donation according to local regulations 22. Having one or more of the following laboratory results: a. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (may be repeated if eGFR is 45–59 mL/min/1.73 m^2) b. ALT or AST $> 3 \times$ upper limit of normal (ULN; may be repeated if 3.1-4 $\times$ ULN) c. Total bilirubin greater than 2 $\times$ ULN (may be repeated if 2.1–3 x ULN), with the exception for patients with Gilbert's disease d. Platelet count ≤ 100 $\times$ 10^9/L (may be repeated if 80–100 $\times$ 10^9/L) e. Abnormalities in hepatic synthetic function tests (PT time, INR, PTT, albumin) as judged by the Investigator to be clinically significant
Investigational product(s), formulation, route of administration	The drug product **CLS12311** consists of autologous red blood cells (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). **Placebo** consists of autologous red blood cells (RBCs) re-suspended in saline (150 ml). CLS12311 and placebo are stored in standard bags for blood transfusions. CLS12311 and placebo will be administered by i.v. infusion typically over a 30 to 60 minutes period.
Dosing	Single/first treatment cycle of CLS12311 will be given as follows: • Group 1 (2 patients): ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] uncoupled RBCs (placebo) ○ Week 3: ▪ Bag 1: [redacted] uncoupled RBCs (placebo) ▪ Bag 2: [redacted] uncoupled RBCs (placebo) manufactured from a single blood donation [redacted] • Group 2 (3 patients): ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] uncoupled RBCs (placebo) ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted][1] uncoupled RBCs (placebo) manufactured from a single blood donation [redacted] • Group 3 (4 patients): ○ [redacted]

	▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] peptide-coupled RBCs (CLS12311) ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] peptide-coupled RBCs (CLS12311) manufactured from a single blood donation [redacted] Second treatment cycle of CLS12311 will be given as follows: • Group 1 (1 patient): ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] uncoupled RBCs (placebo) ○ [redacted] ▪ Bag 1: [redacted] uncoupled RBCs (placebo) ▪ Bag 2: [redacted] uncoupled RBCs (placebo) manufactured from a single blood donation [redacted] • Group 2 (2 patients): ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] uncoupled RBCs (placebo) ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] uncoupled RBCs (placebo) manufactured from a single blood donation [redacted] • Group 3 (3 patients): ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] peptide-coupled RBCs (CLS12311) ○ [redacted] ▪ Bag 1: [redacted] peptide-coupled RBCs (CLS12311) ▪ Bag 2: [redacted] peptide-coupled RBCs (CLS12311) manufactured from a single blood donation [redacted]
Statistical methods	
Sample Size Calculation	As this is an exploratory Phase Ib study focusing on safety and tolerability, 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. The study is not powered for efficacy analyses.
Analysis Populations	• The enrolled analysis set includes all patients who provided informed consent. • The safety analysis set (SAF) includes all patients with blood donation for CLS12311 production.
Safety analysis	Adverse events (AE) will be coded using MedDRA and will be presented by primary System Organ Class (SOC) and Preferred Term. The analysis will focus on the treatment-emergent AEs (TEAE), i.e. AEs which started or worsened after blood donation for CLS12311 production. The frequency of TEAEs by dose group and in total will be summarized by incidences standardized to the number of patients at risk and rates standardized to the total observation time.

	Frequencies of TEAEs by dose group and in total will also be presented by relationship to study treatment and by severity. Additional analyses will be performed for SAE, TESAE, adverse events of special interest (AESIs) and AEs leading to discontinuation. The number and percentages of patients having experienced a centrally confirmed relapse will be presented by dose group and in total. Descriptive summaries of observed values and changes from baseline will be presented for hematology and biochemistry variables by dose group. Each abnormal value will be flagged to show whether it is a value below or above the reference range and assessed by the Investigator for clinical relevance. The assessments of laboratory variables will be tabulated by visit for each clinical laboratory analyte by dose group and in total (frequency tables). The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by dose group and in total (frequency tables). Vital signs will be described by summary statistics (by dose group and in total) for measured values and changes from baseline by visit. The number and percentages of patients with normal/abnormal findings in physical examinations will be presented by visit (by dose group and in total). Additional safety analyses will examine the changes in clinical parameters including EDSS, 9-HPT, T25-FW and SDMT following treatment with CLS12311.
Further analyses	Exploratory analyses will include quantitative and functional aspects of the obtained T cell responses as well as analysis of the influence of dose on other immune cell populations such as regulatory T cells and changes in soluble biomarkers. Biomarker data may also be explored in relation to safety and imaging parameters. All analyses will be exploratory and hypothesis-generating.
Safety analysis timepoints	The safety evaluation will be conducted by the Sponsor's Medical Expert(s) and/or the Data Safety Monitoring Board. Safety will be assessed at different timepoints: <u>Single/First treatment cycle</u> • After each patient in the low dose group completed [redacted] • After each patient in the medium dose group completed [redacted] • After each patient in the high dose group completed [redacted] • After sentinel patients 3 and 6 completed [redacted] • Data Safety Monitoring Board (DSMB) meeting after the last patient in the high dose group completed [redacted] <u>Second treatment cycle</u> • After all patients in the low dose group completed [redacted] • After the first patient (sentinel) in the medium dose group completed [redacted] • After all patients in the medium dose group completed [redacted] • After the first patient (sentinel) in the high dose group completed [redacted] • After the last patient in the high dose group completed [redacted]
Data and Safety Monitoring (DSMB)	A DSMB consisting of at least 3 independent MS- and trial-experienced neurologists will be established to closely monitor the safety of the trial. Besides tolerability and safety of CLS12311, the DSMB will also evaluate

worsening of MS assessed by new lesions on brain MRI and occurrence of relapses and progression of disability based on EDSS.

After the last patient in the high dose group completed [redacted] and [redacted], the DSMB will evaluate all safety data (including MRI and clinical data).
In addition, a DSMB meeting will be required any time during the trial, if any of the criteria mentioned below is met:

- if at least 1 patient experiences AE graded as severe and at least possibly related to the IMP within the same dose level of CLS12311 or placebo
- if at least 3 patients experience AEs graded as 'moderate' and at least possibly related to the IMP within the same dose level of CLS12311/placebo
- If at least 3 patients (irrespective of the dose group) show an increase of >5 new lesions (CEL or new/enlarging T2) at [redacted] compared to the average number of new brain lesions (as defined above) observed during baseline
- if a confirmed relapse (irrespective of the dose group), assessed as severe, occurred within 4 weeks after the last dosing

The DSMB shall give recommendations on the following main outcomes:

- stop further treatment or lower further dosing in individual patients
- stop recruitment and/or treatment or lower dose for a specific treatment arm
- stop recruitment and/or treatment for the clinical trial
- continue the clinical trial as per protocol
- any other trial modification (e.g. additional visits, assessments)

Any recommendation will be explicitly documented in the meeting minutes.
Based on the DSMB recommendations, the Study Steering Committee will decide on actions to be taken as outlined above.
For the DSMB meetings, the DSMB will receive patient listings and statistical summaries, consisting of at least the following in addition to all available data on the patient(s) that made the meeting necessary:

- All patients who experienced SAEs (including relationship and severity)
- All patients who experienced AEs (including relationship and severity)
- All patients who experienced AEs within one day following infusion of CLS12311/placebo including severity and relationship
- All patients who experienced a relapse
- Number of new brain lesions (CEL and new/enlarging T2)
- EDSS scores
- Safety relevant protocol deviations

Detailed requirements on the presentation of listings and summaries and details of the premise and the scope of the DSMB will be specified in the DSMB Charter.

4 SCHEDULE OF EVENTS AND TREATMENT

4.1 Part A

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, T25-FW, SDMT	x						x						x		x	x	x
Eligibility for blood donation[6]	[redacted]																
Blood donation																	

Visit	[redacted]	UV
Week	[redacted]	Unscheduled[12]
Study Phase	BL	Treatment	SFU	
CLS12311/ (Placebo)[7]	[redacted]	
Concomitant medication/procedures		x	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	x
Adverse event assessment	x	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); T25-FW 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 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 V2 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 [redacted] coincides with the phone visit [redacted], the phone consultation of the [redacted] will be skipped.

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

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

5 INTRODUCTION

5.1 Background Information

5.1.1 Overview of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory neurological disease, starting in early adulthood with a female to male ratio of 3:1 [1]. It affects 2.3 million individuals around the world and has a median global prevalence of 33 per 100.000 [2]. Patients with MS have a high risk for future disability, and MS is one the most frequent causes of neurologic impairment in young adults in Europe and North America. The disease is characterized by multifocal inflammatory infiltrates in the brain and spinal cord resulting in an injury to the myelin sheaths, oligodendrocytes and nerve cells and their processes [3]. The clinical presentation and the symptoms of MS are driven by the strategic location of inflammatory lesions triggering a wide spectrum of symptoms and signs, including (but not limited to) focal weakness, sensory deficits, double vision, loss of vision, imbalance, fatigue, urinary and bowel dysfunction, sexual impairment and cognitive decline.

In approximately 80-90% of patients the disease starts with a relapsing-remitting disease course (RRMS), which can convert to a secondary-progressive disease course (SPMS) characterized by a steady increase in disability with or without superimposed relapses [4]. A relapse is an acute episode of a new neurological abnormality or worsening of a previously stable or improving pre-existing neurological abnormality, which lasts for >24h, in the absence of fever or infection (see 12.1.1.2). A subset of MS patients presents with a chronic neurological deterioration from the onset of disease, termed primary progressive MS.

The diagnosis of MS is based on characteristic clinical presentation and neurological findings and supported by the presence of white matter lesions on magnetic resonance images (MRIs) of the brain and spinal cord, as well as signs of chronic inflammation detected in the cerebrospinal fluid (CSF). The diagnosis can be made if standard criteria are fulfilled [5].

Various immunomodulating and/or immunosuppressive therapies are approved for the treatment of MS, including interferon-beta, glatiramer-acetate, dimethyl fumarate, diroximel fumarate, teriflunomide, fingolimod, siponimod, ozanimod, ponesimod, cladribine, natalizumab, ocrelizumab, ofatumumab, alemtuzumab and mitoxantrone. Overall, these treatments reduce the risk of the development of new brain lesions on average by 50-90% and the risk of clinical relapses by 30-60%. These therapies need to be administered for long periods of time and carry the risk of side effects, associated with global immunosuppression.

5.1.2 Autoimmune Pathogenesis of MS and Role of T cells

The pathogenesis of MS is driven by a complex interaction of genetic and environmental factors. Major environmental risk factors include sun exposure, vitamin D deficiency, smoking, obesity, Epstein Barr virus (EBV) infection and particularly infectious mononucleosis during early adulthood. The most important genetic risk factor in MS is the human leukocyte antigen (HLA) DR15 haplotype. Most of the other >200 genetic variants that confer a risk of developing the disease are associated with immune pathway genes [6]. Data from both human and animal studies suggest that the adaptive immune system and in particular autoreactive CD4+ T cells and B cells are important effector cells in the autoimmune pathogenesis of MS [7]. The fact that most of the genetic susceptibility for MS is conferred by the DR15 haplotype, supports the role of CD4+ T cells, since CD4+ T cells recognize antigens in the context of HLA-class II molecules [8]. Further evidence for the importance of autoreactive CD4+ T cells, comes from studies in blood and CSF of MS patients. The frequency of activated CD4+ T cells reactive to main constituents of the myelin sheath, such as myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG), is increased in the peripheral blood of MS patients [9] [10] [11]. In particular, T cells targeting a set of immunodominant peptides from MBP, MOG and PLP (MBP13-32, MBP111-129, MBP146-170, PLP139-154, MOG1-20 and MOG35-55) with high avidity and a Th1 or Th1* (secreting IFN-γ and IL-17) cytokine phenotype, can be found in a large

fraction of RRMS patients [12]. Further evidence for the importance of myelin-reactive T cells comes from a clinical trial in MS, where an experimental therapy induced MBP 83-99-reactive Th1 CD4+ T cells, which caused exacerbation of disease [13].

More recent studies focusing on T cells, which are clonally expanded in brain lesions of MS patients, identified further non-myelin proteins as target antigens of the autoimmune response in MS patients [14; 15].

Analyzing the autologous proliferating T cell compartment in the blood of MS patients identified a T cell clone (TCC), which was also clonally expanded in MS brain lesions and recognized peptides from RAS guanyl-releasing protein 2 (RASGRP2) with high avidity [15]. Importantly, RASGRP2 is expressed in both the brain and in proinflammatory B cells, which are important in the pathogenesis of MS.

Beside analysis of peripheral blood cells, antigen-specific autoimmune responses can be detected in brain- and CSF-infiltrating lymphocytes of MS patients [16]. Brain -infiltrating TCCs isolated from active brain lesions of an MS patients recognized GDP-L fucose synthase (TSTA3) [14]. The T cell reactivity against TSTA3 could be confirmed in the CSF of a large number of MS patients [17].

5.1.3 Peptide-coupled Cell Tolerance in Pre-clinical Models and MS Patients

5.1.3.1 Summary of Preclinical Data

A promising tolerization strategy employs autologous blood cells, which are chemically coupled with antigenic peptides using the cross linker 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC).

The efficacy and mechanism of action of antigen-specific immune tolerance induced by peptide-coupled cells has been studied in various non-clinical models of autoimmune diseases, transplantation and allergies, demonstrating significant therapeutic potential.

Peptide-coupled cells have shown efficacy for either prevention or treatment or both of disease in murine models of autoimmune central nervous system (CNS) demyelination induced by myelin-reactive T cells [12; 18; 19; 20], in the diabetes model in the Non-Obese Diabetic (NOD) mouse [21], and in other models of T cell-mediated autoimmune diseases including experimental thyroiditis, uveitis and neuritis [22; 23; 24], in allograft rejection [25], and allergic disease [26].

In the experimental autoimmune encephalomyelitis (EAE) model, a single i.v. injection of splenocytes or RBC coupled with single- or mixtures of encephalitogenic myelin peptides using the cross-linker EDC is highly efficient in inducing peptide-specific tolerance in vivo [27; 28]. In a relapsing EAE model in SJL mice, induced with a peptide of proteolipid protein (PLP), induction of immune tolerance with peptide-coupled cells not only prevented animals from developing disease but even effectively reduced the onset and severity of all subsequent relapses when given after disease induction, indicating that specific tolerance can downregulate an ongoing autoimmune response [18; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39]. More relevant to the treatment of MS, studies in EAE have shown that tolerance can be simultaneously to induce tolerance to multiple epitopes using a cocktail of encephalitogenic myelin peptides provides the strategy to target autoreactive T cells with multiple specificities [40]. The regimen was superior to tolerance induction by oral, subcutaneous or intraperitoneal administration of antigen. Furthermore, it has been shown that the tolerization with peptide-coupled splenocytes prevent intra- and intermolecular spreading of the autoimmune response, that is the broadening to other than the inducing encephalitogen [37; 41]. While these findings are promising, the potential risks associated with the use of peptide-coupled cells, such as unexpected immune responses or anaphylactic reactions, must be considered when moving to clinical application.

5.1.3.2 Summary of Clinical Data with Peptide-Coupled Cell Based Therapies

The initial clinical application of peptide-coupled cell treatment employed autologous peripheral mononuclear cells (PBMCs) which had been coupled with seven peptides (MBP1, MBP2, MBP3, MBP4, PLP1, MOG1, MOG2) from three myelin proteins (MOG, MBP, PLP). In a first-in-man phase Ib trial (ETIMS), a single infusion of peptide-coupled PBMCs was feasible, safe and well-tolerated in MS patients up to a dose of $3x10^9$ antigen-coupled PBMCs [12]. In patients receiving more than $1x10^9$ peptide-coupled cells, a decrease in antigen-specific T cell responses could be observed [12].

During further clinical development autologous RBCs were introduced as tolerogenic carrier cells. The advantages of using RBCs include: 1) Flexibility to increase the dose with a single blood donation; 2) Available safety profile due to extensive experience with the use of RBCs in medicine; 3) Well-established procedures for collection and storage of RBCs, considered routine and 4) RBCs target the liver as a tolerogenic organ.

An open-label, dose-escalation, phase Ib study (ETIMSred) of a single infusion of autologous RBCs coupled with seven myelin peptides (TOL001) in 10 RRMS patients demonstrated an excellent safety and tolerability profile (Lutterotti et al. in preparation). Three dose groups, including $1x10^{10}$ (2 patients), $1x10^{11}$ (3 patients) and $3x10^{11}$ (5 patients) peptide-coupled RBCs were assessed and patients followed up to 6 months. Mechanistic studies performed in parallel with the trial showed preliminary evidence for induction of antigen-specific immune tolerance, with a reduction in peptide-specific T cell responses, increases in serum levels of IL-10 and the number of induced regulatory T cells. Given the excellent safety and tolerability of a single infusion of [redacted] peptide-coupled RBCs, an extension of the trial was performed, which included five patients from the initial phase Ib trial cohort. These five patients received an intensified regimen consisting of [redacted] peptide-coupled RBCs given [redacted]. The extension of the phase Ib trial confirmed the safety and tolerability of this regimen.

See the Investigator's Brochure for detailed information on relevant non-clinical and clinical studies.

5.1.3.3 Summary of the Investigational Product CLS12311

CLS12311 consists of autologous RBCs chemically coupled with [redacted] peptides [redacted] from [redacted] proteins [redacted], which are re-suspended in saline solution. To date, the optimal dose has not been defined and will be tested during the RED4MS trial. The current dose range is between [redacted] and [redacted] peptide-coupled RBCs.

Pharmaceutical form

CLS12311 is a cell suspension for i.v. infusion, supplied as a sterile and preservative-free solution packaged in a 500 ml standard blood bag (CompoFlex, Fresenius, Germany). The sterile blood bag will be opened by a standard blood infusion kit before infusion. Each bag of CLS12311 contains [redacted] peptide coupled RBCs. CLS12311 is supplied for single-use only.

Mode of administration

CLS12311 will be administered intravenously. Depending on the allocated dose, patients are to receive one or two 150 ml infusion(s) of CLS12311, administered around 30 to 60 min.

5.1.4 Use of Gadolinium-Based Contrast Agents as Auxiliary Medicinal Products

Gadolinium-based contrast agents (GBCAs) will be used as auxiliary medicinal products (AxMPs) in this study to enhance MRI imaging for assessing disease activity in patients with RRMS. Various macrocyclic gadolinium agents, which have been approved for their intended use and are also part of standard medical care in managing RRMS, will be employed based on availability at the participating centers, as the Sponsor does not require the use of a particular agent. These agents have established safety profiles and improve diagnostic accuracy, supporting precise monitoring for the effective evaluation of the investigational medicinal product (CLS12311) in RRMS patients.

5.2 Study Rationale

In the last 20 years there has been considerable progress in the treatment of MS. Not only did the number of approved therapies increase (see section 5.1.1), but also the efficacy in reducing the burden of disease improved.

However, the development of highly active therapies has come at the cost of sometimes limited tolerability and relevant safety concerns, which are particularly related to the lack of specificity and global immunosuppression. Therefore, there remains an unmet medical need for therapies that target the pathogenic immune response with high specificity and maintaining acceptable safety and efficacy profile.

5.2.1 Rationale for the Study Population

Due to their pathogenetic involvement, CD4+ T are one logical target for a highly specific therapeutic intervention. Therefore, early intervention using an antigen-specific tolerance protocol, which targets both activated and naïve autoreactive T cells specific for multiple disease-relevant epitopes, could be an effective therapy for MS with an optimal safety profile. However, it may be important to start the treatment early in the disease process to prevent the diversification of the pathogenic immune response arising via a process called epitope spreading [41].

The trial aims to include RRMS patients. Participants must be off approved therapies at the time of inclusion, have a baseline Expanded Disability Status Scale (EDSS) score of 0 to 5.5. The inclusion of patients who are off approved therapies is considered appropriate since all patients who participate in the treatment phase of the trial will receive active treatment.

During the study patients will be followed for safety and tolerability of CLS12311. Hence, the selection criteria do not include disease activity or prior T cell reactivity to the antigens.

5.2.2 Rationale for the Dosing Regimen

The dose rationale for the starting dose in this first-in-human trial was defined based on preclinical studies using the no observable adverse effect level (NOAEL) and the minimal anticipated biological effect level (MABEL). A toxicological study in rats receiving the highest feasible dose of RBCs coupled with [redacted] peptides from [redacted] proteins [redacted] and given as 3 monthly cycles did not reveal any signs of toxicity. Each cycle consisted of a single injection of [redacted] peptide-coupled RBCs/kg given twice within 24h (total [redacted]/kg within 24h) and repeated at monthly intervals for a total of three cycles. Thus, the NOAEL is set at [redacted] peptide coupled RBCs/kg ([redacted]/60kg) for a single injection and [redacted] peptide coupled RBCs/kg ([redacted]/60kg) for the cycle therapy. The peptide cocktail also included the MOG91-108 peptide, which is encephalitogenic peptide in the specific rat strain (Dark Agouti) to account for potential immunotoxicity. There were no signs of immunotoxicity in the course of the study. Also, a single dose toxicity study in mice with the set of [redacted] peptides coupled to RBCs did not reveal any adverse effects at a dose of [redacted] per mouse (i.e. [redacted]/kg), which equals [redacted] in a 60 kg person.

In an EAE model in mice, we have demonstrated a dose dependent effect of peptide-coupled RBCs in the induction of immune tolerance, with higher efficacy of [redacted]/kg compared to [redacted]/kg, Hence, using the abovementioned conversion method, the MABEL for a 60kg human

can be set at [redacted] cells (see IB 7.1.2). However, in mice a dose dependent effect of peptide-coupled RBCs in the induction of immune tolerance, with higher efficacy of [redacted] peptide-coupled RBCs/kg (equivalent [redacted] cells in 60 kg human) compared to [redacted] peptide-coupled RBCs /kg could be observed. Consequently, also in humans a higher dose of peptide-coupled RBCs might be potentially more effective and is the main reason for testing additional higher dose of [redacted] peptide-coupled RBCs.

In a phase Ib trial of autologous RBCs coupled with seven myelin peptides (ETIMSred trial), repeated dosing of [redacted] peptide coupled RBCs was safe and well tolerated, supporting the rationale for exploring higher doses.

This clinical trial will assess the safety and tolerability of three different doses of CLS12311 from [redacted] to [redacted] peptide-coupled RBCs per treatment cycle (see section 10.2.1). One treatment cycle consists of two treatment days, [redacted]. The IMP is supplied as single bag containing [redacted] peptide coupled RBCs per entity. Consequently, patients in the high dose group ([redacted] peptide-coupled RBCs) will receive two bags of [redacted] peptide-coupled RBCs on each treatment day, [redacted]. This separation of the administration aims to reduce the maximum number of RBCs to be removed in liver and spleen in a short period of time. Pre-clinical data demonstrate removal of peptide-coupled RBCs within 24h after infusion. Under physiological conditions, approx. [redacted] RBCs are removed from the circulation. The administration of [redacted]-coupled RBCs and their fast removal, exceeds this number by [redacted] times. Hence, we decided to split the administration to two doses [redacted]. This approach also allows for assessments of safety and tolerability prior to the next infusion.

Similar to many vaccination schemes, a repetition of dosing in the time frame of 1-3 months is commonly used to render the immune tolerance induction more efficient. Several tolerization modalities, which were tested in MS patients [42; 43; 44] used repetitive applications of the tolerizing antigens. Pre-clinical data with peptide-coupled cells, show high efficacy of the single administration, without further relapses, however in a model of allotransplantation 2 doses of peptide-coupled splenocytes were required [45]. From the above data, we reasoned that the application of the second dosing cycle [redacted].

Patients in the lower dose groups will also receive two infusions containing either CLS12311 or [redacted] autologous RBCs, not coupled with peptides (“placebo”).

5.2.3 Rationale for the Study Design

CLS12311 is given for the first time in humans, hence the clinical trial is designed to assess safety and tolerability of three dose regimens of CLS12311.

The study will provide data on the safety of a single treatment cycle given in an ascending dose of CLS12311 and will further assess the safety and tolerability of a second treatment in a subset of patients.

Initially, the safety and tolerability of a single treatment cycle of CLS12311 will be assessed in three dose groups in a total of 9 patients. Each dose group will start with a sentinel patient, who will inform about the safety of the treatment in the same dose group. To ensure the safety of dosing in the next patient a time frame of at least four days is defined prior to dosing of the next patient. The definition of this time frame is based on preclinical data showing complete processing of peptide-coupled RBCs in the first 24h after infusion (see IB 5.3). Immediate reaction to the therapy, e.g. hyperacute immune activation and cytokine release or thrombotic events, would be expected in the first hours after treatment. Due to the individual manufacturing of each product and related logistics, only one patient will be treated per week. The treatment will start in the lowest dose groups (2 patients). Further dosing in the higher dose groups (mid dose 3 patients, high dose 4 patients) will be initiated only after safety analysis of the respective prior dose group. During the course of the study the safety and tolerability of a second treatment cycle of CLS12311 will be evaluated in 6 of the 9 patients who received a first treatment cycle. The first patient in each dose group (sentinel patient) will not receive a second treatment cycle of CLS12311, only. Further, patients in each dose group will receive a second treatment in [redacted] of the

trial. The time interval between the first and second treatment is supported by preclinical safety studies of repeated dosing in monthly intervals over a period of three months. The time interval also reflects the safety of a [redacted] between autologous blood donations. During dose escalation of the second treatment cycle, the cumulative dose given in each dose group does not exceed the single dose, which has already been applied to patients of the next higher dose group as part of the initial treatment cycle (see 10.2.1). Consequently, the second treatment of patients in the lower dose group will be administered only after confirming the safety of the total dose given to patients in the single ascending dose. Hence, the safety of the total dose in the single/first treatment cycle is confirmed prior to administration of a second treatment cycle. Please refer to section 0 for more details on the study design.

In summary, the study is designed to provide a maximum of safety throughout both single dose escalation and second treatment.
Furthermore, the combination of clinical, MRI and immunological parameters provides a maximum of information as to safety, and tolerability of experimental treatment approaches and is therefore ideal for early-phase development [13].

5.2.4 Rationale for Biomarker Assessments

Cell-, protein-, or RNA-based biomarkers will be analyzed to detect an unwanted immune activation, that is a safety signal, and to investigate the mechanisms of action immune tolerance induction with peptide-coupled RBCs including the assessment of immune reactivity to the peptides contained in CLS12311. Biomarkers may be analyzed in conjunction with safety or efficacy endpoints to identify possible association of the treatment with adverse immune reactions and/or adverse events. Adverse event reports will not be derived from biomarker data by the Sponsor, and biomarker data will not be included in the formal safety analyses for this study. In addition, biomarker data will not inform decisions on patient management.

