AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A Phase 2, double-blind, randomized, placebo-controlled study assessing efficacy and safety of SAR441344, a CD40L-antagonist monoclonal antibody, in participants with relapsing multiple sclerosis**
Protocol number:	**ACT16877**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR441344** **frexalimab**
Brief title:	**Proof-of-concept study for SAR441344 in relapsing multiple sclerosis** **LAMPETIA**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**82 Avenue Raspail, 94250 Gentilly, FRANCE** **Manufacturer: Sanofi-Aventis Recherche & Développement**
Monitoring team's representative name and contact information	**The study centers and the Investigators at each center are listed in a separate document**

Regulatory agency identifier number(s):

IND:	138742
EU trial number:	2024-513527-17
NCT:	NCT04879628
WHO:	U1111-1260-3962
EUDAMED:	Not applicable
Other:	Not applicable

Pediatric investigational plan number: Not applicable

Date: 18-Nov-2024 Total number of pages: 153

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	All	18 November 2024, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	16 November 2023, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	21 February 2023, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	20 May 2021, version 1 (electronic 1.0)
Original protocol		26 November 2020, version 1 (electronic 1.0)

Amended protocol 04 (18 November 2024)

This amended protocol 04 (amendment 04) is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment is subsequent to European Union (EU) clinical trials regulation (CTR) request to update the protocol in line with their requirements. The study intervention in the Part B extension is now clarified to be limited to 40 months, as requested by the Health Authority (HA).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	The Legal registered address updated. EU trial number was added.	Change in new address. EU trial number was added.
1.1 Synopsis 6 Study intervention(s) and concomitant therapy 6.1 Study intervention(s) administered 6.1.3 Auxiliary medicinal product(s) 6.7 Treatment of overdose 6.8 Prior and Concomitant Therapy 7.2 Participant discontinuation/ Withdrawal from the Study 7.3 Lost to Follow Up 8.3.4 Regulatory reporting requirements for SAEs and other safety reporting 8.3.7 Adverse events of special interest 8.3.9 Medication errors, or misuses of medicinal product	Multiple sections updated to align the protocol with EU CTR requirements.	To comply with EU CTR.

Section # and Name	Description of Change	Brief Rationale
8.3.10 Guidelines for reporting product complains 8.5.1 Deoxyribonucleic acid (DNA) 8.5.2 Ribonucleic acid (RNA) 8.6 Biomarkers 8.7 Immunogenicity assessments 8.9 Use of biological samples and data for future research 10.1.1 Regulatory and ethical considerations 10.1.4 Data protection 10.1.6 Dissemination of clinical study data and results 10.1.7 Data quality assurance 10.2 Appendix 2: Clinical Laboratory tests 10.3.1 Definition of AE 10.3.2 Definition of SAE 10.5 Appendix 5: Genetics 10.7 Appendix 7 Country specific/region requirements 10.7.1 Germany 10.7.2 European Union: Safety reporting to the agency 10.8 Appendix 8: Contingency measures for a regional or national emergency that is declared by a governmental agency 10.11 Appendix 11: Collection, storage, and future use of data and human biological samples		
1.1 Synopsis 4.1 Overall Design 4.4 End of Study Definition	Multiple sections updated to reflect the maximum Part B duration of 280 weeks (and not exceeding 296 weeks.)	To limit the extension of Part B to 40 months according to Health Authority request.
1.1 Synopsis 4.1 Overall Design	The sentence “The participant must be followed-up for 24 weeks after the completion of common EOS.” was added to the “overall design” subsection.	To provide better explanation regarding 24-week follow up period.
1.3.2 Schedule of activities for Part B	The clarification “every 12 weeks” was added to the column “Early EOT (Follow up visits planned through EOS)”.	Quartely safety visits instead of monthly.
	Phone calls to evaluate potential severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was removed.	Given the COVID-19 pandemic evolution and previous experience with frexalimab.
	Assessment of immunoglobulin (Ig) levels moved under the Safety procedures.	Clarification.
	The assessments MSIS-29 and PROMIS-Fatigue-MS-8 were updated.	To allow long term assessments.

Section # and Name	Description of Change	Brief Rationale
	The footnotes of the table were updated.	
2.3.1 Risk assessment	Statement “There is no signal of increased risk of thromboembolism in frexalimab clinical program.” added to the Table 2.	Clarification.
3 Objectives and endpoints	Additional timepoints added to exploratory endpoints in Table 4 (study Part B).	To allow long-term assessment for these exploratory endpoints.
8.3.7 Adverse events of special interest	The title was renamed to “Adverse events of special interest”.	Clarification.
10.13 Appendix 13: Protocol amendment history	The Section 10.13 is updated with subsection and Overall rationale and summary of changes for protocol amendment 03 is included in this section in the current amendment.	To be aligned with the current amendment.
Throughout	Minor corrections, template update, clarification.	Minor, therefore, have not been summarized.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2, double-blind, randomized, placebo-controlled study assessing efficacy and safety of SAR441344, a CD40L-antagonist monoclonal antibody, in participants with relapsing multiple sclerosis.

Brief title:

Proof-of-concept study for SAR441344 in relapsing multiple sclerosis

Regulatory agency identifier number(s):

IND:	138742
EU trial number	2024-513527-17
NCT:	NCT04879628
WHO:	U1111-1260-3962
EUDAMED:	Not applicable
Other:	Not applicable

Rationale:

The goal of this Phase 2 study is to assess efficacy and safety of frexalimab, also know as SAR441344 in people with relapsing multiple sclerosis (RMS). Frexalimab is an antagonist monoclonal antibody (mAb) which binds to human cluster of differentiation 40 ligand (CD40L) and blocks the cluster of differentiation 40 (CD40)/CD40L signaling pathway. This pathway is critical for humoral immune response, as well as for proinflammatory cytokines secretion by macrophages and reciprocal costimulation between T lymphocytes (T-cells) and antigen presenting cells. As such, it is relevant to autoimmune diseases in which pathogenic B lymphocyte (B-cells) play a key role, such as multiple sclerosis (MS) (1).

The proposed mechanism of action is that frexalimab should inhibit the formation of new active brain lesions in MS as measured by magnetic resonance imaging (MRI) and is expected to demonstrate efficacy by other clinical endpoints in longer trials to follow. This study will assess frexalimab efficacy by measuring changes in the number of gadolinium (Gd)-enhancing T1-hyperintense (GdE T1) lesions during treatment. This radiographic outcome has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS and has been demonstrated to be a predictive biomarker for clinical efficacy (reduction in annualized relapse rate [ARR]) in studies with other MS treatments (2, 3).

Frexalimab efficacy relative to placebo will be assessed at Week 12 by evaluating inhibition of the formation of new active brain lesions (new GdE T1 lesions) as measured by MRI. The study will also characterize safety and tolerability of frexalimab in participants with RMS.

The ACT16877 study will employ secondary MRI endpoints in an effort to collect supportive data on the potential benefit of frexalimab in neuroinflammation.

Exploratory assessments, such as analysis of neurofilament light chain (NfL) in plasma and advanced MRI methods, are expected to build evidence for frexalimab activity on neuroinflammation and neurodegeneration as well as potential effects on remyelination and tissue preservation.

Additional exploratory biomarkers will be assessed with the aim of:

1. Characterizing activation of the CD40/CD40L signaling pathway by analysis of the mRNA "signature" (levels of expression of genes) in whole blood or in subsets of PBMC in order to study treatment effects (MS CD40/CD40L signature score).
2. Investigating a potential differential response to treatment in patients utilizing biomarker results. This could allow segmentation of the patient population with a potentially higher efficacy of frexalimab in a subpopulation.

Objectives and endpoints

Part A	
Objectives	**Endpoints**
Primary	
• To determine the efficacy of frexalimab as measured by reduction of the number of new active brain lesions.	• Number of new gadolinium (Gd)-enhancing T1-hyperintense (GdE T1) lesions at Week 12 as measured by brain magnetic resonance imaging (MRI).
Secondary	
• To evaluate efficacy of frexalimab on disease activity as assessed by other MRI measures.	• Number of new or enlarging T2 lesions at Week 12. • Total number of GdE T1 lesions at Week 12.
• To evaluate the safety and tolerability of frexalimab.	• Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG), and vital signs during Part A. • Anti-drug antibodies (ADAs).
• To evaluate pharmacokinetics of frexalimab.	• frexalimab plasma concentrations over time. Pharmacokinetic (PK) parameters (maximum concentration [C_{max}], time to C_{max} [t_{max}], area under the curve over the dosing interval [$AUC_{0\text{-}tau}$], and elimination half-life [$t_{1/2}$]).

Part B	
Objectives	**Endpoints**
Secondary	
• To evaluate the long-term safety and tolerability of frexalimab.	• Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG), and vital signs during Part B.
• To evaluate the safety of the 1800 mg SC q4w dose regimen.	• Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG), and vital signs in the 1800 mg SC q4w dose regimen group (Part B2). • Anti-drug antibodies (ADAs).

Part B Objectives	Endpoints
• To evaluate pharmacokinetics of frexalimab beyond 12 weeks of study intervention for SC and IV regimen, including after switch to 1800 mg SC q4w.	• frexalimab plasma concentrations over time. Pharmacokinetic (PK) parameters (maximum concentration [C_{max}], time to C_{max} [t_{max}], area under the curve over the dosing interval [AUC_{0-tau}], and elimination half-life [$t_{1/2}$]).

Overall design:

ACT16877 is a Phase 2, multicenter, randomized, parallel-group, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of 2 doses/routes of administration of frexalimab in participants with RMS (relapsing-remitting MS and secondary progressive MS participants with relapses as per inclusion criteria). The study is open-label for route of administration and dose group and double-blinded for treatment assignment. Independent raters of MRI results will be blinded for study treatment and dose and other participants data.

The study consists of 2 parts:

Part A is a 12-week, double-blind, placebo-controlled part, preceded by a screening period starting not earlier than 4 weeks before Day 1.

At the beginning of Part A, participants will be randomly assigned in a 4:4:1:1 ratio to the frexalimab intravenous (IV) every 4 weeks (q4w) or frexalimab subcutaneous (SC) every 2 weeks (q2w) or IV placebo q4w or SC placebo q2w. Interactive response technology (IRT) will be used to assign treatment to participants. All participants will switch to Part B after the Week 12 visit.

Once the last participant has entered Part B, analysis of Part A data will be performed as the main analysis of the study.

Part B comprises open-label frexalimab treatment of 212 to approximately 280 weeks (approximately 53 to 70 months and not exceeding 296 weeks [74 months]) expected duration for individual participants, in order to allow further analysis of safety and efficacy. Participants from frexalimab treatment arms in Part A will continue their previous IV or SC treatment. Participants from the placebo treatment IV or SC arms in Part A will switch to IV q4w or SC q2w frexalimab treatment, respectively, starting from Week 12 visit. This design will allow reduction of exposure to placebo and allow continuation of assessment of safety and efficacy of frexalimab for a longer period. Treatment will be administered in an open-label fashion from Week 14 until the Common end of study (EOS). Further to Part A results, there will be no dose regimen change for the IV arm. In the SC arm, dose regimen will be modified to 1800 mg q4w (via syringe infusion material). Both regimens will continue until the Common EOS.

For the SC group, Part B will be divided in 2 subparts: Part B1 until individual participant switches to the modified dose regimen and Part B2 after this switch.

Based on the duration of recruitment of Part A and time needed for primary data analysis, it is expected that participants will be treated for a total duration of 292 weeks (73 months) of study intervention (and will not exceed 308 weeks [77 months]) in both parts of ACT16877.

A Common EOS will be planned when the first participant randomized has reached approximately 292 weeks (73 months) of study intervention administration. The participant must be followed-up for 24 weeks after the completion of common EOS (see Section 4.4 for details of common EOS). Upon completion of both Parts A and B of ACT16877, any decision to switch a participant to a locally available RMS treatment (disease-modifying therapy) will be taken by the treating physician, generally after the follow-up period.

Overall, maximum duration of study participation comprising screening period (4 weeks), Part A (12 weeks), Part B (up to 280 weeks and not exceeding 296 weeks), and safety follow-up (24 weeks) is 320 weeks (80 months) and will not exceed 336 weeks (84 months).

Brief summary:

This is a parallel, treatment, Phase 2, double-blind, 4 arms study to assess frexalimab injection compared with placebo injection for efficacy and safety in participants with relapsing multiple sclerosis.

Number of participants:

Approximately 160 participants will be screened to achieve 120 participants randomly assigned to the study intervention (based on a 25% screening failure rate) and 100 evaluable participants (based on an approximately 15% dropout).

Intervention groups and duration:

Part A of the study will last 12 weeks. Participants will receive q4w IV infusions or q2w SC injections of frexalimab or placebo (after a loading dose at Day 1) in a blinded fashion (not blinded for route of administration).

At Week 12, participants in the IV and SC placebo arms will switch to corresponding IV or SC frexalimab treatment.

In Part B, participants will receive study treatment in an open-label fashion:

- In the IV arm, q4w IV infusions until Common EOS.
- In the SC arm:
  - q2w SC injections of frexalimab until amended protocol 02 is approved and the syringe infusion material locally available (Part B1)
  - Then switched to q4w SC infusion via syringe infusion material until the Common EOS (Part B2). The switch to the new SC dose regimen will occur once amended protocol 02 is locally approved and the syringe infusion material is available at site.

Study intervention(s)

Part A:

IV arms: q4w administration of frexalimab (1800 mg on Day 1 followed by 1200 mg doses at Weeks 4 and 8) or matching placebo in a blinded fashion. At Week 12, placebo treatment group participants will receive frexalimab treatment loading dose of 1800 mg, while participants of frexalimab treatment arm will keep on 1200 mg dose on Week 12 in a blinded fashion.

SC arms: q2w administration of frexalimab (600 mg IV infusion loading dose on Day 1 followed by 300 mg SC injections on Weeks 2, 4, 6, 8 and 10) or matching placebo in a blinded fashion. At Week 12 visit, placebo treatment group participants will receive frexalimab treatment loading dose as an IV infusion of 600 mg and a placebo SC injection; while participants in the frexalimab treatment arm remain on the SC 300 mg dose and will receive a placebo IV infusion in a blinded fashion.

Part B:

IV arm: q4w administration of 1200 mg frexalimab IV will be performed in an open-label fashion to all participants from Week 16 onward.

SC arm: q2w administration of 300 mg frexalimab SC (Part B1). Then q4w administration by syringe infusion material of 1800 mg frexalimab SC (Part B2). All these administrations will be performed in an open-label fashion to all participants from Week 14 onward.

Investigational medicinal product(s)

- Formulation: frexalimab will be supplied in single use vials containing 300 mg frexalimab (150 mg/mL; extractable volume: 2 mL) or vials containing [redacted]. A matching placebo will be prepared using the same formulation as frexalimab without the active protein and be supplied in single use vials (extractable volume: 2 mL or [redacted]).
- Route(s) of administration: IV infusion in a 100 mL pre-filled 0.9% saline bag with a duration of administration of approximately 1 hour, SC injection (2 mL undiluted in Part B1) then SC infusion (12 mL undiluted in Part B2).
- Dose regimen: 1800 mg frexalimab (or matching placebo) IV on Day 1 followed by 1200 mg q4w IV for the IV arm; and 600 mg frexalimab (or matching placebo) IV on Day 1 followed by 300 mg q2w SC (Part A and Part B1) and then switch to 1800 mg q4w with the SC syringe infusion material for the SC arm (Part B2).

Auxiliary medicinal products

- Formulation: MRI contrast-enhancing preparations.
- Route(s) of administration: IV.
- Dose regimen: as per respective label.

Posttrial access to study medication

After participants have completed Part A, they will remain in Part B until the Common EOS. Then, post study access to study medication could be provided based on local/country regulations or a decision to switch to a locally available DMT will be made by the treating physician, in agreement with the participant.

Statistical considerations:

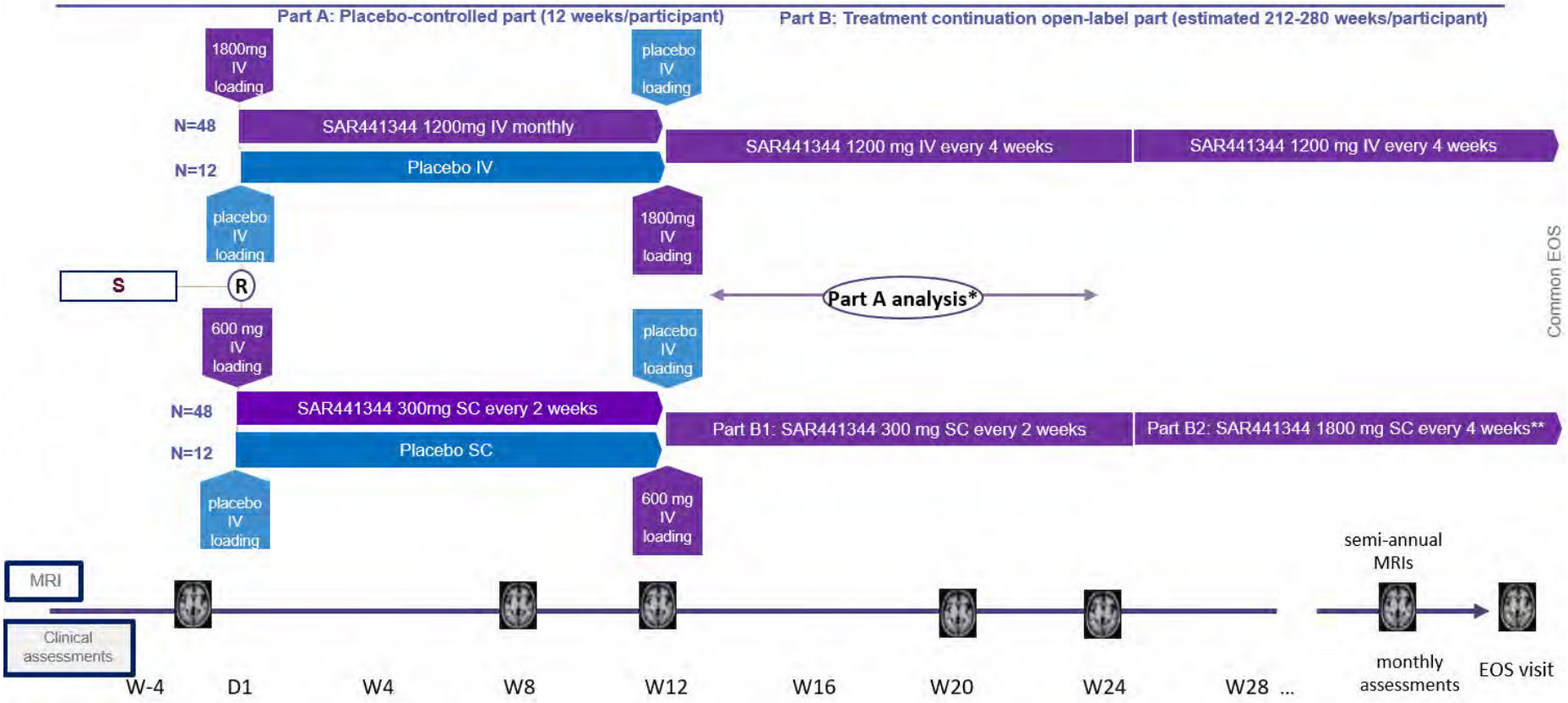
- Primary endpoint: Number of new GdE T1 lesions at Week 12 relative to Week 8 as measured by brain MRI.
- Main secondary endpoints:
  - Number of new or enlarging T2 lesions at Week 12 (relative to Week 8).
  - Total number of GdE T1 at Week 12.

For the primary and main secondary endpoints, the reduction in mean counts for participants treated with frexalimab relative to counts in participants receiving placebo (regardless of the administration route) will be estimated in the Efficacy Population.

Data Monitoring/Other committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: S = screening; R = randomization; N = number of participants; W = week; D = day; IV = intravenous; SC = subcutaneous, MRI = magnetic resonance imaging; EOS = end of study.
N = 120 (for at least 100 evaluable, randomization 4:1:4:1)
Blinding: double-blind for treatment group, open for dose and route of administration; participants receive either IV or SC.
* Further to Part A analysis, to increase its exposure at level similar to the IV arm, the SC arm dose regimen will be modified to 1800 mg q4w (via syringe infusion material). The IV arm will remain unchanged.
** Upon availability of syringe infusion material for SC infusion on site and local approval of amended protocol 02.