Biomarker samples will be obtained from all patients who have given their consent in the study.

Refer to Appendix 24.1 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses, ensuring compliance with both CTR and Swiss regulations.

5.3 Risk-Benefit-Assessment

Although highly active therapies are available in MS, these come at the cost of sometimes limited tolerability and severe safety concerns, which are particularly related to the lack of specificity and global immunosuppression. Thus, there clearly remains an unmet medical need for more specific interventions and better tolerated therapies. The induction of tolerance to target antigens offers the opportunity to attenuate specifically the pathogenic autoimmune response in an effective way with few side effects. In previous phase Ib trial, the application of autologous RBCs coupled with seven myelin peptides was safe and well tolerated. CLS12311 has been developed to include 5 additional novel target antigens, which are important in MS patients. The present trial is conducted as a ascending-dose phase Ib study to assess the safety and tolerability of a higher dose of peptide-coupled RBCs. Both the addition of novel peptides and the higher dose-level are expected to increase the likelihood for efficacy. An independent Data Safety Monitoring Board (DSMB) will be established to monitor safety during the trial. CLS12311 aims at individualizing therapy in two regards. First, the autoimmune response against the tolerizing peptides or the protein containing the peptide respectively, will be tested in all patients participating in the trial. This step greatly increases the likelihood of demonstrating whether antigen-specific immune tolerance is achieved and understanding it by mechanism-of-action-oriented immunological studies. Furthermore, the tolerization by CLS12311 involves the use of autologous cells of the patient, adding to the safety of the treatment. The specificity and pre-clinical safety profile are considered major advantages of this treatment.

Unique advantages of CS12311 therapy are a) the use of a set of peptides that covers a broad set of the immunodominant epitopes of those proteins, which are targeted by autoreactive T cells

in MS, b) different from all other tolerization therapies, peptide-coupled cell tolerance was shown to prevent epitope spreading.

Given the excellent tolerability of peptide-coupled RBCs so far, and the safety-focused design of this Phase I trial, the potential benefits of the expanded peptide pool and increased dose are well balanced to the risks of this development step. To support patient safety, comprehensive safety measures are in place, including regular monitoring during and after infusion, immediate access to supportive care for managing any adverse effects, and thorough eligibility assessments.

Detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of CLS123 is provided in the latest version of the Investigator's Brochure and informed consent form (ICF). The COVID19 pandemic has brought additional uncertainties and risks, particularly to patients with long-term immunosuppressive therapies and thereby increasing the burden of disease considerably. A treatment regimen aiming at induction of antigen-specific immune tolerance and sparing the protective immune responses, might reduce this burden and improve the reactivity to the pathogen and/or a vaccine, aiming to prevent an infection.

Patients participating in the RED4MS trial will remain off immunosuppressive therapies for the duration of the trial. The treatment with CLS12311 is not expected to interfere with an antiviral immune response. Hence participation in RED4MS trial is not expected to increase the risks associated with SARS-CoV-II infection.

The COVID19 pandemic is rapidly evolving requiring flexibility in adapting measures to ensure the safety and well-being of trial participants and the integrity of the trial. During the conduct of the trial all measures will be taken, according to national recommendations and local regulations, to reduce the risk of viral transmission and infection of trial participants. The Sponsor will follow regulatory guidance relevant to the management of the clinical trial in the COVID19 pandemic. The Sponsor together with Steering Committee of the trial will assess the situation on a regular basis and implement any necessary safety measures.

6 STUDY OBJECTIVES AND ENDPOINTS

Table 6-1 Study Objectives and Endpoints

Primary Objectives	Primary Endpoints
Safety objective To assess the safety and tolerability of CLS12311 in patients with RRMS	***Primary Safety Endpoint*** The primary safety endpoint is measured by the number and severity of adverse events (AEs) and serious adverse events (SAEs) and/or worsening of disease measured by clinical (relapses) and imaging (number and size of brain MRI lesions) parameters.
Secondary Objectives	**Secondary Endpoints**
Safety objectives To assess the safety and tolerability of each dose group of CLS12311	***Safety Endpoints*** • Incidence of treatment-emergent AEs (TEAEs) and treatment-emergent SAEs (TESAEs) (number and severity) in each dose group • Number of confirmed relapses in the treatment phase in each dose group • Changes in clinical measures of disease severity: EDSS, T25-FW, 9-HPT, SDMT in each dose group.
Exploratory Objectives	**Exploratory Immunological and Biomarker Measures**
To assess biomarkers indicating unwanted immune activation, and To understand the mechanism/s of action of tolerance induction with peptide-coupled RBCs and to identify biomarkers for measuring immune tolerance induction	• Percentage of patients in each dose group showing a reduction of antigen-specific 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.

7 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 the 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 [redacted] might vary between patients.

If safety and tolerability during the first treatment cycle, a subset of patients will receive a second administration of CLS12311 in a dose escalating second treatment cycle. Additional information on the rationale of the study design is given in section 5.2.3.

7.1 Open Label Treatment Phase: at least 17 weeks

The key measures, which have been implemented to ensure the safety of trial participants are briefly highlighted:

- Single ascending dosing starting with sentinel patient in each dose group
- An interval of at least 4 days between dosing of patients
- Safety assessments between dosing of each patient
- A scheduled DSMB meeting to assess safety of dosing after the last patient completes [redacted]
- Stringent criteria have been defined to trigger immediate DSMB safety assessments at any time during the trial
- Strict enrollment to allow safety assessment of the first treatment cycle prior to administration of second treatment cycle
- The second treatment cycle to be administered only after the safety of the first treatment cycle of the higher dose group has been confirmed
- The cumulative dose during second treatment cycle does not exceed the total dose of the first treatment cycle, for which safety had already been confirmed

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. This time frame is based on preclinical data showing that peptide-coupled RBCs are fully processed in the first 24h after infusion (see IB 5.3). However, due to the individual manufacturing process of each product and related logistics, only one patient will start treatment per week. 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 Sponsor's medical

expert(s). The corresponding data should be entered into the eCRF in timely manner, within 24 hours at the latest.

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 Visit 16 (week 48) according to the schedule of visit (see section 4.1). 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 [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 [redacted] between the first and second treatment cycle is supported by preclinical safety studies of repeated dosing at monthly intervals over a period of three months. The safety of a [redacted] between autologous blood donations is also reflected in the dosing schedule.

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 first treatment cycle, which has already been administered to patients in the next higher dose group (see 5.2.3).

Safety Monitoring and DSMB Review

Safety and tolerability will be assessed using vital sign measurements, clinical laboratory tests (hematology, blood chemistry, and urine tests), physical examinations, and monitoring for (S)AEs and relapses.

Twice, after patient 3 and then after patient 6 have completed [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.

To ensure availability of safety data a stringent enrollment of patients has been defined (Figure 7-1).

Patients 1, 2 and 3 will be enrolled to receive a dose of [redacted] of peptide-coupled RBCs (patients 1 and 2) or [redacted] (patient 3) in the first treatment cycle (see 10.2.1). Only after confirmation of the tolerability and safety of the first treatment cycle in **patient 3** (single dose of [redacted]) at safety assessments visit in [redacted]), the second treatment cycle of patient 2 (total cumulative dose of [redacted]) will be permitted.

Accordingly, patients 4, 5 and 6 will be enrolled [redacted]. Patients 4 and 5 will only receive the second treatment cycle (total cumulative dose of [redacted]) if the [redacted] safety data of **patient 6** (single dose of [redacted]) will support second dosing of CLS12311.

The second treatment cycle of the last three patients (patients 7 - 9) will be administered only after the safety and tolerability of second treatment cycle has been confirmed in **patients 4** or **5.** If safety data of [redacted] from patients 3 or 6 are not available due to prematurely discontinuation, second dosing of patient 2, 4 or 5 need to be postponed until sentinel patients are replaced and safety data are available.

After the last patient in the high dose group has completed [redacted] safety data (including MRI data, relapses and EDSS) of all patients will be evaluated by the DSMB.

If any of the treatment regimens are deemed to be unsafe, the DSMB may recommend protocol modifications or omit any of the dose levels (see Section 19.1.3). A substantial change will be submitted for approval by IRBs/ECs and the regulatory authorities, in accordance with CTR and Swiss ClinO (see Section 19.7).

Dosing schedules and adherence to time frames (as mentioned above) between patients and across different sites and countries will be secured by close coordination between the Sponsor, the manufacturer and participating sites.

For patients who donated blood for study drug manufacturing and/or received at least one dose of study drug but prematurely discontinue treatment period and/or choose not to stay in the study until the [redacted], an Early Discontinuation (ED) visit will be performed (see section 14.1.9) to capture safety data and ensure continued patient monitoring.

Figure 7-1 Patients' enrollment and safety assessments in the treatment phase

7.2 Safety Follow Up Phase: approx. 31 weeks

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 period (Week 20), at Week 24 and at Week 48.

During the SFU, patients will be assessed at clinical visits as per Schedule of Events – please refer to Table 4.1 for further details.

The DSMB will reconvene after the completion of [redacted] to assess the safety outcomes of the trial.

If patients wish to discontinue the unblinded SFU and the last visit has been more than 8 weeks ago, they should be invited for an ED visit to capture safety data and ensure continued patient monitoring.

As the duration of the treatment effect is not known, patients may begin another DMT during the SFU, at the discretion of the investigator. However, every effort should be made to have patients complete the SFU and all related assessments, regardless of whether or not they receive alternative treatment for their MS.

In summary, this Phase Ib trial is designed to provide a maximum of safety throughout both single dose escalation and second treatment cycle.
Safety data will be evaluated by a DSMB after key milestones to assess the overall safety of CLS12311 and the different dose levels tested. A brief overview of the course of the Phase Ib study is shown in Figure 7-2.

Figure 7-2 Study Design

8 STUDY POPULATION

8.1 Patient Population

The study population will consist of patients with a diagnosis of RRMS in accordance with the revised 2017 McDonald Criteria [5]. Given the gender and age distribution typical of MS - where females are affected up to three times more often than males - the study population is expected to reflect a higher proportion of female participants.

Patients previously treated with MS drugs will be allowed to participate in this study, provided that they did not take certain medications within the timeframes defined in the exclusion criteria.
It is mandatory that the decision for discontinuation prior treatments was made by the patient independently of the participation in the RED4MS trial. Patients entered for this study should not be withdrawn from MS therapies for the sole purpose of meeting eligibility for the RED4MS trial.

Screening and enrollment will focus on meeting the inclusion and exclusion criteria before performing the MRI and blood withdrawals required to assess the specific qualification/exclusion criteria.

Patients not eligible for the study will be considered as screening failures, i.e. no further study-related assessments/treatments will be performed on these patients and they will be offered the standard medical care by their physician.

To characterize the study population with respect to key HLA associations in MS, HLA typing for HLA-[redacted] alleles is performed. These alleles are among the most frequently associated with MS,[redacted]. The resulting data may be used for exploratory analyses.

8.1.1 Inclusion Criteria

<u>General inclusion criteria (to be assessed at the beginning of the baseline period based on patient interview and medical history):</u>

1) RRMS according to the 2017 McDonald criteria
2) Male or female patients (assigned at birth) aged 18-55 years inclusive
3) Disease duration (since diagnosis) <10 years
4) EDSS at baseline 0-5.5
5) Untreated patients or patients being off therapy for the time-periods listed under exclusion criterion No. 2. Patients are either not eligible to receive approved therapies or have explicitly chosen not to receive such therapies after being adequately informed by the investigators
6) Only for female patients of childbearing potential (sexually mature, pre-menopausal and not surgically sterile): the patient is willing to use a highly effective method of contraception throughout the treatment phase or at least for 4 weeks after the last dose of the study drug. Accepted methods are:
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device or hormone-releasing intrauterine system
    - Bilateral tubal occlusion or vasectomy of the male partner
7) Male patients willing to use contraception (such as a condoms) throughout the treatment phase or at least for 4 weeks after the last dose of the study drug, unless surgically sterile

8) Basic immunization against SARS-CoV-2, i.e. both doses of two-dose vaccines (or one dose of a vaccine and a SARS-CoV-2 infection before or after vaccination) OR a dose of a single-dose vaccine

8.1.2 Exclusion Criteria

General exclusion criteria (to be assessed at the beginning of the baseline period based on patient interview and medical history) *:

1) Patients with an active chronic disease (or stable but treated with immunomodulatory/-suppressive therapy) of the immune system other than MS (e.g. rheumatoid arthritis, scleroderma, Crohn's disease, ulcerative colitis, etc.) or with a known immunodeficiency syndrome (AIDS, hereditary immune deficiency, drug-induced immune deficiency)
2) Prior treatment with any of the medications below within the specified time-frame:
    a. glatiramer acetate, interferon-beta within 4 weeks prior to screening visit 1
    b. dimethylfumarate, diroximel-fumarate within 4 weeks prior to screening visit 1
    c. teriflunomide within 4 weeks prior to screening visit 1, provided accelerated elimination procedure (eg. cholestyramine) was performed and teriflunomide plasma level are below 0.02 mg/L before randomization
    d. fingolimod, ozanimod within 12 weeks prior to screening visit 1, provided normal lymphocyte counts (see exclusion criterion No. 18)
    e. Siponimod, ponesimod within 8 weeks prior to screening visit 1, provided normal lymphocyte counts (see exclusion criterion No. 18)
    f. natalizumab within 12 weeks prior to screening visit 1
    g. ocrelizumab, ofatumumab, rituximab, alemtuzumab, cladribine, mitoxantrone within 52 weeks prior to screening visit 1
    h. plasma exchange, intravenous immunoglobulin within 8 weeks prior to screening visit 1
    i. azathioprine, methotrexate, cyclophosphamide or any other continuous immunosuppressive therapy within 24 weeks prior to screening visit 1
    j. any other immunosuppressive monoclonal antibody treatment within 24 weeks prior to screening visit 1
    k. Prior autologous hematopoietic stem cell transplantation
    l. Corticosteroid treatment for MS relapse within 4 weeks prior to screening visit 1
    m. Patients who participated in the ETIMSred trial
3) History of HIV, chronic or active Hepatitis C, chronic or active Hepatitis B or Syphilis, which had not been sufficiently treated
4) Long-Covid19 syndrome
5) History of splenectomy or chronic liver disease
6) History of coronary artery disease, chronic heart failure, aortic stenosis
7) Current anticoagulation therapy
8) Uncontrolled grade II hypertension (≥160 systolic and/or ≥100 diastolic blood pressure according to ISH global practice guidelines) despite treatment or without treatment
9) History of stroke
10) Pregnant female confirmed by a positive pregnancy test or breast-feeding

11) History of alcohol or drug abuse within the 1 year prior to screening visit 1
12) History of or existing malignancy within the last 5 years prior to enrollment except history of basal cell carcinoma and melanoma in situ
13) History of or existing relevant central nervous system disorder (other than MS)
14) Allergy to gadolinium-based contrast agents
15) Any other disease or condition, which could interfere with the participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures.

Specific exclusion criteria (to be assessed during the baseline period):

16) Anemia, defined as hemoglobin levels ≤12.5 g/dl (7.25 mmol/l) for female and ≤13.5 g/dl (8.37 mmol/l) for male participants (may be repeated if 11.5-12.5 g/dl in females and 12.5-13.5 g/dl in males)
17) Erythrocyte count <4.0 10^{12}/L in female and <4.5 E12/L in male patients (may be repeated if >3.8 E12/L in female and >4.3 E12/L in male)
18) Lymphopenia with total lymphocyte counts ≤1000/µl (may be repeated if >800/µl)
19) Positive HIV testing
20) Positive results of baseline period testing for serological markers for hepatitis B, C, and Syphilis indicating acute or chronic infection
21) Patient is not eligible for blood donation according to local regulations
22) Having one or more of the following laboratory results:
    a. Estimated glomerular filtration rate (eGFR)< 60 mL/min/1.73 m^2 (may be repeated if eGFR 45–59 mL/min/1.73 m^2)
    b. ALT or AST > 3 × upper limit of normal (ULN; may be repeated if 3.1-4 × ULN)
    c. Total bilirubin greater than 2 × ULN (may be repeated if 2.1–3 x ULN), with the exception for patients with Gilbert's disease
    d. Platelet count ≤ 100 × 10^9/L (may be repeated if 80–100 × 10^9/L)
    e. Abnormalities in hepatic synthetic function tests (e.g. PT, INR, PTT, albumin) as judged by the Investigator to be clinically significant

9 SELECTION AND WITHDRAWAL OF PATIENTS

9.1 Informed Consent

An informed consent, written in accordance with the principles of the Declaration of Helsinki, CTR and applicable national laws of the respective country has to be obtained from all patients. The informed consent forms prepared by the sponsor and approved by the ethics committees and/or competent authorities will be provided to the study centres in the local language. Each patient will sign the Informed Consent Form (ICF) before entering the study, i.e. before any study-related activities (e.g. study-specific blood drawings, baseline assessments). The study's objectives, the procedures involved, the benefits and risks of the study, alternative treatment options and the voluntary nature of participation must be explained to each subject. Patients must be given sufficient time to consider whether they wish to participate in the study. A person designated by the Investigator may give the information, if permitted by local regulations.
A copy of the signed and dated ICF must be given to the subject, while the original signed and dated ICF will be retained with the study records.

The overall process of obtaining informed consent should be documented in the medical record by the Investigator. Should there be any amendments to the Final Protocol that may directly affect

the willingness of the patient's participation in the study e.g. a change to study procedures or when new information becomes available, the ICF must be amended to incorporate this modification and the patient's informed *re*-consent must be obtained.
For any updated Consent Forms, the medical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

9.2 Patient Identification

All patients participating in the study will be assigned a unique, study-specific, patient identification number (Patient ID) at visit 1, which will be kept throughout the study duration. The format of the patient ID is as follows: C-NN-XX, where C is the country number (starting with 1 for the first country, 2 for the second, etc.). NN is the site number (with leading zero as appropriate, starting with 01), and XX is the serial number of the patient (with leading zero as appropriate starting with 01).

Example: The patient ID of the first patient entering the Visit 1 at site 01 in country number one would be: 1-01-01.

Patients will be identified by their Patient ID to ensure data protection and confidentiality. The Investigator must maintain a list of patient names corresponding to the respective patient IDs, stored securely in compliance with both GDPR and Swiss data protection laws. The Patient ID is unique to each participant and cannot be reassigned to another individual.

9.3 Stopping and Discontinuation Criteria

A patient's participation in the study is considered complete when all visits according to the assessments schedule have been performed ("study completers"). Patients who do not fulfil the inclusion or qualification criteria or who fulfil any exclusion criterion will be considered "screening failures". Patients meeting the qualification criteria who leave the study prior completing all scheduled visits will be regarded as "premature discontinuations". In the event of screening failure or premature discontinuation, the reason has to be documented.

If the study as a whole or the participation of an individual trial site is prematurely terminated or suspended, the concerned Investigator(s), independent ethics committee(s) (IEC(s)) and regulatory authority(ies) will be promptly informed by the Sponsor and provided with the reasons for the termination or suspension, in compliance with CTR Article 37 and Swiss ClinO Article 38. Furthermore, the clinical trial patients at the concerned trial site(s) must be immediately informed by the respective Investigator about a premature termination of the clinical trial.

All documentation related to screening failures, premature discontinuations, and trial terminations will be securely stored and made accessible for regulatory inspection.

9.3.1 Discontinuation Criteria Related to the Study

The study can be terminated by the Sponsor Cellerys at any time.
The criteria for early discontinuation / termination of the clinical trial include (not exclusively):

- An unexpected, significant, or unacceptable safety risk to participants enrolled in the study.
- A decision based on recommendation from applicable boards after review of safety data. A DSMB will be implemented to assess safety to provide rationale for discontinuation of the study (section 19.1.3).
- Patients cannot be recruited in sufficient numbers.

In the decision to terminate, Cellerys will always consider participants' welfare and safety. Should early termination be necessary, participants must be seen as soon as possible as described in section 14.1.9.

The Investigator may receive additional procedures to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

For every patient who prematurely discontinues the trial prior to Visit 3 (dose group 1) or Visit 4 (dose groups 2 and 3), an additional patient will be included. Every sentinel patient who discontinues the trial prior to [redacted] has to be replaced. In the mid dose group, safety data of the second treatment cycle should be available from at least one patient (patient 4 or 5).. Any patient with insufficient safety information may be replaced at the discretion of the Sponsor, to maintain the safety integrity of the dose escalation schedule.

For participants who choose to withdraw from the study, all data collected up to the point of withdrawal will be securely stored and analyzed per protocol.

9.3.2 Discontinuation Criteria Related to the Study Site

Discontinuation of the clinical study in an individual study site may occur because of various reasons including but not limited to:

- Failure of Investigator to comply with the ICH-GCP and/or applicable regulatory requirements. This includes failure to adherence to data protection and data security requirements if occurring repeatedly.
- Submission of knowingly false or incomplete information from the site to the Sponsor, study monitor, or the authorities.
- Repeated non-adherence to protocol requirements including insufficient data quality (missing data in (e)CRFs occurring repeatedly).
- Failure of the Investigator at a site to enrol patients into the study/ Excessively slow recruitment.
- Lack of study activity (i.e. all patients have completed the study and all obligations have been fulfilled).

9.3.3 Discontinuation Criteria Related to the Patient

The patients will be advised in the Informed Consent Forms that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Investigator's / Sponsor's discretion at any time.

Withdrawal of individual patients from treatment or from the study respectively is caused by (but is not limited to) the following reasons:

- Pregnancy detected at any time during the study.
- At the discretion of the Investigator
- Disease progression requiring the use of effective MS treatment (DMT)
- Major protocol deviation(s)
- Ineligibility/Development of one or multiple protocol-specified withdrawal criteria
- Adverse Event
- At the specific request of the sponsor
- The patient withdraws of consent
- Lost to follow-up

In case a patient does not reappear to any scheduled visit (i.e. is lost to follow-up) reasonable effort should be made to contact this patient in order to complete assessments and/or to evaluate the reason for non-appearance (possibly implicit withdrawal of consent).These contact attempts

should be documented in the medical records. Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

In the event that a patient withdraws consent or is withdrawn from the study, the study termination page in the (e)CRF should be completed indicating that the study was prematurely terminated. The Investigator should record the date of the withdrawal and the reason for withdrawal.
If a subject wishes to withdraw his/her consent to the testing of his/her samples, the Investigator must inform the Sponsor in writing of the subject's wishes and enter the date of withdrawal in the subject's electronic Case Report Form (eCRF).

Patients who received at least one dose of CLS12311 and prematurely discontinue the treatment phase stay in the study and follow the schedule of assessments in the treatment phase. If a patient withdraws from the study, the patient should be encouraged to return for the ED visit (see section 14.1.9) and asked if he or she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Female patients with a suspected unplanned pregnancy during the study must permanently discontinue the study, contact their study investigator to confirm the pregnancy by urine pregnancy testing.

10 STUDY TREATMENT

Investigational Medicinal Product (IMP) and placebo will be made available to the study sites by TETEC AG, Reutlingen, Germany on behalf of Cellerys AG, Zurich, Switzerland (Sponsor of the study). If defects in the IMP or placebo are observed, the study manager or the monitor is to be informed.

10.1 Name and Description of the Investigational Medicinal Product and Placebo

10.1.1 Qualitative and Quantitative Composition

The IMP, CLS12311, consists of autologous red blood cells (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). [redacted]

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

A detailed description of the IMP and placebo is available in the Investigator Brochure.

RBCs for CLS12311 and placebo will be isolated from 450 - 500 ml of whole blood collected of study qualifying MS patients taken by standard blood donation procedures. The blood bag containing RBCs will be transferred to TETEC AG, Reutlingen, Germany, where CLS12311/placebo will be manufactured in compliance with Good Manufacturing Practice (GMP). A complete Certificate of Analysis (CoA) is available for each batch, including batch numbers, storage conditions, and expiry dates, ensuring full traceability.

Transport and handling protocols have been established to maintain the integrity of RBCs, CLS12311, and placebo samples during the transfer to and from TETEC AG.

Informed consent is obtained from all patients before blood collection, specifically addressing both the main study and the research use of the buffy coat. The consent form outlines that the buffy coat will be sent to Cellerys AG for exploratory research use.

Table 10-1 presents the composition of the Investigational Medicinal Product (IMP) and placebo.

Table 10-1 Composition of drug product (CLS12311) and placebo

Ingredient	**Investigational medicinal test product** ***CLS12311***	***Placebo***
Autologous peptide-coupled RBCs	[redacted] cells (range [redacted])	-
Autologous RBCs (uncoupled)	-	[redacted] cells ([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)

10.1.2 Pharmaceutical Form

CLS12311 and placebo are supplied as a sterile and preservative-free solution for i.v. infusion.

10.1.3 Nature and Content of Container(s)

CLS12311 and placebo are packaged in a 500 ml standard bag (CompoFlex, Fresenius Germany). The sterile bag is made of PVC/DHEP (Polyvinyl chloride).

CLS12311 drug product/placebo is supplied for single-use only.

10.2 Posology and Method of Administration

10.2.1 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 [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 [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 [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) [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) [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 10-1.

[redacted]

10.2.2 Statement on the use of uncoupled RBCs “placebo”

To reach the [redacted] peptide-coupled RBCs for the high-dose group (group 3), two blood bags per dose are required. For this reason, it is aimed that two blood bags per dose are also administered in the low and medium dose groups (groups 1 and 2) to ensure that the cell count administered is equivalent in all patients. Thus, patients in the low and medium dose groups receive a reinfusion of uncoupled RBCs ("placebo").

Administration of uncoupled RBCs is considered important for the evaluation of safety and tolerability of CLS12311, as the re-infusion of RBCs can counteract the risks of iron deficiency and/or anaemia induced by the blood donation. This is particularly relevant for the second treatment cycle, as differences respective lab values would be expected across the dose groups, if the cell number would not be standardized between the treatment arms. In addition, administering uncoupled cells will maintain dose blinding for both patients and investigators and hence provide an unbiased evaluation of CLS12311’s safety and efficacy. The use of autologous uncoupled RBCs will not expose patients to any risk of serious or irreversible harm, ensuring compliance with regulatory requirements for minimizing participant risk while maintaining study integrity.

10.2.3 Method of Administration

Study treatment will be administered on an outpatient basis. The product bag(s) should be taken out from the fridge or cooling box approx. 30 min prior to the application. A bedside test for blood group or cross-matching procedures will be performed according to local regulations and prior to infusion. The administration of CLS12311/placebo is performed by i.v. infusion of the entire product bags over a 30 to 60-minute period using a standard blood component kit with inline filter (40 µm). The infusion should typically run with 5 ml/min, corresponding to approx. 1.7 drops per second. Standard study site guidelines will be followed to ensure sterility of the material and appropriate methods for intravenous administration.