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Schedule of activities for Part A

Period	Screening (up to 4 weeks before Day 1)	Baseline/ Start of IMP	Part A								For participants with premature study discontinuation
									From D1 to W12		
Visit	W-4 to D-1	D1/W0	W2[a]	W4	W6[a]	W8	W10[a]	W12[b]	Unscheduled visits	Early EOT (follow all visits planned through Common EOS[c])	Follow-up visits (4 weeks, 12 weeks, and 24 weeks after EOT)
Window allowed[cc]			±2 days	±2 days	±2 days	±2 days	±2 days	±2 days		±3 days	±3 days
Visit number	1	2	3	4	5	6	7	8			
Informed consent	X										
Inclusion and exclusion criteria	X	X[d]									
Demography	X										
Medical history (includes prior medications)	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Randomization		X[d]									
Phone call to evaluate potential SARS-CoV-2 infection[f]	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration											
frexalimab /placebo[g]		X	X[a]	X	X[a]	X	X[a]	X[h]			
Safety											
Physical examination[i, d]	X	X		X		X		X	X	X	X

Period	Screening (up to 4 weeks before Day 1)	Baseline/ Start of IMP	Part A								For participants with premature study discontinuation
									From D1 to W12		
Visit	W-4 to D-1	D1/W0	W2[a]	W4	W6[a]	W8	W10[a]	W12[b]	Unscheduled visits	Early EOT (follow all visits planned through Common EOS[c])	Follow-up visits (4 weeks, 12 weeks, and 24 weeks after EOT)
Window allowed[cc]			±2 days	±2 days	±2 days	±2 days	±2 days	±2 days		±3 days	±3 days
Visit number	1	2	3	4	5	6	7	8			
Body weight[d], height[e]	X	X		X		X		X	If needed	X	If needed
Body temperature[d]	X	X		X		X		X	X	X	If needed
Vital signs[d]	X	X		X		X		X	X	X	X
12-lead ECG[d]	X	If needed[j]						X	If needed[j]	X	X (2nd and 3rd visit - if needed)
Local tolerability[l]		X	X	X	X	X	X	X			
AE collection and review	<----------										---------->
Safety laboratory											
Serology tests for hepatitis B and C[k], HIV1/HIV2. Serology for other infectious diseases if locally required.	X										
β-HCG test (if applicable)[n, d]	X	X		X		X		X	If needed	X	X
Serum FSH (if applicable)[m]	X										
Tuberculosis test (to be repeated, if needed)[o, p]	X										

Period	Screening (up to 4 weeks before Day 1)	Baseline/ Start of IMP	Part A								For participants with premature study discontinuation
									From D1 to W12		
Visit	W-4 to D-1	D1/W0	W2[a]	W4	W6[a]	W8	W10[a]	W12[b]	Unscheduled visits	Early EOT (follow all visits planned through Common EOS[c])	Follow-up visits (4 weeks, 12 weeks, and 24 weeks after EOT)
Window allowed[cc]			±2 days	±2 days	±2 days	±2 days	±2 days	±2 days		±3 days	±3 days
Visit number	1	2	3	4	5	6	7	8			
Hematology and biochemistry[q, d, r]	X	X		X		X		X	If needed	X	X (2nd and 3rd visit - if needed)
Coagulation[q, d]	X	X		X		X		X	If needed	X	X (2nd and 3rd visit - if needed)
Urinalysis[q, d]	X	X		X		X		X	If needed	X	
Antidrug antibodies[d]		X		X		X		X	In case of relapse	X	X (2nd and 3rd visit)
Pharmacokinetics											
Plasma sample collection[t] (frexalimab concentration)		X[s]		X[t]		X[t]		X[s, u]	In case of relapse	X	X (2nd and 3rd visit)
Efficacy											
MRI[v]	X[w]					X[d]		X[d]		At earliest possibility[x]	
EDSS[d]	X	X						X	If relapse suspected		
Patient-reported outcomes											
MSIS-29[y, d]	X (as close to D1 as possible)	X (if not done at screen)						X		X	

Period	Screening (up to 4 weeks before Day 1)	Baseline/ Start of IMP	Part A								For participants with premature study discontinuation
									From D1 to W12		
Visit	W-4 to D-1	D1/W0	W2[a]	W4	W6[a]	W8	W10[a]	W12[b]	Unscheduled visits	Early EOT (follow all visits planned through Common EOS[c])	Follow-up visits (4 weeks, 12 weeks, and 24 weeks after EOT)
Window allowed[cc]			±2 days	±2 days	±2 days	±2 days	±2 days	±2 days		±3 days	±3 days
Visit number	1	2	3	4	5	6	7	8			
PROMIS-Fatigue-MS-8[y, d]	X (as close to D1 as possible)	X (if not done at screen)						X		X	
PQATv3[y, d]								X		X	
PGIS-Fatigue[y, d]	X (as close to D1 as possible)	X (if not done at screen)						X		X	
PGIC-Fatigue[y, d]								X		X	
Pharmacodynamics/ Biomarkers											
Ig levels[d]		X				X		X		X	
Plasma sample for NfL, CHI3L1, and other biomarkers[d]		X						X		X	
Plasma sample for sCD40L[d]		X[aa]						X		X	X (2nd and 3rd visit)
PBMC substudy in selected centers (immunophenotyping and MS CD40/CD40L signature)[d]		X[z]		X[z]				X[z]		X[z]	

Period	Screening (up to 4 weeks before Day 1)	Baseline/ Start of IMP	Part A								For participants with premature study discontinuation
									From D1 to W12		
Visit	W-4 to D-1	D1/W0	W2[a]	W4	W6[a]	W8	W10[a]	W12[b]	Unscheduled visits	Early EOT (follow all visits planned through Common EOS[c])	Follow-up visits (4 weeks, 12 weeks, and 24 weeks after EOT)
Window allowed[cc]			±2 days	±2 days	±2 days	±2 days	±2 days	±2 days		±3 days	±3 days
Visit number	1	2	3	4	5	6	7	8			
Whole blood (PaxGene sample) (MS CD40/CD40L signature)[d]		X		X				X		X	
Archived blood sample[d, dd]		X									
Archived DNA sample[bb]	X										

Abbreviations: AE = adverse event; β-HCG = beta Human chorionic gonadotropin; CD40 = cluster of differentiation 40; CD40L = CD40 ligand; CHI3L1 = chitinase 3-like 1; D = day; W = week; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; EOS = end of study; EOT = end of treatment; FSH = follicle-stimulating hormone; FU = follow-up; HIV = human immunodeficiency virus; Ig = immunoglobulin; IMP = investigational medicinal product; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS = multiple sclerosis impact scale; NfL = neurofilaments light chain; PBMC = peripheral blood mononuclear cell; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; PROMIS = patient reported outcome measurement information system; PQATv3 = patient's qualitative assessment of treatment version 3; SARS-CovV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous; sCD40L = soluble cluster of differentiation 40 ligand.

a For the SC treatment arms only.

b Week 12 correspond to final assessment for Part A and to beginning of treatment for Part B; all laboratory samples must be collected before any treatment of Week12 (see *s* for PK sampling).

c See also Part B schedule for EOS details. Participants who agree, should continue all the visits scheduled until Common EOS even in case of early EOT, see relevant columns for visits schedule.

d To be performed before administration of IMP.

e At screening only.

f Participants will be contacted before each visit (latest on the day before the visit), by the Investigator or designee, to evaluate for signs and symptoms of a potential SARS-CoV-2 infection. In case of suspicion of such infection, the participant will be asked to not come to the study site and will be referred to a testing facility or his/her primary care physician according to local regulations. If the suspicion of a SARS-CoV-2 infection is excluded and there is no other reason to pause treatment in the judgment of the investigator, the treatment can continue. If the suspicion of a SARS-CoV-2 infection is confirmed, treatment should be stopped.

g Please refer to the administration of IMP by visit detailed in Table 7.

h SC injection must be performed after the predose PK sample is taken and before the start of the IV infusion. Participants receiving placebo are switched to frexalimab at Week 12.

i Full physical examination at screening, brief physical examination for the following visits.

j If suspicion of new cardiovascular event and ECG is needed for monitoring.
k if anti-HBs negative and Anti-HBc positive: perform hepatitis B virus DNA to confirm; if anti-HC IgG positive: IgG, HCV-RNA PCR will be performed.
l Injection/infusion site examination (until 2 hours following administration). Evaluation of SC injection/IV infusion site reactions following IMP administration will be performed by the Investigator or designee (local injection site reaction assessment, see Section 10.9.1) and by participants (pain-verbal descriptor scale, See Section 10.9.2).
m As needed in female of non childbearing potential only.
n Blood test at screening, then blood or urine test. Additional tests performed at the judgment of the investigator.
o Blood testing (eg, QuantiFERON® TB Gold test) is preferred; skin testing (eg, tuberculin skin test) with ancillary testing will be allowed if blood testing is not available and T-SPOT® can also be performed, if available. This test may not be suitable if previous treatment(s) have produced significant immunosuppression.
p Sites must consider assay results availability and perform tests more than 4 days before planned randomization.
q Please see Section 10.2 for details.
r Fasting is preferred if possible where clinical chemistry will be assessed.
s On Day 1 and at Week 12, PK sample collection will take place at 0 (predose), 1 hour (or end of infusion for IV arms), and 4 hours (after the beginning of infusion or later if participants stay longer at site for this visit) after the start of the IMP administration. Samples will be taken in the contralateral arm of that of the IMP infusion.
t Samples taken before IMP administration at Week 4 and Week 8.
u SC injection must be performed after the predose PK sample and before the IV infusion start.
v Magnetic resonance imaging can be performed within a window of ±3 days. If a participant has a confirmed relapse within 7 days prior to the next planned MRI scan, an MRI scan should be performed prior to administration of any corticosteroid treatment to the extent possible.
w Magnetic resonance imaging will be done as close as possible to randomization but not less than 5 days before randomization (considering the minimal duration needed for image submission and QC acceptance). MRI should preferably be performed once all other screening assessments are checked and none of them have excluded the patient.
x If the previous MRI was performed more than 1 month before.
y Patient-reported outcome (PRO) assessments - MSIS-29, PROMIS-Fatigue-MS-8, PGIC-Fatigue, PGIS-Fatigue, and PQATv3 will be completed by each study participant, prior to any treatment, laboratory work, radiological assessments, and discussion with the participant regarding treatment or health status.
z At selected sites. With single cell PBMC samples. PBMC samples from selected participants will be archived for later stage analysis.
aa On Day 1, sCD40L sample collection will take place at 0 (predose) and 1 hour (or end of infusion for IV arms).
bb Optional pharmacogenetic sample.
cc The reference for visit windows calculation is Day 1.
dd This sample will be collected and stored for use if any unexpected safety issue, to ensure that a pre-dose baseline value is available for previously not assessed parameters (eg, serology) and for biomarkers research, if agreed by the participant.

1.3.2 Schedule of activities for Part B

Period	Part B (for SC arm: Part B1 before switch to modified dose regimen, Part B2 after switch[r])											For premature study discontinuation
Visit	W14[a]	W16	W18[a]	W20	W22[a]	W24	q4w visits after W24 to EOS[r, s] W28, W32, W36, W40, W44, W48, W52, W56, W60, W64, W68, W72, W76, W80, W84, W88, W92, W96, W100, W104, W108, W112, W116, W120, W124, W128, W132, W136, W140, W144, W148,…W292[u]	Additional SC injection visits after W24 until switch to the SC q4w regimen[a, r] W26, W30, W34, W38, W42, W46, W50, W54, W58, W62, W66, W70, W74, W78, W82, W86, W90, W94,…	After W12 to EOS			
									Unscheduled visits	Early EOT (Follow up visits planned through EOS [every 12 weeks])[c]	EOS Common study end[c, aa]	Follow-up visits (4 weeks, 12 weeks, and 24 weeks after EOT)
Window allowed[q]	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±5 days	±5 days		±5 days	±5 days	±5 days
Visit number	9	10	11	12	13	14	All visits to EOS	All visits to EOS				
Inform consent							X[v]	X[v]				
Study treatment administration												
frexalimab[d]	X[a]	X	X[a]	X	X[a]	X	X[x]	X[a]				
Safety												
Physical examination[e, b]		X		X		X	Every 3 months[j]		X	X	X	X
Body weight[b]		X		X		X	Every 6 months[f]		If needed	X	X	If needed
Body temperature[b]		X		X		X	Every 3 months[j]		X	X	X	If needed
Vital signs[b]		X		X		X	Every 3 months[j]		X	X	X	X
12-lead ECG[b]						X	Every 6 months[f] if needed		If needed	X	X	If needed
Local tolerability[g]	X[a]	X	X[a]	X	X[a]	X	X	X[a]				
AE collection and review	<----------											---------->
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X
Ig levels[b, z]						X	Every 6 months up to W144, then W192 and W240[f]			X	X	

Period	Part B (for SC arm: Part B1 before switch to modified dose regimen, Part B2 after switch[r])											For premature study discontinuation
Visit	W14[a]	W16	W18[a]	W20	W22[a]	W24	q4w visits after W24 to EOS[r, s] W28, W32, W36, W40, W44, W48, W52, W56, W60, W64, W68, W72, W76, W80, W84, W88, W92, W96, W100, W104, W108, W112, W116, W120, W124, W128, W132, W136, W140, W144, W148,…W292[u]	Additional SC injection visits after W24 until switch to the SC q4w regimen[a, r] W26, W30, W34, W38, W42, W46, W50, W54, W58, W62, W66, W70, W74, W78, W82, W86, W90, W94,…	After W12 to EOS			
									Unscheduled visits	Early EOT (Follow up visits planned through EOS [every 12 weeks])[c]	EOS Common study end[c, aa]	Follow-up visits (4 weeks, 12 weeks, and 24 weeks after EOT)
Window allowed[q]	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±5 days	±5 days		±5 days	±5 days	±5 days
Visit number	9	10	11	12	13	14	All visits to EOS	All visits to EOS				
Safety laboratory												
β-HCG test (if applicable)[h, b]		X		X		X	X		If needed	X	X	X
Hematology and biochemistry[i, b, k]		X		X		X	Every 3 months[j, t]		If needed	X	X	
Coagulation[i, b]						X	Every 3 months[j]		If needed	X	X	
Urinalysis[i, b]						X	Every 6 months[f]		If needed	X	X	
Antidrug antibodies[b]		X		X		X	Every 3 months up to W168 Then every 6 months[t, w]		In case of relapse	X	X	X (2nd and 3rd visit)
Pharmacokinetics												
Plasma sample collection (frexalimab concentration)[l]		X		X		X	Every 3 months up to W168 Then every 6 months[t, w]		In case of relapse	X	X	X (2nd and 3rd visit)
Efficacy												
MRI[m]				X[b]		X[b]	Every 6 months[f, b]			at earliest possibility[n]	X	
EDSS[b]						X	Every 6 months[f]		If relapse suspected		X	
PROs												
MSIS-29[b]						X	Every 12 months from Week 192			X[o]	X	
PROMIS-Fatigue-MS-8[b]						X	Every 12 months from Week 192			X[o]	X	

Period	Part B (for SC arm: Part B1 before switch to modified dose regimen, Part B2 after switch[r])											For premature study discontinuation
Visit	W14[a]	W16	W18[a]	W20	W22[a]	W24	q4w visits after W24 to EOS[r, s] W28, W32, W36, W40, W44, W48, W52, W56, W60, W64, W68, W72, W76, W80, W84, W88, W92, W96, W100, W104, W108, W112, W116, W120, W124, W128, W132, W136, W140, W144, W148,...W292[u]	Additional SC injection visits after W24 until switch to the SC q4w regimen[a, r] W26, W30, W34, W38, W42, W46, W50, W54, W58, W62, W66, W70, W74, W78, W82, W86, W90, W94,...	After W12 to EOS			
									Unscheduled visits	Early EOT (Follow up visits planned through EOS [every 12 weeks])[c]	EOS Common study end[c, aa]	Follow-up visits (4 weeks, 12 weeks, and 24 weeks after EOT)
Window allowed[q]	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±5 days	±5 days		±5 days	±5 days	±5 days
Visit number	9	10	11	12	13	14	All visits to EOS	All visits to EOS				
PGIS-Fatigue[b]						X				X[o]		
PGIC-Fatigue[b]						X				X[o]		
Pharmacodynamics												
Plasma sample for NfL, CHI3L1, and other biomarkers[b]						X	W48, W72; W120 Then NfL and CXCL13 only (W144, W240)			X	X	
Plasma sample for sCD40L[b]											X	X (2nd and 3rd visit)
PBMC substudy in selected centers (immunophenotyping and MS CD40/CD40L signature)[b]						X[p]	W144, W240[p]			X[p]	X[p]	
Whole blood (PaxGene sample) (MS CD40/CD40L signature)[b]						X	W144, W240			X	X	
Archived blood sample[b, y]							W144, W240			X	X	

Abbreviations: AE = adverse event; β-HCG = beta Human chorionic gonadotropin; CD40 = cluster of differentiation 40; CD40L = CD40 ligand; CHI3L1 = chitinase 3-Like 1; W = week; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; EOS = end of study; EOT = end of treatment; FU = follow-up; Ig = immunoglobulin; IMP = investigational medicinal product; M = month; MRI = magnetic resonance imaging; MS = multiple sclerosis; NfL = neurofilament light chain; PBMC = peripheral blood mononuclear cell; PGIS = Patient Global Impression of Severity; PGIC PRO = patient-reported outcome; PROMIS = patient reported outcome measurement information system; MSIS = multiple sclerosis impact scale; PGIC = Patient Global Impression of Change; SARS-CovV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous; sCD40L = soluble cluster of differentiation 40 ligand.

a For additional injection visits in the SC treatment arm only (Part B1). If, in the judgment of the investigator, no adverse reaction have occurred or is suspected, SC injections of frexalimab (from Week 14 on) can be performed at home after appropriate medical training, assessment of the participant's self-injection or partner/caregiver/home healthcare professional capability and technique are done (please refer to product management manual). In the case of any injection site or other adverse reactions, the participant must contact the site as soon as possible to report the injection site reaction or other adverse event. The Investigator must monitor any worsening of events and schedule an on-site visit for evaluation and treatment, if needed. The Investigator will also proactively contact the participant on the day of injection to ensure the best management of injection site reaction or other adverse event, should this occur. Additional SC visit for 300 mg q2w SC regimen continued until switch to 1800 mg q4w SC via syringe infusion material (upon local approval of amended protocol 02 and availability of the syringe infusion material on site). Depending on the switch visit: W98, W102, W106, W110, W114, W118, W122, W126, W130, W134, W138, W142, W146.

b To be performed before administration of IMP.

c Participants should continue with scheduled visits until the Common EOS even in case of EOT. See relevant columns for visits schedule.

d From Week 12 on, participants treated with placebo during Part A will be treated with frexalimab. Please refer to the administration of IMP by visit as detailed in Table 7.

e Brief physical examination.

f Semi-annual visits after Week 24 until Week 144 (W48/M12, W72/M18, W96/M24, W120/M30, W144/M36), then W192/M48 and W240/M60).

g Injection/infusion site examination (2 hours after administration; can be reduced to 1 hour after Week 12 if the Investigator judges this adequate). Evaluation of SC injection/IV infusion site reactions following IMP administration will be performed by the Investigator or designee (local injection site reaction assessment, see Section 10.9.1) and by participants (pain-verbal descriptor scale, See Section 10.9.2).

h Blood or urine tests; additional test if indicated in the judgment of the Investigator.

i Please see Section 10.2 for details.

j Quarterly visits after Week 24 to EOS (W36/M9, W48/M12, W60/M15, W72/M18, W84/M21, W96/M24, W108/M27, W120/M30, W132/M33, W144/M36, W156/M39, W168/M42, W180/M45, W192/M48, W204/M51, W216/M54, W228/M57, W240/M60, W252/M63, W264/M66, W276/M69, W288/M72).

k Fasting is preferred if possible where clinical chemistry will be assessed.

l Samples are to be taken before IMP administration.

m Magnetic resonance imaging can be performed within a window of ±3 days. If a participant has a confirmed relapse prior to 7 days before the next planned MRI scan, an MRI scan should be performed at the time of the relapse confirmation and prior to administration of any corticosteroid treatment, whenever possible.

n If the previous MRI was performed more than 1 month prior.

o If EOT earlier than Week 24.

p At selected sites. With single cell PBMC samples. PBMC samples from selected participants will be archived for later stage analysis.

q The reference for visit windows calculation is Day 1.

r The switch should occur at a q4w visit (not at an additional q2w visit).

s Part B IV and Part B2 SC arm after switch from 300 mg q2w SC to 1800 mg q4w SC via syringe infusion material (upon local approval of amended protocol 02 and availability of the syringe infusion material on site).

t For SC arm in part B2 (after switch from 300 mg q2w SC to 1800 mg q4w SC upon local approval of amended protocol 02 and availability of the syringe infusion material on site), monthly assessments of hematology/biochemistry and PK/ADA for the first 12 weeks. Then resume Part B periodicity of the q4w arm. See Table 1.

u W28/M7, W32/M8, W36/M9, W40/M10, W44/M11, W48/M12, W52/M13, W56/M14, W60/M15, W64/M16, W68/M17, W72/M18, W76/M19, W80/M20, W84/M21, W88/M22, W92/M23, W96/M24, W100/M25, W104/M26, W108/M27, W112/M28, W116/M29, W120/M30, W124/M31, W128/M32, W132/M33, W136/M34, W140/M35, W144/M36, W148/M37, W152/M38, W156/M39, W160/M40, W164/M41, W168/M42, W172/M43, W176/M44, W180/M45, W184/M46, W188/M47, W192/M48, W196/M49, W200/50, W204/M51, W208/M52, W212/M53, W216/M54, W220/M55, W224/M56, W228/M57, W232/M58, W236/M59, W240/M60, W244/M61, W248/M62, W252/M63, W256/M64, W260/M65, W264/M66, W268/M67, W272/M68, W276/M69, W280/M70, W284/M71, W288/M72, W292/M73

v All participants should sign the updated Inform consent form after amended protocol 02 local approval.

w Quarterly visits after Week 24 to Week 144 (W36/M9, W48/M12, W60/M15, W72/M18, W84/M21, W96/M24, W108/M27, W120/M30, W132/M33, and W144/M36) then every 6 months (W192/M48, W216/M54, W240/M60, W264/M66, W288/M72)

x [redacted] and in Part B2 (from 12 weeks after switch) for SC arm, optional home administration may be considered for interim visits between 2 quarterly onsite visits (those with physical examination and laboratory sampling). In this case, home nurse intervention after appropriate medical training and assessment of practical conditions will be required (please refer to product management manual).

y This sample will be collected and stored for use if any unexpected safety issue, to ensure that a post-baseline value is available for previously not assessed parameters (eg, serology) and for biomarkers research, if agreed by the participant.

z In case of low value, retest is allowed within the screening period.

aa For individual participant, the maximum duration of Part B is limited to 296 weeks (74 months).

1.3.3 Schedule of activities for the initial 12 weeks of Part B2

In the SC arm, additional procedures will be done, as described in Table 1.

Table 1 - Additional activities for the first 12 weeks of Part B2 (if not already planned in the Part B SOA)

Period	Part B2	
Visit	**First 4 q4w visits:** • Switch visit, • Switch visit +4 weeks, • Switch visit +8 weeks, • Switch visit +12 weeks.	**Following visits**
Window allowed	**+/-5 days**	**+/-5 days**
Hematology and biochemistry	X	As planned per Part B SoA
Antidrug antibodies	X	
Plasma sample collection (frexalimab concentration)	X	
Other assessments	As previously planned	

2 INTRODUCTION

2.1 STUDY RATIONALE

The goal of this Phase 2 study is to assess the efficacy and safety of frexalimab in people with RMS. Frexalimab also know as SAR441344 is an antagonist mAb which binds to human CD40L and blocks the CD40/CD40L signaling pathway. This pathway is critical for humoral immune response, in particular T-cell-dependent antibody response (TDAR), as well as for reciprocal costimulation between T-cells and antigen-presenting cells, and related proinflammatory cytokines secretion by macrophages. As such, frexalimab may be relevant to autoimmune diseases in which pathogenic B-cells play a key role, such as MS (1).