The Investigator or his representative will document the time and volume of CLS12311/placebo administration for each patient. For incomplete volume administration (e.g. discontinuation due to AE), the reasons must be documented.

CLS12311 (or placebo) infusions should be initiated and supervised by an experienced professional with access to appropriate medical support to manage severe reactions (see Appendix 24.2).

All patients will be observed at the clinical site for at least 2 hours after the completion of the administration of the CLS12311/placebo. After completion of the infusion, the i.v. cannula should remain in situ for at least 2 hours to allow for administration of drugs intravenously, if necessary, in the event of a delayed reaction. If no adverse event occurs during this period of time, the i.v. cannula may be removed, and the patient may be discharged***.**

AEs during administration and observation must be documented according to the procedures outlined in section 13.

***** *In Czech Republic, all patients will be admitted as inpatients and will be observed for 24 hours following administration of CLS12311.*

10.2.4 Duration of Treatment

Patients of all three dose groups will receive treatment with CLS12311 within 13 weeks from enrollment in the study. CLS12311 will be administered at [redacted] for sentinel patients and at [redacted] for all other patients. CLS12311 will be manufactured from blood donations taken in [redacted] for treatments in [redacted] and from blood donation taken in [redacted] for treatments given [redacted]. Due to organizational reasons, the study design and the manufacturing schedule, the treatments may be postponed. However, both treatments of one cycle will be administered with an [redacted]. The sponsor and the manufacturer of the IMP will closely coordinate with the sites and other involved parties to organize all respective study visits, ensuring the adherence to the protocol. A minimum interval of [redacted] between the two blood donations will be maintained.

10.3 Labelling

The labels for CLS12311/placebo and protective containers will be designed in accordance with GMP annex 13 and relevant regulatory requirements, including CTR and applicable national regulations. At a minimum, the study treatment label will include a study reference code, drug identifier, patient identifier, lot number, expiry or use-by date and time. In addition, the patient's name (surname, first name) and date of birth will be listed on the label in order to comply with transfusion medicine regulations for autologous red blood cell products.

10.4 Packaging

CLS12311/ placebo is manufactured by TETEC AG and is supplied as a sterile liquid drug product for i.v. administration. It is provided in blood bags, each containing 150 ml CLS12311 or placebo.

The IMP/ placebo is shipped to the sites in temperature-controlled cooling boxes, designed to keep the product at 2-10°C during transport.

To ensure the integrity of the product, each shipment will include a temperature monitoring device to verify that the product remained within the required temperature range throughout the transport process.

10.5 Storage

Upon arrival at the site, the IMP/placebo must be stored in a temperature-controlled fridge at 2-8°C, if not directly administered. The IMP/placebo must be kept restricted to authorized personnel, and the product must be stored in a secure, locked area to prevent unauthorized access. Correct storage is essential for the IMPs to retain their safety and potency for the duration of their assigned shelf life.

Detailed instructions on the storage conditions and handling procedures are provided in the Logistics Manual, including requirements for temperature monitoring and documentation of any deviations.

Strict adherence to the storage requirements will be monitored through regular site monitoring and temperature log reviews.

10.6 Investigational Medicinal Product Accountability

The IMPs required for completion of this study (CLS12311 [or placebo] will be provided by the Sponsor. The study site (i.e. investigator or other authorized personnel e.g. pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP use in each patient, and disposition of any unused IMP. This ensures reconciliation of all IMPs received and guarantees that patients are provided with doses as specified by the protocol.

The study site should follow all instructions included with each IMP shipment. The investigator or authorized designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure and monitored (manual or automated) area in accordance with the labelled storage conditions, with access limited to the investigator and authorized staff. Further details are described in the Logistics Manual.

Only patients enrolled in the study may receive IMPs, and only authorized staff may administer IMPs. Accurate records of all IMPs received, dispensed and disposed of at the study site should be recorded on the Drug Accountability Form.
These Drug Accountability Forms should include dates and time of administration, dose completeness (complete or incomplete dose), batch numbers, expiration dates, and the unique code numbers assigned to study patients.

Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

Copies of the completed Drug Accountability Forms must be retained in the Investigator's Site Files (ISF), and the document must be filed in the Sponsor Trial Master File (TMF) at the latest after the completion of the study.

10.7 Destruction / Retrieval of Surplus Investigational Medicinal Products

Unused or surplus IMP/Placebo will be disposed of at the study site as medical waste in conformity with national regulations. The destruction has to be recorded accordingly on the study specific destruction form.

11 CONCOMITANT THERAPY

A concomitant medication is any treatment (e.g. prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) received by the patient during the study aside from the IMP/placebo.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator or Study Physician and must be recorded in the eCRF.

Symptomatic therapies such as treatments for spasticity, bladder dysfunction, depression, or fatigue are not restricted, but should be optimized as early as possible during baseline and pre-treatment in an attempt to maintain consistent treatment for the duration of the study.

Patients who use oral contraceptives or hormone-replacement therapy should continue their use.

11.1 Therapies not allowed during the Study

Any of the drugs mentioned under Exclusion Criterion No. 2 (see Section 8.1.2) will not be allowed during the study.

Patients may not receive systemic corticosteroid therapy except for the treatment of relapses (see section 11.2).

Patients may not receive any other investigational product including investigational symptomatic therapies for MS and investigational therapies for non-MS indications.

In the Safety Follow Up period there are no restrictions regarding concomitant medication.

11.2 Standardized Acute Therapy for Relapses during the Study

Relapses are to be treated with standard i.v. corticosteroids if clinically necessary according to the Investigator's judgement. The standard treatment regimen is i.v. methylprednisolone 1g, daily for 3-5 days. If required a second cycle may be given.

Impact of corticosteroid treatment on scheduled MRIs:

MRIs will be performed as per schedule irrespective of corticosteroid treatment.

Impact of corticosteroid treatment on blood donation and study drug administration:

If relapse treatment is started prior to blood donation or IMP administration the visit shall be postponed until the end of corticosteroid therapy, i.e. the visit can be performed the day after the last corticosteroid dose at the earliest.

Use of steroid treatment must be recorded on the concomitant medications eCRF.

12 DEFINITION OF THE PRIMARY AND SECONDARY VARIABLES

12.1 Primary Variable(s)

12.1.1 Safety Variables

The primary safety outcome is the number and severity of AEs and SAEs and/or worsening of disease measured by clinical (relapses) and imaging (number and size of brain lesions) parameters, following different doses of CLS12311.

12.1.1.1 Adverse Events (AEs)

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. AEs will have to be documented throughout the trial as described in Section 13. Event description, start/stop dates, severity, relationship to treatment (i.e. blood donation, CLS12311 or placebo), outcome and seriousness (yes or no) will be recorded.

Of particular interest are the following classes of AEs:

- Treatment related AEs
- Treatment related SAEs
- AEs of special interest (AESIs) are AEs considered severe and related to the IMP occurring within one day (i.e. occurring on the treatment day or on the day after treatment) following infusion of CLS12311/placebo: dyspnea, tachycardia, fever, chills, malaise, shock, infection, allergic reaction, renal or liver failure.

12.1.1.2 MS Relapse

MS relapse definition: 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 [5]. The abnormality must have been 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. A patient may report symptoms indicative of a relapse at a scheduled visit or at any other time.

Patients will be instructed to contact the Investigator if he/she develops new or reoccurring or worsening neurological signs/symptoms indicative of relapse. At each scheduled visit, the patient will also be asked whether such symptoms have occurred. If a patient reports new neurological symptoms or worsening of previous symptoms, a relapse assessment will be performed and sent for confirmation to the Medical Monitor.

Reporting of relapse: MS relapses should not be recorded as adverse events. However, MS relapses will be recorded on a separate relapse form in the eCRF. In addition, all relapses reported by the Investigators in the eCRF will be reviewed individually on an ongoing basis by an expert neurologist to decide whether the event qualifies for a true relapse in the context of this study (see definition above).

Occasional isolated symptoms that according to the Investigator are caused by MS, but do not constitute a full MS relapse, should be reported as an adverse event.

12.1.1.3 Safety MRI

A safety MRI will be performed at [redacted]). Additionally, MRIs performed at [redacted] will also add information on the safety of the treatment, in particular with regard to inflammatory disease activity. The safety MRI will also be assessed centrally..

All patients will undergo MRI scanning of the brain as described in Section 14. MRIs will be sent to the central imaging facility and interpreted by independent neuroradiologists immediately after image acquisition.

The treating physician must be contacted in case of unexpected findings (not consistent with MS, e.g. bleeding) detected on the MRI scan for safety actions and AE reporting. New MS lesions do not need to be reported as AEs.

Prior to the start of the study, the MRI technician (or other designated person) will receive an MRI Manual, outlining technical implementation, image quality requirements and MRI administrative procedures. The exact definition of the MRI measures, their sequence and handling and transmission of the scans are included in the MRI manual.

12.2 Secondary Variables

12.2.1 Secondary Variables – Safety

12.2.1.1 Physical Examination

A complete physical examination will be performed at planned and unscheduled visits as described in Section 14, and will include an assessment of head and neck, lungs/chest, heart/cardiovascular system, abdomen, skin and mucosae, lymph nodes, musculoskeletal system and nervous system, and, if applicable, others.

All significant findings that are present prior to the start of the study should be reported under the relevant medical history/current medical conditions item in the eCRF. Physical examination abnormalities after baseline considered as AE (see Section 13.1.1) should be documented in the AE section in the eCRF.

12.2.1.2 Vital Signs

Vital sign measurements will include blood pressure (BP, systolic and diastolic, mmHg), heart rate (HR, beats/minute) and body temperature. Body temperature will be measured in degrees Celsius using a suitable clinical thermometer. It has to be ensured by the site that the same way of temperature and blood pressure measurement should be applied for every patient throughout the study. As far as possible, patients must remain in the same body position for 5 minutes prior to having their heart rate and blood pressure taken.

Vital signs will be assessed at planned and unscheduled visits as described in the schedule of assessments in the study synopsis and Section 14 of the protocol.

Any vital sign abnormalities considered as AE (see Section 13.1.1) should be documented in the AE section of the eCRF.

12.2.1.3 Safety Laboratory Evaluations

A central laboratory will be used for analysis of all specimens collected. The respective samples will be collected at scheduled and unscheduled visits as described in Section 14.

Specimen collection, packaging and shipment will be described in the laboratory manual.

The Investigator will review the laboratory reports upon receipt from the central laboratory for clinically relevant values. Laboratory values which are out of normal ranges should be documented as ‘not clinically relevant’ or ‘clinically relevant’ on the laboratory report. Additionally, values will be documented in the eCRF. Laboratory abnormalities considered as AEs (see Section 13.1.1) should be additionally documented in the AE section in the eCRF.

The laboratory reports should be signed and dated by the Investigator and filed in the patient files.

Hematology

The parameters assessed will include complete blood count with differential and platelet count, Coombs test, coagulation studies (PT, PTT, INR) and sedimentation rate. Blood group (only at visit 1).

Clinical chemistry

The parameters assessed will include sodium, potassium, creatinine, eGFR, urea, total bilirubin, GGT, ALT/GPT, AST/GOT, alkaline phosphatase, total protein, albumin, lactate dehydrogenase, fibrinogen, CRP, iron, ferritin, haptoglobin. eGFR at visit 1 only.

Urinalysis

The parameters assessed will include specific gravity, pH, glucose, protein, ketones, nitrite, leukocytes and blood.

Urinalysis with dipstick will be performed centrally. Microscopic analysis at the central laboratory (leukocytes, erythrocytes, casts, bacteria) will only be performed, in case of a positive dipstick test result.

Routine clinical samples will be destroyed no later than the time of completion of the study.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 19.11.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

12.2.1.4 Assessment of Disability

In general, assessment of disability should be performed by the Investigator or Study Physician. Except for the EDSS, disability assessment can also be delegated to an individual (e.g. nurse/study coordinator), who has been instructed in the appropriate administration of the test. Advisory instructions on the application of the respective tests will be provided as protocol's appendices.

Disability assessment as outlined below will be performed at planned and unscheduled visits as described in Section 14.

Expanded Disability Status Scale (EDSS)

EDSS will be determined, based on neurological examination, by the Investigator or Study Physicians. The EDSS is an ordinal scale used for assessing neurologic impairment in MS based on a neurological examination. It consists of scores in each of seven functional systems (FSs) that are then combined to determine the EDSS steps (ranging from 0 (normal) to 10 (death due to MS). The FSs are visual, brain stem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral functions and ambulation. The FSs and EDSS steps will be assessed in a standardized manner. EDSS is a widely used and accepted instrument to evaluate disability status at a given time and longitudinally to assess disability progression in clinical studies in MS. Any worsening on the EDSS scale may indicate progression of the disease. To exclude any incidental/unrelated changes, the increase in EDSS score should be confirmed at the next visit with scheduled EDSS assessment (Appendix 24.3).

Nine Hole Peg Test (9-HPT)

The 9-HPT 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 from each hand will be used for further analysis. The 9-HPT will be administered as described in the Multiple Sclerosis Functional Composite (MSFC) Administration and Scoring Manual [53]. The psychometric validity of the test has been demonstrated in MS patients [54]. It has been demonstrated that a 20% change in the time to perfom the 9-HPT is clinically meaningful. Hence, in the RED4MS trial a 20% increase in the timing of the 9-HPT is defined as an indicator for an increase of disease severity (Appendix 24.4).

Timed 25-Foot Walk (T25-FW)

The Timed 25-Foot Walk 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 is immediately administered again by having the patient walk back the same distance. The score for the T25-FW is the average of the two completed trials. Patients may use assistive devices (i.e. cane or wheelchair) when performing the task. The T25-FW will be administered as described in the MSFC Administration and Scoring Manual [53]. The psychometric validity of the test has been demonstrated in MS patients [55]. It has been demonstrated that a 20% change in walking speed during the T25-FW is clinically meaningful. Hence, in the RED4MS trial a 20% deterioration in the T25-FW is defined as an indicator for an increase of disease severity (Appendix 24.5).

Symbol Digit Modalities Test (SDMT)

The symbol digit modalities test (SDMT) assesses processing speed, which is considered an important measure of cognitive dysfunction in MS patients. The psychometric validity of the test for assessing cognitive dysfunction in MS has been demonstrated [56]. The SDMT is brief, is easy to administer, and involves a simple substitution task. Using a reference key, the examinee 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 represents a clinically meaningful change in cognitive processing. In the RED4MS trial a 4-point deterioration in the SDMT is an indicator for increase of disease severity (Appendix 24.6).

12.3 Exploratory Variables – Immunological and Biomarker Efficacy

To assess immunological disease activity, to understand the mechanism/s of action of tolerance induction with peptide-coupled RBCs, and to identify biomarkers for measuring immune tolerance induction, the following biomarkers will be assessed.

12.3.1 T Cell Reactivity

Samples for antigen-specificity testing of T cells will be collected at scheduled visits as described in Section 14.

The goal is to assess the percentage of patients in each dose group showing an increase or reduction of antigen-specific T cells against the peptide/s or respectively target protein/s they responded to prior to study entry.

Blood collection, packaging and shipment will be described in the laboratory/logistics manual.

12.3.1.1 Other Markers Related to Tolerance Induction

Other biomarkers indicative of tolerizing effects include but are not limited to surface- and intracellular markers of proinflammatory and regulatory T cell populations, cytokines and transcription factors known to be secreted or expressed by proinflammatory or regulatory T cells or other cell populations.

12.3.2 Biomarkers of Disease Activity

The presence of markers related to disease activity in the serum can indicate increase or attenuation respectively of target tissue damage (neurofilament-light chain is one example), inflammation in the brain (chitinase 3-like protein 1 is one example) or activation and damage of glial cells (glial fibrillary acidic protein is one example) among others. These markers will be measured before and following CLS12311 treatment at scheduled visits as described in Section 14.

Mechanistic profiling of serum and blood cells may be complemented by applying broad-based methods including but not limited to multi-analyte measurements, transcriptomics and proteomics.

Biomarker samples will be sent to the Sponsor or a designee for analysis.

Biosamples collected for biomarker research will be stored for at least five years unless patients request that they are destroyed, or regulatory authorities require a shorter storage period for the specimens.

The information obtained from the samples up to the time of withdrawal will continue to be used.

Sample collection, packaging and shipment will be described in the laboratory/logistics manual.

12.4 Other Variables

Other variables including the time of assessment are detailed in Table 12-1.

Table 12-1 Other variables including time of assessment and description

Variable	To be assessed at Visit	Description
Demography	1	Age, sex, race.
Tobacco use	1	Smoking yes/no
MS history	1	Date of first MS symptom, date of first MS diagnosis, prior relapses, prior disease modifying therapies and symptomatic therapies
Medical history (except MS)	1	Past and present medical conditions other than MS at the time of informed consent.
Previous medication (except MS)	1	Medications and their indications for treatment, taken within 30 days before V1 or taken regularly for chronic medical conditions will be recorded.
Height	1	Body height will be measured in cm, in standing patients with bare feet.
Weight	1	Body weight (indoor clothing but without shoes) will be measured in kg.
Body mass index (BMI)	1	The BMI will be calculated in kg/m^2.
Electrocardiogram (ECG)	1	At least a 6-lead ECG acceptable. Pathologic findings need to be recorded in the eCRF.
Childbearing potential	1	Women are considered post-menopausal and/or not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to baseline.
HLA typing	1	Analyzed for the HLA [redacted] alleles.

Variable	To be assessed at Visit	Description
Pregnancy test	All visits except5, 6, 8, 12 and 14	Urine pregnancy tests will be performed locally at all visits only in female patients of childbearing potential.
Infectious disease screen & Eligibility Criteria	1/2 9	Infectious disease screening will be performed locally according to local regulations. However, the minimum panel to be tested is Anti-HIV-1/2, HBsAg, Anti-HBc, Anti-HCV and screening for syphilis. In addition, in Switzerland only, anti-HTLV-1/2 testing will be performed.
History of COVID19 disease or vaccination	1	Prior History of COVID19 disease or vaccination against SARS-CoV-2 should be documented and confirmed by patient`s certificate.
Concomitant medications and concomitant procedures (e.g. surgery, diagnostic procedures)	Continuously	Concomitant medications (including changes in dose) and concomitant procedures (e.g. surgeries, diagnostic procedures related to MS) started/performed after signing the informed consent form until the last scheduled visit will be recorded. Homeopathic medicinal products, phytotherapeutics and dietary supplements (e.g. vitamins, minerals) should also be documented.

12.5 Source Documents

For definitions of source documents and data see section 17.

All information that will be captured by the eCRF should be represented in the patient records as source data.

13 ASSESSING, RECORDING AND REPORTING OF ADVERSE EVENTS

13.1 Adverse Event Reporting and Classification

This section defines adverse events (AEs) and serious adverse events (SAEs) in alignment with CTR, Swiss regulations (specifically ClinO), and Good Clinical Practice (GCP) standards.

13.1.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP or study treatment/procedures.

The findings from physical examinations will be compared with those at baseline (screening visit 1) and all new findings and deterioration of baseline findings will be documented as AEs.

Vital sign, laboratory or ECG abnormalities should not be documented as AEs unless they are accompanied by clinical symptoms, require treatment, fulfil any SAE criterion, cause a change in the study schedule or are considered clinically significant in the Investigator's judgment.

In case the vital sign / laboratory / ECG abnormalities are a sign of a medical condition, the condition should be documented as an AE and not the abnormal sign (e.g. elevated blood pressure → primary hypertension; blood glucose increased → type 2 diabetes mellitus).

MS Relapse and new MS lesions are not considered AEs (see 12.1.1.2).

AE collection will occur from the start of study through the end of the follow-up period.

13.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that, at any dose

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event

More than one of the above criteria can be applicable to the same event.

AEs/ARs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardise the patient or may require intervention to prevent serious outcome as defined above, are also classified as serious. Example: Any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction.

NOTE:

Death: is the outcome of an AE. The event to be reported comprehensively is the medical condition leading to death, e.g. underlying disease, accident.

Life-threatening: the definition of a SAE or SAR refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalization is defined as inpatient care of more than one calendar day (overnight admission). Admission for ambulant diagnostic procedures, overnight survey visits or ambulant visits to an emergency ward, e.g. during weekends are not considered 'hospitalization' in the sense of the criteria for SAE / SAR, unless any of the other criteria for seriousness is met.

13.1.3 Adverse Event Intensity

The intensity or severity of an adverse event will be classified based on the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0, 2017) (Table 13-1). Care needs to be taken to avoid confusing the term "severe" with the classification of "serious" (see section 13.1.2). Appropriate training should be provided to the investigational site staff as required.

Table 13-1 Adverse event intensity classification

Severity	Explanation
Mild (Grade 1)	• Asymptomatic or mild symptoms • Clinical or diagnostic observations only • Intervention not indicated
Moderate (Grade 2)	• Minimal, local or non-invasive intervention indicated • Limiting age-appropriate instrumental activities of daily living (ADL)

Severity	Explanation
Severe (Grade 3)	• Severe or medically significant but not immediately life-threatening • Hospitalization or prolongation of hospitalization indicated • Disabling • Limiting self-care activities of daily living
Life-threatening (Grade 4)	• Life-threatening consequences • Urgent intervention indicated
Death (Grade 5)	• Death related to AE

13.1.4 Adverse Event Causality

The adverse event causality, i.e. the causal relationship of an adverse event with CLS12311/placebo or the related blood donation, is classified as 'related' or 'not related' (Report of CIOMS Working group VI "Management of Safety Information from Clinical Trials" (2005; Chapter 4.c.2). AE causality will be assessed according to the definitions given in Table 13-2.

Table 13-2 Adverse event causality classification

Causality Code	Definition
Not related (no reasonable possibility)	A clinical event, including laboratory test abnormality, which is temporally unreasonable with regard to the administration of the investigational medicinal product/placebo or the related blood donation **and/or** can be reasonably explained by • Previous or concomitant disease(s) • Previous or concomitant other treatment(s) • Protocol related procedure(s)
Related (reasonable possibility)	A clinical event, including laboratory test abnormality, which is temporally reasonable **and** can be reasonably explained by the administration of the investigational medicinal product/placebo or the related blood donation **and/or** is unlikely attributed to • Previous or concomitant disease(s) • Previous or concomitant treatment(s) • Protocol related procedure(s) **and/or** the response to withdrawal of the investigational medicinal product is clinically reasonable **and/or** the causality assessment is missing

When an Investigator fails to provide a causality assessment, the event will always be considered 'related' to the study product.

13.1.5 Adverse Event Outcome

The outcome will be classified as follows:

- **Recovered/Resolved:** The patient has fully recovered from the event, or the condition has returned to the level observed at baseline.
- **Recovering/Resolving:** The patient is improving but is still not fully recovered.
- **Not recovered/Not resolved:** As a final outcome, the condition is still present after appropriate follow-up. Improvement has not been observed and is no longer expected.
- **Recovered/Resolved with sequelae:** As a result of the AE, the patient suffers persistent and significant disability/incapacity (e.g. became blind, deaf or paralyzed).
- **Fatal:** The patient died due to the event. If the patient died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (e.g. not recovered or recovering).
- **Unknown:** If outcome is not known or not reported.

13.1.6 Adverse Reaction (AR)

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable suspected causal relationship to a medicinal product qualify as ARs. The reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship (see 0). If a patient experiences both a local and systemic reaction to the study drug, each reaction should be recorded separately on the Adverse Event form of the eCRF. The expectedness of ARs will be assessed by the Sponsor against the Reference Safety Information (RSI) in the Investigator's Brochure.

13.1.7 Unexpected Adverse Reactions

An AR, the nature or severity not consistent with the RSI. In the current trial the Reference Safety Information is given in the current version of the Investigators' brochure. Expectedness will be assessed by the Sponsor.

13.1.8 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected AR to an investigational medicinal product (the tested IMP or placebo) which occurs and is assessed as both unexpected based on the RSI and serious.

13.2 Recording and Reporting of Adverse Events

13.2.1 Recording of Adverse Events

The Investigator must record in detail all AEs (signs and symptoms) which are either volunteered by patients or observed following inclusion to the trial (signature of the ICF) on the appropriate (e)CRF page. Included in the description should be:

- The nature of the sign or symptom
- The date of onset; date of resolution (duration)
- Seriousness
- The severity / intensity (for definition see section 13.1.3)
- The Investigator's judgement on possible causal relationship to the investigational medicinal product or protocol related procedures (for definition see section 13.1.4)
- The outcome

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquial language and abbreviations.

All SAEs must be additionally documented on a 'Serious Adverse Event Report' form including a description of the event in medical terms.

Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. In the case of SAEs, component signs and symptoms may be recorded in addition to a diagnosis if they further clarify the clinical picture. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All patients experiencing AEs, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice until a satisfactory explanation is found or the Investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied, if possible. If the same AE occurs in the same patient more than once, each occurrence must be documented and assessed separately. If an AE increases in severity, the event will be reported at the higher severity grade as a new AE. The onset date of the new AE will be the date that the severity increased. A decrease in severity should not be reported as a new AE. The same applies to SAEs.

13.2.2 Reporting of Serious Adverse Events

All SAEs must be reported in the format detailed by the Serious Adverse Event Report Form to the SCOPE International Pharmacovigilance by email or fax within 24 hours of the Investigator becoming first knowledge (Note: If local regulations require shorter reporting timelines, the stricter requirement will apply).

SAEs must be reported within 24h to

email: safety@scope-international.com or

Fax: +370 523 27903

Any information not available at the time of the initial SAE report (e.g. an end date for the AE or laboratory values received after the report) must be documented on a SAE report form, with the box "Follow-up" indicated under "Report type". AEs initially reported as non-serious but later assessed as serious, must be forwarded immediately to SCOPE International Pharmacovigilance on a SAE report form.
SCOPE on behalf of the Sponsor will notify the competent authorities, IECs/IRBs and all Investigators of any suspected SARs that are unexpected (SUSARs) and other significant safety issues in line with applicable legal requirements.

All reporting of adverse events must strictly adhere to relevant data protection regulations to ensure patient confidentiality.

13.3 Period of Observation

For the purposes of this study, the observation period for collecting of AEs extends from the time the patient provides informed consent until the last patient visit. AEs occurring prior to Visit 1 (screening) should be recorded as part of the patient's medical history and will not require separate reporting. This approach streamlines the reporting process and ensures that only relevant AEs occurring during the study period are documented.

Any serious AE occurring during this study must be monitored beyond the observation period until:

- It has been shown to be unrelated to the Investigational Medicinal Product (IMP) or placebo
- The event has resolved

- There has been improvement or no further improvement is expected, and the case has been fully explained and assessed.

Medical conditions diagnosed at the screening visit will only be documented as AEs, if they are known to have started or are suspected to have started after the ICF has been signed. All other medical findings during examinations at the screening visit will be documented as medical history. Medical judgment should be exercised to estimate if a condition likely began between the signing of the informed consent and the date/time of the medical examination. Adverse Events will be followed up throughout the course of the clinical trial, in compliance with ICH GCP guidelines and local regulatory requirements.

13.4 Potential Risks and Potential Adverse Events

The risk to patients in this trial will be minimized by compliance with inclusion/exclusion criteria, close clinical and imaging monitoring during the study, assessment of the nature, frequency, and severity of adverse events, avoidance of prohibited treatments and adherence to Investigator guidance. In addition, guidelines for managing severe allergic reactions are provided in the Appendix 24.2. Detailed criteria for study discontinuation are given in section 9.3 and post-treatment observational periods defined in sections 10.2.3 and 14.5. Furthermore, safety will be closely monitored on an ongoing basis by a Data and Safety Monitoring Board (DSMB) as outlined in section 19.1.3.

13.4.1 Risks of Blood Drawing

Adverse events associated with drawing blood for RBC donation include vasovagal syncope with needle insertion and in rare cases hypotension secondary to volume depletion. Exclusion of patients with a history of cardiovascular disease further reduces the risk of this complication. Infection is a potential risk but is unlikely due to the closed system and the maintenance of sterile technique. Clinically significant iron deficiency and anemia may occur as a consequence of the blood donation.

13.4.2 Risks of Leukapheresis

Possible risks comprise hematoma at the puncture site, an infection due to venous puncture (the tubing system for the withdrawal is a sterile one-way system), prickling paresthesia due to anti-coagulating agents, which are added during the centrifugation of the blood. Further, break into a sweat, nausea, vomiting or hypotension and faint as expression of vasovagal response can occur. Exclusion criteria for leukapheresis: pregnancy and difficult peripheral venous access.

13.4.3 Risks of Lumbar Puncture

Effusions, stiffness, irritation of the tissue due to the injection, post-puncture headache, in very rare cases post-puncture infection. Headaches or irritation of a nerve root can occur but are rare (headaches) or very rare (nerve root irritation, hematoma).

13.4.4 Risks of MRI

Gadolinium is used as a contrast agent with MRI approved by the Swissmedic and European Medicines Agency (EMA). No serious side effects have been associated with its use. Approximately 5 to 10 percent of patients develop transient headaches following administration, but it is not clear whether the headaches are associated with the drug. The effect of gadolinium on the developing fetus remains partly unknown. Animal studies have shown a delay in development but no developmental abnormalities. Consequently, women of childbearing potential will be entered into this study only if an effective means of birth control is in use. A pregnancy test will be done prior to beginning the study and at each follow-up visit. The risk of nephrogenic systemic fibrosis is increased in patients with profoundly impaired renal function (glomerular filtration rate <30mL/minute).

13.4.5 Risks of Therapy

The tolerance protocol that is proposed here has been extensively used in rodents for many years, with no major safety issues arising. For a complete summary of safety information, refer to the Investigator's Brochure. From the extensive experience with peptide-coupled cells we do not expect any significant hematopoietic or organ toxicity in humans. Data from two phase I trials with myelin peptide-coupled cells in MS patients are consistent with this assumption and did not reveal any signs of toxicity in any of the nineteen patients who have been treated [57]; ETIMSred Trial unpublished).

Aggregates: The formation of aggregates is a major concern in cell-based therapies. Aggregates might cause thromboembolic events, particularly in the lungs after intravenous infusion, but also other venous and arterial vascular compartments. The peptide-coupling procedure induces changes in the deformability of RBCs and the surface of the membrane, which might cause thromboembolism. Pre-clinical studies did not reveal any thromboembolic events following single or repeated administrations of peptide-coupled RBCs. In line with preclinical experience two prior studies in MS patients using either PBMCs coupled with seven myelin peptides or RBCs coupled with seven myelin peptides were tolerated well in MS patients. The following measures were taken to reduce the risk of embolism: 1) formation of aggregates will be carefully checked and excluded in every product prior to release and infusion, and 2) peptide-coupled RBCs as well as uncoupled RBCs will pass through a 40 µm filter in a standard blood transfusion kit. Appropriate monitoring of patients during and after infusion is mandatory to ensure appropriate medical care.

Hypersensitivity and cytokine response: In pre-clinical experiments and two phase I trials (Lutterotti et al., 2013; ETIMSred Trial unpublished) the i.v. use of peptide-coupled cells did not show any risk of anaphylaxis. Cytokine response to the drug product has not been observed in animals, and our in vitro data in human cells did not reveal any cytokine response. Patients will be monitored to provide immediate adequate medical measures in case anaphylaxis should occur (see section 14.5). In case of severe allergic (anaphylactic) reactions, standardized medical treatment should be applied. An example for an emergency treatment is given in the Appendix 24.2.

Risk of a transfusion reaction will be mitigated by thorough tracking of the autologous blood product.

Immune activation and disease exacerbation: The aim of the therapy is the downregulation of an autoreactive immune response through the induction of immune tolerance. However, the induction of an immune response leading to exacerbation of disease cannot be fully excluded. The type of trial, which is based on using MRI measures of inflammation as a sensitive safety measure, is considered optimal in this regard, and clear rules triggering safety data review by a DSMB (see section 19.1.3) have been defined to minimize risks and enable medical actions at the earliest possible time point.

Risk of infection: Some biologic and non-biologic therapies for the treatment of MS have been associated with an increased risk of infection. As a measure of precaution, the Investigator or study physicians are required to carefully monitor for any signs or symptoms of infection (see section 14.5).

Carcinogenicity: Peptide-coupled RBCs are mature autologous cell populations and do not have a cell nucleus and thus do not have the ability to proliferate. It has not been described that MS patients have increased risks to develop tumors [58]. [redacted]

Reproductive and developmental toxicity: Reproductive and developmental toxicity was not assessed in pre-clinical studies. Available data do not suggest any reproductive or developmental toxicity or influence on reproductive performance to arise from the single injection of autologous

cells. Nevertheless, the patients will be informed about the remote potential of such risks and will have to sign an informed consent that they have to use acceptable methods of contraception.

Injection site reactions: Peptide-coupled RBCs will be administered by IV infusion. The medication will be released slowly as a drip from a bag and into a tube that is attached to the needle. It is common for a patient to experience reactions at the injection site as a side effect of the venous puncture. Common skin reactions include redness, bruising, pain, or swelling. These symptoms usually resolve on their own within a short period. Slowing of the infusion rate may be necessary in the event of an infusion reaction.

13.4.6 Risks of Manufacturing and Transportation

The IMP/placebo will be manufactured, tested, and released in compliance with GMP requirements including appropriate sterility testing. Nonetheless, there is still a risk that manufacturing of the IMP/placebo will have to be stopped or that the final product will not be conforming to specifications and can be not released for use. Despite all due care, there is a certain risk of the possible transmission of germ components. Furthermore, there is also the risk of damage to the starting product or the final product due to incorrect handling or exceeding of the expiry date e.g. due to prolonged transport times so that the starting product can no longer be used for manufacturing, or the final product can no longer be used for infusion. In these cases, study treatment cannot be carried out as scheduled. The management of positive sterility test results during manufacturing and after administration of IMP to a patient is illustrated in Appendix 24.7.

There is also a minor risk of mixing up patient blood and IMP/placebo. Safety measures have been taken to minimise the risk and to ensure that the patient will receive the own IMP/placebo. This also includes serological crossmatch or bedside testing immediately prior to each infusion according to the local regulations. In case of incompatibility the IMP/placebo will not be infused.

If study treatment cannot be carried out as scheduled, the patient will stay on study and receive his/her next treatment according to the study schedule.

13.5 Pregnancies

Female patients should take all appropriate precautions to avoid becoming pregnant during this study. As such, women of childbearing potential should use adequate contraception throughout the trial, including the treatment phase and for 4 weeks after the last dose of CLS12311. Regular pregnancy tests will be performed during the study. Patients who become pregnant at any time during the study will be instructed to immediately inform the investigator and come in for an unscheduled visit. A positive pregnancy test must be confirmed by a urine pregnancy test at the central laboratory.

The Investigator has to document any pregnancy occurring in a female patient after the first study dose until patient's last study visit on the Pregnancy Report Form and submit to the Sponsor`s designee immediately (i.e. no more than 24 hours after learning of the pregnancy), either by faxing or by emailing:

SCOPE International Pharmacovigilance
email: safety@scope-international.com
Fax: +370 523 27903

Pregnant patients who received at least one dose of CLS12311 and prematurely discontinue the study prior to the last scheduled visit have to perform the early discontinuation (ED) visit (see section 12.1.9), except for the MRI examination and pregnancy testing.

After the birth, the investigator will contact the patient, who become pregnant to obtain data on pregnancy outcomes. The Investigator has to email or fax the Pregnancy Report Form to SCOPE International Pharmacovigilance when updated information on the course and outcome of the pregnancy becomes available. In addition, patients may volunteer further information regarding child health at 12 months after birth using the validated infant health questionnaire (ASQ-3). After

a pregnancy has been confirmed, an informed consent will be sought regarding collecting information on the health and well-being of the infant.

Pregnancy per se does not classify as an AE. However, any AEs related to a pregnancy have to be reported like any other AEs in eCRF Adverse Event page. SAEs related to pregnancy and any abnormal outcome (i.e. congenital anomalies, spontaneous abortion or fetus death, adverse reactions in the neonate that are classified as serious) have to be reported on the SAE Report Form within 24 hours to SCOPE PV and documented in the eCRF Adverse Event page.

13.6 Ongoing Safety Assessment

An external, independent Data and Safety Monitoring Board (DSMB) will review safety data throughout the study as outlined in section 19.1.3.

14 VISIT SCHEDULE AND ASSESSMENTS

14.1 Procedures at Each Visit

14.1.1 Baseline [redacted]

Baseline evaluations and data collection will be used to determine eligibility for enrollment and to document patient clinical status prior to treatment. Information to be collected includes:

- Date of informed consent
- Demography
- Tobacco use
- Height and weight
- MS history (date of first MS symptom, date of first MS diagnosis, prior relapses, prior disease modifying therapies and symptomatic therapies)
- SARS-CoV-2 vaccination status
- Medical history (except MS history)
- Current medication except for MS (taken regularly for chronic conditions, or within the past 30 days)
- Physical examination
- Vital signs
- ECG (at least a 6-lead)
- Childbearing potential and ask patient if she is pregnant (pregnancy is an exclusion criterion)
- Urinary pregnancy test
- Central labs: Infectious Disease Screen (no extra blood sample needed)
- Hematology: complete blood count with differential and platelet count, Coombs test, coagulation studies (PT, PTT, INR) and sedimentation rate, blood group
- Clinical chemistry: Sodium, potassium, creatinine, eGFR, urea, total bilirubin, GGT, ALT/GPT, AST/GOT, alkaline phosphatase, total protein, albumin, lactate dehydrogenase, fibrinogen, CRP, iron, ferritin, haptoglobin, eGFR
- Urinalysis: specific gravity, pH, glucose, protein, ketones, nitrite, leukocytes and blood

- HLA typing HLA-[redacted] alleles (no extra blood sample needed; will be taken from blood collected for antigen specificity testing)
- Antigen specificity: collect 30 ml of EDTA blood
- Biomarker: collect one serum tube (5 ml)
- **Cranial MRI (contrast enhanced)**; (can be performed within 5 days after V1, latest on the same day prior to the blood donation)
- EDSS
- 9-HPT
- T25-FW
- SDMT
- Adverse events
- Assessment of inclusion/exclusion criteria

14.1.2 Visit [redacted]: Blood donation

In case it is not possible to perform the visit at the study site directly before the blood donation, e.g. if the BDU is located at another facility, the respective visit at the study site may be performed on the day before the blood donation.

- Vital signs
- Urinary pregnancy test in women of childbearing potential
- Eligibility for blood donation according to local law, including blood count, hemoglobin and infectious disease screen
  - Sample for analysis may be taken from the blood donation itself, or a separate blood sample taken prior to blood donation according to local regulations
  - However, the minimum panel to be tested is Anti-HIV-1/2, HBsAg, Anti-HBc, Anti-HCV and screening for syphilis
  - For Switzerland blood needs additionally to be tested for HTLV-1/2
- **Blood donation for IMP/Placebo production**
- MS relapse assessment
- Concomitant medication
- Adverse events

14.1.3 Visits [redacted] IMP administration

- Vital signs will be recorded: within 15 min pre-dose, 15 min after Infusion start, Infusion end, 1h and 2h post-dose
- Urinary pregnancy test in women of childbearing potential
- **IMP/Placebo (see section 10.2.1):** A bedside test for blood group or cross-matching procedures will be performed according to local regulations and prior to each infusion.
- MS relapse assessment
- Concomitant medication
- Adverse events **(a telephone-based assessment of AEs will be done on the next working day after IMP administration.** If the phone consultation of the [redacted] coincides with the phone visit [redacted], the phone consultation of the [redacted] will be skipped.)*

** In the Czech Republic, AEs will be recorded on the day after visit 3 and visit 4, as patients will be observed of 24 hours in the hospital.*

14.1.4 Visit [redacted] Safety assessments

- Physical examination
- Vital signs
- MS relapse assessment
- Concomitant medication
- Adverse events

14.1.5 Visit [redacted] End of Treatment (EOT)/ Early Discontinuation (ED) visit

- Physical examination
- Vital signs
- Urinary pregnancy test
- Hematology: complete blood count with differential and platelet count, Coombs test, coagulation studies (PT, PTT, INR) and sedimentation rate
- Clinical chemistry: Sodium, potassium, creatinine, eGFR, 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
- Antigen specificity: collect only 10 ml EDTA blood [redacted] and 30 ml EDTA blood [redacted]
- Biomarker: collect one serum tube (5 ml)
- **Cranial MRI (contrast enhanced)**; (can be performed +/- 5 days of the visit. If the MRI will be performed before [redacted], urinary pregnancy test has to be performed at the site prior to the MRI.
- EDSS
- 9-HPT
- T25-FW
- SDMT
- MS relapse assessment
- Concomitant medication
- Adverse events

14.1.6 Visit [redacted] Telephone interviews

*****A telephone interview will be conducted 3-5 days after the first dose of study drug has been administered. The purpose of this interview is to identify and collect information on changes in the patient's health status that warrant an unscheduled visit (e.g., new or worsening neurological symptoms). During the telephone interview, patients will be asked questions related to potential adverse events (AEs) or if they noticed any change in neurological functions. Concomitant medications will be recorded. The telephone interview will be conducted by the principal

investigator or a delegate from the study team. All clinically significant findings will be reported in the appropriate eCRF.

14.1.7 Visit [redacted] Safety Follow Up

- Physical examination
- Vital signs
- Urinary pregnancy test in women of childbearing potential
- Hematology: complete blood count with differential and platelet count, Coombs test, coagulation studies (PT, PTT, INR) and sedimentation rate
- Clinical chemistry: Sodium, potassium, creatinine, eGFR, 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
- **Cranial MRI (without contrast);** can be performed +/- 5 days of the [redacted] and up to 5 days before [redacted]. If the MRI will be performed before the respective visit, urinary pregnancy test has to be performed at the site prior to the MRI.
- EDSS
- 9-HPT
- T25-FW
- SDMT
- MS relapse assessment
- Concomitant medication
- Adverse events

14.1.8 Unscheduled Visit

In case of symptoms that suggest a possible relapse, i.e. new neurological symptoms or worsening of previous symptoms, the following assessments will be performed during an unscheduled visit:

- Physical examination
- Vital signs
- Urinary pregnancy test in women of childbearing potential
- **Cranial MRI (without contrast)**; (can be performed ±5 days). If the MRI will be performed before the UV urinary pregnancy test has to be performed at the site prior to the MRI
- Hematology: complete blood count with differential and platelet count, Coombs test, coagulation studies (PT, PTT, INR) and sedimentation rate
- Clinical chemistry: Sodium, potassium, creatinine, eGFR, 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
- EDSS
- 9-HPT, T25-FW, SDMT

- MS relapse assessment
- Concomitant medication
- Adverse events
- In case of symptoms not related to a potential relapse, it is up to the Investigator to decide which of the abovementioned assessments should be performed during the unscheduled visit.

14.1.9 Last Visit in Patients who Prematurely Discontinue the Study (ED Visit)

Patients who received at least one dose of study drug and prematurely discontinue the treatment period will be investigated immediately (but not earlier than 2 weeks after the last dose) according to the premature discontinuation visit (ED). This will also apply to patients who have prematurely discontinued the safety follow-up phase and whose last visit has been more than 8 weeks ago.

At the ED visit an MRI needs to be performed unless a previous MRI had been performed less than 2 weeks prior to the ED visit. The MRI at the ED visit needs to be with contrast.

14.1.10 Re-screening of patients

A patient may be re-screened once if any inclusion criterion is not met, or any exclusion criterion is met during the first screening attempt . In case of re-screening, all parameters which have already been assessed during initial screening with the exception of HLA typing must be reassessed.

Note: In case of narrowly missed safety laboratory values during screening as defined in Section 8.1.2 ‘exclusion criteria’, repeat samples may be drawn once. This repetition of laboratory values is not regarded as re-screening.

14.2 Tabular Overview of Treatment Schedule

A tabular summary of the treatment schedule and assessments in this study is given in the study synopsis at the beginning of the clinical study protocol.

14.3 Windows for Scheduled Visits

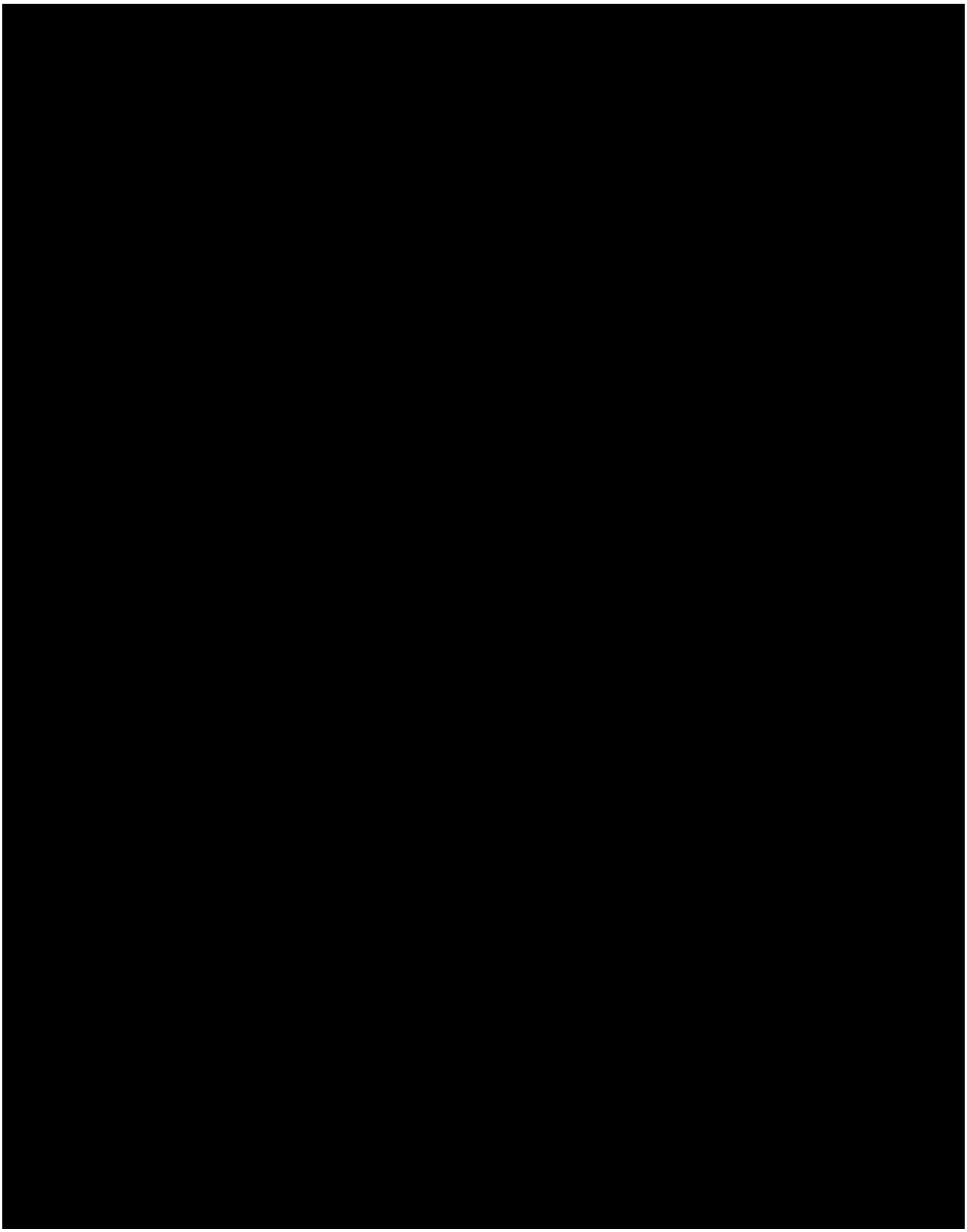
Baseline visit (visit 1) of the patients will be scheduled to review inclusion and exclusion criteria. Time point of [redacted] blood donation start of the IMP administration will be coordinated centrally to ensure appropriate safety assessments between dosing of patients. [redacted]

Due to organizational reasons, the study design and the manufacturing schedule, the treatments could be postponed as well. However, both treatments of one cycle will be administered [redacted]

All safety visits will be planned and performed based on the previous visit, e.g. if there is a postponement of one week, the following visit will also be postponed at least by one week.

It is ensured that there is [redacted] between the two blood donations.

Table 14-1 Windows for scheduled visits



14.4 Assessment of Compliance

Patients are expected to maintain compliance with the visit schedule within the permitted study visit windows. Site staff must have regular contact with each patient throughout the study to ensure that contact information is correct and to remind them of upcoming visits.

14.5 Special Warnings and Precautionary Measures

Allergic/anaphylactic and other infusion-related reactions: As a precautionary measure, patients must be kept under medical supervision for at least 2 hours following IMP/placebo administration during the first treatment cycle to allow for an adequate observation and adequate treatment in case of potential allergic or other infusion related reactions. During the second treatment cycle the observation period is 1h following IMP administration. Furthermore, during the first treatment cycle, a telephone-based assessment of AEs will be done the day after IMP/placebo administration. In case of severe allergic (anaphylactic) reactions, standardized medical treatment should be applied. An example for an emergency treatment is given in the Appendix 24.2.

Infection: Some biologic and non-biologic therapies for the treatment of MS have been associated with an increased risk of infection. As a measure of precaution, the Investigator or Study Physicians are required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, sweats, cough, dyspnea etc.

A **Data and Safety Monitoring Board (DSMB)** has been established to assess safety of patients treated in the study (for details on DSMB responsibilities see section 19.1.3).

Investigators are instructed not to proceed with the next IMP infusion if:

- the study participant is pregnant
- the study participant experienced allergic reaction in prior IMP administration
- the study participant experienced a severe infusion-related reaction in prior IMP administration
- the study participant experienced a serious AR to prior IMP administration
- the study participant experiences an SAE at the time of IMP infusion or any other serious medical condition, which poses a threat to the safety of IMP administration
- the Sponsor or Steering Committee or DSMB have decided to not continue IMP administration in the trial arm concerned

In case of questions or uncertainties regarding IMP administration following adverse events, the Investigator should contact the medical monitor (primary contact) or the Sponsor's Medical Representative. Contact details are given at the beginning of the study protocol.

15 STUDY AND TREATMENT DURATION

15.1 Duration per Patient

The total duration of study participation for each subject will be at least 48 weeks. Subject eligibility will be determined at Baseline. Patients who meet all criteria for enrollment will be centrally allocated to the dose group. Hence, the timing of the visit 2 (1st blood donation) will depend on sequential allocation and respective safety periods defined between IMP administrations. Subsequently, a 17-week treatment phase begins, followed by a 31-week safety follow up phase.

15.2 Duration of Whole Study

The maximum duration of the study - from the screening of the first patient to the study's completion, defined as the last patient's last visit (LPLV), is expected to be approximately 20 months.

In addition, the Sponsor may decide to terminate the study at any time or extend its duration.

To ensure adherence to the study timeline and maintain data integrity, monitoring activities will be conducted throughout the study, as outlined in Section 18.1.2. These activities are essential for evaluating compliance with the protocol and safeguarding participant safety.

16 STATISTICS

16.1 Statistical Methods

This section gives an overview of the statistics planned for the study. All programming of tables, figures, listings and statistical analyses will be performed using the statistical software package SAS V 9.4. The planned statistics will be performed in accordance with the principles outlined by the guideline ICH E9.

A Statistical Analysis Plan (SAP) will be finalized before database lock. It will include all details of all planned analyses, the statistical methods and any protocol amendments. In case a protocol amendment is passed after finalization of the SAP an amendment to the SAP is to be performed accordingly. No interim analysis is planned for this study. However, safety analysis will be performed to provide the data to the DSMB, this safety analysis will be defined prior to including the first patient in the trial (see section 19.1.3).

As this is a Phase Ib study, all statistical analyses will be of exploratory in nature.

16.1.1 Analysis Populations

- The enrolled analysis set includes all patients who provided informed consent.
- The safety analysis set (SAF) includes all patients with blood donation for CLS12311 production.

16.1.2 Safety Analysis

A comprehensive safety evaluation will be performed after all patients have completed the last scheduled visit.

Safety will be assessed through summaries of exposure to blood donation, study treatment, adverse events, changes in laboratory test results, changes in neurological function, vital signs and MS relapses.

The safety data will be listed and summarized using all safety data available.

Adverse events (AE) will be coded using MedDRA and will be presented by primary System Organ Class (SOC) and Preferred Term. The analysis will focus on the treatment-emergent AEs

(TEAE), i.e. AEs which started or worsened after blood donation for CLS12311 production. The frequency of TEAEs by dose group and in total will be summarized by incidences standardized to the number of patients at risk and rates standardized to the total observation time.

Frequencies of TEAEs by dose group and in total will also be presented by relationship to study treatment and by severity. Additional analyses will be performed for SAE, TESAE, AESIs (see section 12.1.1.1), AEs leading to discontinuation.

The number and percentages of patients having experienced a centrally confirmed relapse will be presented by dose group and in total.

Descriptive summaries of observed values and changes from baseline will be presented for hematology and biochemistry variables by dose group. Each abnormal value will be flagged to show whether it is a value below or above the reference range and assessed by the Investigator for clinical relevance. The assessments of laboratory variables will be tabulated by visit for each clinical laboratory analyte by dose group and in total (frequency tables).

The assessment of categorical urinalysis variables will be tabulated by visit for each urine parameter by dose group and in total (frequency tables).