The proposed mechanism of action for frexalimab is inhibition of T-cells interaction with B-cells and antigen-presenting cells and suppression of autoimmune pathologic processes such as formation of new active focal brain lesions in MS as well as diffuse inflammation in brain tissue. Focal active brain lesions can be measured by MRI. frexalimab reduction or amelioration of these would be predictive of clinical efficacy in MS patients. This study will assess frexalimab efficacy by measuring changes in the number of GdE T1 lesions. This radiographic outcome has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS and has been demonstrated to be a predictive biomarker for clinical efficacy (reduction in ARR and disability worsening) studies with other MS treatments (2, 3).

Treatment efficacy for lesion reduction will be assessed at Week 12 comparing frexalimab and placebo treatment groups. Frexalimab efficacy relative to placebo will be assessed by evaluating inhibition of the formation of new active brain lesions (new GdE T1 lesions) as measured by MRI. The study will also characterize safety and tolerability of frexalimab in participants with RMS.

This ACT16877 study will employ secondary MRI endpoints in an effort to collect additional data on other potential benefits of frexalimab.

Important data is expected from the exploratory objective of characterizing activation of the CD40/CD40L signaling pathway by analysis of mRNA “signatures” (levels of expression of genes) in blood. This will facilitate study of treatment effects, including changes in expression of ‘signature genes’ (‘MS CD40/CD40L signature’ score) and assessment of correlation of the “CD40/CD40L mRNA signature” with efficacy of frexalimab on the primary and other study endpoints. Identification of a subpopulation with increased CD40/CD40L signaling might allow targeting frexalimab to those who could most benefit.

Other exploratory assessments, such as quantification of levels of NfL and Chi3L1 in blood and advanced MRI methods, are expected to support evidence for frexalimab activity on neuroinflammation and neurodegeneration as well as potential effects on tissue preservation. Immunophenotyping and other biomarker assessments will allow better understanding of frexalimab effects on immune system and on neuroinflammation processes of MS.

2.2 BACKGROUND

Immunomodulatory drugs are the mainstay of MS therapy. Recently, clinical studies have demonstrated very good efficacy of agents that target B-cells, especially B-cell-depleting agents like ocrelizumab or ofatumumab (anti-CD20) (4, 5). New treatments that are specific, non-depleting, and provide new mechanisms of action are needed to further reduce disease progression and improve long-term outcome in MS.

Beyond the existing strategy of modulating the cellular elements of adaptive immunity, there is mounting evidence that innate immunity, mediated by myeloid cell lineages (bone-marrow-derived monocytes/macrophages and central nervous system [CNS] -resident microglial cells), is responsible for many of the neurodegenerative aspects of MS that persist despite the effectiveness of approved disease-modifying therapies in preventing acute relapses (6, 7).

There is still a significant unmet need for therapies that target neuroinflammation in the CNS with a goal of halting long-term disability and neurodegeneration in people with RMS a well as in those with progressive forms of MS (primary progressive multiple sclerosis [PPMS] and secondary progressive multiple sclerosis [SPMS]). Even the most recent high-efficacy disease-modifying therapies act mainly on adaptive immunity in the periphery with only modest or temporary ability to halt neuroinflammatory and neurodegenerative processes and stop disease progression. Therefore, development of MS treatments with new modes of action involving not only adaptive but also innate immunity is of interest.

Through its interactions with CD40, CD40L is best known for its role as an immunologic second signal, it is expressed on T-cells and is required for B-cell activation/maturation and dendritic cell maturation (8). CD40L loss of function is associated with development of hyper-immunoglobulin (Ig) M syndrome characterized by inhibition of B-cell maturation, loss of germinal center formation, absence of isotype switching, affinity maturation and somatic hypermutation, and inability to form long-lived plasma and memory B-cells (9). In addition to its role in B-cell maturation, CD40L is thought to enhance macrophage effector function and aid in the development of CD8+ memory T-cells. Disruption of the CD40/CD40L pathway in autoimmune diseases, particularly those where pathogenic B-cell responses are a key hallmark of disease, as in MS, would be predicted to impact both cellular and humoral responses and have therapeutic benefit.

Importance of CD40/CD40L pathway in immune signaling in MS can indirectly be supported by observed increase of soluble CD40L in people with MS (10). Higher levels of soluble CD40L are observed in people with RRMS as compared to patients with SPMS (11), suggesting different involvement of this pathway activation and which is found related to CD40L expression increase on immune cells (12).

Given the critical role of CD40L in the adaptive immune response, anti-CD40L therapies are being developed for the treatment of diseases such as immune thrombocytopenic purpura, and systemic lupus erythematosus with some early signs of efficacy. Unfortunately, first generation anti-CD40L therapies are associated with increased thromboembolic events in clinical trials and ultimately resulted in the discontinuation of their development (“thromboembolic” event or

"thromboembolism" are used in this document to denote any arterial or venous thrombotic or embolic events). Elevated thromboembolic risk seen with first generation anti-CD40L mAb therapies resulted from platelet activation triggered by FcγRIIa activation by higher order immune complexes containing the anti-CD40L mAb and CD40L (membrane or soluble forms), expressed by platelets (13, 14).

Understanding fragment crystallizable (Fc)-mediated thromboembolic risk resulted in the engineering of second-generation anti-CD40L therapies that either did not contain an Fc or contained a modified Fc with low FcγRIIa binding, with the goal of eliminating thromboembolic risk. Frexalimab has a modified Fc region. In the first-in-human clinical trial with frexalimab (TDU15525/TDR15526) and ongoing Phase 2 clinical trials, no thromboembolic event has occurred.

Frexalimab is derived from the humanized mAb IDEC-131, with 2 major modifications: 1) affinity maturation of the variable region, and 2) mutations in the Fc region to inhibit binding to the FcγRIIa receptor. Similar to the first-generation IDEC-131, frexalimab, binds to CD40L and prevents binding to and signaling via CD40. Additional information on frexalimab may be found in the Investigator's Brochure (IB). CD40L is a member of the tumor necrosis factor alpha superfamily. It is transiently expressed on the surface of cells and platelets as a homotrimer and may be released in a biologically active form into circulation (15). CD40L is also expressed on a variety of other cell types including T-helper (Th) cells, platelets, endothelial cells, smooth muscle cells, macrophages, and antigen presenting cells.

Nonclinical studies: The frexalimab nonclinical package, as described in the IB, demonstrated that thromboembolism is not an identified hazard of the frexalimab toxicology profile. The frexalimab toxicology profile is consistent with its pharmacology and includes decreased cellularity in germinal centers, moderate decrease in B-cells and decreased TDAR to keyhole limpet hemocyanin (KLH) antigen. Effects on immune system and potential opportunistic infections are expected hazards of frexalimab. These effects on the immune system are monitorable and are expected to resolve after antibody discontinuation. Antidrug antibody (ADA) formation was generally observed at lower doses in frexalimab toxicology studies, but the frexalimab mechanism of action should reduce the impact of ADA formation at higher doses.

The no-observed-adverse-effect level (NOAEL) from the 6-month Good Laboratory Practice (GLP) toxicity study in cynomolgus monkeys was 100 mg/kg/week IV, with a Day 169 area under the curve (AUC) from hour 0 to 168 hours ($AUC_{0\text{-}1\ week}$) of 468 000 µg*h/mL. The maximum concentration (C_{max}) achieved was 5210 µg/mL. For details on the non GLP and GLP toxicity studies performed within the nonclinical assessment of frexalimab, please refer to the IB.

Based on the 6-month GLP toxicology study in the non-human primate, the PK exposure ($AUC_{0\text{-}4\ weeks}$) of 1 872 000 µg*h/mL and C_{max} of 5210 µg/mL are considered safe. The predicted exposure of 1800 mg IV loading dose followed by 1200 mg IV q4w dose regimen in clinical trials are estimated at 222 000 µg*h/mL for $AUC_{0\text{-}4\ weeks}$ (at steady state) and 650 µg/mL for C_{max} (reached after the IV loading dose), leading to a safety margin of 8 compared to the NOAEL. For the initial SC treatment, with 600 mg IV loading dose followed by 300 mg SC q2w, predictive exposure corresponds to 3-fold less exposure than for the q4w IV treatment (with $AUC_{0\text{-}4\ weeks}$ at steady state and C_{max} after IV loading dose of 75 000 µg*h/mL and 217 µg/mL respectively), so

its safety margin is even larger. In part B2, with the SC dose regimen 1800 mg SC q4w, $AUC_{0\text{-}4\ weeks}$ (at steady state) are predicted to be similar to those obtained with the 1200 mg q4w IV regimen with a lower C_{max} estimated as 450 µg/mL versus 650 µg/mL.

Phase 1 first-in-human study:

TDU15525 (single ascending dose study)

TDU15525 study is a Phase 1, double-blind, randomized, parallel design, placebo-controlled single ascending dose study conducted to evaluate the safety, tolerability, PK, and PD of IV doses of frexalimab in healthy adult participants. Five sequential ascending single doses of frexalimab (200, 600, 1200, 2100, or 3000 mg) or matching placebo were diluted to a final volume of approximately 100 mL in 0.9% normal saline and administered on Day 1 by IV infusion over approximately 1 hour. All participants were immunized with a single dose of KLH on Day 4. A total of 40 healthy adult participants, including 22 (55.0%) males and 18 (45.0%) females received the investigational medicinal product (IMP). Each cohort consisted of 8 participants, 6 receiving frexalimab and 2 receiving placebo.

Overall, a single IV dose of frexalimab between 200 and 3000 mg was safe and well tolerated. There were no SAEs or severe treatment-emergent adverse events (TEAEs). No trends in vital signs, electrocardiograms (ECGs) or laboratory values were identified, including assays aimed at identifying potential increased risks for thromboembolism or infections.

The t_{max} for frexalimab was observed between 1 hour (end of infusion) to 2 hours postdose. frexalimab exposure increased with no deviation from dose proportionality from 200 to 3000 mg. Mean terminal half-lives ranged from 25 to 35 days over the dose range.

While there were fewer anti-KLH IgG values above the lower limit of quantification in all active treatment groups relative to placebo, the anti-KLH IgG response was weak and variable, even in participants receiving placebo. A likely explanation is that only 1 dose of KLH was administered which induced variable levels of IgG. Therefore, no formal dose-response relationship was established in this study.

TDR15526 (multiple ascending dose study)

TDR15526 was a Phase 1, double-blind, randomized, parallel design, placebo-controlled multiple ascending dose study investigating 5 dose levels of frexalimab or placebo controls in healthy adult participants. Five multiple doses (3 injections, q2w) of frexalimab (150 mg [10 participants], 300 mg [8 participants], 600 mg [9 participants], 1200 mg [9 participants], and 2100 mg [8 participants]) or matching placebo (12 participants) were administered via the SC route on Days 1, 15, and 29. All participants were immunized with KLH on Days 4 and 32. A total of 56 healthy adult participants, including 46 (82.1%) males and 10 (17.9%) females received the IMP.

Overall, 5 dose levels of frexalimab between 150 and 2100 mg administered SC as 3 doses q2w in healthy male and female adult participants were safe and well tolerated. There were no serious or severe TEAEs. Three participants discontinued treatment due to AEs of elevated transaminases (alanine aminotransferase [ALT] increase up to approximately 2.5 × ULN) (frexalimab 150 mg), pityriasis (placebo), and presyncope (frexalimab 2100 mg).

No trends in vital signs, ECGs, or laboratory values were identified, including assays aimed at identifying potential increased risks for thromboembolism or infections. Three participants have developed a positive ADA during the study (2 from the 150 mg dose cohort and 1 from the 2100 mg dose cohort).

After single and repeated SC administration of frexalimab, median t_{max} ranged from 3 to 7 days postdose. Frexalimab exposure increased with no deviation from dose proportionality from 150 to 2100 mg. Steady state was not reached after the third administration. Accumulation ratio estimates ranged from 1.90 to 2.43 for C_{max} and from 2.09 to 3.05 for $AUC_{0\text{-}2\ weeks}$. Mean terminal half-lives were estimated at 22 days at the lowest dose of 150 mg and between 29 and 33 days for doses ranging from 300 mg to 2100 mg.

In participants receiving placebo, the 2 doses of KLH administered in this multiple ascending dose study induced a strong TDAR response, as measured by anti-KLH IgG levels in the majority of participants. frexalimab administration resulted in a dose-dependent inhibition of the TDAR response, with partial inhibition in the 150 mg and 300 mg cohorts (84% and 92%, respectively), and near complete (>97%) inhibition in the 600 mg, 1200 mg, and 2100 mg dose cohorts. The extent of inhibition at each dose level at steady state would be anticipated to be more extensive than the values observed in this study after 3 administrations.

ACT16877 Part A

ACT16877 Part A was a Phase 2, double-blind, randomized, parallel design, placebo-controlled study investigating 2 dose levels of frexalimab or placebo controls in participants with relapsing MS. Fifty-two participants were exposed to frexalimab 1200 mg IV q4w, 51 to frexalimab 300 mg q2w SC, and 26 to placebo.

The analysis of the Part A of ACT16877 demonstrated a reduction in the number of new active GdE T1 lesions after 12 weeks (relative to Week 8) with frexalimab as compared to the placebo group. A 89% reduction (95%CI: 62% - 97%) in the adjusted mean monthly count of new GdE T1 lesions was observed in the frexalimab IV group as compared to the placebo group meeting the predefined criteria for positive conclusions (see Section 9.3.2). A 79% reduction (95%CI: 44% - 92%) in the adjusted mean monthly count was observed in the frexalimab SC group as compared to the placebo group, but it did not meet the predefined criteria.

Overall, the dose levels of frexalimab (1200 mg IV q4w and 300 mg q2w SC) administered to adult participants with RMS were safe and well tolerated. A higher percentage of participants who reported at least 1 TEAE was observed in the frexalimab low dose (SC) group versus frexalimab high dose (IV) group and placebo groups (23 [45.1%] in the frexalimab SC group versus 15 [28.8%] in the frexalimab IV group and versus 8 [30.8%] in the placebo groups). This was mainly driven by the TEAEs of coronavirus disease 19 (COVID19) (5 [9.8%] in the frexalimab low dose group versus 0 in the frexalimab high dose group and versus 0 in the placebo groups). There were no TEAEs leading to death nor treatment-emergent SAEs, nor severe TEAEs. One participant in the frexalimab low dose group had TEAE of COVID-19 that led to study intervention discontinuation, as per protocol procedure. Six participants had treatment emergent AESIs: 5 participants had non-serious COVID-19 and 1 participant had non-serious alanine aminotransferase (ALT) increase. All AESIs were resolved. There were no participants with TEAEs of TE events or severe infection.

Mean exposure between Week 8 and Week 12 (AUC_{W8-W12}) was 3-fold higher in participants receiving frexalimab 1200 mg IV q4w than in participants receiving frexalimab 300 mg SC q2w.

2.3 BENEFIT/RISK ASSESSMENT

Frexalimab is a novel, potent CD40L inhibiting antibody that is being developed for several autoimmune diseases including MS. The disruption of the CD40/CD40L pathway in autoimmune diseases pathogenic B-cell responses, a key hallmark of disease, is predicted to impact both cellular and humoral responses and have therapeutic benefit.

2.3.1 Risk assessment

Although first generation anti-CD40L therapies were discontinued due to thromboembolic events, the second-generation therapies, including frexalimab, have addressed this risk by modifying the Fc region to prevent FcγRIIa binding and platelet activation. No safety signal of thromboembolic events has emerged in public data from clinical trials of second-generation anti-CD40L therapies. In addition, the frexalimab nonclinical package did not identify thromboembolic events as a hazard.

Human exposure to frexalimab is limited to the completed Phase 1 first-in-human (FIH) study in healthy participants and the 3 ongoing Phase 2 clinical studies (ACT16877 in MS, ACT16618 in pSjS, and ACT17010 in SLE). Overall, the study drug was considered generally safe and well-tolerated following both a single dose administration of up to 3000 mg IV (TDU15525) and up to 2100 mg SC q2w for 3 doses (TDR15526). No SAEs and no clinically significant abnormalities in vital signs, ECG parameters, or laboratory changes in healthy participants who received at least one dose of the study drug were reported, including assays aimed at identifying potential increased risks for thromboembolism or infections. No significant safety findings in the ongoing Phase 2 clinical studies have been identified so far. More information can be found in the IB.

Due to limited information on the safety and efficacy of frexalimab, the nature, severity, and frequency of potential adverse drug reactions have not been characterized. Based on nonclinical data, Phase 1, unblinded ACT16877 Part A and ongoing Phase 2 studies clinical data from frexalimab and safety profiles of the same class of compounds in development, the following are the potential risks anticipated in humans:

Table 2 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
Thromboembolic events	The first -generation anti-CD40L therapies were associated with an increased risk of thromboembolic events. The frexalimab nonclinical package did not identify thromboembolism as a hazard. The nonclinical package included:	**Risk assessment:** • Regular monitoring of platelet counts and AEs which may suggest possible thromboembolic events. • Confirmed thromboembolic event to be reported as AESI.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	• In vitro assessment of the Fc gamma receptor binding profile of frexalimab. • Repeat-dose studies (up to 100 mg/kg weekly) in monkeys. • Platelet activation potential assessment in vitro in blood of healthy subjects, and MS and SLE patients. Platelet count and D-dimer were monitored throughout the FIH Study (TDU15525, TDR15526) and while transient abnormal values were occasionally noted, there were no clinically significant sustained changes from baseline. No frexalimab-related thromboembolic events have been observed in the completed Phase 1 and Phase 2, and ongoing Phase 1 and Phase 2 clinical studies with frexalimab (PKM17227, ACT16877, ACT16618, and ACT17010). There is no signal of increased risk of thromboembolism in frexalimab clinical program.	**Risk Minimization:** • Removal or modification of the Fc region has addressed the thromboembolic risk as indicated by second-generation therapies showing no elevated risk in nonclinical models or clinical studies. • Exclusion of participants with any history of clinically significant[a] thromboembolic events, as well as myocardial infarction, stroke, antiphospholipid syndrome, and/or participants requiring antithrombotic treatment.
Infection including opportunistic infections	Frexalimab inhibits CD40/CD40L interactions which plays a key role in the adaptive immune response, particularly humoral immunity. Based on the findings of the 13-week GLP toxicology study and knowledge of the CD40L loss of function phenotype in humans, inhibition of CD40L may increase the risk of upper and lower respiratory infections and gastrointestinal infections as well as opportunistic infections. In the 13-week GLP toxicology study, a moderate decrease in B-cells was noted, without a significant decrease in cell numbers and recovered after a 10-week recovery period. In the 6-month GLP toxicology study without a recovery period dose-independent slight to moderate decreases in absolute counts of B-cells were observed with statistical significance for all frexalimab treated groups. Treatment with anti-CD40L therapies is associated with modest reductions in IgG in clinical studies. Both were not detected in the completed Phase 1 studies (TDU15525, TDR15526).	**Risk assessment:** • Adverse event reporting. Severe infections, including opportunistic infections, are considered AESI. • Baseline detection and exclusion of TB, HIV, hepatitis tests. To be repeated in case of suspicion. **Risk minimization:** • Exclusion of participants with active or latent tuberculosis with TB test, HIV infection, chronic viral hepatitis or other known opportunistic infection, history of severe parasitic infections, as well as active infections or chronic ongoing infections of any course. • Clinical vigilance for infections, including prompt diagnosis and treatment. • Temporary treatment discontinuation can be considered in participants with any acute infections on a case-by-case basis at the discretion of investigator after evaluation of severity based on clinical and laboratory assessments. Decision to continue treatment after discontinuation can be made if the investigator considers from his/her clinical judgment that the participant has recovered from infection, based on absence of residual symptoms and/or available lab results confirming infection resolution. • No live vaccines/live components.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	SARS-COV-2 infection/COVID-19: No detailed data available on the specific role of CD40L in the course of a SARS-CoV-2 infection/COVID-19. Currently, there is no evidence that CD40L is relevant for the viral infection with SARS-CoV-2. There is evidence that the development of viral clearance and a potential protective immunity follow the generation of an adaptive immune response, including the production of neutralizing antibodies, in which the CD40/CD40L interaction plays a key role. Therefore, blocking CD40L may prevent antibody formation and immune response in case of an acute SARS-CoV-2 infection and might prevent long-term immunity. No serious TEAEs of COVID-19 were reported in the ongoing Phase 1 and Phase 2 clinical studies (PKM17227, ACT16877, ACT16618, and ACT17010) that were conducted during or after the start of the pandemic.	**Risk assessment:** • All diagnosed and biologically proven SARS-CoV-2 infections are considered AESI. • Monitoring the local, regional, national and global situation of COVID-19 spread. **Risk minimization:** • Exclusion of high risk populations for COVID-19 due to the general selection of study participants for the current studies. • Exclusion of participants who live in long-term care facilities and nursing homes. • Exclusion of patients with significant lymphopenia and significant neutropenia. • The IMP may permanently be discontinued if according to the Investigator a permanent IMP discontinuation is necessary in the best interest of the participant. • Temporary study intervention discontinuation can be considered in case of SARS-CoV-2 suspicion and/or biologically confirmed SARS-CoV-2 infection (positive antigen and/or PCR test). Decision to resume treatment after discontinuation can be made if the investigator considers from his/her clinical judgment that the participant has recovered from the Covid-19 infection, based on absence of residual symptoms and available negative PCR test results. • Study sites need to apply protective measures according to local guidance.
Immunogenicity/ hypersensitivity	Due to its mechanism of action, frexalimab may reduce the risk of ADA formation in humans. Nevertheless, ADA may result in alterations in frexalimab exposure and in extreme cases could result in a Type III hypersensitivity reaction. In total, only 4 subjects developed ADA (TDU15525: One participant after 200 mg IV single infusion; TDR15526: 2 participants after 150 mg SC 3 × q2w, 1 participant in the 2100 mg SC 3 × q2w group only at EoS). There were no SAEs relevant to this risk in the ongoing Phase 2 studies.	**Risk assessment:** • Antidrug antibodies detection during the study through 4 elimination half-lives. • Hypersensitivity reactions will be systematically monitored (eg, chills, rash, urticaria, hypotension). • Anaphylactic reaction/acute allergic as well as infusion related reaction to be reported as an AESI. **Risk minimization:** • Intravenous administration of 1 hour minimum with a monitoring period of 3 hours at the study site afterwards. • Symptomatic treatment of any immunogenicity related AEs. • Antidrug antibodies will be checked if there is a safety concern.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Injection site reaction/local tolerability at injection site	IV administration in study TDU15525 has been well tolerated up to 3000 mg IV. Subcutaneous administration in TDR15526 up to 14 mL was overall well tolerated, with 3 frexalimab-treated subjects showing mild injection site reactions. There were no SAEs of injection site reactions in the ongoing Phase 1 and 2 clinical studies.	**Risk assessment:** • Thorough medical examination of the injection sites and implementation of assessment scale. • Severe injection and infusion site reaction will be reported as AESI. **Risk minimization:** • Loading dose will be administered IV to avoid large volume SC injection. • For administration of high SC doses (1800 mg in 12 mL), SC infusions will be administered via syringe infusion material to allow slow delivery. • Monitoring of the injection site after IMP injection.
Other		
Gadolinium contrast agent injection	Allergic reaction	Exclusion of patients with known history of allergy to any contrast medium

Abbreviations: ADA = antidrug antibodies, AE = adverse event, AESI = adverse event of special interest, CD40 = cluster of differentiation 40, CD40L = cluster of differentiation 40 ligand, EOS = end of study, FIH = first in human, GLP = Good Laboratory Practice, HIV = human immunodeficiency virus, Ig = immunoglobulin, IMP = investigational medicinal product, IV = intravenous, q2w = once every 2 weeks, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SC = subcutaneous, TB = tuberculosis.

a The term "significant" refers to risks and events with major clinical implications, affecting patient morbidity or mortality. "Non-significant" events are those with lower clinical impact, often self-limiting or manageable conservatively (eg, superficial thrombophlebitis during immobilization without prophylaxis). Examples of significant TE risks: hypercoagulable states (factor V Leiden, protein C/S deficiency, antiphospholipid syndrome), chronic diseases (cancer, atrial fibrillation, heart failure, autoimmune diseases, diabetes, hyperlipidemia), lifestyle (smoking, obesity), surgery (orthopedic, abdominal, pelvic), trauma (fractures in pelvis, hip, leg). Examples of significant TE events: pulmonary embolism, deep vein thrombosis, ischemic stroke, myocardial infarction, arterial embolism.