Vital signs will be described by summary statistics (by dose group and in total) for measured values and changes from baseline by visit.

The number and percentages of patients with normal/abnormal findings in physical examinations will be presented by visit (by dose group and in total).

Additional safety analyses will examine the changes in clinical parameters like EDSS, 9-HPT, T25-FW and SDMT.

16.1.3 Further Exploratory Biomarker Analysis

Exploratory analyses will be performed based on immunological data and soluble biomarkers collected. Biomarkers will be assessed at baseline (V1) and subsequent timepoints following administration of CLS12311 (or placebo). Immunological analyses will include descriptive summaries of T cell reactivity to CLS12311 peptides and/or their respective source proteins, as well as quantitative and functional assessments of T cell- and other immune cell populations . In addition, the influence of dose on T cell- and other immune cell population, such as regulatory T cells, may be explored. Changes in biomarkers of disease activity, such as neurofilament light chain (NFL), will be analyzed descriptively. Furthermore, biomarker levels may be compared with safety and imaging parameters to assess potential prognostic or predictive properties.

All exploratory biomarker analyses are intended to identify potential safety signals, that is proinflammatory immune activation, and to be hypothesis-generating.

16.2 Statistical Hypotheses

Due to their exploratory character, no formal statistical hypotheses have been defined.

16.3 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.

16.4 Data Handling

All data will be listed. Whenever applicable, all tables, figures and listings will use patient identification (ID) and time of evaluation to ensure clear tracking of individual data points. Patients will be listed according to their enrollment and dose group as applicable.

Tables, figures and listings will be produced in accordance with the principles outlined by the ICH E3 guideline, ensuring that all data is organized and reported consistently and in compliance with legal requirements.

16.5 Criteria for the Termination of the Study

Refer to section 9.3

16.6 Patient Selection for Analyses

All safety analyses will be based on the SAF.

Demographic and baseline characteristics will be presented for the SAF population.

All collected data will be presented in the listings.

17 SOURCE DATA AND SOURCE DOCUMENTS

17.1 Definitions

17.1.1 Source Documents

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments involved in clinical study). Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 19.9).

17.1.2 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Direct Access

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical study.

17.2 Permission of Access

The Investigator will permit study-related monitoring, audits, IRB / IEC review and regulatory inspections, providing direct access to primary patient data (i.e. source data) which supports the data on the eCRFs for the study, e.g. general practice charts, hospital notes, appointment books, original laboratory records.

Because this enters into the realm of patient confidentiality, this fact must be included in the Informed Consent Form to be signed by the patient, in line with pertinent data protection legislation.

Any party (e.g. domestic and foreign regulatory authorities, the Sponsor and/or authorized representatives of the Sponsor such as monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Sponsor proprietary information.

18 QUALITY CONTROL AND QUALITY ASSURANCE

18.1 Quality Control

18.1.1 Definition

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

18.1.2 Study Monitoring

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Any changes to source data must be traceable, should not obscure the original entry, and be explained if necessary (e.g. with an audit trail). Authorized, qualified representatives of the Sponsor will visit investigational sites at regular intervals during the study and after the study has been completed, as appropriate. clinical site monitoring plan will detail who performs the monitoring, how often it occurs, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes. During these visits, eCRFs, supporting documentation, and essential study-related documents will be reviewed and any discrepancies or omissions will be addressed. Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

To enable adequate monitoring, it is essential that the Investigator enters the data into the eCRF in a timely manner. In case the monitor identifies non-adherence to protocol or legal requirements including data protection and data security requirements, a re-training will be performed. Adherence to the protocol will be strictly controlled to ensure compliance with all relevant guidelines and regulations. This process supports the overall study timeline, as outlined in Section 15.2 and ensures that any issues are promptly addressed, facilitating a smooth path toward the study's completion.

18.2 Quality Assurance

18.2.1 Definition

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed, and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements.

18.2.2 Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Cellerys AG and/or the CRO Scope International. This initiation visit will include a detailed review of the protocol and study procedures.

18.2.3 Protocol deviations

The Investigator should document and explain any protocol deviations as required by the Clinical Trial Regulation (CTR). The Investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations

and assess whether any represent a serious breach and require reporting to the reviewing institutions in each participating country as mandated by regulatory requirements.

18.2.4 Audit

An audit is a systematic and independent review of study-related activities and documents to determine that the study related activities have been conducted, and the data has been recorded, analyzed and accurately reported according to the protocol, designated Standard Operating Procedure (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

An independent audit of a study site may take place at any time during or after the study. Refer also to section 17.2.

18.2.5 Inspection

An Inspection is defined as an official review conducted by a regulatory authority of documents, facilities, records and any other resources related to the clinical study. The inspection may be located at a study site, the Sponsor's facilities, the clinical research organization's facilities, or any other location deemed appropriate by the regulatory authorities.

Refer also to section 17.2.

19 ETHICAL AND LEGAL CONSIDERATIONS

19.1 Committees and Boards

19.1.1 Independent Ethics Committee (IEC)

This is an independent body (a review board or a committee, institutional, regional, national or international) constituted of medical/scientific professionals and non-medical/non-scientific members. Its responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in the study and to provide public assurance of that protection. This is achieved by reviewing and providing a favourable opinion on the study protocol, suitability of the Investigator, facilities adequacy and the methods and material used in obtaining and documenting informed consent from study patients.

The legal status, composition, function, operations and regulatory requirements pertaining to the Independent Ethics Committee may vary across all participating countries but should allow the Ethics Committee to act in agreement with GCP and applicable EU and national regulations.

Regarding the conduct of the present study and involvement of IEC, refer to section 17.2.

19.1.2 Institutional Review Board (IRB)

This is an independent body constituted of medical scientific and non-scientific members responsible to ensure the protection of the rights, safety and well-being of human subjects involved in a study by reviewing, approving and providing continued review of the study protocol and amendments as well as of the methods and material used in obtaining and documenting informed consent of the study patients, in alignment with EU and national legal requirements.

19.1.3 Data Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) consisting of at least 3 independent MS- and trial experts will be chartered to review the safety of the trial. Beside tolerability and safety of CLS12311, the DSMB will also evaluate signs of worsening of MS assessed by new lesions on brain MRI and occurrence of relapses and disability progression based on EDSS.

After both patients in the low dose group and all three patients in the medium dose group have completed [redacted], the Sponsor’s medical expert(s) will decide based on (S)AEs and relapses, whether the next dose level of the treatment can be applied.

As soon the last patient in the high dose group has completed [redacted] safety data (including MRI data, relapses and EDSS) of all patients will be evaluated by the DSMB. Finally, after the last patient in the high dose group has completed [redacted] the DSMB will meet again to evaluate safety of the 12-week follow-up after the second treatment cycle in all patients.

The DSMB shall give recommendations on the following main outcomes:

- stop further treatment or lower further dosing of individual patients
- stop recruitment and/or treatment or lower dose for a specific dose group
- stop recruitment and/or treatment for the clinical trial
- continue the clinical trial as per protocol
- any other trial modification (e.g. additional visits, assessments)

Any recommendation will be explicitly documented in the meeting minutes.

Based on the DSMB recommendations, the Study Steering Committee, consisting of the Sponsor and selected country Investigators, will decide on actions to be taken as outlined above.

For the DSMB meetings, the DSMB will receive patient listings and statistical summaries, consisting of at least the following in addition to all available data on the patient(s) that made the meeting necessary:

- All patients who experienced SAEs (including relationship and severity)
- All patients who experienced AEs (including relationship and severity)
- All patients who experienced AEs within one day following infusion of CLS12311/placebo including severity and relationship
- All patients who experienced a relapse
- Number of new brain lesions (CEL and new/enlarging T2)
- EDSS scores
- Safety relevant protocol deviations

Detailed requirements on the presentation of listings and summaries, as well as details of the premise and the scope of the DSMB, will be specified in the DSMB Charter.

19.1.4 Steering Committee

A Steering Committee consisting of at least the Sponsor and selected country Investigators, or other experts will be established to provide oversight of the conduct of the trial. This includes oversight of the practical aspects of the study as well as ensuring that the study is conducted in a way which is both safe for the patients and provides appropriate safety and efficacy data to the Sponsor and Investigators.

Specific responsibilities of the Steering Committee may include, but are not limited to, the following:

- to provide overall supervision of the trial, including compliance with regulatory standards
- to discuss steps to reduce deviations from the protocol
- periodic review of the study progress
- to review safety data; in a blinded manner. This review is typically done blinded to treatment allocation

- to resolve any differences within the research team or between research team and Sponsor regarding data management and monitoring procedures in the trial or any recommendation for modifications to the protocol.
- The Steering Committee provides guidance to the Sponsor regarding modifications of the trial conduct based on DSMB recommendations, e.g. prematurely stopping recruitment and/or treatment, reducing the dose for a specific dose group or terminating the clinical trial.

Details regarding composition of the Steering Committee, its premise and scope will be specified in the Steering Committee charter. Members will agree their commitment to the charter in writing prior to the start of the study.

19.2 Conduct of Study and Ethical Considerations

This clinical study will be conducted in accordance with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in compliance with this protocol, Good Clinical Practice (ICH E6 (R2)), and designated SOPs. The study will also adhere to all applicable national laws, including the Swiss ClinO relevant to the use of investigational new drugs in the country of conduct.

Before initiating a study, the Investigator should have written and dated approval/favourable opinion from the Ethics Committee (EC), as required by the Clinical Trials Regulation (CTR) for EU Member States or the ClinO for Switzerland. This approval should cover the study protocol (including any amendments), the written informed consent form and updates, patient recruitment procedures (e.g. advertisements), and any other written information to be provided to patients. The approval will be documented in writing, with reference to the final protocol number and date. Details of the IEC's constitution including names of its members and their function in the committee (e.g. chairman, specialist, lay-member) should be made available to the Sponsor for inclusion in the Trial Master File.

During the study all documents that are subject to review should be provided to the EC by the Sponsor or the Investigator in line with national provisions.

19.3 Responsibilities

The responsibilities of the Investigator, Monitor and Sponsor regarding data handling of data, storage of data, study planning, assessment and quality assurance are regulated by the recommendations in "ICH Topic E6(R2) Guideline for Good Clinical Practice" of the "International Conference on Harmonisation" (ICH), which are fully applicable to this clinical trial.

19.4 General reporting obligation

The Sponsor shall apply for the authorization of the clinical study to the relevant regulatory authorities and ethics committees in each participating Member State prior to the study's start and provide written notification to the relevant local authorities. These notifications will ensure that the trial is fully compliant with applicable national and local regulations and with the requirements of the participating sites.

19.5 Financing and Insurance

The costs necessary for the conduct of the study will be agreed upon with each Investigator and will be documented in a separate financial agreement, signed by both the Investigator and the Sponsor (or the Sponsor's representative), prior to the study initiation.

The Sponsor has obtained subject insurance for all patients taking part in the trial, the Sponsor's. Each Investigator will receive a copy of the insurance certificate, along with the full insurance terms and conditions. This insurance coverage meets all requirements under applicable national regulations.

19.6 Personal Data and Data Protection

All data collected in the context of the clinical trial are subject to data protection in compliance with the CTR, GDPR, and Swiss data protection law. Cellerys maintains rigorous confidentiality standards by “coding” (all subjects enrolled in the clinical study as described in 19.11, ensuring no identifiable information is included in data sets transmitted to the Sponsor.

The Investigator must assure that patients’ anonymity is maintained and that their identities are protected from unauthorized access. It must be ensured that eCRFs or other documents (e.g. copies of reports on special findings) transmitted to the Sponsor contain only study-specific identifiers, such as patient number, year of birth and/or a random code.

The storage of data for statistical assessment will be performed only under the patient’s study identification. Only authorized personnel, such as the Investigator and designated study team members will have access to data that could identify participants.

All blood samples, which are analyzed by contract laboratories, are destroyed after the study's completion and/or during the analysis process, following standard operating procedures (SOPs).

Specimens available for biomarker discovery will be transferred to a new tube at Cellerys and labelled with a new random number, a process referred to as Double Coding to enhance confidentiality and will be stored for at least five years either at the Research Laboratory of Cellerys AG or, if delegated, at another laboratory that fulfills the required standards and has been designated by the Sponsor.

The autologous red blood cell product, and the IMP will be labelled with the patient's (full) name and date of birth. Access to personal data will be restricted to designated individuals at TETEC AG, Germany involved in the production of the IMP.

If it becomes necessary in the course of the study to identify a patient’s name for medical reasons, all individuals involved are obliged to maintain confidentiality.

19.6.1 Data Breach Management

In the event of a data breach, the Sponsor’s team will promptly assess the breach's nature and scope. If personal data is affected, the incident will be reported to relevant regulatory authorities as required by data protection laws. Participants will be promptly notified if there is a significant risk to their data privacy. Mitigation measures, including retraining personnel and enhancing monitoring systems, will be implemented to prevent future incidents. All details of the breach, including its impact, response actions, and preventive strategies, will be documented and reviewed to continuously improve data protection practices, ensuring compliance with regulations in each participating country.

19.7 Protocol Amendments

Any protocol amendments will be prepared by the Sponsor and assessed to determine whether they are “substantial” according to the applicable criteria and have to be submitted to the ethics committees and/or regulatory authorities to ensure compliance with EU Regulation No. 536/2014 (CTR), Swiss ClinO and all applicable national regulations across participating countries. Protocol amendments that affect subject safety, the study scope or the scientific integrity of the study must be approved prior to implementation.

Cellerys AG may implement measures at any time to address an immediate hazard to a subject, even if not in line with this protocol. In such cases, the appropriate regulatory authorities and/or ethics committees will be notified without delay and if applicable a substantial modification will subsequently be submitted.

If any protocol revision also necessitates changes to the Informed Consent Form (ICF), these updates will be implemented following the principles outlined in Section 9.1. This approach ensures that participants are informed of all study risks, benefits, and any new information impacting their participation, in alignment with ethical standards.

19.8 Investigator's Brochure

The Investigator shall be informed about the preclinical and clinical state of knowledge concerning the Investigational Medicinal Products.

In the present study this will be done by means of the Investigators' Brochure. This document should serve as the basis for the assessment of expectedness of an adverse reaction (see section 13.1.7).

19.9 Completion of (electronic) Case Report Forms

This study will be performed using an electronic Case Report Form (eCRF) for data collection. The electronic system will comply with Good Clinical Practice (GCP) and all applicable laws to ensure data protection, integrity, and confidentiality. The Investigator and study site staff will receive eCRF completion guidelines, training and support for the use of the eCRF. The electronic system will be validated according to regulatory standards to ensure accuracy, reliability, and consistent performance.

Data reported in the eCRF that are derived from source documents should be consistent with the source documents. Any discrepancies between the source documents and the eCRF entries should be explained.

All data entry, modification or deletion will be recorded in an electronic audit trail. The audit trail will automatically capture the following information: patient identifier, original data value, new data value, reason for data change, user who made the change and when the change was made. This audit trail will ensure transparency and traceability of all data changes, with means to locate prior values.

The system will be secured to prevent unauthorized access to the data or the system. This will include the unique user ID and password to enter or change data and role-based access controls to restrict system permissions. The Investigator will maintain a list of individuals who are authorized to enter, modify or review data.

All electronic data entered by the site (including an electronic audit trail) as well as computer hardware and software (for accessing the data) will be maintained or made available at the site in compliance with applicable record retention regulations, such as Article 58 of the CTR. The computerized system is able to generate accurate and complete copies of the trial records in human-readable form for inspection, review and copying by regulatory authorities, as well as by monitors or auditors authorized by the Sponsor.

Following data entry into the eCRF, the Investigator or a designated Study Physician will review and verify the accuracy of each patient's data. The validity of the data will be confirmed through the use of an electronic signature, which will comply with regulatory standards for electronic signatures.

The Sponsor will retain the original eCRF data and audit trail. A copy of all completed eCRFs with history of data discrepancies and audit trail will be provided to the Investigator.

19.10 Archiving

Essential documents are to be retained for either:

- the periods required by ICH-GCP; that is for at least 2 years after the last approval of a marketing application in an ICH region when there are no further pending or contemplated marketing applications in an ICH region or for at least 2 years after formal discontinuation of clinical development of the Investigational Medicinal Product (CPMP/ICH/135/95);

or

- the periods defined in the relevant national legal requirements, that is for at least 25 years after completion or termination of the clinical study in the EU community as required by the Clinical Trial Regulation536/2014 and for at least 30 years after completion or termination of the clinical study as required by the Federal Act on Medicinal Products and Medical Devices in Switzerland.

The final report shall be retained for at least 2 years after the Investigational Medicinal Products are removed from the last market.

The informed consent forms and all the original (raw) data are to be retained by the Investigator as required by any institutional requirements or local laws or regulations *(e.g. for at least 25 years)*.

19.11 Confidentiality

The aim, content and results of this study are to be treated as confidential by all persons involved in the clinical trial.

The Sponsor will maintain confidentiality standards in compliance with CTR and Swiss regulations and Section 19.6 of this protocol, which also includes information on data protection. Each patient enrolled in the study is assigned of a unique patient identification number to protect patient confidentiality. This means that patient names or other directly identifiable information are not included in data sets transmitted to the Sponsor or its representatives.

Patient medical information obtained in this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law. Data generated by this study must be available for inspection upon request by national and local health authorities, Sponsor monitors, representatives, collaborators, and the IRB/EC for each study site, in compliance with applicable regulations.

Study data, which may include infection data, may be shared with government agencies, companies, or other groups not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnosing disease.

Given the complexity and exploratory nature of biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available on study data publication.

20 FINAL REPORT AND PUBLICATION POLICY

After the completion of the study (as defined in section 15.2), a clinical study report (CSR) will be prepared by the Sponsor or its delegate in accordance with applicable regulatory requirements, including EU Regulation 536/2014 and other relevant guidelines. The CSR will include a statistical analysis and an appraisal of the results from a scientific and medical viewpoint, ensuring transparency and quality reporting. This report shall be based on the items listed in this study protocol.

The Sponsor retains the rights to all data and information generated by this study and will ensure that the study is registered and results are disclosed in a publicly accessible database such as Clinicaltrials.gov and EudraCT and other registries as required by both EU and Swiss regulations, where applicable. The publication or presentation of trial results or any other trial-related data is permitted only upon consultation and written agreement of the Sponsor. The Sponsor retains the right to review and edit all proposed manuscripts, abstracts, publications, and presentations based upon this study or its results prior to submission to any organization, business, agency, person, publisher, society, or other entity.

The results of this study are expected to be presented at scientific meetings and/or published in peer-reviewed scientific journals. Any formal presentation or publication of data from this trial will be considered as a joint publication by the Investigator(s) and appropriate Sponsor personnel. Authorship for any publication will be determined in line with the International Committee of Medical Journal Editors (ICMJE) recommendations and with due consideration of the recruitment contributions from each investigational site.

Data derived from biomarker specimen analysis on individual subjects will not be provided to Study Investigators, except where explicitly stipulated in a study protocol. Exceptions may be granted (e.g. if biomarker data would be linked to safety issues). Any inventions and resulting patents, improvements and/or know-how originating from the use of the biomarkers will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

21 FURTHER REQUIREMENTS AND GENERAL INFORMATION

21.1 External Contract Organizations

Cellerys AG will ensure oversight of any study-related duties and functions delegated to external organizations, in accordance with applicable regulatory requirements, including but not limited to EU and Swiss regulations. All duties and functions transferred to such external contract organizations will be specified in writing, and the Sponsor retains responsibility for the quality and integrity of all trial-related activities, ensuring compliance with the CTR and Good Clinical Practice (GCP) standards.

21.1.1 Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, site monitoring, data management and safety reporting (including Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)) in accordance with applicable regulatory requirements, including Article 42 of the CTR. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and study site staff, ensuring their compliance with the protocol and regulatory requirements.

21.1.2 Electronic Data Capture

Subject information will be captured and managed by study sites using eCRFs via a web-based electronic data capture (EDC) tool developed by the EDC vendor and configured by the CRO. The EDC system must comply with data protection regulations (including GDPR) and ensure the integrity, confidentiality, and security of subject data. The Sponsor will ensure oversight of the EDC system to guarantee data accuracy, traceability, and proper handling of trial data.

21.1.3 Central Laboratories for Laboratory Assessments

Central laboratories selected by Cellerys AG will be responsible for the analysis of blood chemistry, hematology, urine samples as well as other biological such as HLA-typing collected for this study. Antigen specificity and biomarkers will be analyzed at Cellerys AG. Contracted laboratories will operate under a contractual agreement that ensures compliance with GCP and relevant quality standards. The Sponsor will oversee the quality of laboratory assessments and ensure that the data provided by these laboratories, including those analyzed at Cellerys AG, meet the requirements of the study and regulatory authorities.

21.1.4 Central Facility for Other Assessments

A central MRI reader has been selected to read and interpret all MRI scans for this study. The Sponsor will ensure oversight of the MRI reader's activities to maintain the quality, consistency, and regulatory compliance of the imaging data used in the study.

22 REFERENCES

[1] C.W. Noonan, S.J. Kathman, and M.C. White, Prevalence estimates for MS in the United States and evidence of an increasing trend for women. Neurology 58 (2002) 136-8.

[2] P. Browne, D. Chandraratna, C. Angood, H. Tremlett, C. Baker, B.V. Taylor, and A.J. Thompson, Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology 83 (2014) 1022-4.

[3] H. Wekerle, Immunopathogenesis of multiple sclerosis. Acta Neurol (Napoli) 13 (1991) 197-204.

[4] F.D. Lublin, S.C. Reingold, J.A. Cohen, G.R. Cutter, P.S. Sorensen, A.J. Thompson, J.S. Wolinsky, L.J. Balcer, B. Banwell, F. Barkhof, B. Bebo, Jr., P.A. Calabresi, M. Clanet, G. Comi, R.J. Fox, M.S. Freedman, A.D. Goodman, M. Inglese, L. Kappos, B.C. Kieseier, J.A. Lincoln, C. Lubetzki, A.E. Miller, X. Montalban, P.W. O'Connor, J. Petkau, C. Pozzilli, R.A. Rudick, M.P. Sormani, O. Stuve, E. Waubant, and C.H. Polman, Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83 (2014) 278-86.

[5] A.J. Thompson, B.L. Banwell, F. Barkhof, W.M. Carroll, T. Coetzee, G. Comi, J. Correale, F. Fazekas, M. Filippi, M.S. Freedman, K. Fujihara, S.L. Galetta, H.P. Hartung, L. Kappos, F.D. Lublin, R.A. Marrie, A.E. Miller, D.H. Miller, X. Montalban, E.M. Mowry, P.S. Sorensen, M. Tintore, A.L. Traboulsee, M. Trojano, B.M.J. Uitdehaag, S. Vukusic, E. Waubant, B.G. Weinshenker, S.C. Reingold, and J.A. Cohen, Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17 (2018) 162-173.

[6] C. International Multiple Sclerosis Genetics, C. Wellcome Trust Case Control, S. Sawcer, G. Hellenthal, M. Pirinen, C.C. Spencer, N.A. Patsopoulos, L. Moutsianas, A. Dilthey, Z. Su, C. Freeman, S.E. Hunt, S. Edkins, E. Gray, D.R. Booth, S.C. Potter, A. Goris, G. Band, A.B. Oturai, A. Strange, J. Saarela, C. Bellenguez, B. Fontaine, M. Gillman, B. Hemmer, R. Gwilliam, F. Zipp, A. Jayakumar, R. Martin, S. Leslie, S. Hawkins, E. Giannoulatou, S. D'Alfonso, H. Blackburn, F. Martinelli Boneschi, J. Liddle, H.F. Harbo, M.L. Perez, A. Spurkland, M.J. Waller, M.P. Mycko, M. Ricketts, M. Comabella, N. Hammond, I. Kockum, O.T. McCann, M. Ban, P. Whittaker, A. Kemppinen, P. Weston, C. Hawkins, S. Widaa, J. Zajicek, S. Dronov, N. Robertson, S.J. Bumpstead, L.F. Barcellos, R. Ravindrarajah, R. Abraham, L. Alfredsson, K. Ardlie, C. Aubin, A. Baker, K. Baker, S.E. Baranzini, L. Bergamaschi, R. Bergamaschi, A. Bernstein, A. Berthele, M. Boggild, J.P. Bradfield, D. Brassat, S.A. Broadley, D. Buck, H. Butzkueven, R. Capra, W.M. Carroll, P. Cavalla, E.G. Celius, S. Cepok, R. Chiavacci, F. Clerget-Darpoux, K. Clysters, G. Comi, M. Cossburn, I. Cournu-Rebeix, M.B. Cox, W. Cozen, B.A. Cree, A.H. Cross, D. Cusi, M.J. Daly, E. Davis, P.I. de Bakker, M. Debouverie, B. D'Hooghe M, K. Dixon, R. Dobosi, B. Dubois, D. Ellinghaus, et al., Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 476 (2011) 214-9.

[7] M. Sospedra, and R. Martin, Immunology of multiple sclerosis. Annu Rev Immunol 23 (2005) 683-747.

[8] J. Hillert, and O. Olerup, Hla and Ms. Neurology 43 (1993) 2426-2426.

[9] K. Ota, M. Matsui, E.L. Milford, G.A. Mackin, H.L. Weiner, and D.A. Hafler, T-cell recognition of an immunodominant myelin basic protein epitope in multiple sclerosis. Nature 346 (1990) 183-7.

[10] K.W. Wucherpfennig, I. Catz, S. Hausmann, J.L. Strominger, L. Steinman, and K.G. Warren, Recognition of the immunodominant myelin basic protein peptide by autoantibodies and HLA-DR2-restricted T cell clones from multiple sclerosis patients - Identity of key contact residues in the B-cell and T-cell epitopes. J Clin Invest 100 (1997) 1114-1122.

[11] N. Kerlero de Rosbo, M. Hoffman, I. Mendel, I. Yust, J. Kaye, R. Bakimer, S. Flechter, O. Abramsky, R. Milo, A. Karni, and A. Ben-Nun, Predominance of the autoimmune response to myelin oligodendrocyte glycoprotein (MOG) in multiple sclerosis: reactivity to the extracellular domain of MOG is directed against three main regions. Eur J Immunol 27 (1997) 3059-69.

[12] A. Lutterotti, S. Yousef, A. Sputtek, K.H. Sturner, J.P. Stellmann, P. Breiden, S. Reinhardt, C. Schulze, M. Bester, C. Heesen, S. Schippling, S.D. Miller, M. Sospedra, and R. Martin, Antigen-specific tolerance by autologous myelin peptide-coupled cells: a phase 1 trial in multiple sclerosis. Sci Transl Med 5 (2013) 188ra75.

[13] B. Bielekova, B. Goodwin, N. Richert, I. Cortese, T. Kondo, G. Afshar, B. Gran, J. Eaton, J. Antel, J.A. Frank, H.F. McFarland, and R. Martin, Encephalitogenic potential of the myelin basic protein peptide (amino acids 83-99) in multiple sclerosis: Results of a phase II clinical trial with an altered peptide ligand. Nature Medicine 6 (2000) 1167-1175.

[14] R. Planas, R. Santos, P. Tomas-Ojer, C. Cruciani, A. Lutterotti, W. Faigle, N. Schaeren-Wiemers, C. Espejo, H. Eixarch, C. Pinilla, R. Martin, and M. Sospedra, GDP-L-fucose synthase is a CD4(+) T cell-specific autoantigen in DRB3*02:02 patients with multiple sclerosis. Sci Transl Med 10 (2018).

[15] I. Jelcic, F. Al Nimer, J. Wang, V. Lentsch, R. Planas, I. Jelcic, A. Madjovski, S. Ruhrmann, W. Faigle, K. Frauenknecht, C. Pinilla, R. Santos, C. Hammer, Y. Ortiz, L. Opitz, H. Gronlund, G. Rogler, O. Boyman, R. Reynolds, A. Lutterotti, M. Khademi, T. Olsson, F. Piehl, M. Sospedra, and R. Martin, Memory B Cells Activate Brain-Homing, Autoreactive CD4(+) T Cells in Multiple Sclerosis. Cell 175 (2018) 85-100 e23.

[16] M. Sospedra, Y.D. Zhao, M. Giulianotti, R. Simon, C. Pinilla, and R. Martin, Combining positional scanning peptide libraries, HLA-DR transfectants and bioinformatics to dissect the epitope spectrum of HLA class II cross-restricted CD4+T cell clones. J Immunol Methods 353 (2010) 93-101.

[17] C. Cruciani, M. Puthenparampil, P. Tomas-Ojer, I. Jelcic, M.J. Docampo, R. Planas, P. Manogaran, R. Opfer, C. Wicki, M. Reindl, I. Jelcic, A. Lutterotti, R. Martin, and M. Sospedra, T-Cell Specificity Influences Disease Heterogeneity in Multiple Sclerosis. Neurol Neuroimmunol Neuroinflamm 8 (2021).

[18] A.A. Vandenbark, M. Vainiene, K. Ariail, S.D. Miller, and H. Offner, Prevention and treatment of relapsing autoimmune encephalomyelitis with myelin peptide-coupled splenocytes. J Neurosci Res 45 (1996) 430-8.

[19] M. Krogsgaard, K.W. Wucherpfennig, B. Cannella, B.E. Hansen, A. Svejgaard, J. Pyrdol, H. Ditzel, C. Raine, J. Engberg, and L. Fugger, Visualization of myelin basic protein (MBP) T cell epitopes in multiple sclerosis lesions using a monoclonal antibody specific for the human histocompatibility leukocyte antigen (HLA)-DR2-MBP 85-99 complex. J Exp Med 191 (2000) 1395-412.

[20] G.R. Cutter, M.L. Baier, R.A. Rudick, D.L. Cookfair, J.S. Fischer, J. Petkau, K. Syndulko, B.G. Weinshenker, J.P. Antel, C. Confavreux, G.W. Ellison, F. Lublin, A.E. Miller, S.M. Rao, S. Reingold, A. Thompson, and E. Willoughby, Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 122 (Pt 5) (1999) 871-82.

[21] B.T. Fife, I. Guleria, M. Gubbels Bupp, T.N. Eagar, Q. Tang, H. Bour-Jordan, H. Yagita, M. Azuma, M.H. Sayegh, and J.A. Bluestone, Insulin-induced remission in new-onset NOD mice is maintained by the PD-1-PD-L1 pathway. J Exp Med 203 (2006) 2737-47.

[22] H. Braley-Mullen, J.G. Tompson, G.C. Sharp, and M. Kyriakos, Suppression of experimental autoimmune thyroiditis in guinea pigs by pretreatment with thyroglobulin-coupled spleen cells. Cell Immunol 51 (1980) 408-13.

[23] H.S. Dua, D.S. Gregerson, and L.A. Donoso, Inhibition of experimental autoimmune uveitis by retinal photoreceptor antigens coupled to spleen cells. Cell Immunol 139 (1992) 292-305.

[24] S.K. Gregorian, L. Clark, E. Heber-Katz, E.P. Amento, and A. Rostami, Induction of peripheral tolerance with peptide-specific anergy in experimental autoimmune neuritis. Cell Immunol 150 (1993) 298-310.

[25] K. Kaneko, A.E. Morelli, Z. Wang, and A.W. Thomson, Alloantigen presentation by ethylcarbodiimide-treated dendritic cells induces T cell hyporesponsiveness, and prolongs organ graft survival. Clin Immunol 108 (2003) 190-8.

[26] C.B. Smarr, C.L. Hsu, A.J. Byrne, S.D. Miller, and P.J. Bryce, Antigen-fixed leukocytes tolerize Th2 responses in mouse models of allergy. J Immunol 187 (2011) 5090-8.

[27] S.D. Miller, D.M. Turley, and J.R. Podojil, Antigen-specific tolerance strategies for the prevention and treatment of autoimmune disease. Nat Rev Immunol 7 (2007) 665-77.
[28] D. Turley, Dual mechanism for antigen-specific peripheral tolerance induction as a therapy for experimental autoimmune encephalomyelitis, ProQuest Dissertations & Theses - Gradworks, Northwestern University, http://gradworks.proquest.com/33/33/3333009.html, 2007.
[29] T.N. Eagar, N.J. Karandikar, J.A. Bluestone, and S.D. Miller, The role of CTLA-4 in induction and maintenance of peripheral T cell tolerance. Eur J Immunol 32 (2002) 972-81.
[30] W.J. Karpus, K.J. Kennedy, W.S. Smith, and S.D. Miller, Inhibition of relapsing experimental autoimmune encephalomyelitis in SJL mice by feeding the immunodominant PLP139-151 peptide. J Neurosci Res 45 (1996) 410-23.
[31] M.K. Kennedy, M.C. Dal Canto, J.L. Trotter, and S.D. Miller, Specific immune regulation of chronic-relapsing experimental allergic encephalomyelitis in mice. J Immunol 141 (1988) 2986-93.
[32] M.K. Kennedy, L.J. Tan, M.C. Dal Canto, and S.D. Miller, Regulation of the effector stages of experimental autoimmune encephalomyelitis via neuroantigen-specific tolerance induction. J Immunol 145 (1990) 117-26.
[33] M.K. Kennedy, L.J. Tan, M.C. Dal Canto, V.K. Tuohy, Z.J. Lu, J.L. Trotter, and S.D. Miller, Inhibition of murine relapsing experimental autoimmune encephalomyelitis by immune tolerance to proteolipid protein and its encephalitogenic peptides. J Immunol 144 (1990) 909-15.
[34] L. Pope, P.Y. Paterson, and S.D. Miller, Antigen-specific inhibition of the adoptive transfer of experimental autoimmune encephalomyelitis in Lewis rats. J Neuroimmunol 37 (1992) 177-89.
[35] L.J. Tan, M.K. Kennedy, M.C. Dal Canto, and S.D. Miller, Successful treatment of paralytic relapses in adoptive experimental autoimmune encephalomyelitis via neuroantigen-specific tolerance. J Immunol 147 (1991) 1797-802.
[36] L.J. Tan, M.K. Kennedy, and S.D. Miller, Regulation of the effector stages of experimental autoimmune encephalomyelitis via neuroantigen-specific tolerance induction. II. Fine specificity of effector T cell inhibition. J Immunol 148 (1992) 2748-55.
[37] C.L. Vanderlugt, K.L. Neville, K.M. Nikcevich, T.N. Eagar, J.A. Bluestone, and S.D. Miller, Pathologic role and temporal appearance of newly emerging autoepitopes in relapsing experimental autoimmune encephalomyelitis. J Immunol 164 (2000) 670-8.
[38] X.M. Su, and S. Sriram, Treatment of chronic relapsing experimental allergic encephalomyelitis with the intravenous administration of splenocytes coupled to encephalitogenic peptide 91-103 of myelin basic protein. J Neuroimmunol 34 (1991) 181-90.
[39] A.A. Vandenbark, B. Celnik, M. Vainiene, S.D. Miller, and H. Offner, Myelin antigen-coupled splenocytes suppress experimental autoimmune encephalomyelitis in Lewis rats through a partially reversible anergy mechanism. J Immunol 155 (1995) 5861-7.
[40] C.E. Smith, and S.D. Miller, Multi-peptide coupled-cell tolerance ameliorates ongoing relapsing EAE associated with multiple pathogenic autoreactivities. J Autoimmun 27 (2006) 218-31.
[41] C.L. Vanderlugt, and S.D. Miller, Epitope spreading in immune-mediated diseases: implications for immunotherapy. Nat Rev Immunol 2 (2002) 85-95.
[42] J. Chataway, K. Martin, K. Barrell, B. Sharrack, P. Stolt, D.C. Wraith, and A.-M.S. Group, Effects of ATX-MS-1467 immunotherapy over 16 weeks in relapsing multiple sclerosis. Neurology 90 (2018) e955-e962.
[43] H. Garren, W.H. Robinson, E. Krasulova, E. Havrdova, C. Nadj, K. Selmaj, J. Losy, I. Nadj, E.W. Radue, B.A. Kidd, J. Gianettoni, K. Tersini, P.J. Utz, F. Valone, L. Steinman, and B.H.T.S. Group, Phase 2 trial of a DNA vaccine encoding myelin basic protein for multiple sclerosis. Ann Neurol 63 (2008) 611-20.
[44] A. Walczak, M. Siger, A. Ciach, M. Szczepanik, and K. Selmaj, Transdermal application of myelin peptides in multiple sclerosis treatment. JAMA Neurol 70 (2013) 1105-9.

[45] X. Luo, K.L. Pothoven, D. McCarthy, M. DeGutes, A. Martin, D.R. Getts, G. Xia, J. He, X. Zhang, D.B. Kaufman, and S.D. Miller, ECDI-fixed allogeneic splenocytes induce donor-specific tolerance for long-term survival of islet transplants via two distinct mechanisms. Proc Natl Acad Sci U S A 105 (2008) 14527-32.

[46] B. Bielekova, M.H. Sung, N. Kadom, R. Simon, H. McFarland, and R. Martin, Expansion and functional relevance of high-avidity myelin-specific CD4+ T cells in multiple sclerosis. J Immunol 172 (2004) 3893-904.

[47] B. Bielekova, N. Richert, T. Howard, G. Blevins, S. Markovic-Plese, J. McCartin, J.A. Frank, J. Wurfel, J. Ohayon, T.A. Waldmann, H.F. McFarland, and R. Martin, Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proc Natl Acad Sci U S A 101 (2004) 8705-8.

[48] J. Gold, M. Marta, U.C. Meier, T. Christensen, D. Miller, D. Altmann, D. Holden, L. Bianchi, R. Adiutori, D. MacManus, T. Yousry, K. Schmierer, B. Turner, and G. Giovannoni, A phase II baseline versus treatment study to determine the efficacy of raltegravir (Isentress) in preventing progression of relapsing remitting multiple sclerosis as determined by gadolinium-enhanced MRI: The INSPIRE study. Mult Scler Relat Disord 24 (2018) 123-128.

[49] K.H. Sturner, J.P. Stellmann, J. Dorr, F. Paul, T. Friede, S. Schammler, S. Reinhardt, S. Gellissen, G. Weissflog, T.D. Faizy, O. Werz, S. Fleischer, L.A.I. Vaas, F. Herrmann, O. Pless, R. Martin, and C. Heesen, A standardised frankincense extract reduces disease activity in relapsing-remitting multiple sclerosis (the SABA phase IIa trial). J Neurol Neurosurg Psychiatry 89 (2018) 330-338.

[50] C.H. Polman, S.C. Reingold, F. Barkhof, P.A. Calabresi, M. Clanet, J.A. Cohen, G.R. Cutter, M.S. Freedman, L. Kappos, F.D. Lublin, H.F. McFarland, L.M. Metz, A.E. Miller, X. Montalban, P.W. O'Connor, H. Panitch, J.R. Richert, J. Petkau, S.R. Schwid, M.P. Sormani, A.J. Thompson, B.G. Weinshenker, and J.S. Wolinsky, Ethics of placebo-controlled clinical trials in multiple sclerosis - A reassessment. Neurology 70 (2008) 1134-1140.

[51] H.F. Mcfarland, J.A. Frank, P.S. Albert, M.E. Smith, R. Martin, J.O. Harris, N. Patronas, H. Maloni, and D.E. Mcfarlin, Using Gadolinium-Enhanced Magnetic-Resonance-Imaging Lesions to Monitor Disease-Activity in Multiple-Sclerosis. Annals of Neurology 32 (1992) 758-766.

[52] P.S. Albert, H.F. McFarland, M.E. Smith, and J.A. Frank, Time series for modelling counts from a relapsing-remitting disease: application to modelling disease activity in multiple sclerosis. Stat Med 13 (1994) 453-66.

[53] J.S. Fischer, R.A. Rudick, G.R. Cutter, and S.C. Reingold, The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. Mult Scler 5 (1999) 244-50.

[54] P. Feys, I. Lamers, G. Francis, R. Benedict, G. Phillips, N. LaRocca, L.D. Hudson, R. Rudick, and C. Multiple Sclerosis Outcome Assessments, The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler 23 (2017) 711-720.

[55] R.W. Motl, J.A. Cohen, R. Benedict, G. Phillips, N. LaRocca, L.D. Hudson, R. Rudick, and C. Multiple Sclerosis Outcome Assessments, Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler 23 (2017) 704-710.

[56] R.H. Benedict, J. DeLuca, G. Phillips, N. LaRocca, L.D. Hudson, R. Rudick, and C. Multiple Sclerosis Outcome Assessments, Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler 23 (2017) 721-733.

[57] A. Lutterotti, S. Yousef, A. Sputtek, K. Stürner, J. Stellmann, P. Breiden, S. Reinhardt, C. Schulze, M. Bester, C. Heesen, S. Schippling, S. Miller, M. Sospedra, and R. Martin, Antigen-specific Tolerance by Autologous Myelin Peptide-Coupled Cells – A Phase I Trial in Multiple Sclerosis. Science Translational Medicine 5 (2013).

[58] C. Lebrun, M. Debouverie, P. Vermersch, P. Clavelou, L. Rumbach, J. de Seze, S. Wiertlevski, G. Defer, O. Gout, F. Berthier, and A. Danzon, Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis. Mult Scler 14 (2008) 399-405.

[59] 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.

[60] M.P. Sormani, P.D. Molyneux, F. Barkhof, D.H. Miller, and M. Filippi, MRI enhancing lesion frequency from patients with MS enrolled in the placebo arms of clinical trials or in natural history studies. Magn Reson Imaging 17 (1999) 1236-7.

23 SIGNATURES

Sponsor Signature Page

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

PROTOCOL: RED4MS

VERSION: 7.0

DATE: 2025-05-09

Clinical Study Protocol was approved by:

9 MAY 2025
Date

[redacted]
(CMO and Medical Expert, Cellerys AG)

9 May 2025
Date

[redacted]
(Statistician)

Investigator Signature Page

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

PROTOCOL: RED4MS

VERSION: 7.0

DATE: 2025-05-09

SPONSOR: Cellerys AG

I have read the foregoing protocol and agree to conduct this study in accordance with the protocol, the ICH GCP guidelines, the applicable laws and regulatory requirements. I will ensure that all personnel involved in this study under my supervision are informed of their responsibilities and obligations.

I will maintain confidentiality of all information obtained from participation in this study unless otherwise agreed in writing.

.....
Date

.....
Principal Investigator's Signature

.....
Principal Investigator's Name (print)

.....
Site No.

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or their designee.

24 APPENDICES

24.1 Exploratory Biomarker Study

Introduction

Knowledge about the mechanisms of action of the different tolerance-inducing approaches in MS is limited, not only in animal models, but even more so in patients (Lutterotti et al., 2021). Different from type 1 diabetes (T1D; antibodies against islet cell antigens), there is no diagnostic biomarker for MS; there is also no response biomarker in MS like glucose levels as a direct measure for remaining beta cell function in T1D. Furthermore, there is no T cell/cell-mediated immunity biomarker for any autoimmune disease, and not a single validated assay for any of the aspects that is important to consider for tolerance induction (phenotypic alterations, pharmacodynamic-related biomarkers (e.g. interleukin-10, IL-10), antigen specificity testing, Treg phenotype and numbers). MRI outcome measures and recently also the CNS damage-related marker neurofilament light chain (NfL) are validated and estimates can be built on them, but this is not possible for any of the other markers (Disanto et al., 2017) (Kuhle et al., 2019). RED4MS offers the unique opportunity of gaining insights into tolerization mechanisms including biomarkers validation and discovery.

The primary objective of the RED4MS Phase Ib study is to assess the safety and tolerability of peptide-coupled RBC tolerization in patients with MS.

In addition to safety assessments, exploratory biomarker analyses will be conducted based on blood samples to investigate immunological effects of the treatment. These analyses are intended to support further understanding of the treatment's biological activity and inform the design of future studies.

[redacted]

Biomarker samples (serum and plasma) will be obtained at different time points of the study protocol. The bio samples (serum, plasma) will be collected by standard venipuncture.

Sampling procedures and shipment conditions instructions are described in the Logistics Manual, which will be provided to each study site.

Sample handling

Biomarker samples will be obtained from all patients who have given their consent in the study. Sampling for the biomarker research is contingent on written informed consent and review and approval for the exploratory biomarker assessments by the appropriate regulatory authorities (depending on the country where the study is performed) and the ethics committees (ECs). If a regulatory or EC does not approve the sampling for the exploratory biomarker analyses, this part of the study will not be conducted at the respective site.

Biosamples collected for biomarker research will be stored for at least five years unless patients request that they are destroyed, or regulatory authorities require a shorter storage period for the specimens. The samples will be stored either at the laboratory of Cellerys or, if delegated, at a laboratory appointed by the Sponsor that meets the required regulatory and quality standards.

Participants have the right to withdraw their specimen at any time for any reason. Upon withdrawal, all untested biomarker samples will be destroyed. However, the information obtained from analyzed samples up to the time of withdrawal will continue to be used. Withdrawal the biomarker sampling does not affect participation in the study.

All samples provided to Cellerys AG will be coded, so that no conclusions can be drawn about individual patients. Incoming samples at Cellerys will be processed, labelled and stored following standard operating procedures. The cryopreserved samples will be stored at -80°C, cells at -196°C in the laboratory of the Cellerys. All steps and storage locations in the respective freezers or liquid nitrogen tanks are recorded in a GLP-compliant lab software (eLab, elabjournal.com) with an audit trail to meet ISO standards. The access to sample storage rooms is restricted to authorized persons only. The freezers and liquid nitrogen tanks are equipped with temperature sensors, for continuous monitoring. An emergency power unit and alarm plan ensure their proper storage in case of power failure.

Any data obtained from the sample will be stored in at least 3 different locations: a physical NAS server, the ISO-certified Microsoft Sharepoint Cloud, and a backup provided by an IT provider. The access to this data is limited to authorized lab members only.

All data stored within eLab is saved under ISO approved measures that ensure data traceability and integrity. Each sample's information is linked to analysis results, with all deviations noted. Raw files will be linked to their respective analyses and any further changes made to any analysis are documented through eLab auditable software. If such changes are made, they will be stored and written as a new version and annotated with details of who has made the changes to the analysis. Data arising from sample analysis will be subject to the confidentiality standards described in Section 19.11 of the study protocol.

If required for analysis, samples can be distributed to external collaborating laboratories that comply with relevant data privacy laws. Cellerys will ensure that all data transfers to collaborating labs are conducted in accordance with applicable legislations on data privacy.

Data protection and control of data access are integral parts of sample management processes.

Data analysis

The mechanistic/biomarker program has exploratory and hypothesis-generating character.

The main goals include:

- To explore immunological and biomarker changes associated with administration of CLS12311,
- To assess whether specific biomarker patterns are associated with safety outcomes,
- To gather preliminary data for potential identification of responder characteristics.

Descriptive biostatistics methods will be applied to each program component, e.g. the variation of percentages of certain immune cell subtypes or a biomarker such as NfL.

The analysis of the biomarker samples will be performed on samples provided to Cellerys' laboratory with study IDs, without personal identifiers, ensuring compliance with data privacy requirements. The result of the biomarker analyses may only be linked to individual patient identifiers during the study conduct. Linkage to individual data will only occur after database lock and completion of the primary safety analysis, if needed.

Biomarker data will not be included in the formal safety analysis of the this study. In addition, biomarker data will not affect patient management.

Given the complexity and exploratory nature of biomarker analyses, results will not be provided to study investigators or patients unless required by law. Results will be presented in a separate exploratory report, which may be included as an appendix to the Clinical Study Report (CSR).

Any inventions and resulting patents, improvements and / or know- how originating from the use of the biomarker will become and remain the exclusive and unburdened property of Cellerys, except when agreed otherwise.

References

Bronge, M., Högelin, K.A., Thomas, O.G., Ruhrmann, S., Carvalho-Queiroz, C., Nilsson, O.B., Kaiser, A., Zeitelhofer, M., Holmgren, E., Linnerbauer, M., Adzemovic, M.Z., Hellström, C., Jelcic, I., Liu, H., Nilsson, P., Hillert, J., Brundin, L., Fink, K., Kockum, I., Tengvall, K., Martin, R., Tegel, H., Gräslund, T., Al Nimer, F., Guerreiro-Cacais, A.O., Khademi, M., Gafvelin, G., Olsson, T., Grönlund, H., 2022. Identification of four novel T cell autoantigens and personal autoreactive profiles in multiple sclerosis. Sci. Adv. 8, eabn1823. https://doi.org/10.1126/sciadv.abn1823

Bronge, M., Kaiser, A., Carvalho-Queiroz, C., Nilsson, O.B., Ruhrmann, S., Holmgren, E., Olsson, T., Gafvelin, G., Grönlund, H., 2019. Sensitive detection of antigen-specific T-cells using bead-bound antigen for in vitro re-stimulation. MethodsX 6, 1635–1641. https://doi.org/10.1016/j.mex.2019.07.004

Disanto, G., Barro, C., Benkert, P., Naegelin, Y., Schädelin, S., Giardiello, A., Zecca, C., Blennow, K., Zetterberg, H., Leppert, D., Kappos, L., Gobbi, C., Kuhle, J., the Swiss Multiple Sclerosis Cohort Study Group, 2017. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis: Serum NfL as a Biomarker in MS. Ann. Neurol. 81, 857–870. https://doi.org/10.1002/ana.24954

Docampo, M.J., Lutterotti, A., Sospedra, M., Martin, R., 2022. Mechanistic and Biomarker Studies to Demonstrate Immune Tolerance in Multiple Sclerosis. Front. Immunol. 12, 787498. https://doi.org/10.3389/fimmu.2021.787498

Kuhle, J., Kropshofer, H., Haering, D.A., Kundu, U., Meinert, R., Barro, C., Dahlke, F., Tomic, D., Leppert, D., Kappos, L., 2019. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. Neurology 92, e1007–e1015. https://doi.org/10.1212/WNL.0000000000007032

Lutterotti, A., Hayward-Koennecke, H., Sospedra, M., Martin, R., 2021. Antigen-Specific Immune Tolerance in Multiple Sclerosis - Promising Approaches and How to Bring Them to Patients. Front. Immunol. 12, 640935. https://doi.org/10.3389/fimmu.2021.64093

24.2 Acute management of severe allergic reactions (anaphylaxis)

Acute management of severe systemic allergic reactions (anaphylaxis, grade II-IV)	
Anaphylaxis is a life-threatening emergency IF WORKING ALONE, CALL FOR ASSISTANCE	
1	Stop the CLS12311 infusion.
2	Give oxygen Lie patient flat and give oxygen by face mask at the highest possible flow rate (> 6 L/minute).
3	Give adrenaline Immediately inject adrenaline 1:1000 intramuscularly in the lateral thigh. < 50 kg . . . . . give 0.25 - 0.50 mL > 50 kg . . . . . give 0.50 mL (See Notes 1, 2)
4	Start rapid fluid resuscitation Establish an intravenous line and infuse normal saline or Hartmann's solution (20 mL/kg). Continue as necessary.
5	Give further adrenaline If necessary, repeat intramuscular dose every 5 minutes. Large doses of adrenaline may be needed, up to a maximum of 5 mL (5 mg). If the patient remains shocked after two intramuscular doses, consider an adrenaline infusion to restore blood pressure. (See Notes 3, 4)
6	Ventilate If there is severe respiratory and circulatory collapse or coma, ventilate the patient. (See Note 5)
7	Additional measures Bronchodilators . . . . . For bronchospasm, give salbutamol or terbutaline by nebuliser, or aerosol with spacer device. In severe cases use continuously. Corticosteroids . . . . . Give hydrocortisone 2-6 mg/kg or dexamethasone 0.1-0.4 mg/kg intravenously. (See Note 6) Nebulised adrenaline. . . . . (5 mL of 1:1000) May be tried in laryngeal edema and may ease upper airway obstruction. However, do not delay intubation if upper airway obstruction is progressive.
8	Supportive treatment Observe vital signs frequently and, if possible, monitor electrocardiogram and pulse oximetry. Keep patient in hospital for observation for at least 4-6 hours after the complete resolution of abnormal symptoms and signs, as biphasic reactions may occur. (See Note 7)

Notes

1. Adrenaline is life-saving and must be used promptly. Withholding adrenaline due to misplaced concerns of possible adverse effects can result in deterioration and death of the patient. It is safe and effective.
2. Adrenaline 1:1000 contains 1000 microgram in 1 mL (1 mg/mL). The volumes of adrenaline recommended for adults approximate to 5-10 microgram/kg.
3. If critical care facilities are not immediately available, give the following adrenaline infusion:
   - Mix 1 mg adrenaline (1 ampoule) in 1000 mL of normal saline
   - Start infusion at 5 mL/kg/hour (approx. 0.1 microgram/kg/minute)
   - Titrate rate up or down according to response.
4. Some cases are resistant to adrenaline, especially if the patient is taking beta blocking drugs. If adequate doses of adrenaline are not improving the situation, give glucagon 1-2 mg intravenously over 5 minutes.
5. Drug-assisted intubation for impending airway obstruction is a very high-risk procedure and should only be attempted by an expert.
6. Corticosteroids may modify the overall duration of a reaction and may prevent relapse. However, onset of action will be delayed. Never use these to the exclusion of adrenaline.
7. Keep patient in hospital longer if there is a history of asthma or previous allergy, or if the patient needed repeated doses of adrenaline. All patients must be followed up to investigate possible provoking factors and for further management.