The potential risks associated with frexalimab are well defined, and appropriate risk mitigation strategies have been put into place for all ongoing and future clinical studies. Therefore, the overall benefit-risk balance is considered favorable for further clinical development of frexalimab.

Risk assessment and mitigation in the context of SARS-CoV-2

Risk assessment

A potential risk for infections is already described for frexalimab. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a pandemic, with uncertainties regarding the epidemiology, clinical course and immunity remaining. The relevance of immunosuppression for the entire course of the disease is currently unclear, but could represent a potential risk.

Assessment of the infectious risk of other anti-CD40L or CD40L compounds, which were or are in clinical development, is limited to information from early clinical trials with small sample sizes performed before the SARS-CoV-2 (COVID-19) pandemic. Overall, these data showed only a slight increase of upper respiratory tract infections but did not reveal significant increased infection rates.

Although CD40/CD40L interaction is important for B-cell differentiation, there is currently no evidence, based on nonclinical and clinical data from the FIH study, that frexalimab is B-cell depleting. A slight decrease in B-cells was noted in the 13-week GLP toxicology study, which reversed in the recovery period. The same was seen in a 6-month GLP study, which was run without a recovery period (GLP studies described in Section 2.2). Throughout the FIH, no decrease in B-cells was observed. Therefore, comparison with B-cell-depleting drugs, such as rituximab and ocrelizumab, in terms of infectious risk, is limited. However, it is important to note that, although viral and respiratory tract infections are very common during treatment with these compounds, severe infections are limited.

Although the general role of CD40L in immune response is well established, there are no detailed data available on the specific role of CD40L in SARS-CoV-2 infection/COVID-19. Currently, there is no evidence that CD40L is relevant for SARS-CoV-2 infection. There is evidence that the development of viral clearance and a potential protective immunity follow the adaptive immune response, including the production of neutralizing antibodies, in which the CD40/CD40L interaction plays a key role (16, 17, 18, 19, 20, 21). Therefore, blocking CD40L may prevent antibody formation and immune response in case of acute SARS-CoV-2 infection and may prevent long-term immunity.

Considering the potential risk of increased infection rates based on the mode of action of frexalimab and knowledge of similar and related compounds, and the potential role of CD40L for adaptive immune response to a SARS-CoV-2 infection, an increased risk for study participants in the context of the COVID-19 pandemic can be assumed; hence appropriate risk mitigation is being implemented.

Risk mitigation

One potential risk of frexalimab is increased rate of infections. During pandemic, this risk is additionally increased. Because of this, risk mitigation actions have been established to address the risk of infection for participants in this clinical trial.

Clear protective measures to mitigate the SARS-CoV-2 spread and reduce the risk of infection are given by global health agencies such as the World Health Organization (22), as well as on national and local levels. Study sites should ensure that, before study start and throughout, the study local guidance is applied to the conduct of the study at the site level.

Stopping rules are implemented to provide guidance for Investigators:

- In case of suspicion of COVID-19 (eg, fever, cough, shortness of breath in a context of possible contact with an infected person), temporary discontinuation of the IMP will be considered by the Investigator in accordance with Section 7.1.3, considering the following to evaluate individual benefit-risk of continuation or stop of IMP: the probability of COVID-19, the possibility of rapid diagnosis, the severity of symptoms, and risk factors.
- In case of investigational site closure or complete regional or national lock down due to a local epidemic or international pandemic, the study may be suspended by the Sponsor completely or at selected sites or in selected regions. Every effort will be made to continue to follow up already recruited participants as close to the SoA as possible.

Temporary treatment discontinuations and adaptions of the follow-up period may be considered in exceptional cases as described in Section 7.1.3.

Participants will be contacted before each visit by an Investigator or designee, for evaluation of signs and symptoms of a potential SARS-CoV-2 infection. In case of suspicion of infection, the participant will be asked to not come to the study site and will be referred to a testing facility or his/her primary care physician according to local regulations.

If the suspicion of SARS-CoV-2 infection is excluded, and there is no other reason to pause treatment according to the Investigator's judgment, treatment can continue.

If suspicion of SARS-CoV-2 infection is confirmed, temporary treatment discontinuation can be considered. Decision to resume treatment after discontinuation can be made if the investigator considers from his/her clinical judgment that the participant has recovered from the COVID-19 infection, based on absence of residual symptoms and available negative PCR test results. The IMP may permanently be discontinued if according to the Investigator a permanent IMP discontinuation is necessary in the best interest of the participant.

Severe illnesses can occur in otherwise healthy individuals at any age, but it predominantly occurs in adults with underlying medical comorbidities including: chronic lung disease, cardiovascular disease, diabetes mellitus, hypertension, obesity, and cancer (22, 23, 24, 25, 26, 27, 28). High risk populations for COVID-19 are excluded in the general selection of study participants for this proof-of-concept study, according to the inclusion/exclusion criteria, eg, I01: excluding participants >55 years, I04: partly limiting morbid obesity, E03, E10, E12, and E13: excluding certain concomitant pathologies, such as recent malignancies, active infections, history of opportunistic infections, human immunodeficiency virus (HIV) infection. (Section 5.1 and Section 5.2).

According to exclusion criteria E 03 (Section 5.2), participants with acute infection or having a high risk for an asymptomatic SARS-CoV-2 infection (eg, living with a person that is currently infected) should not be included in the study.

Taking into account the potential increased infectious risk due to lymphopenia and potential relevance in SARS-CoV-2 infection (29), people with a significant lymphopenia or neutropenia will be excluded from this study (see E 10 in Section 5.2).

Extensive assessment of the risk of the COVID-19 pandemic has been performed. This has led to a risk mitigation plan including stopping rules, which take into account the current knowledge and also potential uncertainties, including plans for lock-down situations. Participant selection that limits the inclusion of the population at risk of severe COVID-19 should reduce the risk for participants included in this study.

2.3.2 Benefit assessment

Dysregulation of cellular and humoral immune responses and benefits of immunotherapies have been clearly demonstrated in MS (30). Due to the role of the CD40/CD40L signaling pathway's role in modulating adaptive and innate immune response, as evidenced by the frexalimab pharmacodynamic effect on TDAR in the Phase 1 clinical trial, frexalimab is anticipated to reduce brain inflammation, which will be monitored by evaluating formation and count of new GdE T1 lesions and volume and count of new or enlarging T2 lesions.

Risk of MS relapse, the clinical manifestation of neuroinflammation, is expected to be decreased due to the anti-inflammatory activity of frexalimab. Due to the short duration of the treatment period in Part A and general low frequency of MS relapses, no significant differences in relapse count between groups or compared to the placebo period is expected. Nevertheless, MS relapse and Expanded Disability Status Scale (EDSS) data to monitor disability due to MS will be collected in Parts A and B to detect any possible changes. This will be used as a baseline for long-term observations in this study, open to all participants in ACT16877.

Magnetic resonance imaging brain volume data acquired during Part B as well as serum biomarker such as NfL data, and additional biomarkers (including analysis of the mRNA signature of the CD40/CD40L pathway, PBMC immunophenotyping, Chi3L1 and soluble CD40L) will also allow evaluation of any effect on neuroinflammation underlying CNS damages.

The analysis of the Part A of ACT16877 demonstrated a reduction in the number of new active GdE T1 lesions after 12 weeks (relative to Week 8) with frexalimab as compared to the placebo group. A 89% reduction (95%CI: 62% - 97%) in the adjusted mean monthly count of new GdE T1 lesions was observed in the frexalimab IV group as compared to the placebo group meeting the predefined criteria for positive conclusions (see Section 9.3.2). A 79% reduction (95%CI: 44% - 92%) in the adjusted mean monthly count was observed in the frexalimab SC group as compared to the placebo group, which did not meet the predefined criteria.
Both frexalimab groups showed reduction in new/enlarging T2-lesions and total gadolinium-enhancing T1-lesions, with larger effect of the high dose. Frexalimab was well tolerated.
The most common adverse events (≥4% in any frexalimab group) were COVID-19 and headache.
No serious adverse events were reported.

2.3.3 Overall benefit: risk conclusion

No safety or tolerability concerns have been identified in the completed Phase 1 FIH clinical study and in the Phase 2 experience so far. Phase 1 results indicate that frexalimab treatment with the dose chosen for the study can lead up to more than 95% inhibition of TDAR, which supports the potential for clinical efficacy. More detailed information on the known and expected benefits and risks and reasonably expected AEs of frexalimab may be found in the IB.

In the single ascending dose study (TDU15525), the C_{max} after the highest IV dose (3000 mg) was 1120 µg/mL and AUC_{inf} was 22 800 µg*day/mL. Overall, a single IV dose of frexalimab between 200 to 3000 mg was safe and well tolerated.

In the multiple ascending dose study (TDR15526), at Day 29, the C_{max} after the highest SC dose (2100 mg) was 531 µg/mL and $AUC_{0\text{-}2\ weeks}$ was 5940 µg*day/mL. Overall, 5 dose levels of frexalimab between 150 and 2100 mg administered as 3 SC doses q2w were safe and well tolerated.

Estimated exposures for ACT16877 are similar to those observed in the Phase 1 study and are well below the NOAEL observed in the non-human primate study.

The results from Part A of ACT16877 demonstrated a reduction in the number of new Gd-enhancing T1-hyperintense brain lesions detected by brain MRI after 12 weeks of treatment. There was an 89% relative reduction in lesions at 12 weeks in the IV 1200 mg dose group as compared with placebo. Potential benefits include the following:

- Decrease of annualized relapse rate (ARR).
- Reduction in the accumulation of confirmed disability worsening.
- Reduction of disease activity as assessed by MRI.

Taking into account the measures taken to minimize risk to participants in Study ACT16877, the potential risks identified in association with frexalimab are justified by the anticipated benefits that may be afforded to participants with MS. The continuation of Part B is confirmed and its prolongation is justified by the positive results of Part A.

3 OBJECTIVES AND ENDPOINTS

Table 3 - Part A objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the efficacy of frexalimab as measured by reduction of the number of new active brain lesions.	• Number of new gadolinium (Gd)-enhancing T1-hyperintense (GdE T1) lesions at Week 12 as measured by brain magnetic resonance imaging (MRI).
Secondary	
• To evaluate efficacy of frexalimab on disease activity as assessed by other MRI measures.	• Number of new or enlarging T2 lesions at Week 12. • Total number of GdE T1 lesions at Week 12.
• To evaluate the safety and tolerability of frexalimab.	• Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG), and vital signs during Part A. • Anti-drug antibodies (ADAs).
• To evaluate pharmacokinetics of frexalimab.	• frexalimab plasma concentrations over time. Pharmacokinetic (PK) parameters (maximum concentration [C_{max}], time to C_{max} [t_{max}], area under the curve over the dosing interval [$AUC_{0\text{-}tau}$], and elimination half-life [$t_{1/2}$]).
Exploratory	
• To evaluate efficacy of frexalimab on disease activity, assessed by clinical, imaging measures, and patient-reported outcomes.	• Change from baseline to Week 12 in volume, number, and intensity (T1) of slowly evolving lesions (SEL). • Change in number of phase rim lesions in susceptibility weighted imaging (SWI) MRI from baseline to Week 8 and Week 12 (subset of centers with capacity of 3 Tesla MRI). • Change in total number of T1-hypointense lesions from baseline to Week 8 and Week 12. • Proportion of participants with no new MRI disease activity at the end of 12 weeks of treatment. • Number of new or enlarging T2 lesions at Week 12. • Number of relapses (annualized relapse rate) over 12 weeks of treatment. • Proportion of relapse-free participants at the end of 12 weeks of treatment Change in EDSS from baseline to Week 12. • Change in MSIS-29 physical and psychological domains scoring from baseline to Week 12. • Change in PROMIS-Fatigue-MS-8 scoring from baseline to Week 12. • Descriptive summaries of PQATv3 scores by treatment arm at Week 12. • PGIC-Fatigue value at Week 12. • Change in PGIS-Fatigue from baseline to Week 12.
• To explore genetic and plasma-based biochemical biomarkers that correlate with disease pathophysiology.	• Analysis of messenger ribonucleic acid (mRNA) signature of cluster of differentiation 40/cluster of differentiation-40 ligand (CD40/CD40L) pathway activation in blood. • Change in immune cell at Week 12 compared to baseline. • Change in plasma neurofilament light chain (NfL) at Week 12 compared to baseline. • Change in serum chitinase-3-like 1 (CHI3L1) at Week 12 compared to baseline. • Change in sTREM2 at Week 12 compared to baseline.

Objectives	Endpoints
	• Change in CXCL13 at Week 12 compared to baseline. • Change in IgG, IgM at Week 12 compared to baseline. • Soluble CD40L (sCD40L) in plasma (at baseline, Week 12, and during 24 weeks of follow-up after EOT). • Presence of SNPs in genes related to CD40/CD40L signaling pathway or MS disease.

Table 4 - Part B objectives and endpoints

Objectives	Endpoints
Secondary	
• To evaluate the long-term safety and tolerability of frexalimab.	• Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG), and vital signs during Part B.
• To evaluate the safety of the 1800 mg SC q4w dose regimen.	• Adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities (PCSAs) in laboratory tests, electrocardiogram (ECG), and vital signs in the 1800 mg SC q4w dose regimen group (Part B2). • Anti-drug antibodies (ADAs).
• To evaluate pharmacokinetics of frexalimab beyond 12 weeks of study intervention for SC and IV regimen, including after switch to 1800 mg SC q4w.	• Frexalimab plasma concentrations over time. Pharmacokinetic (PK) parameters (maximum concentration [C_{max}], time to C_{max} [t_{max}], area under the curve over the dosing interval [$AUC_{0\text{-}tau}$], and elimination half-life [$t_{1/2}$]).
Exploratory	
• To evaluate efficacy of frexalimab on disease activity, assessed by clinical, imaging measures, and patient-reported outcomes.	• Number of new GdE T1 lesions at Week 24, Week 48, and over time. • Number of new or enlarging T2 lesions at Week 24, Week 48, and over time. • Change in volume, number, and intensity (T1) of slowly evolving lesions (SEL) from baseline to Week 12 and Week 48, from Week 48 to Week 96, from Week 96 to Week 192. • Change in number of phase rim lesions in susceptibility weighted imaging (SWI) MRI from baseline over time (subset of centers with capacity of 3 Tesla MRI). • Change in magnetization transfer imaging (MTR) of GdE T1 lesions from Week 8 and Week 12 to Week 24, from Week 20 and Week 24 to Week 96, from Week 120, Week 144, and Week 192 to Week 240 (selected centers). • Change in volume of T2 lesions from baseline over time. • Change in brain volume, including regional changes, from baseline to EOS. • Change in total number of T1-hypointense lesions from baseline over time. • Proportion of participants with no new MRI disease activity over time. • Number of relapses (annualized relapse rate) over time. • Proportion of relapse-free participants over time.

Objectives	Endpoints
	• Change in EDSS from baseline over time. • Change in MSIS-29 physical and psychological domains scoring from baseline at Week 24, Week 192, Week 240, Week 288, and at EOS. • Change in PROMIS-Fatigue-MS-8 scoring from baseline at Week 24, Week 192, Week 240, Week 288, and at EOS. • PGIC-Fatigue value at Week 24. • Change in PGIS-Fatigue from baseline at Week 24.
• To explore genetic and plasma-based biochemical biomarkers that correlate with disease pathophysiology.	• Analysis of messenger ribonucleic acid (mRNA) signature of cluster of differentiation 40/cluster of differentiation-40 ligand (CD40/CD40L) pathway activation in blood at Week 24. • Change in immune cell over time compared to baseline. • Change in plasma neurofilament light chain (NfL) over time compared to baseline. • Change in serum chitinase-3-like 1 (CHI3L1) over time compared to baseline. • Change in sTREM2 over time compared to baseline. • Change in CXCL13 over time compared to baseline. • Change in IgG, IgM over time compared to baseline. • Soluble CD40L (sCD40L) in plasma during 24 weeks of follow-up after EOT and Common EOS.

3.1 APPROPRIATENESS OF MEASUREMENTS

Because MS results in a leaky blood-brain barrier, accumulation of Gd contrast agent in brain tissue is related to inflammatory activity in MS patients. This radiographic outcome has been established as a highly-reliable predictive biomarker for clinical efficacy in pivotal studies in MS.

The number of new GdE T1 lesions at Week 12 as measured by brain MRI (primary endpoint) is a validated and established outcome measurement for therapeutic efficacy in RMS.

Central review will be used to identify new GdE T1 lesions not present at the previous MRI scans. The total count of GdE T1 lesions will also be used as a secondary endpoint to detect any effect on pre-existing inflammatory foci. The number of new and enlarging T2-hyperintense lesions, another MRI marker of disease activity in MS, will also be evaluated as secondary endpoint to collect additional efficacy data.

In terms of safety, TEAEs, SAEs, adverse events of special interest (AESIs), ECG, vital signs, and laboratory analyses will be reported, and local tolerability will be examined. Frexalimab will be administered SC or IV after an initial IV loading dose. Measurement of local tolerability will be done with a verbal descriptor scale (VDS) and Investigator rating, described in Section 8.2.5. Antidrug antibodies will be measured as well, although the mechanism of action of frexalimab (prevention of CD40/CD40L interaction) is expected to decrease the risk of ADA formation (see Section 2.2).

Due to the short duration of the study Part A, ARR and changes in EDSS score will be assessed as tertiary endpoints.

In addition, exploratory assessments, such as analysis of genetic and plasma-based biochemical biomarkers and advanced imaging methods are expected to build evidence for frexalimab activity on neuroinflammation and neurodegeneration as well as potential effects on remyelination and tissue preservation.

Each of the clinical outcome assessments selected for inclusion in this study is considered relevant and fit for purpose in the target populations for the context of use. The multiple sclerosis impact scale-29 items (MSIS-29) measure is an established and relevant MS Impact Scale used to measure the physical and the psychological impact of MS from the patient's perspective.
The patient reported outcome measurement information system-Fatigue-MS-8 (PROMIS-Fatigue-MS-8) measure is a patient-reported outcome (PRO) questionnaire being qualified by the Food and Drug Administration (FDA) in the target population in order to support a label claim for fatigue; the Patient Global Impression of Severity-Fatigue (PGIS-Fatigue) and Patient Global Impression of Change-Fatigue (PGIC-Fatigue) are each single-item whose measures are used as anchors for validating the PROMIS-Fatigue-MS-8. The patient's qualitative assessment of treatment version 3 (PQATv3) is a generic measure developed to provide early patient insights on benefits and disadvantages of drugs received within a clinical trial and patient preferences for route of administration (ie, SC versus IV).

4 STUDY DESIGN

4.1 OVERALL DESIGN

ACT16877 is a Phase 2, multicenter, randomized, parallel-group, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of 2 doses/routes of administration of frexalimab in participants with RMS (relapsing-remitting MS and secondary progressive MS participants with relapses as per inclusion criteria). The study is open-label for route of administration and dose group, double-blinded for treatment assignment. Independent MRI raters will be blinded for study treatment and dose and other participant data.

The study consists of 2 parts:

Part A is a 12-week, double-blind, placebo-controlled part, preceded by a screening period starting not earlier than 4 weeks before Day 1.

At the beginning of Part A, participants will be randomly assigned in a 4:4:1:1 ratio to the frexalimab IV q4w or frexalimab SC q2w or IV placebo q4w or SC placebo q2w. Interactive response technology will be used to assign treatments to participants. All participants will switch to Part B after the Week 12 visit.

Once the last participant has entered Part B, analysis of Part A data will be performed as the main analysis of the study.

Part B is an open-label frexalimab treatment part of 212 to approximately 280 weeks (approximately 53 to 70 months, and not exceeding 296 weeks [74 months]) expected duration for individual participants to allow further safety and efficacy analysis. Frexalimab treatment arms from Part A will continue the participant's previous IV or SC treatment routes. Participants from the placebo treatment IV or SC arms in Part A will transition to IV q4w or SC q2w frexalimab treatment respectively, at Week 12. Further to Part A analysis results, there will be no change of dose regimen for the IV arm. In the SC arm, dose regimen will be modified to 1800 mg q4w (via syringe infusion material) (for rationale, see Section 4.3). Both treatment arms (IV and SC) will be continued until the Common end of study (Common EOS). This design will allow for reduction of exposure to placebo and continuation of the evaluation of safety and efficacy of frexalimab for a longer period. Treatment will be administered in an open-label fashion from Week 14 till the Common EOS.

For the SC group, Part B is divided in 2 subparts: Part B1 until individual participant switch to the modified dose regimen and Part B2 after this switch.

Based on the expected duration of recruitment of Part A, time needed for primary data analysis, it is expected that individual participant treatment duration in both parts of Study ACT16877 will be up to 292 weeks (73 months) of study intervention (and will not exceed 308 weeks [77 months]).

Investigational medicinal product administration will be performed on-site in Part A. In the judgment of the Investigator, if no injections site reactions or adverse events has occurred or is suspected, SC injections of frexalimab (from Week 14 onward in Part B1, up to switch to Part B2) could be performed at home after appropriate medical training, evaluation of participant's self-injection (or partner/caregiver/home healthcare professional) capability and technique are done (please refer to product management manual).

[redacted] and in Part B2 (from 12 weeks after switch) for SC arm, optional home administration may be considered for interim visits between 2 quarterly onsite visits (those with physical examination and laboratory sampling). In this case, home nurse intervention after appropriate medical training and assessment of practical conditions will be required (please refer to product management manual).

In case of any injection site reactions or other adverse events, the participant must contact the site as soon as possible for reporting, timely monitoring of any worsening of the events, and decision for best evaluation/treatment by the Investigator (including on-site visit if needed). Investigator will also proactively contact the participant the day of injection to assure absence of any events or to assure their best management if such occur.

In case of travelling restrictions impacting IMP administration on-site, an in-home Investigator visit (or a visit by a qualified physician in communication with the Investigator) may be performed in Part B after the agreement of the Sponsor with each concerned site and with the establishment of all technical means for such visits.

A Common EOS will be planned when the first participant randomized has reached approximately 292 weeks (73 months) of study intervention administration. The participant must be followed-up for 24 weeks after the completion of common EOS (see Section 4.4 for details of common EOS). Upon completion of both Parts A and B of this study, post study access to study medication could be provided based on local/country regulations or participants will be managed individually by their regular caregiver for their future MS therapy, generally after the follow-up period. These participants would need to take appropriate RMS treatment (disease-modifying therapy) available in their countries per decision of their treating physicians.

Overall, maximum duration of study participation comprising screening period (4 weeks), Part A (12 weeks), Part B (up to 280 weeks and not exceeding 296 weeks), and safety follow-up (24 weeks) is 320 weeks (80 months) and will not exceed 336 weeks (84 months).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A Parallel group design was chosen for this study, providing comparable arms with data collected in the same time period for evaluation of efficacy and safety. Randomization of 4:4:1:1 to high IV dose, low SC dose, placebo IV, and placebo SC arms was chosen to collect information on 2 different doses as well as 2 different routes of administration, while keeping the placebo group small to minimize participant exposure to placebo. The study is not blinded for route of administration and dose group, but is double blinded within each of the SC and IV groups for frexalimab or placebo assignment. This allows simplification of the study design while avoiding double-dummy additional IMP administration, but maintains the blind for treatment, allowing adequate frexalimab evaluation.

Duration of the main assessment period of 3 months is expected to be sufficient for efficacy signal detection based on the primary endpoint (new T1 GdE lesions in MRI). Duration of 3 months has proved to be sufficient to show a meaningful efficacy signal of potent MS treatments (5, 31).

Choice of the short duration of the placebo comparator is driven by consideration of sample size and attempting to minimize participant exposure to the placebo. It is known that treatment effect size related to that of placebo can be demonstrated with smaller participant numbers that is required for an active comparator. In an attempt to decrease the number of participants receiving placebo to a minimum, a randomization ratio of 4:1 was chosen, meaning a participant has only a 20% chance to be assigned to a placebo arm. For the same reason, placebo data from the SC and IV arms will be pooled for all main analyses, allowing sufficient study power with a small placebo group. A main study period of 3 months is rather short and carries a limited risk of disease advancement for participants in the placebo arms, keeping in mind the chronic nature of RMS and somewhat rare frequency of clinical relapses and generally slow progression.

This study will assess frexalimab efficacy by measuring number of new GdE T1 lesions, which are associated with inflammation. This radiographic outcome has been established as a highly reliable predictive biomarker for clinical efficacy in pivotal studies in MS and has been demonstrated to be a predictive biomarker for clinical efficacy (reduction in ARR and disability worsening) in studies with other MS treatments (2, 3).

Two secondary efficacy endpoints have been chosen: number of new or enlarging T2 lesions at the end of 12 weeks of frexalimab treatment and the number of GdE T1 lesions at the end of 12 weeks of frexalimab treatment.

The number of new or enlarging T2 lesions is a recognized to reflect MS inflammatory activity and resulting brain tissue lesions. It will provide supportive objective data for efficacy evaluation through MRI imaging. The total number of T1 lesions, widely used assessment of inflammatory activity in MS trials, will also provide additional support for the primary endpoint.

Safety and tolerability endpoints including AEs, vital signs, ECG and clinical laboratory evaluation are elected as secondary endpoints and will be assessed as per standard practice in clinical trials.

4.3 JUSTIFICATION FOR DOSE

The selected doses for Part A and Part B until analysis of Part A are 1200 mg q4w (with an IV loading dose of 1800 mg on Day 1) for the IV arm and 300 mg q2w (with an IV loading dose of 600 mg) for the SC arm.

In healthy participants, administration of a single IV dose of frexalimab up to 3000 mg (TDU15525) and repeated SC doses (q2w, 3 administrations) of frexalimab up to 2100 mg (TDR15526) were safe and well tolerated. Of note, a maximal tolerated dose was not reached in either of these clinical studies. There were no serious or severe TEAEs. No trends in vital signs, ECGs or laboratory values were identified, including assays aimed at identifying potential increased risks for thromboembolism or infections.

In the multiple ascending dose study in healthy participants (TDR15526), 150, 300, 600, 1200, and 2100 mg doses administered as 3 SC injections q2w were tested. frexalimab inhibited KLH-TDAR in a dose dependent manner after 3 doses SC q2w and the sequential administration of 2 doses of KLH (Days 4 and 32). Frexalimab administration resulted in a dose-dependent inhibition of the TDAR response, with partial inhibition after 3 SC doses of 150 mg and 300 mg cohorts (84% and 92%, respectively), and near complete (>97%) inhibition after 3 doses of 600 mg, 1200 mg, and 2100 mg. After 3 doses, the steady state was not reached. At steady state, complete TDAR suppression is to be expected with a dose of 300 mg SC q2w. Thus, a high probability of clinical efficacy for this dose is expected.

A high dose of 1200 mg IV q4w was chosen to assure good target engagement in peripheral compartment, but also targeting brain tissue, where drug penetration due to the altered blood-brain barrier in MS cannot be ruled out.

For the dose of 1200 mg IV q4w, expected exposures ($AUC_{0\text{-}4\ weeks}$) is equivalent to a dose of 900 mg SC q2w at steady state, 3-times higher than that of the low dose of 300 mg q2w SC planned in the study.

At the high dose the predicted exposure at steady state, in terms of $AUC_{0\text{-}4\ weeks}$ (222 000 µg*h/mL), will not reach the exposure observed at the highest dose in the TDR15526 repeat dose study (SC q2w dose of 2100 mg, estimated $AUC_{0\text{-}4\ weeks}$ approximately 250 000 µg*h/mL).
The predicted C_{max} of 650 µg/mL (after the loading dose) is approximatively 2-fold lower than the C_{max} observed in healthy participants after a single dose of 3000 mg IV. Based on preliminary PK analysis of the Part A , after the 3rd and last dose, approximatively 90 % of the steady state was achieved and $AUC_{0\text{-}4weeks}$ was estimated as 190 000 µg*h/mL.

The rationale of utilizing a loading dose is that, in its absence, steady state is predicted to be reached only after 12 weeks. An IV loading dose of double the SC maintenance dose or 1.5-fold higher than the IV maintenance dose on Day 1 would assure a plasma concentration close to steady state would be reached after the second administration.

Predicted exposure at steady state in the high dose arm of frexalimab 1200 mg IV q4w has a safety margin of 8 relative to the exposure at NOAEL in the chronic toxicology non-human primate study.

The analysis of Part A supports a dose-exposure-response effect. It shows that the efficacy of the IV 1200 mg dose is superior to the efficacy of the SC 300 mg dose, with a larger effect size on the primary endpoint, new Gd-enhancing T1 lesions (respectively 89% and 79% reduction), and secondary endpoints (data on file). The two doses were safe and well tolerated, with no increase in frequency or intensity of adverse events. The data therefore support a higher benefit/risk ratio for a high dose. Furthermore, it is important to maximize effect in MS when possible.

In consequence, the open-label period, on the basis of amendment 2, will continue with administration of a dose having shown better benefit/risk. Therefore, the starting route of administration in each group, IV or SC, will be kept in order to maintain the same route of administration for the participants, and PK and safety information will be collected with the administration of higher SC doses in participants with RMS.

In the IV group, the dose will therefore be unchanged, ie 1200 mg q4W. In the SC group, the frequency of administration is reduced (from q2w to q4w) for better convenience to the participants, and the change in dose from 300 mg to 1800 mg will allow to reach the exposure of the IV arm. The volume to be administered, 12 mL, necessitates an infusion, which will be done using a syringe infusion material. Details on the administration will be provided in the pharmaceutical manual. Such administration has been performed in Phase 1, with administration up to 2100 mg per SC syringe infusion/pump infusion (maximum 0.67 mL/min), with good tolerability (more information can be found in the IB). PK sampling and laboratory tests will be done every 4 weeks in the 12 weeks following the dose modification (see Table 1).

With the new proposed SC regimen, 1800 mg q4w, the predicted AUC0-4weeks are similar to those at 1200 mg q4w IV (222 000 µg*h/mL compared at steady state), the C_{max} is predicted to be lower (450 µg/mL versus 650 µg/mL) and C_{trough} slightly higher (250 µg/mL versus 220 µg/mL). The simulations were conducted using a population PK model (POH0693) developed with frexalimab plasma concentration data from 73 healthy subjects included in Phase 1 who received either single IV doses (TDU15525) or multiple SC doses (TDR15526). This model is a 2 compartmental model and with a linear elimination, the bioavailability after SC administration is estimated as 0.7. The preliminary PK data of the Part A of the two arms (SC and IV) showed that the predictions in RMS patient population using this model are accurate.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit/last contact of the last participant in the study or the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

Should a participant not consent to transition to the Part B2 modified SC dose regimen, then the participant would be withdrawn from the study.

A Common EOS will be planned when the first participant randomized in the study has reached a total duration of approximately 292 weeks (73 months) of study intervention (and will not exceed 308 weeks [77 months]). The participant must be followed-up for 24 weeks after the completion of Common EOS.

Routine q4w visits falling into this period will be performed as EOS visits.

The EOS visit must be performed for every participant as per the SoA (Section 1.3) and must be performed for any participant withdrawing consent to continue in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit/last contact.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. The participant must have been diagnosed with RMS (relapsing-remitting MS or secondary progressive MS participants with relapses) according to the 2017 revision of the McDonald diagnostic criteria (32).

I 03. The participant must have at least 1 documented relapse within the previous year, or ≥2 documented relapses within the previous 2 years, or ≥1 active Gd-enhancing brain lesion on an MRI scan in the past 6 months and prior to screening.

Weight

I 04. Body weight within 45 to 120 kg (inclusive) and body mass index (BMI) within the range 18.0 to 35.0 kg/m^2 (inclusive) at Screening.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 05. All

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants:

Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 24 weeks after the last administration of study intervention:

- Refrain from donating sperm

PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception/barrier as detailed below

- A male condom and an additional highly effective contraceptive method as described in Section 10.4.2 when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

b) Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.1.

    OR
  - Is a woman of childbearing potential (WOCBP) and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.4.2 during the study intervention period and for at least 24 weeks after the last administration of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first administration of study intervention, see Section 8.2.6 Pregnancy testing. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Informed Consent

I 06. Capable of giving signed informed consent as described in Section 10.1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative.

Other inclusions

Not applicable.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. The participant has been diagnosed with PPMS according to the 2017 revision of the McDonald diagnostic criteria (32) or with non-relapsing SPMS (33).

E 02. The participant has conditions or situations that would adversely affect participation in this study, including but not limited to:

- A short life expectancy due to preexisting health condition(s) as determined by judgment of investigator or their treating physician.
- Medical condition(s) or concomitant disease(s) making them nonevaluable for the primary efficacy endpoint or that would adversely affect participation in this study, as judged by the Investigator.
- A requirement for concomitant treatment that could bias the primary evaluation by judgment of investigator.
- Contraindication for MRI, ie, presence of pacemaker, metallic implants in high-risk areas (ie, artificial heart valves, aneurysm/vessel clips), presence of metallic material (eg, shrapnel) in high-risk areas, known history of allergy to any contrast medium, or history of claustrophobia that would prevent completion of all protocol scheduled MRI.
- Contraindications to use MRI Gd contrast-enhancing preparations.

E 03. The participant has a history of or currently has concomitant medical or clinical conditions that would adversely affect participation in this study, including but not limited to:

- A history of T-lymphocyte or T-lymphocyte-receptor vaccination, transplantation (including solid organ, stem cell, and bone marrow transplantation) and/or antirejection therapy.
- A history of diagnosis of progressive multifocal leukoencephalopathy (PML) or evidence of findings suggestive of PML on the baseline MRI.
- Serious systemic viral, bacterial, or fungal infection (eg, pneumonia, pyelonephritis), infection requiring hospitalization or IV antibiotics or significant chronic viral, bacterial, or fungal infection (eg, osteomyelitis) 30 days before and during screening.
- Participants with a history of invasive opportunistic infections, such as, but not limited to histoplasmosis, listeriosis, coccidioidomycosis, candidiasis, pneumocystis jirovecii, and aspergillosis, regardless of resolution.
- Symptomatic herpes zoster within 3 months prior to screening.
- Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest X-rays (posterior anterior and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration <5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin [BCG] or other vaccination history) or a positive (not indeterminate) QuantiFERON®-TB Gold test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.

- Any other active infections that would adversely affect participation or IMP administration in this study, as judged by the Investigator.
- A history of malignancy within 10 years prior to the first screening visit, except effectively treated carcinoma in situ of the cervix or adequately treated nonmetastatic squamous or basal cell carcinoma of the skin.
- A history of alcohol or drug abuse within 1 year prior to the first screening visit.
- A history of any psychiatric disease, behavioral condition, or depression requiring hospitalization within 2 years prior to the first screening visit.
- Presence of any screening laboratory or ECG values outside normal limits that are considered in the Investigator's judgment to be clinically significant.
- Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

E 04. History, clinical evidence, suspicion, or significant risk for thromboembolic events, as well as myocardial infarction, stroke and/or antiphospholipid syndrome and any participants requiring antithrombotic treatment.

E 05. Allergies to humanized monoclonal antibodies or severe post-treatment hypersensitivity reactions other than localized injection site reaction, to any biological molecule (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).

Prior/concomitant therapy

E 06. The participant has received any of the following medications/treatments within the specified time frame before any baseline assessment (no wash-out is required for interferons beta or glatiramer acetate treatments):

Medication	Exclusionary if used/used within required wash-out period
Systemic corticosteroids, adrenocorticotropic hormone	1 month prior to screening MRI scan
Dimethyl fumarate	1 month prior to randomization
Intravenous (IV) immunoglobulin, plasmapheresis, fingolimod, natalizumab (participants who have discontinued natalizumab in the 6 months prior to randomization should be evaluated to rule out PML)	2 months prior to randomization
Teriflunomide	3 months prior to randomization. No time restriction if accelerated elimination procedure is done[a]
B-cell-depleting therapies such as ocrelizumab and rituximab	6 months prior to randomization or until return of B-cell counts to normal levels, whichever is longer
Mildly to moderately immunosuppressive/chemotherapeutic medications such azathioprine and methotrexate	6 months prior to randomization
Highly immunosuppressive/chemotherapeutic medications: mitoxantrone up to 120 mg/m^2 body surface area, cyclophosphamide, cladribine	2 years prior to randomization
Alemtuzumab	4 years prior to randomization

Medication	Exclusionary if used/used within required wash-out period
Other MS-disease modifying treatments	5 half-lives or until end of pharmacodynamics activity, whichever is longer
Lymphoid irradiation, bone marrow transplantation, mitoxantrone (with evidence of cardiotoxicity following treatment, or cumulative lifetime dose >120 mg/m^2), other strongly immunosuppressive treatments with very long-lasting effects	Any time (not eligible for enrollment)
Any live (attenuated) vaccine (including but not limited to varicella zoster, oral polio, and nasal influenza)	3 months prior to randomization

Abbreviations: MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy; IV = intravenous.

a Teriflunomide accelerated elimination procedure must be followed per locally approved product information.

Prior/concurrent clinical study experience

E 07. The participant has taken other investigational drug within 3 months or 5-half-lives, whichever is longer, before the screening visit.

Diagnostic assessments

E 08. The participant has an EDSS score >5.5 at the first screening visit.

E 09. The participant has had a relapse in the 30 days prior to randomization.

E 10. Positive human immunodeficiency virus (HIV) serology (anti HIV1 and anti HIV2 antibodies) or a known history of HIV infection, active or in remission.

E 11. Abnormal laboratory test(s) at Screening:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 × ULN.
- Bilirubin >1.5 × ULN; unless the participant has documented Gilbert syndrome (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
- Hemoglobin <11 g/100 mL for males and <10 g/100 mL for females.
- Lymphocytes <1000/mm^3.
- Neutrophils <1500/mm^3 (except <1000/mm^3 for participants of African descent) .
- Platelets <140 000/mm^3.
- Estimated Glomerular filtration rate <60 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD]).

E 12. Presence of hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antibodies (anti-HBc Ab) at screening or within 3 months prior to first dose of study intervention. If anti-HBs negative and anti-HBc positive: perform hepatitis B virus DNA test to confirm.

Positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention. NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

Other exclusions

E 13. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 14. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 7 (Section 10.7) of the protocol.

E 15. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 16. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the international conference of harmonization [ICH]-good clinical practice [GCP] Ordinance E6).

E 17. Any specific situation during study implementation/course that may raise ethics considerations.

E 18. Known hypersensitivity to any of the study interventions, or components thereof, or to a drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 19. Any participant with a known history of ADA to a monoclonal antibody-based biologic.

E 20. Any participant who has previously received frexalimab.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

No specific dietary restrictions are applicable throughout the study. Fasting is preferred if possible in those visits where clinical chemistry (laboratory) will be assessed, as per the SoA (Section 1.3). Fasting is defined as no food/no drinks beside water without any supplements for at least 10 hours. Fasting/non-fasting status will be recorded at the time of blood collection.

5.3.2 Caffeine, alcohol, and tobacco

During the study, it is recommended that participants should try to abstain from drinking alcohol and using tobacco products as much as possible. No recommendations or restrictions apply regarding caffeine.

5.3.3 Activity

No restriction is required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, if criterion at cause can be expected to change (eg, mild laboratory abnormality).

There is no requirement for a waiting period between the screen failure date and the rescreen date. Participants who are rescreened must sign a new informed consent and all Screening visit procedures must be repeated, if they were performed more than 4 weeks prior to the new Day 1 (except DNA test and previously positive serology tests for infectious diseases).

If participant was not eligible due to abnormal parameter(s) which was(were) retested during screening period and eligibility was confirmed, participant may be randomized and will not be considered as screen failure.

5.5 CRITERIA FOR TEMPORARILY DELAYING RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Section 10.8.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified IMPs, AxMPs, and medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

Home administration will not be considered in the Part A of this clinical trial, particularly as this is a first study in people with MS. In Part B1, for additional SC injection visits only (from Week 14 onward) if, in the judgment of the Investigator, no injection site reactions or adverse events have occurred, participants may perform SC injections of frexalimab at home after appropriate medical training, evaluation of participant's self-injection or partner/caregiver/home healthcare professional capability and technique are done (please refer to product management manual). Visiting nurse may be also solicited for at home injection.

[redacted] and in Part B2 (from 12 weeks after switch) for SC arm, optional home administration may be considered for interim visits between 2 quarterly onsite visits (those with physical examination and laboratory sampling). In this case, home nurse intervention after appropriate medical training and assessment of practical conditions will be required (please refer to product management manual).

In case of any injection site reaction or other adverse event, participant must contact the site as soon as possible for reporting, timely monitoring of any worsening of the events and decision for best evaluation/treatment by the Investigator (including on-site visit if needed). Investigator or designee will also proactively contact the participant the day of injection to assure absence of any events or to assure their best management if such occur.