Published as an insert to *Australian Prescriber* 2007, Vol.30, No.5.

Severity grading of anaphylactic reactions

Grade	Skin	Abdomen	Airways	Cardiovascular system
I	Itch Flush Urticaria Angioedema	–	–	–
II	Itch Flush Urticaria Angioedema	Nausea Cramps	Rhinorrhea Hoarseness Dyspnea	Tachycardia (increase by ≥ 20/min) Hypotension (decrease by 20mm Hg systolic pressure) Arrhythmia
III	Itch Flush Urticaria Angioedema	Vomiting Defecation	Laryngeal edema Bronchospasm Cyanosis	Schock
IV	Itch Flush Urticaria Angioedema	Vomiting Defecation	Respiratory arrest	Cardiac arrest

Classification according to the most severe symptom, no symptom is mandatory.
Ring et al., Guideline (S2k) on acute therapy and management of anaphylaxis: 2021 update. Allergo J Int (2021) 30:1–25

24.3 Expanded Disability Status Scale (EDSS)

neurostatus scoring

Definitions for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52

4031 Basel, Switzerland; Version 04/10.2

EQUIVALENCE WITH PREVIOUS VERSIONS

This version of the neurostatus scoring guidelines is fully compatible with previous versions. Additional help is provided by clarifying some definitions and by introducing an ambulation score in order to reduce measurement noise. But these changes do not imply changes in scoring levels.

GENERAL GUIDELINES

To ensure unbiased EDSS assessment in controlled clinical trials, the EDSS rater should not inquire about the patients' condition except as necessary to perform the EDSS assessment. Patients must be observed to walk the required distance.
The functional system and EDSS scores should reflect the MS related deficits only. In case of doubt the examining physician should assume a relation to MS.
Temporary signs or symptoms that are not due to multiple sclerosis, e.g. temporal immobilisation after fracture of one limb, as well as permanent signs or symptoms that are not due to multiple sclerosis, e.g leg amputation after accident, will not be taken into consideration when assessing the FS scores and EDSS steps, but need to be noted in neurostatus and commented by adding "P" next to the respective field on the scoring sheet for permanent findings and "T" for temporary findings.

FUNCTIONAL SYSTEMS (FS)

A neurostatus score "signs only" is noted when the examination reveals signs of which the patient is unaware.
A score of 1 in a Functional System implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities. However, this general rule does not apply to the Visual, Bowel/Bladder and Cerebral FS.

EXPANDED DISABILITY STATUS SCALE (EDSS)

The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS before conversion.

EDSS steps from 0 up to 4.0 should not change compared to the previous examination, unless there is a change by one grade in at least one FS score.
EDSS steps from 0 up to 1.5 can only apply if ambulation is "unrestricted".
EDSS steps from 2.0 up to 5.0 are defined by the Functional System (FS) scores and/or walking range restriction. As an example, EDSS step 5.0 is possible with an unrestricted ambulation. EDSS steps from 2.0 up to 4.0 does only apply in individuals when at least "fully ambulatory" (able to walk ≥500 meters). If ambulation is assessed as "restricted" the pyramidal or cerebellar FS must be ≥2.
EDSS steps ≥ 5.5 are exclusively defined by the ability to ambulate, the assistance required or the use of a wheelchair.

1 VISUAL (OPTIC) FUNCTIONS

VISUAL ACUITY

The visual acuity score is based on the line in the Snellen chart at 20 feet (5 meters) for which the patient makes no more than one error, using best available correction. Alternatively, best corrected near vision can be assessed, but this should be noted and consistently performed during follow-up examinations. Switching from near to distance visual acuity measurements should be avoided in follow-up examinations.

VISUAL FIELDS

0 normal
1 signs only: deficits present only on formal (confrontational) testing
2 moderate: patient aware of deficit, but incomplete hemianopsia on examination
3 marked: complete homonymous hemianopsia or equivalent

SCOTOMA

0 none
1 small: detectable only on formal (confrontational) testing
2 large: spontaneously reported by patient

* DISC PALLOR

0 not present
1 present

NOTE

When determining the EDSS step, the Visual FS score must be converted to a lower score as follows:

Visual FS Score	6	5	4	3	2	1
Converted Visual FS Score	4	3	3	2	2	1

FUNCTIONAL SYSTEM SCORE

0 normal
1 disc pallor and/or small scotoma and/or visual acuity (corrected) of worse eye less than 20/20 (1.0) but better than 20/30 (0.67)
2 worse eye with maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
3 worse eye with large scotoma and/or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.21)
4 worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.2–0.1);
grade 3 plus maximal acuity of better eye of 20/60 (0.33) or less
5 worse eye with maximal visual acuity (corrected) less than 20/200 (0.1);
grade 4 plus maximal acuity of better eye of 20/60 (0.33) or less
6 grade 5 plus maximal visual acuity of better eye of 20/60 (0.33) or less

* = optional part of the examination.

2 BRAINSTEM FUNCTIONS

EXTRAOCULAR MOVEMENTS (EOM) IMPAIRMENT

0 none
1 signs only: subtle and barely clinically detectable EOM weakness, patient does not complain of blurry vision, diplopia or discomfort
2 mild: subtle and barely clinically detectable EOM weakness of which patient is aware; or obvious incomplete paralysis of any eye movement of which patient is not aware
3 moderate: obvious incomplete paralysis of any eye movement of which patient is aware; or complete loss of movement in one direction of gaze in either eye
4 marked: complete loss of movement in more than one direction of gaze in either eye

NYSTAGMUS

0 none
1 signs only or mild: gaze evoked nystagmus below the limits of "moderate" (equivalent to a Brainstem FS score of 1)
2 moderate: sustained nystagmus on horizontal or vertical gaze at 30 degrees, but not in primary position, patient may or may not be aware of the disturbance
3 severe: sustained nystagmus in primary position or coarse persistent nystagmus in any direction that interferes with visual acuity; complete internuclear ophthalmoplegia with sustained nystagmus of the abducting eye; oscillopsia

TRIGEMINAL DAMAGE

0 none
1 signs only
2 mild: clinically detectable numbness of which patient is aware
3 moderate: impaired discrimination of sharp/dull in one, two or three trigeminal branches; trigeminal neuralgia (at least one attack in the last 24 hours)
4 marked: unable to discriminate between sharp/dull or complete loss of sensation in entire distribution of one or both trigeminal nerves

FACIAL WEAKNESS

0 none
1 signs only
2 mild: clinically detectable facial weakness of which patient is aware
3 moderate: incomplete facial palsy, such as weakness of eye closure that requires patching overnight or weakness of mouth closure that results in drooling
4 marked: complete unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids

HEARING LOSS

0 none
1 signs only: hears finger rub less in one or both sides and has lateralized Weber test but does not complain of any hearing problem
2 mild: as in 1 but is aware of hearing problem
3 moderate: does not hear finger rub on one or both sides, misses several whispered numbers
4 marked: misses all or nearly all whispered numbers

DYSARTHRIA

0 none
1 signs only
2 mild: clinically detectable dysarthria of which patient is aware
3 moderate: obv. dysarthria during ordinary conversation that impairs comprehensibility
4 marked: incomprehensible speech
5 inability to speak

DYSPHAGIA

0 none
1 signs only
2 mild: difficulty with thin liquids
3 moderate: difficulty with liquids and solid food
4 marked: sustained difficulty with swallowing; requires a pureed diet
5 inability to swallow

OTHER CRANIAL NERVE FUNCTIONS

0 normal
1 signs only
2 mild disability: clinically detectable deficit of which patient is usually aware
3 moderate disability
4 marked disability

FUNCTIONAL SYSTEM SCORE

0 normal
1 signs only
2 moderate nystagmus and/or moderate EOM impairment and/or other mild disability
3 severe nystagmus and/or marked EOM impairment and/or moderate disability of other cranial nerves
4 marked dysarthria and/or other marked disability
5 inability to swallow or speak

3 PYRAMIDAL FUNCTIONS

REFLEXES

0 absent
1 diminished
2 normal
3 exaggerated
4 nonsustained clonus (a few beats of clonus)
5 sustained clonus

Cutaneous Reflexes
0 normal
1 weak
2 absent

*Palmomental Reflex
0 absent
1 present

Plantar Response
0 flexor
1 neutral or equivocal
2 extensor

LIMB STRENGTH

The weakest muscle in each group defines the score for that muscle group. Use of optional functional tests (hopping on one foot and walking on heels/toes), is highly recommended in order to assess BMRC grades 3–5.

BMRC RATING SCALE

0 no muscle contraction detected
1 visible contraction without visible joint movement
2 visible movement only on the plane of gravity
3 active movement against gravity, but not against resistance
4 active movement against resistance, but not full strength
5 normal strength

FUNCTIONAL TESTS

*Pronator Drift (upper extremities) Pronation and downward drift:
0 none
1 mild
2 evident

*Position Test (lower extremities – ask patient to lift both legs together, with legs fully extended at the knee) Sinking:
0 none
1 mild
2 evident
3 able to lift only one leg at a time (grade from the horizontal pos. at the hip joints…°)
4 unable to lift one leg at a time

*Walking on heels/toes
0 normal
1 impaired
2 not possible

*Hopping on one foot
0 normal
1 6–10 times
2 1–5 times
3 not possible

LIMB SPASTICITY (AFTER RAPID FLEXION OF THE EXTREMITY)

0 none
1 mild: barely increased muscle tone
2 moderate: moderately increased muscle tone that can be overcome and full range of motion is possible
3 severe: severely increased muscle tone that is extremely difficult to overcome and full range of motion is not possible
4 contracted

GAIT SPASTICITY

0 none
1 barely perceptible
2 evident: minor interference with function
3 permanent shuffling: major interference with function

OVERALL MOTOR PERFORMANCE

0 normal
1 abnormal weakness (as compared to peers) in performing more demanding tasks, e.g. when walking longer distances, but no reduction in limb strength on formal (confrontational) testing
2 Reduction in strength of individual muscle groups at confrontational testing

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 minimal disability: patient complains of motor-fatigability or reduced performance in strenuous motor tasks (motor performance grade 1) and/or BMRC grade 4 in one or two muscle groups
3 mild to moderate paraparesis or hemiparesis: usually BMRC grade 4 in more than two muscle groups;
and/or BMRC grade 3 in one or two muscle groups (movements against gravity are possible);
and/or severe monoparesis: BMRC grade 2 or less in one muscle group
4 marked paraparesis or hemiparesis: usually BMRC grade 2 in two limbs or monoplegia with BMRC grade 0 or 1 in one limb;
and/or moderate tetraparesis: BMRC grade 3 in three or more limbs
5 paraplegia: BMRC grade 0 or 1 in all muscle groups of the lower limbs;
and/or marked tetraparesis: BMRC grade 2 or less in three or more limbs;
and/or hemiplegia;
6 tetraplegia: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs

4 CEREBELLAR FUNCTIONS

HEAD TREMOR

0 none
1 mild
2 moderate
3 severe

TRUNCAL ATAXIA

0 none
1 signs only
2 mild: swaying with eyes closed
3 moderate: swaying with eyes open
4 severe: unable to sit without assistance

LIMB ATAXIA (TREMOR/DYSMETRIA AND RAPID ALTERNATING MOVEMENTS)

0 none
1 signs only
2 mild: tremor or clumsy movements easily seen, minor interference with function
3 moderate: tremor or clumsy movements interfere with function in all spheres
4 severe: most functions are very difficult

TANDEM (STRAIGHT LINE) WALKING

0 normal
1 impaired
2 not possible

GAIT ATAXIA

0 none
1 signs only
2 mild: problems with balance realized by patient and/or significant other
3 moderate: abnormal balance with ordinary walking
4 severe: unable to walk more than a few steps unassisted or requires a walking aid or assistance by another person because of ataxia

ROMBERG TEST

0 normal
1 mild: mild instability with eyes closed
2 moderate: not stable with eyes closed
3 severe: not stable with eyes open

OTHER CEREBELLAR TESTS

0 normal
1 mild abnormality
2 moderate abnormality
3 severe abnormality

NOTE

The presence of severe gait and/or truncal ataxia alone (without severe ataxia in three or four limbs) results in a Cerebellar FS score of 3.
If weakness or sensory deficits interfere with the testing of ataxia, score the patient's actual performance. To indicate the possible role of weakness make an "X" after the Cerebellar FS score.

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 mild ataxia and/or moderate station ataxia (Romberg) and/or tandem walking not possible
3 moderate limb ataxia and/or moderate or severe gait/truncal ataxia
4 severe gait/truncal ataxia and severe ataxia in three or four limbs
5 unable to perform coordinated movements due to ataxia
X pyramidal weakness (BMRC grade 3 or worse in limb strength) or sensory deficits interfere with cerebellar testing

5 SENSORY FUNCTIONS

SUPERFICIAL SENSATION (LIGHT TOUCH AND PAIN)

0 normal
1 signs only: slightly diminished sensation (temperature, figure-writing) on formal testing of which patient is not aware
2 mild: patient is aware of impaired light touch or pain, but is able to discriminate sharp/dull
3 moderate: impaired discrimination of sharp/dull
4 marked: unable to discriminate between sharp/dull and/or unable to feel light touch
5 complete loss: anaesthesia

VIBRATION SENSE (AT THE MOST DISTAL JOINT)

0 normal
1 mild: graded tuning fork 5–7 of 8; alternatively, detects more than 10 seconds but less than the examiner
2 moderate: graded tuning fork 1–4 of 8; alternatively, detects between 2 and 10 sec.
3 marked: complete loss of vibration sense

POSITION SENSE

0 normal
1 mild: 1–2 incorrect responses, only distal joints affected
2 moderate: misses many movements of fingers or toes; proximal joints affected
3 marked: no perception of movement, astasia

*LHERMITTE'S SIGN

Does not contribute to the Sensory FS score
0 negative
1 positive

*PARAESTHESIAE (TINGLING)

Does not contribute to the Sensory FS score
0 none
1 present

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild vibration or figure-writing or temperature decrease only in one or two limbs
2 mild decrease in touch or pain or position sense or moderate decrease in vibration in one or two limbs;
and/or mild vibration or figure-writing or temperature decrease alone in more than two limbs
3 moderate decrease in touch or pain or position sense or marked reduction of vibration in one or two limbs;
and/or mild decrease in touch or pain or moderate decrease in all proprioceptive tests in more than two limbs
4 marked decrease in touch or pain in one or two limbs;
and/or moderate decrease in touch or pain and/or marked reduction of proprioception in more than two limbs
5 loss (essentially) of sensation in one or two limbs;
and/or moderate decrease in touch or pain and/or marked reduction of proprioception for most of the body below the head
6 sensation essentially lost below the head

6 BOWEL AND BLADDER FUNCTIONS

URINARY HESITANCY AND RETENTION

0 none
1 mild: no major impact on lifestyle
2 moderate: urinary retention; frequent urinary tract infections
3 severe: requires catheterisation
4 loss of function: overflow incontinence

URINARY URGENCY AND INCONTINENCE

0 none
1 mild: no major impact on lifestyle
2 moderate: rare incontinence occurring no more than once a week; must wear pads
3 severe: frequent incontinence occurring from several times a week to more than once a day; must wear urinal or pads
4 loss of function: loss of bladder control

BLADDER CATHETERISATION

0 none
1 intermittent self-catheterisation
2 constant catheterisation

BOWEL DYSFUNCTION

0 none
1 mild: no incontinence, no major impact on lifestyle, mild constipation
2 moderate: must wear pads or alter lifestyle to be near lavatory
3 severe: in need of enemata or manual measures to evacuate bowels
4 complete loss of function

*SEXUAL DYSFUNCTION

Male
0 none
1 mild: difficulty to maintain erection during intercourse, but achieves erection and still has intercourse
2 moderate: difficulty to achieve erection, decrease in libido, still has intercourse and reaches orgasm
3 severe: marked decrease in libido, inability to achieve full erection, intercourse with difficulty and hypoorgasmia
4 loss of function

Female
0 none
1 mild: mild lack of lubrication, still sexually active and reaches orgasm
2 moderate: dysparunia, hypoorgasmia, decrease in sexual activity
3 severe: marked decrease in sexual activity, anorgasmia
4 loss of function

NOTE

When determining the EDSS step, the Bowel and Bladder FS score must be converted to a lower score as follows:

Bowel and Bladder FS Score	6	5	4	3	2	1
Converted Bowel and Bladder FS Score	5	4	3	3	2	1

Sexual dysfunction can be documented but in general does not impact on FS score because of obvious difficulties in assessment by examining physician

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild urinary hesitancy, urgency and/or constipation
2 moderate urinary hesitancy/retention and/or moderate urinary urgency/incontinence and/or moderate bowel disfunction
3 frequent urinary incontinence or intermittent self-catheterisation; needs enemata or manual measures to evacuate bowels
4 in need of almost constant catheterisation
5 loss of bladder or bowel function; external or indwelling catheter
6 loss of bowel and bladder function

7 CEREBRAL FUNCTIONS

° DEPRESSION AND EUPHORIA

0 none
1 present: Patient complains of depression or is considered depressed or euphoric by the investigator or significant other.

° Depression and Euphoria are documented on the scoring sheet but are not taken into consideration for FS and EDSS calculation.

DECREASE IN MENTATION

0 none
1 signs only: not apparent to patient and/or significant other
2 mild: Patient and/or significant other report mild changes in mentation. Examples include: impaired ability to follow a rapid course of association and in surveying complex matters; impaired judgement in certain demanding situations; capable of handling routine daily activities, but unable to tolerate additional stressors; intermittently symptomatic even to normal levels of stress; reduced performance; tendency toward negligence due to obliviousness or fatigue.
3 moderate: definite abnormalities on brief mental status testing, but still oriented to person, place and time
4 marked: not oriented in one or two spheres (person, place or time), marked effect on lifestyle
5 dementia, confusion and/or complete disorientation

+FATIGUE

0 none
1 mild: does not usually interfere with daily activities
2 moderate: interferes, but does not limit daily activities for more than 50 %
3 severe: significant limitation in daily activities (> 50 % reduction)

+Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

FUNCTIONAL SYSTEM SCORE

0 normal
1 signs only in decrease in mentation; mild fatigue
2 mild decrease in mentation; moderate or severe fatigue
3 moderate decrease in mentation
4 marked decrease in mentation
5 dementia

8 AMBULATION

Unrestricted ambulation means the patient is able to walk a distance without assistance that is regarded as normal, compared with healthy individuals of similar age and physical condition. In this case the EDSS step can be anything between 0 and 5.0, depending on the FS scores.

Fully ambulatory means at least 500 meters of ambulation without assistance, but not unrestricted. The EDSS step can be anything between 2.0 and 5.0, depending on the FS scores. In this case, the pyramidal and/or cerebellar FS must be ≥2 to reflect this „restriction" of ambulation.

If ambulation is < 500 meters, the EDSS step must be ≥ 4.5 depending on the walking ranges provided by the ambulation score (see next page) and combination of FS scores. EDSS steps 5.5 to 8.0 are exclusively defined by the ability to ambulate and type of assistance required, or the ability to use a wheelchair.

If assistance is needed, the definitions of EDSS steps 6.0 or 6.5 include both a description of the type of assistance required when walking and the walking range. Assistance by another person is equivalent to bilateral assistance.

NOTE

The ambulation score represents both a description of walking range and the type of assistance required for ambulation. The score replaces the former use of several checkboxes (paragraph 8 ambulation on the scoring sheet) but does NOT introduce new definitions. The use of wheelchair can now be scored on the scoring sheet.
Please indicate the reported distance and time for the patient in the appropriate field on the scoring sheet, followed by the type of assistance and the walking distance measured during the assessment.

DISTANCE AND TIME REPORTED BY PATIENT

Maximal unassisted walking distance reported by patient (in meters) without rest or assistance and time required to walk max. distance according to patient (in minutes)

ASSISTANCE

0 Without help or assistance (allowing the use of an ankle foot orthotic device, without any other type of assistive device)
1 Unilateral assistance: one stick/crutch/brace
2 Bilateral assistance: two sticks/crutches/braces or assistance by another person
3 Wheelchair

DISTANCE

Measure the distance the patient is able to walk im meters.
Unassisted: observe the patient walking unassisted for a minimum distance of 500 meters and measure the time needed, if possible.
Assisted: observe the patient walking with the assistive device or help by another person for a minimum distance of 130 meters, if possible.

AMBULATION SCORE

0 Unrestricted
1 Fully ambulatory
2 ≥ 300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0)
3 ≥ 200 meters, but < 300 meters, without help or assistance (EDSS 5.0)
4 ≥ 100 meters, but < 200 meters, without help or assistance (EDSS 5.5)
5 Walking range < 100 meters without assistance (EDSS 6.0)
6 unilateral assistance, ≥ 50 meters (EDSS 6.0)
7 bilateral assistance, ≥ 120 meters (EDSS 6.0)
8 unilateral assistance, < 50 meters (EDSS 6.5)
9 bilateral assistance, ≥ 5 meters, but < 120 meters (EDSS 6.5)
10 Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)
11 Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)
12 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0)

9 EXPANDED DISABILITY STATUS SCALE

0 normal neurological exam (all FS grade 0)
1.0 no disability, minimal signs in one FS (one FS grade 1)
1.5 no disability, minimal signs in more than one FS (more than one FS grade 1)
2.0 minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5 minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0 moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5 fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1);or fully ambulatory with five FS grade 2 (others 0 or 1)
4.0 ambulatory without aid or rest for ≥500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
4.5 ambulatory without aid or rest for ≥300 meters; up and about much of the day, characterised by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0 ambulatory without aid or rest for ≥200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5 ambulatory without aid or rest for ≥100 meters
6.0 unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting (see chapter 8, Ambulation)
6.5 constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting (see chapter 8, Ambulation)
7.0 unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5 unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5 essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0 helpless bed patient; can communicate and eat
9.5 totally helpless bed patient; unable to communicate effectively or eat/swallow
10 death due to MS

neurostatus scoring

Scoring Sheet for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

STUDY NAME

PERSONAL INFORMATION
Patient
Date of Birth (04-Jun-1980)
Centre Nr/Country
Name of EDSS rater
Date of Examination

SYNOPSIS
1. Visual
2. Brainstem
3. Pyramidal
4. Cerebellar
5. Sensory
6. Bowel/Bladder
7. Cerebral
Ambulation Score
EDSS Step
Signature

1. VISUAL (OPTIC) FUNCTIONS
OPTIC FUNCTIONS — OD — OS
Visual acuity — CC SC
Visual fields
Scotoma
* Disc pallor
FUNCTIONAL SYSTEM SCORE

2. BRAINSTEM FUNCTIONS
CRANIAL NERVE EXAMINATION
Extraocular movements (EOM) impairment
Nystagmus
Trigeminal damage
Facial weakness
Hearing loss
Dysarthria
Dysphagia
Other cranial nerve functions
FUNCTIONAL SYSTEM SCORE

3. PYRAMIDAL FUNCTIONS
REFLEXES — R — >< — L
Biceps
Triceps
Brachioradialis
Knee
Ankle
Plantar response
Cutaneous reflexes
* Palmomental reflex
LIMB STRENGTH — R — L
Deltoid
Biceps
Triceps
Wrist/finger flexors
Wrist/finger extensors
Hip flexors
Knee flexors
Knee extensors
Plantar flexion (foot/toes)
Dorsiflexion (foot/toes)
* Position test UE, pronation
* Position test UE, downward drift
* Position test LE, sinking
* Able to lift only one leg a time (grade in °)
* Walking on heels
* Walking on toes
* Hopping on one foot
SPASTICITY
Arms
Legs
Gait
OVERALL MOTOR PERFORMANCE
FUNCTIONAL SYSTEM SCORE

CC = corrected
SC = without correction
* = optional part of the examination
¹ = converted FS Score

4. CEREBELLAR FUNCTIONS
CEREBELLAR EXAMINATION — R — L
Head tremor
Truncal ataxia
Tremor/dysmetria UE
Tremor/dysmetria LE
Rapid alternating movements UE impairment
Rapid alternating movements LE impairment
Tandem walking
Gait ataxia
Romberg test
Other, e. g. rebound
FUNCTIONAL SYSTEM SCORE

5. SENSORY FUNCTIONS
SENSORY EXAMINATION — R — L
Superficial sensation UE
Superficial sensation trunk
Superficial sensation LE
Vibration sense UE
Vibration sense LE
Position sense UE
Position sense LE
* Lhermitte's sign
* Paraesthesiae UE
* Paraesthesiae trunk
* Paraesthesiae LE
FUNCTIONAL SYSTEM SCORE

6. BOWEL/ BLADDER FUNCTIONS
Urinary hesitancy/retention
Urinary urgency/incontinance
Bladder catheterisation
Bowel dysfunction
* Sexual dysfunction
FUNCTIONAL SYSTEM SCORE

7. CEREBRAL FUNCTIONS
MENTAL STATUS EXAMINATION
* Depression
* Euphoria
Decrease in mentation
* Fatigue
FUNCTIONAL SYSTEM SCORE

AMBULATION
Distance reported by patient (in meters)
Time reported by patient (in minutes)
Assistance
Distance measured (in meters)
AMBULATION SCORE

* = optional part of the examination
¹ = converted FS Score
* Depression and Euphoria are not taken into consideration for FS and EDSS calculation.
* Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

UE = upper extremities
LE = lower extremities

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983;33,1444-52
©2011 Ludwig Kappos, MD, Neurology, University Hospital Basel, 4031 Basel, Switzerland; Version 04/10.2

neurostatus.net

Independent Internet Platform for training and certification of physicians participating in projects that use a standardized, quantified neurological examinationand Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

neurostatus training

Interactive Training DVD-ROM for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

neurostatus e-test

Interactive Test and Certification Tool for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

neurostatus forum

Forum for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

www.neurostatus.net

24.4 Instruction for the 9-Hole Peg Test

Description

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. It is composed of a square board with 9 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 9-HPT will be administered as described in the Multiple Sclerosis Functional Composite (MSFC) Administration and Scoring Manual. Both the dominant and non- dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand). It is important that the 9-HPT be administered on a solid table and that the small rubber feet are fixed under the 9-HPT apparatus (or the apparatus be anchored by other method). The testing environment should be the same room or area and the potential for distractions should be minimized as much as possible.

Material needed

9-HPT apparatus, stopwatch, 9-HPT Record Form

Time limit per trial

5 minutes (300 seconds)

Discontinue Rules:

- If the patient cannot complete one trial of the 9-HPT in 5 minutes.
- If the patient cannot complete a trial with his or her dominant hand within 5 minutes, move on to the trials with the non-dominant hand.
- If the patient cannot complete a trial with his or her non-dominant hand.