In case of direct to patient (DTP) IMP delivery, it will be performed directly to the participant's home. The IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant. Under no other circumstances will the Investigator supply the IMP to a third party, allow the IMP to be used other than as directed by this clinical study protocol, or dispose of IMP in any other manner.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 5 - Investigational medicinal product(s) administered

Intervention label	frexalimab IV	Placebo IV	frexalimab SC	Placebo SC
Intervention name	frexalimab	placebo	frexalimab	placebo
Type	Drug	Drug	Drug	Drug
Dose formulation	[redacted]: frexalimab solution for injection 150 mg/mL: [redacted]	Same as active without frexalimab protein	[redacted]: frexalimab solution for injection 150 mg/mL: [redacted]	Same as active without frexalimab protein
Unit dose strength(s)	300 mg/2 mL [redacted]	2 mL	300 mg/2 mL [redacted]	2 mL
Dosage level(s)	IV arm: 1800 mg loading dose; then 1200 mg q4w SC arm: 600 mg loading dose	Not applicable	Part B1[a]: 300 mg every 2 weeks after 600 mg IV loading dose Part B2: 1800 mg every 4 weeks	Not applicable
Route of administration	IV infusion	IV infusion	Part B1[a]: SC injection after IV infusion Part B2[a]: SC infusion	SC injection
Use	Experimental active	placebo	Experimental active	placebo
Packaging and labeling	Study Intervention will be provided in 1 vial treatment box (ie, 1 vial per treatment box). Each vial and box will be labeled as required per country requirement	Study Intervention will be provided in 1 vial treatment box (ie, 1 vial per treatment box). Each vial and box will be labeled as required per country requirement	Study Intervention will be provided in 1 vial treatment box (ie, 1 vials per treatment box). Each vial and box will be labeled as required per country requirement	Study Intervention will be provided in 1 vial treatment box (ie, 1 vials per treatment box). Each vial and box will be labeled as required per country requirement
[Current/Former name(s) or alias(es)]	Not applicable	Not applicable	Not applicable	Not applicable

Abbreviations: IV = intravenous; SC = subcutaneous.

a Part B1 until switch from 300 mg q2w SC to 1800 mg q4w SC, Part B2 after switch. Switch will occur after amended protocol 02 is approved and syringe infusion material is available on site

b [redacted]

Table 6 - Arms and associated interventions

Arm name	IV frexalimab - frexalimab arm	IV placebo- frexalimab arm	SC frexalimab - frexalimab arm	SC placebo- frexalimab arm
Associated interventions (intervention label[s])	frexalimab IV, placebo IV	frexalimab IV, placebo IV	frexalimab IV, frexalimab SC, placebo IV	frexalimab IV, frexalimab SC, placebo IV, placebo SC

Abbreviations: IV = intravenous; SC = subcutaneous.

The administration of IMP by visit is detailed in Table 7.

Table 7 - IMP administration by visit [redacted]

Arm	Day 1	other Part A visits	Week 12	Part B visits
IV frexalimab - frexalimab	6 vials frexalimab IV	4 vials frexalimab IV every 4 weeks	4 vials frexalimab IV +2 vials placebo IV	4 vials frexalimab IV every 4 weeks
IV Placebo- frexalimab	6 vials placebo IV	4 vials placebo IV every 4 weeks	6 vials frexalimab IV	4 vials frexalimab IV every 4 weeks
SC frexalimab - frexalimab	2 vials frexalimab IV	1 vial frexalimab SC every 2 weeks	1 vial frexalimab SC and +2 vials placebo IV[a]	1 vial frexalimab SC every 2 weeks (Part B1[b]) 6 vials frexalimab SC every 4 weeks (Part B2[b])
SC Placebo- frexalimab	2 vials placebo IV	1 vial placebo SC every 2 weeks	1 vial placebo SC and 2 vials frexalimab IV[a]	1 vial frexalimab SC every 2 weeks (Part B1[b]) 6 vials frexalimab SC every 4 weeks (Part B2[b])

Abbreviations: IMP = investigational medicinal product; IV = intravenous; SC = subcutaneous.
Frexalimab vials contain 300 mg/2 mL of frexalimab.
Placebo vials contain 2mL of matching placebo.
a Subcutaneous injections should be done after PK sampling and before IV infusion start.
b Part B1 until switch from 300 mg q2w SC to 1800 mg q4w SC, Part B2 after switch. Switch will occur after amended protocol 02 is approved and once syringe infusion material is available on site.

Table 8 - [redacted]

Abbreviations: IMP = investigational medicinal product; IV = intravenous; SC = subcutaneous.

[redacted]

6.1.1 Frexalimab

Frexalimab is a humanized mouse monoclonal IgG1 antagonist antibody against CD40L, with a modification to the Fc region to prevent binding to FcγRIIa and associated platelet activation.

[redacted] drug product is a sterile, non pyrogenic, clear to opalescent solution for injection essentially free of visible particles. It is packaged in an ISO 2R USP/Ph. Eur. Type I borosilicate glass vial, stoppered with a 13 mm USP/Ph. Eur. elastomeric stopper and sealed with an aluminum seal. Each frexalimab product single use vial contains a nominal volume of 2 mL of 150 mg/mL frexalimab solution. An overfill volume of 0.35 mL is included to allow for withdrawal of 2 mL of solution (300 mg frexalimab). The composition of frexalimab [redacted] drug product solution includes frexalimab, [redacted]. The pH of the formulated solution is [redacted].

[redacted]

6.1.2 Placebo

Each matching placebo is packaged as described for frexalimab and is of the same composition as the active drug without the monoclonal antibody as described in Section 6.1.2.

There is no apparent differences between frexalimab and placebo, so they cannot be distinguished by the site staff and participant.

6.1.3 Auxiliary medicinal product(s)

- Formulation: MRI contrast-enhancing preparations
- Route(s) of administration: IV
- Dose regimen: as per respective label.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

A complete description of IMP preparation for IV and SC administration will be provided in the product management manual available to the clinical site.

The product must be stored at 2°C to 8°C (36°F to 46°F) and protected from light prior to preparation with limited shaking (no vortex). The IMP should not be frozen. Light exposure is permitted during preparation and administration. Sites are requested to maintain a temperature log to ensure storage temperature remains within acceptable limits.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants randomized in the study may receive the study intervention, and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.10).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply the IMP to a third party (except for direct to patient [DTP] shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.2.1 Intravenous preparation and handlings

The IMP will be administered by IV infusion over a minimum of 60 minutes. The necessary number of vials of IMP will be diluted in a pre-filled 0.9% saline bag to constitute approximately 100 mL per single infusion. A system flush needs to be performed after the end of infusion to assure that complete dose is administered. A complete and detailed description can be found in the product management manual.

[redacted]

6.2.2 Subcutaneous preparation and handlings

The IMP should be prepared in an appropriate syringe (details are provided in the product management manual).

In Part B1, each SC dose will require 1 injection with 2 mL IMP per injection. All SC IMP injections should be administered in the abdomen. At Week 12 visit SC injection must be performed after the predose PK sample and before the start of IV infusion. For additional injection visits in the SC treatment arm only (Part B1). If, in the judgment of the investigator, no adverse reaction have occurred or is suspected, SC injections of frexalimab (from Week 14 on) can be performed at home after appropriate medical training, assessment of the participant's self-injection or partner/caregiver/home healthcare professional capability and technique are done (please refer to product management manual).

For the q4w SC infusion in Part B2, a syringe infusion material will be used (details are provided in the product management manual). To administer the 1800 mg dose, 6 vials of [redacted] will be used. The infusion rate for the first infusion should be in line with the TDR15526 study (maximum rate 0.67 mL/min, ie, approximately 18 min for 12 mL). Then the flow rate can be adjusted depending on tolerability. The first SC infusion must be performed at site, under staff supervision. Then, after 12 weeks under modified SC dose regimen, home administration may be considered if deemed appropriate by the investigator. In this case, home nurse intervention after appropriate medical training and assessment of practical conditions will be required (please refer to product management manual).

It is recommended that SC injection sites are alternated between the 4 quadrants of the abdomen with the injection sites at least 2 cm from the umbilicus.

A complete and detailed description can be found in the product management manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

A randomized treatment kit number list will be generated centrally by Sanofi for the IMPs. The IMPs (frexalimab or matching placebo) will be packaged in accordance with the list. The Sponsor's Clinical Supply Chain team will provide the randomized treatment kit number list to the centralized treatment allocation system (IRT). This centralized treatment allocation system will generate the participant randomization list according to which it will allocate the IMP to the participants. The Investigator or designee will obtain the treatment kit number(s) and route of administration at randomization (Day 1, baseline) and subsequent scheduled dosing visits via an IRT that will be available 24 hours/day. Although the kit number(s) will vary for the individual participant, the treatment group assignment and randomization will not change throughout the study.

Randomization will take place at baseline (on Day 1) with no stratification factor.

A participant who has been allocated to a randomized study intervention will be considered a randomized participant, regardless of whether the treatment kit was used (ie, the participant was registered by the IRT). A participant cannot be randomized more than once in the study.

Unblinding

The IRT will be programmed with blind-breaking instructions. In the case of an emergency, the Investigator has the sole responsibility for determining if the unblinding of a participant's intervention assignment is warranted (eg, in case of an AE, the code must only be broken in circumstances when the knowledge of the IMP is required for treating the participant). Participant safety must always be the first consideration when making such a decision. If the Investigator decides that the unblinding is warranted, the Investigator, at his/her discretion, may contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment, unless this could delay emergency treatment of the participant. Code breaking can be performed at any time by using the proper module of the IRT. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date, time of the day, and reason that the blind was broken must be recorded in the source documentation and electronic case report form (e-CRF), as applicable. If the code is broken by the Investigator, the participant must be withdrawn from the study treatment.

Methods of blinding

This study is blinded for treatment allocation (frexalimab or placebo). Vials of frexalimab and placebo will be identical. Due to ethical considerations, placebo duration is restricted to 12 weeks, which will allow more objective evaluation of safety events at the beginning of the study period and will also add to objectivity of evaluation of clinical endpoints.

There are no apparent differences between frexalimab and placebo, so they cannot be distinguished by the site staff and participant.

Blinded IMPs will be supplied for treatment in Part A. Participants will receive frexalimab or matching placebo IV or SC as per random assignment. At Week 12, a switch of IV and SC placebo groups to IV and SC frexalimab groups, respectively, will take place. Participants will receive frexalimab with placebo double-dummy masking as needed in a double-blind fashion as specified in Table 7.

The bioanalyst and the pharmacokineticist responsible for sample analysis and PK evaluation will be unblinded. However, they will agree not to disclose the randomization schedule or the individual unblinded analytical results before the official opening of the randomization schedule. Preliminary PK data, if needed and available during the study, will refer to means with descriptive statistics, and individual data will not be associated to any individual randomization numbers or participant numbers.

Laboratory assessments of the Part A for biomarkers in the SoA (see Section 1.3), as well as of ADA and PK data, will be blinded to study teams, Investigators, and participants from baseline/Day 1 throughout the study. In case of a safety concern, unblinding can be performed by the Investigator and/or Sponsor for biomarkers. Dedicated Sponsor's team members will be also unblinded for technical integration of laboratory data into the database before the database lock of Part A.

Investigators will not have access to MRI data except for any safety-related findings, which will be communicated in order to evaluate the safety of the participant. The local radiology service for the site will be in charge of timely reporting of any safety-related findings on MRI scans to the Investigator. In addition, in accordance with standard clinical practice, the Investigator may access full report of MRI performed from Week 24 through the local radiologist.

Independent raters of MRI will be blinded for study treatment and dose and other participant data.

6.4 STUDY INTERVENTION COMPLIANCE

When participants are treated at the site, they will receive the study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose and route of administration of the study intervention and study participant identification will be confirmed at the time of treatment by a member of the study site staff other than the person administering the study intervention. Details on administration of the IMP and recording of the IMP administration can be found in the product management manual.

The same verifications will be performed before dispensing IMP for SC at-home administration (see Section 4.1 for detail) at the site or by an authorized third party.

6.5 DOSE MODIFICATION

Dose reduction is not foreseen in this study. Participants, Investigators, and the Sponsor's team will be blinded with respect to assigned treatments (frexalimab or placebo), but not blinded for administration route and dose group. Treatment may need to be interrupted or permanently discontinued if deemed necessary due to an AE (Section 7 and Section 8.3).

A participant may switch to the other arm after evaluation of results of Part A, if it is decided to close one arm. This may occur at a different time in the Part B for an individual participant, depending on the time of recruitment to the study.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Upon completion of Parts A and B of this study, post study access to study medication could be provided based on local/country regulations or participants will be managed by their treating physician who will decide the best DMT appropriate for the participant.

6.7 TREATMENT OF OVERDOSE

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as:

- Intravenous doses:
  - Increase of at least 30% of the dose to be administered or the dose is administered in less than 30 minutes.
  - At least twice the intended dose within 20 days.
- Subcutaneous doses:
  - q2w regimen: at least twice the intended dose within 8 days.
  - q4w regimen: at least twice the intended dose within 20 days.

Of note, asymptomatic overdose has to be reported as a standard AE.

The Sponsor does not recommend a specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Sponsor immediately.
2. Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or dosing schedule modified.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities at least for 3 months.
4. Obtain a plasma sample for PK analysis if requested by the Sponsor (determined on a case-by-case basis).
5. Document appropriately in the e-CRF.

6.8 PRIOR AND CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The same data will be collected for all prior medications received during the 4 weeks before enrollment, also for all prior MS treatments and treatments considered clinically important to assess MS or concomitant disease.

Multiple sclerosis relapses should be treated as per local practices: eg, with high-dose IV methylprednisolone for 3 to 5 days, or other equivalent treatment, per local guidance or routine.

Non-essential systemic corticosteroid use should be avoided, especially in Part A, if other equivalent treatments can be used without additional risk for the participant.

6.8.1 Prohibited medication

In addition to the medicines excluded in Section 5.2, the following medications are prohibited throughout the study:

- Other MS disease-modifying treatments.

6.8.2 Rescue medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

The study intervention should be continued whenever possible.

In rare instances, it may be necessary for a participant to permanently discontinue the study intervention. If the study intervention is permanently discontinued, the participant will remain in the study to be followed until the Common EOS. During this extended participation in the study without study intervention, the participant can be treated for RMS according to local clinical practices and the best judgment of the investigator, generally after the follow-up period.
The participant must be followed-up for 24 weeks and shall be asked to perform the key efficacy visits until the Common EOS (that may occur after the 24 weeks follow-up period).

If the participant does not agree to continue until the Common EOS, the 3 additional follow-up visits must be performed for 24 weeks after the last administration of the IMP (see SoA, Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Prescription of subsequent disease-modifying therapy for RMS should generally be made after the 24-week follow-up period, depending on individual circumstances.

In case of the following events, a definitive discontinuation of the IMP is mandatory. This list is not intended to be exhaustive:

- At the request of the participant: ie, withdrawal of consent for the study.
- Pregnancy of a female participant.
- Thromboembolic events including, but not limited to, deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke.
- Any serious opportunistic infections (eg, PML [see Section 10.6]).
- Occurrence of any malignancy.
- Severe hypersensitivity or anaphylactic reaction.
- Severe injection site reaction.
- Any AE, per Investigator judgment, that may jeopardize the safety of the participant, or if discontinuation of the study intervention is considered necessary by the Investigator and/or participant.
- Continuous need for chronic use of prohibited medication (ie, other disease-modifying treatments).

- Any code breaking performed by the Investigator.
- At the specific request of the Sponsor.
- The participant is no longer deriving a therapeutic/clinical benefit in the opinion of the Investigator

Discontinuation of the IMP for laboratory abnormalities should be considered by the Investigator when a participant meets one of the conditions outlined in Appendix 6 (Section 10.6) or if the Investigator believes that it is in the best interest of the participant.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision regarding possible definitive IMP discontinuation for the concerned participant. All efforts should be made to reassess, in a clinically relevant timeframe (using either a local or central laboratory), the clinical significance of laboratory abnormalities and corrective actions before making a decision of definitive discontinuation of the IMP for the concerned participant.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, participants will be assessed using the procedure normally planned for the last day of treatment with the IMP including PK and ADA samples. MRI should be performed as early as possible after discontinuation of the IMP if the last MRI was performed earlier than 1 month before. Afterwards, the participant will be asked to attend all planned visits until the Common EOS, if possible. The Investigators should encourage the participant to attend primarily visits with efficacy assessments until Common EoS. If the participant does not agree to continue until the Common EOS, he/she will be followed-up for 24 weeks after the last administration of the IMP.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm in Section 10.6 or in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the Investigator believes that it is in the best interest of the participant.

7.1.3 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs. The Investigator should record the duration of all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF. Planned visits should take place as scheduled, if possible, during this period of discontinuation.

In case of suspected COVID-19 (eg, fever, cough, shortness of breath in the context of possibly infected contact), temporary discontinuation of the IMP can be considered. The following should be considered to evaluate individual benefit-risk assessment for resuming or stopping of the IMP: probability of COVID-19 disease, possibility of rapid diagnosis, severity of symptoms, and risk factors. If the COVID-19 diagnosis is confirmed, the IMP will be suspended until the participant recovers (ie, becomes asymptomatic), and presents a negative PCR test, after which IMP can be continued (or resumed if a dose was skipped) (Section 7.1.1).

A discontinuation of the IMP of greater than 45 days during Part A will be considered definitive and relevant e-CRF sections should be populated. If this occurs in Part B, the Sponsor must be contacted to decide mutually on further treatment continuation.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.8.

7.1.4 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered, according to his/her best medical judgment that the responsibility of the IMP(s) for the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (see Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.8.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason), or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons.
- A participant not willing consenting to switch to Part B2 modified SC dose regimen would also be withdrawn.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent from the study, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent as per applicable clinical regulation(s).
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend, which are all visits with efficacy assessments until Common EOS. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

Discontinuation of specific sites of the study as a whole are handled as part of Appendix 1 (Section 10.1.9).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, serology tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or to other blinded personnel until the final database lock.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed approximately 890 mL, in case of longest possible participation in the study of 73 months. Maximum amount of blood collected during 12 weeks in Part A will not exceed approximately 225 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.8.

8.1 EFFICACY ASSESSMENTS

Planned time points for all assessments are provided in the SoA (Section 1.3).

8.1.1 Magnetic resonance imaging assessments

Cranial (brain) MRI before and after administration of Gd contrast agent will be performed.

- The basic MRI will be performed at all sites and will consist of the following sequences: T2- and T1-weighted sequences before and after administration of Gd contrast agent (if there is no contraindication).
- An expanded MRI protocol will be conducted using additional MRI sequences such as magnetization transfer ratio (MTR) (all centers) and susceptibility-weighted imaging (SWI) (subset of centers with capacity of 3T MRI).

- Basic MRI sequences will be used to evaluate MRI-related endpoints of change in T2-hyperintense lesion volume, new and enlarging T2-hyperintense lesion count, number and volume of T1-hypointense lesions, brain volume loss rate, volume, number, and intensity (T1) of slowly evolving lesions, and GdE T1 lesion count (see Section 3). The expanded MRI protocol will be used to evaluate Gd enhancement recovery (MTR) and phase rim lesions (SWI). Additional details about MRI assessments will be provided in a separate manual.

Due to a potential safety risk related to deposition of certain IV Gd contrast agents in the brain, these agents should be used in accordance with local recommendations/regulations (34).

As the use of systemic corticosteroids for treatment of MS relapse or any other medical reasons could interfere with the MRI findings, performing of MRI on or close to such treatment needs to be avoided. If a study MRI is planned within 7 days of the initiation of treatment, it should be rescheduled to be performed prior to the initiation of corticosteroid treatment when possible.

A separate manual, containing instructions for brain MRI standard image acquisition requirements, MRI acquisition validation, data transfer to the central review center, archiving and shipping, and the image approval process, will be provided to all participating sites. Study site personnel will undergo training regarding MRI acquisition and data handling procedures. Training will be documented, and adherence to the manual will be monitored throughout the study with retraining performed as necessary.

Unless specified otherwise, the screening brain MRI scan will be used as the reference to assess all MRI-derived endpoints. Standardized endpoint evaluation is assured by central review of brain MRI scans. A blinded MRI central review will be performed for all MRI-derived endpoints. All MRI reviewers will be blinded to treatment assignments and to other participant data. Details of MRI scanning and central review will be described in the manual.

Magnetic resonance imaging scans need to be reviewed by a local radiologist for any non-MS pathology to assure safety reporting as per Section 8.3.8. In the event of the identification of MRI findings relevant to participant safety, the local radiologist will provide a report to the Investigator. Expected MS findings on MRI scans, not reflecting an acute safety concern for the participant, should not be disclosed to the Investigator or to the site team if not relevant to any safety concern. Any safety concern noted on MRI, whether related to MS or not, shall be provided to the Investigator. In addition, in accordance with standard clinical practice, the Investigator may access reports of MRI performed as from Week 24 through the local radiologist.

8.1.2 Multiple sclerosis relapse assessment

8.1.2.1 Definition of multiple sclerosis relapse

For the purposes of this study, MS relapse is defined as a monophasic, acute or subacute onset of, new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms must:

- Be attributable to MS.
- Last for ≥24 hours, with or without recovery.
- Be present at normal body temperature (ie, no infection, excessive exercise, or excessively high ambient temperature), and
- Be preceded by ≥30 days of clinical stability (including no previous MS relapse).

Note: An exacerbation or recurrence of symptoms and signs in a participant with MS that can be reasonably attributed to transient impairment of conduction in previously demyelinated pathways due to drugs (such as rarely occurs a few hours after injections of interferon beta), or raised core body temperature (the Uhthoff phenomenon) will not be considered to be a relapse.

Confirmation of MS relapse will be based on the EDSS score (see Section 8.1.3), based on the following definition:

- A confirmed MS relapse is one accompanied by a clinically relevant change in the EDSS score performed by the Investigator, ie, an increase of at least 0.5 points in the EDSS score, an increase of 1 point on 2 functional scores, or an increase of 2 points on 1 functional score, excluding changes involving bowel/bladder and cerebral functional score compared to the previously available rating (the last EDSS rating that did not occur during a relapse).

Refer to Section 8.3.6 for details regarding MS relapse reporting.

8.1.2.2 Unscheduled assessment visits

Participants must be instructed to immediately report new neurological symptoms and recurring or worsening of previous symptoms to the Investigator. Any reported symptoms will be recorded. If a participant reports symptoms that may be consistent with relapse, an unscheduled assessment visit with the Investigator must be scheduled as soon as possible (whenever possible within 7 days after onset of symptoms). The assessment, management, and reporting of MS relapse is performed by the Investigator.

Diagnosing MS relapses during the study: The Investigator will assess whether the reported episode is consistent with the definition of MS relapse, per protocol. If it is consistent with the definition of MS relapse or if there is any doubt and the possibility of relapse cannot be ruled out, the standard neurological examination (for the EDSS score) will be performed. If an EDSS rating is not performed, this will be documented with an explanation of the reason. Whenever possible, the EDSS rating should be performed the same day of unscheduled visit.

All MS relapses are to be reported on the MS relapse e-CRF page. Multiple sclerosis relapse should not be reported as an AE unless, in the judgment of the Investigator, it is unusually severe, medically unexpected, or matches the definition of a SAE.

Safety laboratory tests are optional for the unscheduled assessment visit if no intercurrent disease is suspected. If any intercurrent disease is diagnosed, it will be reported as an AE as per the safety reporting rules.

The participant will be also asked to report possible relapse symptoms during scheduled quarterly visits. If relapse is suspected, the above decision-making and reporting rules apply.

8.1.3 Expanded disability status scale

The Investigator/rater will perform the EDSS evaluation (35). All Investigators/raters must be qualified to perform neurological assessment as per local requirement. In addition they must be trained and certified to perform the EDSS in a consistent manner (Neurostatus® training version 04/10.2).

The EDSS score will be captured. Quality control measures will be put in place to ensure scoring error detection and thus minimize the impact of any scoring and calculation errors. Details will be included in training materials.

The Investigator/rater will rate functional systems in the context of a standard neurological examination and will report these ratings as per the EDSS score reporting instructions together with information on the participant's mobility, gait, and use of assistive devices. Standard EDSS assessments of 7 functional domains (visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder) will be performed by assessing neurological symptoms in each of these domains. Ambulation will be scored to conclude the evaluation. The fatigue evaluation may be optionally recorded, but it will not contribute to assignment of the EDSS score. The total EDSS score will be assigned according to EDSS scoring rules.

A screening EDSS assessment must be completed to confirm eligibility, and the EDSS assessment must be repeated at the randomization visit.

Participants will not be informed of their EDSS scores.

Additional details on EDSS assessment and EDSS score reporting will be provided in training materials.

8.1.4 Patient-reported outcome and health-related quality-of-life parameters

Patient-reported outcome assessments will be performed in this study in line with the SoA (see Section 1.3). These outcome assessments are to be administered prior to treatment and prior to discussion of a participant's health status. It is important that participants complete the outcome assessments after ICF is signed and prior to any treatment- or study-related activities, including administration of study treatment, laboratory work, radiological assessments, discussion with the participant regarding their treatment or health status, and similar activities. This ensures the objectivity of the data. Detailed site training on the outcome assessments will be provided.

8.1.4.1 Multiple sclerosis impact scale (MSIS)-29

The Multiple Sclerosis Impact Scale with 29 items (MSIS-29) was developed to evaluate the specific physical and the psychological impact of MS from a patient's perspective (36). The MSIS-29 has two subscales; 1/ a physical impact score (20 items) and 2/ a psychological impact score (9 items). The physical and psychological impact subscales of the MSIS-29 range from 0 to 100, with higher scores indicating greater physical or psychological impact.

8.1.4.2 Patient reported outcome measurement information system (PROMIS)-Fatigue-MS-8

The PROMIS-Fatigue-MS-8 is an 8-item short form derived from the Patient-Reported Outcomes Measurement Information System® (PROMIS®) Fatigue Item Bank (37). PROMIS measures were developed for use with both the general population and individuals living with chronic conditions (38). The measures are based on calibrated item banks from which short forms can be derived. The PROMIS-Fatigue-MS-8 is scored on a T score metric, with a mean of 50 and a SD of 10. A higher PROMIS T-score represents more fatigue.

8.1.4.3 Patient's qualitative assessment of treatment version 3 (PQATv3)

The PQAT is a new patient-reported outcome measure designed to evaluate patient-perceived benefits and disadvantages of treatment and their willingness to continue/discontinue treatment based on their experience. The PQATv2 collects qualitative and quantitative data on the benefits and disadvantages of treatment (39). A modified version of the PQATv2; the PQATv3 will be utilized in the study. The PQATv3 has 4 additional questions that assess past IV and SC patient experience, and patient preferences for IV or SC depending on IV/SC past experience.

8.1.4.4 Patient global impression of change and severity scale (PGIC-Fatigue and PGIS-Fatigue measures)

The Patient Global Impression scale (PGI), also known as Subject Global Impression (SGI), is the PRO counterpart to the Clinical Global Impressions scale, (CGI), which was published in 1976 by the National Institute of Mental Health (US). It consists of one item based on the CGI and adapted to the patient. It mainly measures change in clinical status (PGI-C) but can also measure disease severity (PGI-S). Over the years, PGI scales were used in a broad range of diseases and have been modified for clinical settings (item label, number of response options and response options) (40). Two global measures, the PGIC, specific to fatigue (PGIC-Fatigue), and the PGIS, specific to fatigue (PGIS-Fatigue) will be utilized as an anchors to assess changes in fatigue status and in fatigue severity, in order to establish the measurement properties (scoring, clinically meaningful change scores) of the PROMIS-Fatigue-MS-8.

The PGIC-Fatigue and PGIS-Fatigue will be used as anchors to validate the PROMIS-Fatigue-MS-8 questionnaire. Additional details on scoring will be provided in the SAP.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events, which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the skin, oral cavities, eyes and cardiovascular, respiratory, gastrointestinal, musculoskeletal, lymphoid, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical symptom-based physical examination will include organ systems, which are deemed, at the discretion of the Investigator, necessary to be evaluated. Neurological examination will be also to be performed, if EDSS full assessment is not done or needs additional testing (adapted as needed).
- Investigators should pay special attention to clinical signs related to previous serious illnesses and thromboembolic events.
- Any new finding or worsening of a previous finding should be reported as a new AE.

Height and weight

- Height (in cm) will be measured only at Screening.
- Weight (in kg) should be taken with the participant wearing light clothing and no shoes. The same scale should be used throughout the study.
- Body mass index will be calculated automatically at each visit when weight is measured as per the SoA (Section 1.3).

8.2.2 Vital signs

- Vital signs will be measured in a sitting position after 5 minutes of rest and will include tympanic temperature, respiratory rate, systolic and diastolic blood pressure, and pulse.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- A single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3).
- Electrocardiogram parameters will be based upon the automatic reading of the device. These ECG parameters and morphology need to be reviewed by the Investigator. If the device does not provide automatic reading, then the ECG parameters will need to be determined and interpreted by the Investigator.

- At post randomization visits, ECGs will be performed prior to IMP administration. All ECGs will be performed with the participant in a reclining position. Electrocardiogram parameters include heart rate, QRS duration, PR, QT, and QTc interval.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the e-CRF. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 24 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the e-CRF.

8.2.5 Local tolerability

The evaluation of SC injection/IV infusion site reactions following IMP administration will be performed by the Investigator or designee and the participant.

On-site injections/infusions

Local tolerability will be assessed by both Investigator or designee and participant.

Findings at the local injection/infusion site such as, but not limited to tenderness, erythema, and swelling will be recorded in the e-CRF in 4 different grades (mild/moderate/severe/very severe) based on instructions in Section 10.9.1. Participants will be asked to report sensations at the administration site, which will then be evaluated by the Investigator or a designee (and reported as AE if criteria of a local administration site reaction are met, at the discretion of the Investigator or designee).

In addition, self-evaluation of pain will use a pain- verbal descriptor scale before IMP administration, after completion of the IMP administration, and 2 hours post-administration (see Section 10.9.2).

Home injections

The local tolerability will be assessed by participant using the same pain-verbal descriptor scale described above.

In the case of any injection site or other adverse reactions, the participant must contact the site as soon as possible to report the injection site reaction or other adverse event. The Investigator must monitor any worsening of events and schedule an on-site visit for evaluation and treatment, if needed. The Investigator will also proactively contact the participant on the day of injection to ensure the best management of injection site reaction or other adverse event, should this occur.

8.2.6 Pregnancy testing

- Refer to Section 5.1 Inclusion criteria for pregnancy testing entry criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at q4w visits during intervention (additional tests, if needed).
- Pregnancy testing (urine or serum as required by local regulations) should be conducted corresponding with the time frame for female participant contraception in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as deemed necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.2.7 Suicidal ideation and behavior risk monitoring

Not applicable.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.7.

Adverse events will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the EOS at the time points specified in the SoA (Section 1.3).

All SAEs and AESIs (defined in Section 8.3.7) will be recorded and reported to the Sponsor or designee immediately. Under no circumstance should the time lag exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and AESIs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs and other safety reporting

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- Serious adverse events that are considered expected will be specified in the reference safety information (see the IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.
- For the European Union, safety reporting to the agency is described in Section 10.7.2.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the EOS visit.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention or be withdrawn from the study.

8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Multiple sclerosis relapses, determined from the evaluations described in Section 8.1.2, as with all efficacy endpoints, will be exempt from being reported as AEs except when they meet the definition of a SAE or are unusually severe or medically unexpected. Hospitalization for MS relapse, if done routinely at the site (eg, for high dose IV methylprednisolone administration), will not be considered as a seriousness criterion for this study. Data for MS relapses will be collected on the e-CRF and be analyzed as part of the efficacy analysis. Other worsening of neurological symptoms that do not meet the definition of MS relapse will be reported as AEs according to general safety reporting rules.

8.3.7 Adverse events of special interest

Adverse events of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed by protocol amendment during a study.

For AESIs, the Sponsor is to be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Appendix 3 (Section 10.3), even if a seriousness criterion is not met, using the corresponding pages of the case report form (to be sent) or screens in the e-CRF:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP:
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, study intervention should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Section 8.3.5).
- Symptomatic overdose (serious or nonserious) with IMP (see definition of overdose in Section 6.7):
- Increase in alanine transaminase (ALT) : If increase in ALT >3 × ULN, see the "Increase in ALT" flow chart in Appendix 6 (Section 10.6)
  - However, if the increase in ALT is ≥2 × the baseline value (with baseline ALT ≥ULN) but ≤3 × ULN, then ALT should be retested within 72 hours of initial sample to determine if the retest value meets the AESI criterion of ALT > 3 × ULN. If so, proceed as above and follow the guidelines of Appendix 6 (Section 10.6). If not, monitoring of the laboratory findings will be up to the medical judgment of the Investigator.

- Other project specific AESI(s)
  - Confirmed diagnosis of an arterial and/or venous thrombotic or embolic event. All signs and symptoms, clinical or biological, suggestive of a thromboembolic event should be investigated immediately (eg, D-dimer, venous ultrasound and other radiological investigations) as needed, as per Investigator clinical judgment and/or local regulation. Only confirmed thromboembolic events should be reported as an AESI.
  - Anaphylaxis.
  - Severe infusion related reactions.
  - Severe IMP injection or infusion site reaction.
  - Severe infections including opportunistic infections.
  - Tuberculosis or suspected tuberculosis leading to initiation of medications.
  - Diagnosed and biologically proven SARS-CoV-2 infection.

8.3.8 Reporting of safety findings from magnetic resonance imaging

Magnetic resonance imaging scans need to be reviewed locally for any pathology. In case of clinically significant findings, the MRI report needs to be provided to the Investigator for appropriate safety reporting. When available, a diagnosis of pathology at cause of such MRI findings or the findings themselves will be reported as an AE until the diagnosis is clear. Multiple sclerosis findings from MRI scans do not need to be reported unless they are deemed unusual and thus a distinct safety finding.

8.3.9 Medication errors, or misuses of medicinal product

All reports of medication error, or misuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor's representative following standard processes.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

8.3.10 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

Frexalimab concentrations at selected time points will be reported using descriptive statistics. Additional PK parameters such as C_{max}, t_{max}, $t_{1/2z}$, and $AUC_{0\text{-}tau}$ will be estimated using a population PK approach. These parameters will be presented in a separate standalone report.

- Blood samples will be collected for measurement of plasma concentrations of frexalimab as specified in the SoA Section 1.3. Detailed procedures of sample preparation, storage, and shipment will be described in the specific laboratory manual.
- A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of frexalimab. Each plasma sample will be divided into 2 aliquots. Samples collected for analyses of frexalimab plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples unless consent for this was signed by the participant. Participant confidentiality will be maintained.

Pharmacokinetic samples may be used for testing analytical method performance such as comparability and incurred sample reproducibility.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the final database lock.

8.5 GENETICS AND PHARMACOGENOMICS

8.5.1 Deoxyribonucleic acid (DNA)

Whole blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study at Baseline. The DNA isolated from this sample will be stored from consenting participants.

A targeted analysis for genetic polymorphisms in specific loci in CD40 and components of downstream signaling pathways known to be associated with increased risk of MS as potential predictive markers of response to frexalimab is planned. Further, this sample and the DNA isolated from this sample may be used to determine possible relationships between other genes and response to treatment with frexalimab, how the body processes frexalimab, possible side effects to frexalimab, and/or genes that may potentially be involved in MS or other autoimmune diseases. The DNA, and any remaining whole blood, will be stored for up to 25 years from the completion of the clinical study report (CSR) of the present study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

8.5.2 Ribonucleic acid (RNA)

At the study visits specified in the SoA (Section 1.3), RNA blood samples will be collected and stored from all participants for isolation of RNA. In selected sites additional peripheral blood mononuclear cells (PBMCs) will be collected. The samples and any RNA isolated from the samples will be used to study expression levels of genetic transcripts by methods such as NanoString and RNA sequencing.

An analysis of RNA isolated from whole blood for expression of a CD40/CD40L gene signature to evaluate correlation between CD40L activation scores and response to frexalimab is planned. Additionally, RNA isolated from PBMCs will be used to measure the cell type-specific activation state of CD40/CD40L signaling pathway to characterize the CD40/CD40L pathway activation in adaptive and innate immune cells and confirm the treatment effect on innate immunity. Further, the samples may be used to determine possible relationships between RNA transcripts and response to treatment with frexalimab, how the body processes frexalimab, possible side effects of frexalimab, and/or transcripts that may potentially be involved in MS and other autoimmune diseases. The PBMC sample and/or isolated RNA samples from blood or PBMCs may be stored for up to 25 years from the completion of the CSR of the present study.

Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual. See Appendix 5 (Section 10.5) for information regarding genetic research.

Details on processes for collection and shipment and destruction of these samples will be provided to sites.

8.6 BIOMARKERS

Collection of biological samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Whole blood samples for assessing expression of a CD40/CD40L gene signature by bulk RNA sequencing analysis as indicated in Section 8.5.2. Expression levels of a panel of genes associated with CD40 pathway activation will be measured to assess their association with the observed clinical responses to frexalimab treatment. Collection is specified in the SoA (Section 1.3).
- Serum samples will be tested for IgG and IgM as potential biomarkers.
- Soluble CD40L in plasma:
  - To be evaluated as a potential marker of inflammatory activity in MS patients at baseline measurements and for a potential relationship with CD40/CD40L mRNA signature expression.
  - Increase is expected after frexalimab administration based on previous studies. To be used to assess frexalimab target occupancy.
- Plasma samples will be tested for C-X-C chemokine ligand 13 (CXCL13):
  - Biomarker to evaluate germinal center activity in response to frexalimab.
  - CXCL-13 protein levels are expected to show a decrease with frexalimab treatment, indicative of reduced B-cell activity and activation.
- Plasma samples will be tested for NfL:
  - Biomarker to assess changes in the level of neuroaxonal damage in response to frexalimab.
  - NfL protein levels are expected to show a decrease with frexalimab treatment, indicative of reduced disease activity.
- Plasma samples will be tested for chitinase-3-like protein 1 (CHI3L1):
  - Biomarker to assess changes in neuroinflammation activity in response to frexalimab.
  - Chitinase-3-like protein 1 levels are expected to show a decrease with frexalimab treatment, indicative of reduced disease activity.
- Plasma samples will be tested for soluble Triggering receptor expressed on myeloid cells 2 (sTREM2):
  - Biomarker to assess changes in microglial activation and neuroinflammation activity in response to frexalimab.
  - sTREM2 protein levels are expected to show a decrease with frexalimab treatment, indicative of reduced disease activity.
- Analysis of mRNA isolated from PBMCs for assessing expression of a CD40/CD40L gene signature from selected participants (to be chosen based on bulk RNA sequencing results). To be performed on participants from selected sites capable of rapid PBMC isolation.

- Immunophenotyping of subpopulations of interest (such as naïve, effector, helper, regulatory cell subsets among B and T-cells, pro-inflammatory and regulatory monocyte, DC1, and DC2 cell subtypes) from PBMCs collected from participants at selected sites capable of rapid PBMC isolation.
- Biomarkers will be tested to evaluate disease-specific changes and their association with the observed responses to frexalimab as judged by the primary MRI endpoint.
- In addition, optional archival DNA samples for future analysis (see SoA [Section 1.3]) will be collected and stored for up to 25 years from the completion of the CSR of the present study. Analysis of DNA isolated from whole blood may be performed to assess presence of gene variants involved in the CD40/CD40L signaling pathway, as well as those thought to play a role in the pathogenesis and treatment of MS and related autoimmune disease (see Section 8.5.1).
- Remaining samples from the study may be used for additional research of biomarkers related to MS or to the CD40/CD40L signaling or to frexalimab effects or prognosis of its efficacy.
- Samples collected for biomarker analyses and their derivatives will be stored for a period of up to 25 years after last participant's last visit for potential re-analyses.

8.7 IMMUNOGENICITY ASSESSMENTS

Antibodies to frexalimab will be evaluated in serum samples collected from all participants according to the SoA (see Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to frexalimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to frexalimab and/or further characterize the immunogenicity of frexalimab.

The detection and characterization of antibodies to frexalimab will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to frexalimab will also be evaluated for frexalimab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to frexalimab.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of medicines.

Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Coded study data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of data/sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

A specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

Data protection – Processing of coded clinical data

The study participant will be provided with all mandatory details of the data processing in Section 2 of the core ICF. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples and additional samples for future research

Leftover biological samples (eg, remaining and backup PK and biomarker samples) and additional samples (eg, optional DNA samples) will be collected as defined in the SoA (see Section 1.3) and can be used for future research during the study conduct or at the end of the study if consent provided in Part 3 of the Core ICF.

Biological samples for future use will be stored for up to 25 years after the end of the study. Any samples remaining at the end of the retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such cases, samples will be destroyed and related coded data will be anonymized, unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

The sample size was derived by applying the frequentist approach of the Quantitative Decision Making method described by Quan et al (41). This approach is based on the comparison of the lower (LL) and upper limits (UL) of an asymmetric confidence interval of the treatment difference, with target (TV) and lower reference (LRV) values.

Using the following features:

- TV: 90% reduction
- LRV: 70% reduction
- Significance criterion: 86% (P(Non-negative conclusion| LRV)≈14%)
- Relevance criterion: 15% (P(Negative conclusion| TV)≈15%).

And, assuming the following:

- The number of new GdE T1 lesions by month follows a negative binomial distribution with a mean of 0.1 in the frexalimab group and a mean of 1 in the placebo group (that is, 90% reduction of mean lesions count in the frexalimab group relative to that of the placebo group).
- The dispersion parameter of the negative binomial distributions equals 2 (estimated from Week 12 placebo data from the vatelizumab [SAR339658] DRI13839 study).

Then, with 40 evaluable participants in the frexalimab group, and 20 evaluable participants in the placebo group, the probability for the asymmetric confidence interval of the relative reduction in mean new GdE T1 lesions count at Week 12 in participants receiving frexalimab compared to that of those receiving placebo to be located in the “Positive” conclusion area is approximately 71%, and the probability to be located in the “Negative” conclusion area is approximately 15%. Conclusion rules are detailed in Table 11.

Assuming that IV and SC placebo arms can be pooled for comparison with either frexalimab 1200 mg IV q4w arm or frexalimab 300 mg SC every 2 weeks arm, and as no adjustment for multiplicity of doses is planned, approximately 160 people will be screened to achieve 120 participants randomly assigned to study intervention and 100 evaluable participants for an estimated total of 40 and 10 evaluable participants per frexalimab and placebo intervention in each of the dose groups respectively.

It is planned to perform subgroup analysis according to CD40/CD40L pathway activation as measured by mRNA signature in peripheral blood cells. With this sample size and assuming 40% of participants classified as participants with the activated pathway at baseline (CD40/CD40L+) and assuming the absence of effect on primary endpoint in the placebo group, the comparison of 16 participants CD40/CD40 + treated with frexalimab versus 20 participants receiving placebo will results in an overall probability for a positive conclusion of approximately 53% and a negative conclusion of less than 15%. Assuming a 95% reduction of mean lesion

counts versus placebo in this sub-population, the probability of positive conclusion increases to 64% and negative conclusion decreases to 5% with 31 % probability of intermediate outcome.

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 9 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Efficacy	All participants from the ITT population who take all Part A doses of study intervention (one SC dose skipped is allowed) and with an evaluable primary endpoint. The primary endpoint is evaluable when the following conditions are met: • Availability of the blinded MRI central assessment of the primary endpoint. • No systemic corticosteroids administration 30 days before baseline MRI and during Part A period. Participants will be analyzed according to the intervention they actually received.
Safety	All randomized participants who take at least 1 dose (regardless of the amount) of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All randomized and treated participants (safety population) with at least one post-baseline PK sample with adequate documentation of dosing and sampling dates and times. Participants will be analyzed according to the intervention they actually received.
Open-Label Extension (OLE)	All participants who received at least one dose of intervention during the open-label extension phase.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear if they took the study intervention will be considered to be exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

9.3 STATISTICAL ANALYSES

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. A statistical analysis plan (SAP) will be finalized prior to the database lock and will include a more technical and detailed description of the statistical analyses described in this section.

9.3.1 General considerations

A statistical analysis plan (SAP) will be finalized prior to the database lock and it will include a more technical and detailed description of the statistical analyses described in this section.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, Q1, Q3 and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of participants in each treatment group.

The baseline value is defined as the last available value before the first dose of double-blind IMP. For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

Unless otherwise specified, Part A analyses will be performed by initial intervention group, ie, placebo, frexalimab 1200 mg IV q4w, frexalimab 300 mg SC every 2 weeks (and overall for baseline and demographics characteristics).

The observation period will be divided into 4 segments:

- The **pre-treatment period** is defined as the period up to the first IMP administration.
- The **treatment-emergent period** is defined as the period from the first IMP administration to the last IMP administration +180 days. The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP +24 days (maximal administration interval allowed by the protocol) for the SC group or 38 days for the IV group.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.

The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

Unless otherwise specified, Part B analyses will be performed by initial intervention group, ie, Placebo 1200 mg IV q4w, Placebo 300 mg SC q2w, frexalimab 1200 mg IV q4w, frexalimab 300 mg SC q2w.

Analyses specific to Part B2 will be performed by the initial intervention group, in participants treated with frexalimab 1800 mg SC q4w in Part B2.