Methods

Dominant Hand - Trial 1

- Make sure that the stopwatch is set to 0:00. Introduce this section by saying, “Now, we’re going to be measuring your arm and hand function.”
    - If this is the first visit, ask the patient whether he is right- or left-handed. Make a note of the dominant hand for subsequent instructions.
- Place the 9-HPT apparatus on the table directly in front of the patient.
    - Arrange the apparatus so that the side with the pegs is in front of the hand being tested and the side with the empty pegboard is in front of the hand not being tested.
- Read the following instructions to the patient: “On this test, I want you to pick up the pegs one at a time, using one hand only, and put them into the holes as quickly as you can in any order until all the holes are filled. Then, without pausing, remove the pegs one at a time and return them to the container as quickly as you can. We’ll have you do this two times with each hand. We’ll start with your [DOMINANT] hand. You can hold the peg board steady with your [NON-DOMINANT] hand. If a peg falls onto the table, please retrieve it and continue with the task. If a peg falls on the floor, keep working on the task and I will retrieve it for you. See how fast you can put all of the pegs in and take them out again. Are you ready? Begin.”

- Start timing as soon as the patient touches the first peg and stop timing when the last peg hits the container.
    - If a peg drops on the floor, the examiner may retrieve it and put it back in the peg box. However, if a peg drops onto the table, allow the patient to retrieve it.
    - If the subject stops after having put all the pegs into the holes, prompt the subject to remove them as well. If the subject begins to remove more than one peg at a time, correct him/her by saying, “Pick up one peg at a time.”
    - Record the patient’s time under Dominant hand - Trial 1.

Dominant Hand - Trial 2

- After the first trial with the dominant hand, say, “Good. Now, I’d like you to do the same thing again, using again your [DOMINANT] hand. See how fast you can put all of the pegs in and take them out again. Ready? Begin.”
- Again, start timing as soon as the patient touches the first peg, and stop timing when the last peg hits the container.
- Record the patient’s time under Dominant hand - Trial 2.

Non-Dominant Hand -Trials 1 and 2

- After the second trial with the dominant hand, rotate the apparatus 180 degrees such that the side with the pegs is now in front of the non-dominant hand and the empty peg-board is in front of the dominant hand.
- Then say, “OK. Now I’d like you to switch and use your [NON-DOMINANT] hand. This time, you can use your [DOMINANT] hand to stabilize the peg board. Ready? Begin.”
- Administer, time, and record the two non- dominant hand trials following the procedures described above for dominant hand trials.

Completing the Record Form:

Record any circumstances that you believe may have affected the patient’s performance. These are factors that may have affected the trial, but were not severe enough to necessitate repetition of the trial. Examples include, but are not limited to:

- The patient dropped a peg
- The patient has a cold
- The patient forgot eyeglasses and had difficulty seeing pegs
- The patient talked during the task

If a trial is repeated, indicate this and specify the reason it had to be repeated. Examples of reasons to repeat a trial include, but are not limited to:

- The patient knocked entire apparatus on the floor
- The examiner forgot to start or stop stopwatch
- The examiner forgot to reset the stopwatch in between trial

Record only the times for the two successfully completed trials for each hand on the 9-HPT. If the patient could not complete one or both of the trials for either hand of the 9-HPT, record this in the appropriate section of the Record Form.

If the patient's disease has progressed and/or physical limitations prohibit him or her from completing the trial, the examiner should mark "Unable to complete trial due to physical limitations," and then record any specifics that can be observed (e.g., patient unable to use right hand, patient could not complete within time limit, etc.).

Site number	Subject Number	Randomization Number	Visit	Protocol no:
___ - ___ ___	___ - ___ ___ - ___ ___	___ ___ ___	Visit No. _____ Visit Date: ___ ___ - ___ ___ ___ - ___ ___	MSB-IG-H-2101 (RED4MS)

9 HOLE PEG TEST

DOMINANT HAND *(Check one)*: Right ☐ Left ☐

DOMINANT HAND	NON-DOMINANT HAND
Trial 1	**Trial 1**
☐☐☐ ☐ seconds For a complete trial, record any circumstances that affected the patient's performance: _____ _____ If trial was not completed *(mark one)*: ☐ Unable to complete trial due to physical limitations ➡ Specify: _____ _____ ☐ Other ➡	☐☐☐ ☐ seconds For a complete trial, record any circumstances that affected the patient's performance: _____ _____ If trial was not completed *(mark one)*: ☐ Unable to complete trial due to physical limitations ➡ Specify: _____ _____ ☐ Other ➡
Trial 2	**Trial 2**
☐☐☐ ☐ seconds For a complete trial, record any circumstances that affected the patient's performance: _____ _____ If trial was not completed *(mark one)*: ☐ Unable to complete trial due to physical limitations ➡ Specify: _____ _____ ☐ Other ➡	☐☐☐ ☐ seconds For a complete trial, record any circumstances that affected the patient's performance: _____ _____ If trial was not completed *(mark one)*: ☐ Unable to complete trial due to physical limitations ➡ Specify: _____ _____ ☐ Other ➡
Did it take more than two attempts to get two sucessful trials? ☐ Yes ☐ No If Yes, please specify reason(s) for more than two attempted trials:	Did it take more than two attempts to get two sucessful trials? ☐ Yes ☐ No If Yes, please specify reason(s) for more than two attempted trials:

24.5 Instructions for the timed 25-foot walk

Description

The Timed 25-Foot Walk is a quantitative measure of lower extremity function. The T25-FW will be administered as described in the MSFC Administration and Scoring Manual. The patient is directed to one end of a clearly marked 25-foot (7.62 m) course and is instructed to walk 25 feet (7.62 meter) as quickly as possible, but safely. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task. The testing environment should be the same room or area and the potential for distractions should be minimized as much as possible.

Material needed

Stopwatch, Tape measure (for measuring the 25-Foot walking path), Duct-Tape (for marking the 25-Foot walking path), Timed 25-Foot Walk Record Form.

Measure the walking distance of 25-foot (7.62 m) with the tape measure and mark the beginning and the end of the path with a piece of duct tape, either on the floor or on a wall. Make sure the stopwatch is set to 0:00.

Time limit per trial

3 minutes (180 seconds)

Discontinue Rules

- If patient cannot complete Trial 2 after a 5-minutes rest period
- If patient cannot complete trial in 3 minutes

Methods

Trial 1

- In order to start the timed 25-foot Walk Test the patient should be directed to one end of the marked path and instructed to stand behind the starting line.
- The examiner should point out the end of the 25-foot course and instruct the patient as follows: “I’d like you to walk 25 feet as quickly as possible, but safely. Do not slow down until after you`ve passed the finish line. Ready? Go.”
- Begin timing when the lead foot is lifted and crosses the starting line.
    - The examiner should walk along with the patient as s/he completes the task.
- Stop timing when the lead foot crosses the finish line.
    - The examiner should then record the subject’s walk time to within 0.1 second, rounding as needed. Round up to the next tenth if hundredth’s place is > = .05, round down if hundredth’s place is <0.5 (e.g., 32.45” would round to 32.5” but 32.44” would round to 32.4”). Once the time is recorded, be sure to reset the stopwatch.

Trial 2

- After completing the first timed walk, position the patient just behind the line where s/he is now standing, repeat the same instructions, and have the patient immediately complete the walk again.

Assistive Devices

In clinical trials and other serial studies, the goal is to use the same assistive device at each study visit. In general, patients should use their customary assistive device(s), NOT the least assistance possible to complete the test. For patients with significant gait impairment, the treating neurologist should have the patient use a rolling walker even if this is not the patient's customary device. In general, non-wheeled walkers should not be used. If a patient does use an assistive device, this should be noted on the Record Form.

Completing the Record Form

Record any circumstances that you believe may have affected the patient's performance. These are factors that may have affected the trial but were not severe enough to necessitate repetition of the trial. Examples include, but are not limited to:

- The patient had a cold or reports not feeling well.
- The patient tripped but did not fall.

If a situation arises that necessitates the repetition of a trial, indicate the reason a trial had to be repeated on the Record Form. Examples of reasons to repeat a trial include, but are not limited to:

- The patient fell during the walk.
- Examiner forgot to start or stop stopwatch.
- Examiner forgot to reset stopwatch in between trials.
- The patient stopped to talk to someone while walking, or another person/thing somehow interfered with walk.

Record only the times for the two successfully completed trials of the Timed 25-Foot Walk. If the patient could not complete one or both of the trials of the Timed 25-Foot Walk, record this in the appropriate section of the Record Form.

Site number	Subject Number	Randomization Number	Visit	Protocol no:
___ - ___ ___	___ - ___ ___ - ___ ___	___ ___ ___	Visit No. _____ Visit Date: ___ ___ - ___ ___ ___ - ___ ___	MSB-IG-H-2101 (RED4MS)

TIMED 25-FOOT WALK TEST

Did patient wear an AFO? ☐ Yes ☐ No

Was assistive device used? ☐ Yes ☐ No

Assistive device used *(mark one)*:

☐ Unilateral Assistance ☐ Cane ☐ Crutch

☐ Bilateral Assistance ☐ Cane ☐ Crutch ☐ Walker/Rollator

Trial 1

Time for 25-Foot Walk ☐☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one)*: Specify:

☐ Unable to complete trial due to physical limitations ➡

☐ Other ➡

Trial 2

Time for 25-Foot Walk ☐☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one)*: Specify:

☐ Unable to complete trial due to physical limitations ➡

☐ Other ➡

Did it take more than two attempts to get two successful trials?
If yes, please specify reason(s) for more than two attempted trials:

24.6 Instructions for the Symbol Digit Modalities Test (SDMT)

Description

The SDMT is a sensitive and specific test to assess processing speed, which are typically affected domains in cognitively impaired MS patients.

The SDMT requires the examinee to substitute a geometric figure with a number. The appropriate number is shown in a key containing the Arabic numbers 1 through 9, each of which is paired with a different geometric symbol.

The testing environment should be the same room or area and the potential for distractions should be minimized as much as possible. No one other than the examiner and the patient should be in the testing room during the SDMT. Any disruption must be kept to a minimum.

The SDMT is applied according to the Manual from Western Psychological Services (WPS).

Material needed

Stopwatch, SDMT Form, SDMT Record Form

Time limit per trial

90 seconds

Methods

- Hand the test form to the examinee and read the following instructions to the examinee:
    - *"Please look at these boxes at the top of the page. You can see that each box in the upper row has a little mark in it. Now look at the boxes in the row just underneath the marks. Each of the boxes under the marks has a number. Each of the marks in the top row is different, and under each mark in the bottom row is a different number. Now look at the next line of boxes* (examiner points to line of boxes) *just under the top two rows. Notice that the boxes on the top have marks, but the boxes underneath are empty. You are to fill each empty box with the number that should go there according to the way they are paired in the key at the top of the page. For example, if you look at the first mark, and then look up at the key, you will see that the number 1 goes in the first empty box. So write the number 1 in the first box. Now, what number should you put in the second box?* (Number 5) *That's right.*
      So write the number 5 in the second box. What number goes in the third box? (Number 2) *Two, right. That is the idea. You are to fill each of the empty boxes with the numbers that should go in them according to the key. Now for practice, fill in the rest of the boxes until you come to the double line. When you come to the double line, stop."*
- The examiner should check to see that the examinee understands the task. Any errors made in the first 10 practice responses should be immediately pointed out by the examiner and corrected by the examinee.
    - If an examinee has not understood the nature of the task, the instructions are repeated with further examples until the nature of the test is clearly understood. The examiner then continues with the following instructions:

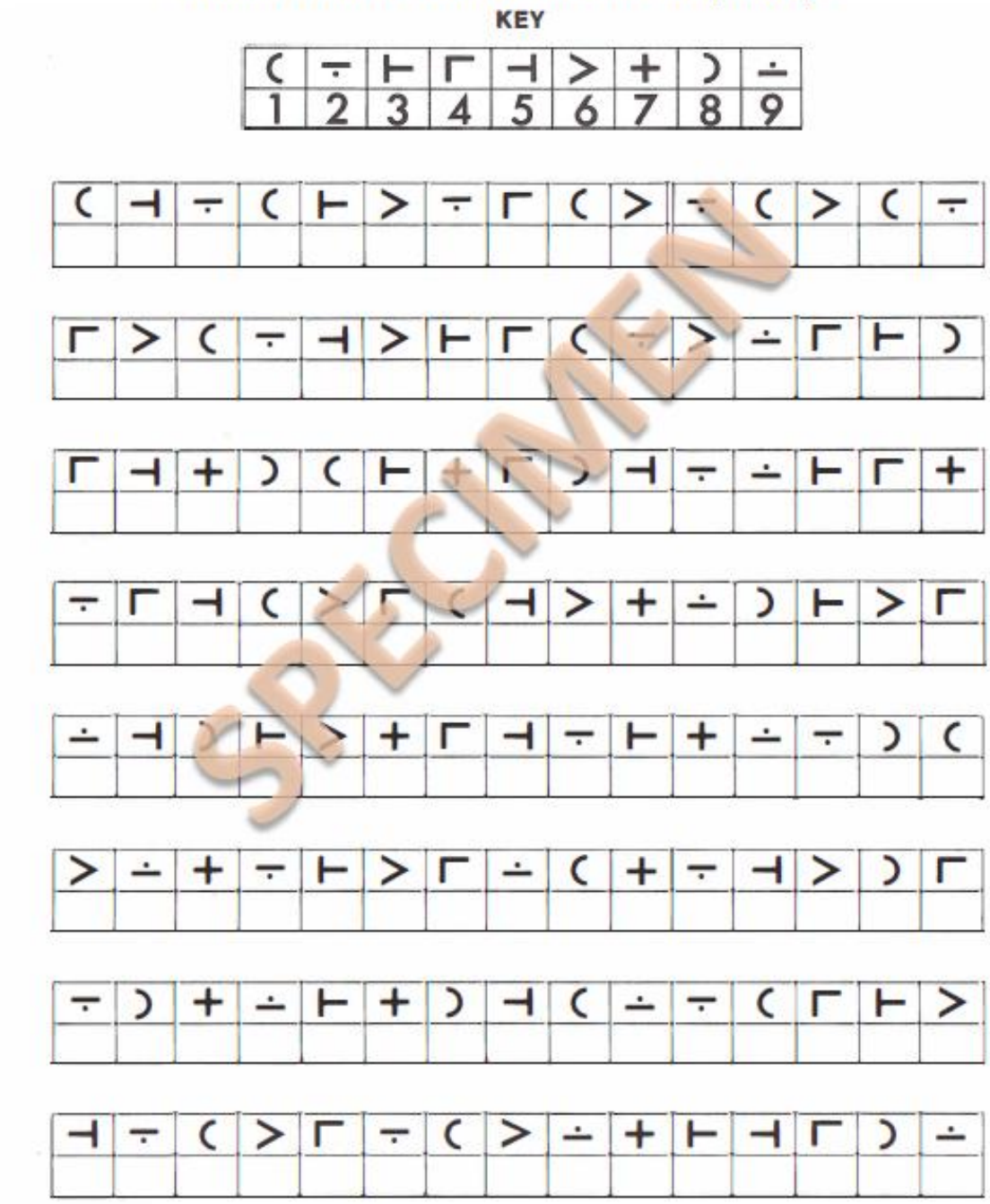
- *Now when I say" Go!" write in the numbers just like you have been doing as fast as you can until I say "Stop!" When you come to the end of the first line, go quickly to the next line without stopping, and so on. If you make a mistake, do not erase, just write the correct answer over your mistake. I repeat, DO NOT ERASE, as you will waste time. Just write the correct answer over your mistake. Do not skip any boxes and work as quickly as you can. Ready? Go!"*
- Exactly 90 seconds from starting, the examiner says: *"STOP!"*

Scoring

The score of the test is the number of correct substitutions in each 90-second interval. This does not include those substitutions made during the practice period (i.e. the first 10 boxes). The total number of correct responses can be easily found by separating the top sheet upon which the examinee has written his or her responses and counting the number of responses that correctly match the number printed above each box on the second sheet. This score is recorded as a proportion of the total number of responses. For example, a score of 36/39 indicates that the examinee made a total of 39 responses, 36 correct and 3 incorrect. The total score provides a measure of the speed and accuracy of symbol-digit substitutions.

Site number	Subject Number	Randomization Number	Visit	Protocol no:
__-__	__-__ __-__	__ __ __	Visit No. _____ Visit Date: __ __-__ __ __-__ __	MSB-IG-H-2101 (RED4MS)

SYMBOL DIGIT MODALITIES TEST (SDMT)



Symbol Digit Modalities Test

Page 1 of 2

Site number	Subject Number	Randomization Number	Visit	Protocol no:
__-__ __	__-__ __ __-__ __	__ __ __	Visit No. _____ Visit Date: __ __-__ __ __-__ __	MSB-IG-H-2101 (RED4MS)

SYMBOL DIGIT MODALITIES TEST (SDMT)

Written Score

Oral Score

2	1	6	1	2

Item Numbers → 1 2 3 4 5

4	6	1	2	5	6	3	4	1	2	6	9	4	3	8
6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

4	5	7	8	1	3	7	4	8	5	2	9	3	4	7
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35

2	4	5	1	6	4	1	3	6	7	9	8	3	6	4
36	37	38	39	40	41	42	43	44	45	46	47	48	49	50

9	5	8	3	6	7	4	5	2	3	7	9	2	8	1
51	52	53	54	55	56	57	58	59	60	61	62	63	64	65

6	9	7	2	3	6	4	9	1	7	2	5	6	8	4
66	67	68	69	70	71	72	73	74	75	76	77	78	79	80

2	8	7	9	3	7	8	5	1	9	2	1	4	3	6
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95

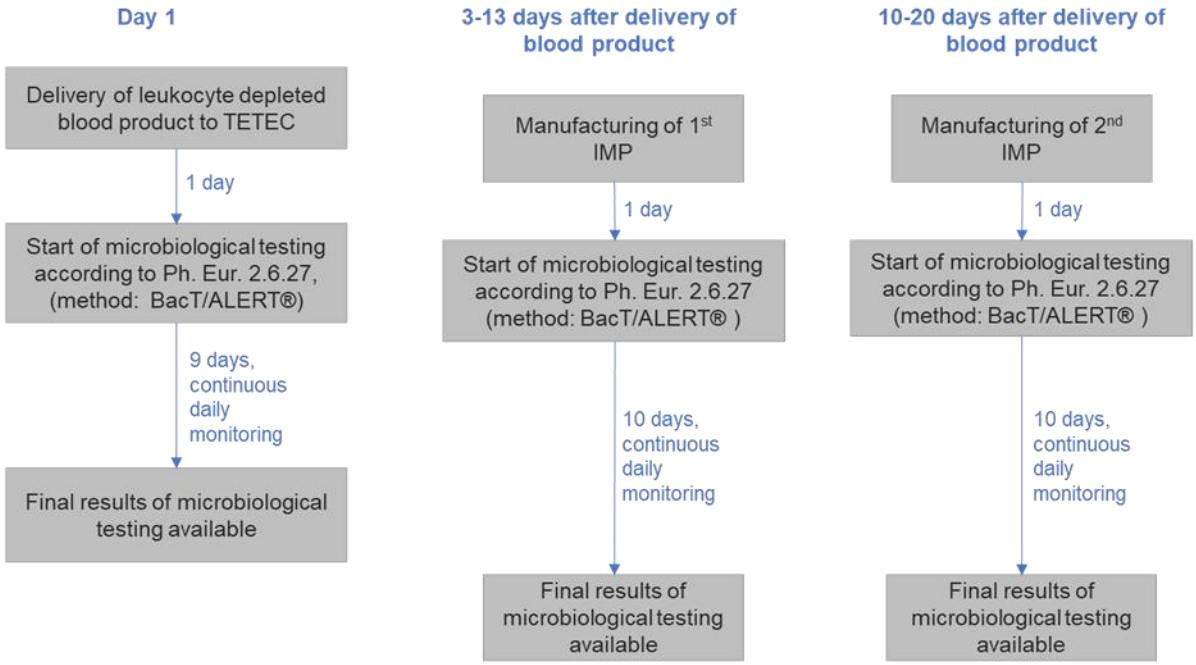
5	2	1	6	4	2	1	6	9	7	3	5	4	8	9
96	97	98	99	100	101	102	103	104	105	106	107	108	109	110

Symbol Digit Modalities Test

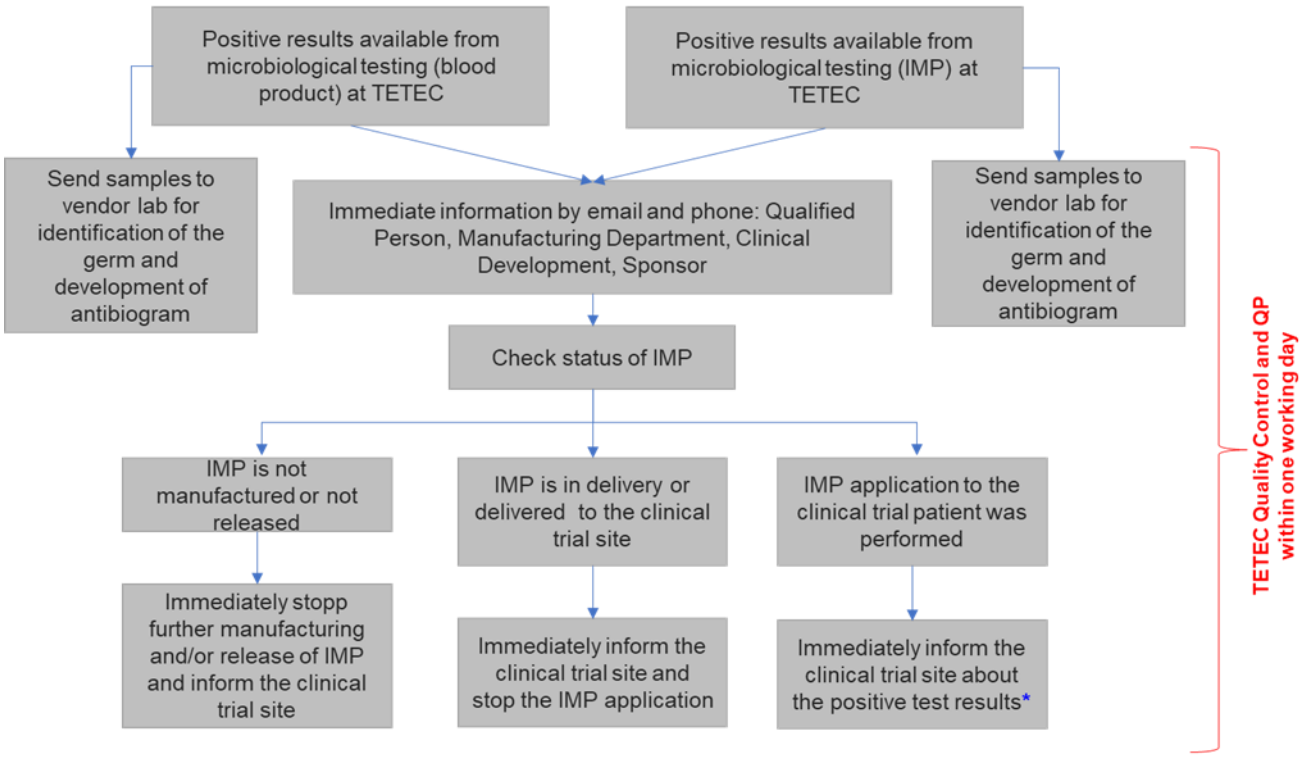
Page 2 of 2

24.7 Handling of sterility testing positive results in/during manufacturing and after IMP administration

Part 1: Overview about microbiological testing

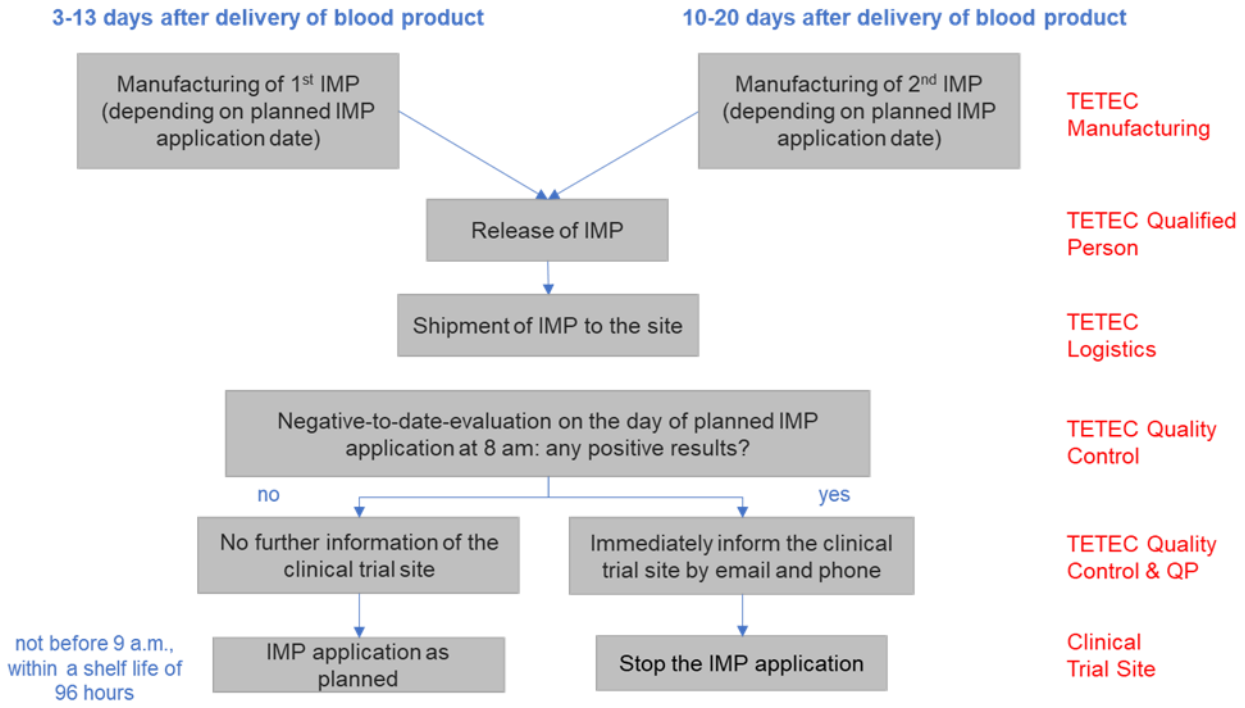


Part 2: Handling of positive results - responsibilities of the manufacturer of the IMP



* Further action steps of trial site illustrated on slide 4

Part 2: Additional negative-to-date evaluation on the day of planned IMP application



Part 3: Handling of positive results – responsibilities of the clinical trial site