9.3.2 Primary endpoint (Part A)

Primary analysis:

Table 10 - Primary endpoint analysis

Primary Endpoint	Statistical Analysis Methods
Number of new[a] GdE T1 lesions at Week 12 as measured by brain MRI.	The number of new GdE T1 lesions will be analyzed by a negative binomial regression model including terms for between treatment and baseline lesion activity (presence/absence). The relative reduction in each frexalimab group compared to placebo will be estimated, with a 95% confidence interval.

Abbreviations: GdE T1 = gadolinium-enhancing T1-hyperintense; MRI = magnetic resonance imaging.
a "new" lesions compared with Week 8 MRI

The primary analysis of the number of new GdE T1 lesions at Week 12 will be performed in the Efficacy Population through a negative binomial regression model.

This model will include natural (base e) logarithm of the baseline GdE T1 lesion activity (presence/absence) as a covariate and treatment as factor. The duration (in months) between the Week 12 MRI and the previous MRI will be also taken into account as an offset variable after natural logarithm transformation.

The mean number of new GdE T1 lesions at Week 12 in each treatment group, as well as the relative reduction under treatment with frexalimab when compared to placebo will be estimated (estimates and 95% confidence intervals) respectively through exponentiated least squared means and exponentiated least squared means differences.

For Quantitative Decision Making methodology, the asymmetric confidence interval of the relative reduction in each frexalimab group compared to placebo will be also obtained through exponentiated least squared means differences. Using a significance criterion of 86% (P [Non-negative conclusion| LRV]≈14%), upper limits of these asymmetric confidence intervals will correspond to upper limits of one-sided 86% confidence intervals. Using a relevance criterion of 15% (P [Negative conclusion|TV]≈15%), the lower limits of the asymmetric confidence intervals will correspond to lower limits of one-sided 85% confidence intervals. The evaluation will be based on cut-offs described in Table 11.

Table 11 - Conclusion rules

Lower limit of the asymmetric confidence interval	Upper limit of the asymmetric confidence interval	Outcome
< TV	< LRV	Positive
< TV	≥ LRV	Intermediate
≥ TV	< LRV	Intermediate
≥ TV	≥ LRV	Negative

TV=0.1 (ie, 90% relative reduction to placebo) – LRV=0.3 (ie, 70% relative reduction to placebo) and additionally LRV=0.25 (ie, 75% relative reduction to placebo)

Supportive analyses:

As a sensitivity analysis, the primary analysis model will be rerun on Efficacy Population but adjusting for the continuous covariate baseline GdE T1 lesion count instead of the categorical covariate baseline GdE T1 lesion activity.

The imbalance between treatment groups in term of participants without new GdE T1 lesions at Week 12 will be analysed in the ITT population through a logistic regression model considering participants without the primary endpoint or with ≥1 new lesions at Week 12 as failures.
This model will include the same factors as that included in the primary analysis model. Odds ratios of success (success = "no new GdE T1 lesions at Week 12") versus placebo will be provided for each frexalimab group (estimates and 95% confidence intervals).

Besides, a negative binomial regression including the baseline GdE T1 activity (presence/absence) and the baseline score of activation of CD40/CD40L pathway as covariates, and treatment as factor will be done on the Efficacy Population.

In addition, the number of new GdE T1 lesions at Week 12 will be summarized in the ITT Population as categorical data (number of participants with a specific lesion count), adding categories for main reasons for non-available primary endpoint.

Exploratory analysis:

It is hypothesized that the efficacy of frexalimab may depend on the activation of CD40/CD40L pathway. A pre-defined threshold will be determined based on the baseline activation score distribution (percentile). In addition, exploratory analyses detailed Section 9.3.6.2 will aim to determine a refined threshold for the activation score above which participants could better benefit from frexalimab treatment. Once determined, the frexalimab effect on the primary endpoint in this subgroups of participants will be estimated in the Efficacy Population using a similar model and population as that utilized for the primary analysis, but including additionally the categorized CD40/CD40L pathway activation score (score above predefined threshold Y/N) and categorized CD40/CD40L pathway activation score by treatment interaction. Frexalimab effect will be estimated through the categorized CD40/CD40L pathway activation score by treatment interaction. The mean number of new lesions at Week 12 in frexalimab treatment groups in each subgroup, as well as the relative reduction compared to placebo group (whatever the score) will be estimated (estimates and 95% confidence intervals) using linear function of the least squares means obtained through this model and exponential transformation.

In the subset of participants from the Efficacy Population including frexalimab participants with CD40/CD40L pathway activation scores greater than the pre-defined threshold, and all placebo participants: frexalimab effect on the primary endpoint will be estimated using a negative binomial regression including the baseline GdE T1 activity (presence/absence) and treatment as factors. Same asymmetric confidence intervals as above will be also provided for Quantitative Decision Making methodology. The frexalimab effect in this subgroup of participants will be also estimated in the ITT Population using the same logistic regression model described above but only included the baseline GdE T1 activity (presence/absence) as a covariate.

9.3.3 Secondary endpoint(s)

Part A

For the MRI secondary endpoints (number of new or enlarging T2 lesions at Week 12; total number of GdE T1 lesions at Week 12) similar analyses as for the primary endpoint will be provided (Quantitative Decision Making methodology excepted).

Table 12 - Key secondary endpoints analyses

Secondary endpoint	Statistical analysis methods
Number of new or enlarging[a] T2 lesions at Week 12.	(See primary endpoint analysis)
Total number of Gd-enhancing T1-hyperintense lesions (GdE T1) at Week 12.	(See primary endpoint analysis)

a "new or enlarging" lesions compared with Week 8 MRI.

Part B

Secondary endpoints are safety related. Details are provided in Section 9.3.4.

9.3.4 Safety analysis

All the safety analyses will be performed using the Safety Population, unless otherwise specified, using the following common rules:

- Safety data in participants who do not belong to the Safety Population (eg, exposed but not randomized) will be listed separately.
- The baseline value is defined as the last measurement collected on or before the randomization visit (Day 1) prior to initiation of the first dose of the study intervention.
- Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA analyses will be performed based on the PCSA list in effect at Sanofi at the time of the database lock).
- PCSA criteria will determine which participants had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The number of all such participants will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of participants assessed for that given parameter in the TEAE period by treatment group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group.

The analysis of safety variables will be essentially descriptive. No systematic analysis is planned. The summary of safety results will be presented by initial treatment group separately for Part A, Part B (including B1 and B2) and B2 (only in participants treated with frexalimab SC in Part B).

9.3.4.1 Adverse events

General common rules for adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version in use by the Sponsor at the time of database lock).

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

Similarly, deaths will be analyzed in the pre-treatment, treatment-emergent, and post-treatment periods.

Treatment-emergent AEs will be assigned to the treatment received as per the Safety Population.

If the onset date (or time) of an AE (occurrence, worsening, or becoming serious) is incomplete or missing, the AE will be considered as a TEAE unless a partial date (or time) shows it as a pre- or post-treatment event.

Analysis of all adverse events

Adverse event incidence tables will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent AESIs (defined with a PT or a prespecified grouping), all treatment-emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

Adverse event summaries will be generated with number (%) of participants experiencing at least one event.

Deaths will also be analyzed.

Table 13 - Safety analyses

Safety measures	Statistical analysis methods
Adverse events • AEs • SAEs • AEs leading to IMP or study discontinuation • AEs leading to death • AESIs • PCSAs	Treatment-emergent adverse event incidence tables will be presented by system organ class and preferred term for each treatment group and overall, showing the number (n) and percentage (%) of participants experiencing a TEAE. Proportion of participants with at least 1 TEAE, treatment emergent SAEs, TEAE leading to death, and TEAEs leading to definitive treatment discontinuation will be tabulated by treatment group and overall. The incidence of PCSAs occurring during the TEAE period will be summarized by treatment group overall and by baseline status.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; IMP = investigational medicinal product; PCSA = potentially clinically significant abnormality; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Immunogenicity

Antidrug antibodies to frexalimab will be summarized by visit.

9.3.4.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

For laboratory variables, vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided for each planned visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only for laboratory variables and ECG variables.

Analyses according to PCSA

PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central and either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs, and ECG variables, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing.
- Abnormal.

9.3.5 Tertiary/exploratory endpoint(s)

Part A

In addition to exploratory analysis described in Section 9.3.2, other tertiary/exploratory endpoint will be presented as descriptive data. Additional analysis may be done and will be detailed in the SAP.

Part B

Exploratory endpoints will be summarized using descriptive statistics. Further details will be provided in the Statistical Analysis Plan.

9.3.6 Other analysis

9.3.6.1 Pharmacokinetics

Summaries will be provided separately for Part A, Part B (including Part B1 and Part B2) and Part B2 (only in participants treated with frexalimab SC in Part B).

For each above period, plasma concentration over time will be summarized by time window using the number of available data, mean, geometric mean, standard deviation (SD), median, minimum and maximum for each frexalimab dose group.

Other analyses performed, as specified in Section 8.4, to estimate PK parameters and other PK/PD analyses with the main efficacy parameters, will be presented in a separate report.

9.3.6.2 Responder population identification and characterization with biomarker data (Part A)

It is hypothesized that the efficacy of frexalimab may depend on the activation of CD40/CD40L pathway. In consequence, below exploratory analyses will be performed to identify threshold of the activation score of the CD40/CD40L pathway above which participants would better benefit from frexalimab treatment.

The expected number of new GdE T1 lesions at Week 12 will be modeled through a negative binomial regression with the baseline GdE T1 activity (presence/absence) and treatment as effects and score by treatment interaction, in the Efficacy Population. The non-responder patients are assumed to have a non-substantial relative reduction of new GdE T1 lesions count per month in the intervention group compared to the placebo group. The relative reduction for

the non-responders is assumed to be less than 70% (and 90% as a second approach). A threshold in the activation score can be calculated by solving the following equation: E[GdE T1 lesion count|treatment, covariates]/E[GdE T1 lesion count| placebo, covariates]<0.3 (0.1 in the second approach). Bootstrap 95% CI will be provided with the threshold estimation.

9.3.6.3 Other biomarkers

Other biomarker analyses will be reported separately.

9.4 INTERIM ANALYSES

No interim analysis is planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable.
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws.
  - Any other applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, [IDFU] and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

- Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
  - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
  - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
  - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
  - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

As applicable, according to requirements of the Regulation No 536/2014 of the European Parliament and the Council of the European Union, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48h after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that

a (suspected) serious breach is promptly reported to the Sponsor through the contacts (email address or telephone number) provided by the Sponsor.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

For the ICF and the optional future use of sample ICF, the following applies:

- The Investigator or his/her representative will explain the nature of the study to the participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participants or their legally authorized representative, where applicable.

Participants who are rescreened must sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research.

Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.8.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)". They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel,

study participants or their relatives, healthcare professionals, etc), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers.
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO – 46 avenue de la Grande Armée - 75017 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

Not applicable.

10.1.6 Dissemination of clinical study data and results

Study participants

After the end of the double-blind Part A of the clinical study, the Sponsor may publish the intermediate study results in scientific journal(s) and/or at scientific conference(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (euclinicaltrials.eu), and sanofi.com, as well as some national registries. For adult trials, the results will generally be

submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF completion guideline.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality check of the data.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in trainings materials or study manuals.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

In case of investigational site closure or complete regional or national lock-down due to a local epidemic or international pandemic, the study may be suspended regionally or nationally at the affected sites. Every effort will be kept to continue the follow-up of already recruited participants as close to the SoA as possible.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.

- Discontinuation of further study intervention development.

- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 14 will be performed by the central laboratory, if feasible, unless local laboratory use is specified, per laboratory manual.
- Local laboratory results are required for some tests listed in Table 14. Local laboratories may also be used in the event that the central laboratory results are not available or are not feasible to result in time for either study intervention administration and/or response evaluation. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the e-CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations (eg, D-dimer, in case of suspicion of thromboembolic event).

- Pregnancy testing: For Screening, a HCG blood test which will be obtained from all female participants, must be deemed negative (see Section 5). During the study, blood or urine HCG testing will be performed for women of childbearing potential (WOCBP), if the urine test is positive or non conclusive, a blood test will be taken and sent to the central laboratory, if feasible, per laboratory manual.

Table 14 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	MCV
	MCH
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Coagulation	
	International normalized ratio (INR), activated partial thromboplastin time (aPTT).
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine (for estimated glomerular filtration rate calculation, according to Modification of Diet in Renal Disease [MDRD])
	Serum glucose[b]
	Potassium
	Sodium
	Calcium
	Chloride
	Bicarbonate
	Phosphorous
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Creatine phosphokinase
	Total and direct bilirubin
	Albumin
	Total protein

Laboratory tests	Parameters
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase (performed by dipstick locally at the site), quantitative measurement for glucose, protein, erythrocytes, and leukocytes count will be required if the urine sample test is positive for any of the above parameters by urine dipstick and rated clinically significant by the Investigator (sample will be sent to central laboratory) • Microscopic examination (if blood or protein is abnormal)
Urine pregnancy testing	• β-human chorionic gonadotropin (HCG) for women of childbearing potential (performed locally at the site)[c]
Other screening tests	• Follicle-stimulating hormone (as needed in postmenopausal women) • Highly sensitive serum β-HCG pregnancy test • Serology: human immunodeficiency virus 1 and 2 antibodies, hepatitis B surface antigen (HBsAg), hepatitis B core antibody, (HBc Ab), and hepatitis C antibody (HCV-Ab); if anti-HBs negative and anti-HBc positive: perform hepatitis B virus DNA to confirm; if anti-HC IgG positive: IgG, HCV-RNA PCR will be performed • Tuberculosis test (local or central by country)[d]
PD/Genetics/Biomarkers[e]	• IgM, IgG • Anti-drug antibodies • Plasma sampling for proteinic exploratory biomarkers • Whole blood for mRNA sequencing • (Subset of sites) whole blood for PBMC isolation • Whole blood for DNA analysis

NOTES :

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 and Appendix 6 (Section 10.6).

b Fasting glucose is preferred. Fasting/non fasting status will be recorded at the time of blood collection for glucose assessment.

c Local urine testing is accepted after screening for the protocol unless serum testing is required by local regulation or IRB/IEC.

d Blood testing (eg, QuantiFERON TB Gold test) is preferred; skin testing (eg, tuberculin skin test) with ancillary testing will be allowed if blood testing is not available, T-SPOT can also be performed, if available.

e The Investigator and study site will be blinded for these parameters. Unblinding is appropriate in case of a safety issue.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the final database lock (see Section 6.3).

Unblinding is appropriate in case of a safety issue and deemed necessary by the Investigator.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse and abuse with the IMP.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

A) Results in death

B) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

C) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

E) Is a congenital anomaly/birth defect

F) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
    - Intensive treatment in an emergency room or at home for:
        - Allergic bronchospasm.
        - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc).
        - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
    - Development of drug dependence or drug abuse.
    - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN.
    - Suicide attempt or any event suggestive of suicidality.
    - Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
    - Bullous cutaneous eruptions.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the investigator site file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator site file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range must be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

- If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - Intravaginal
  - Transdermal
  - Injectable

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - Oral
  - Injectable
- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

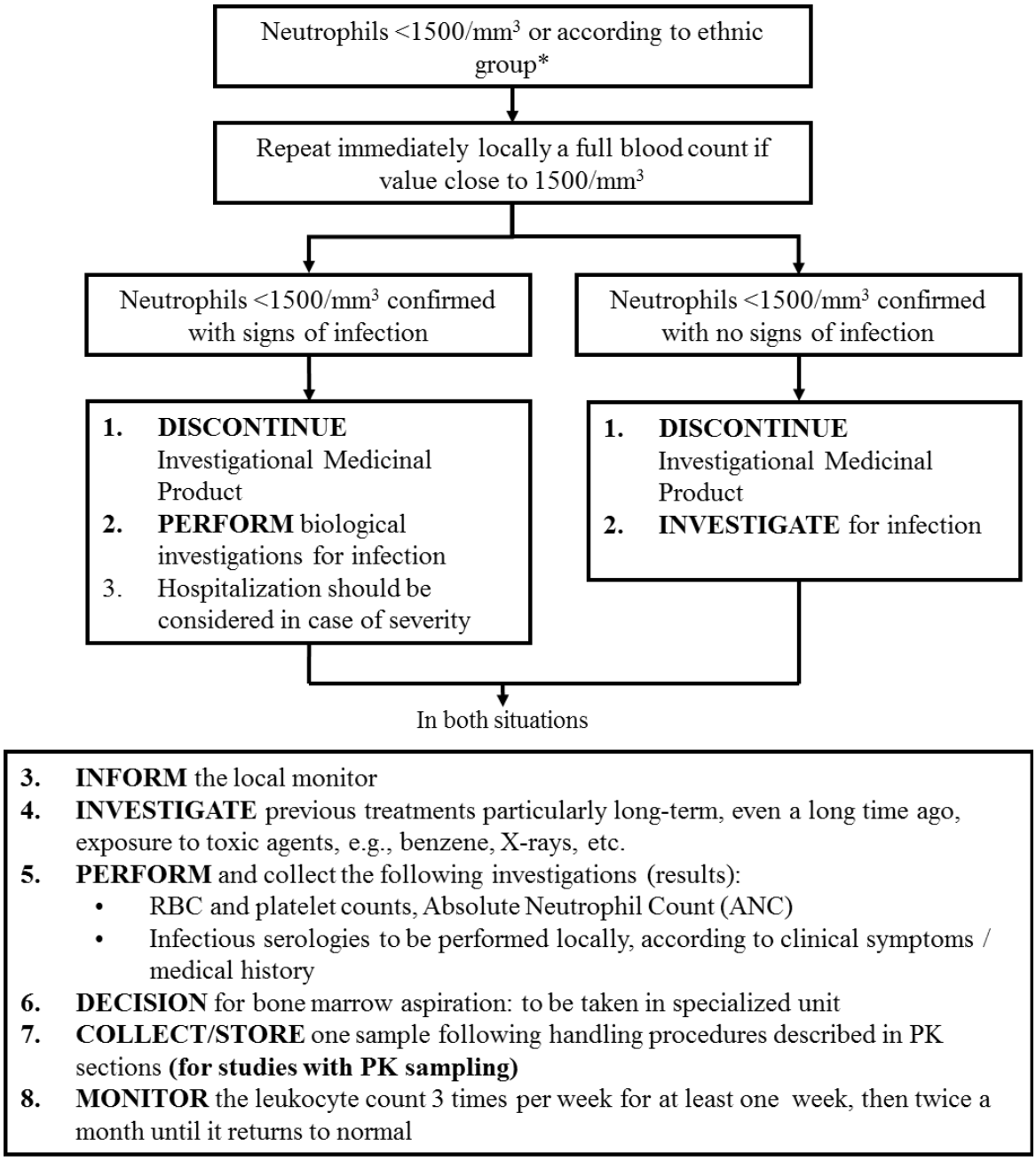
10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to frexalimab or multiple sclerosis and related diseases. They may also be used to develop tests/assays including diagnostic tests related to frexalimab and/or interventions of this drug class and frexalimab. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for genetic polymorphisms such as relevant to MS. Analysis of polymorphisms in CD40 and CD40L and associated genes may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to frexalimab or study interventions of this class to understand MS or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on frexalimab or study interventions of this class or indication continues but no longer than 25 years or other period as per local requirements.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

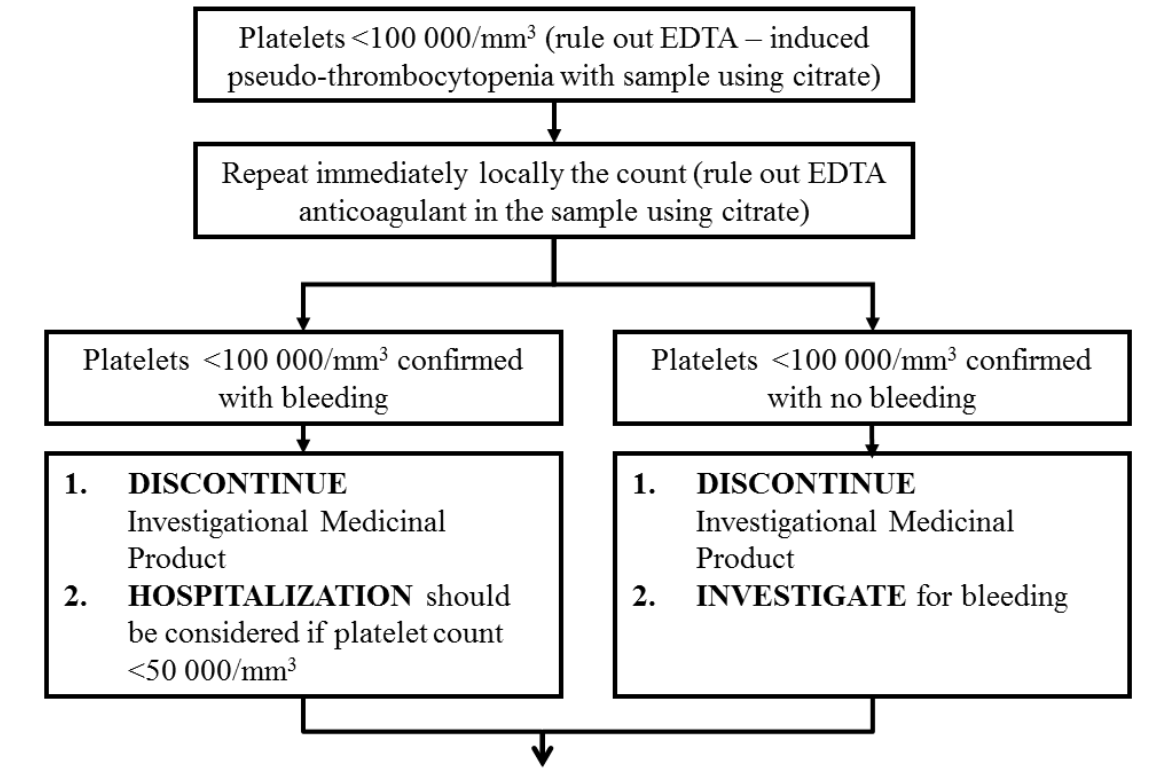
NEUTROPENIA



* For individuals of African descent, the relevant value of concern is <1000/mm³

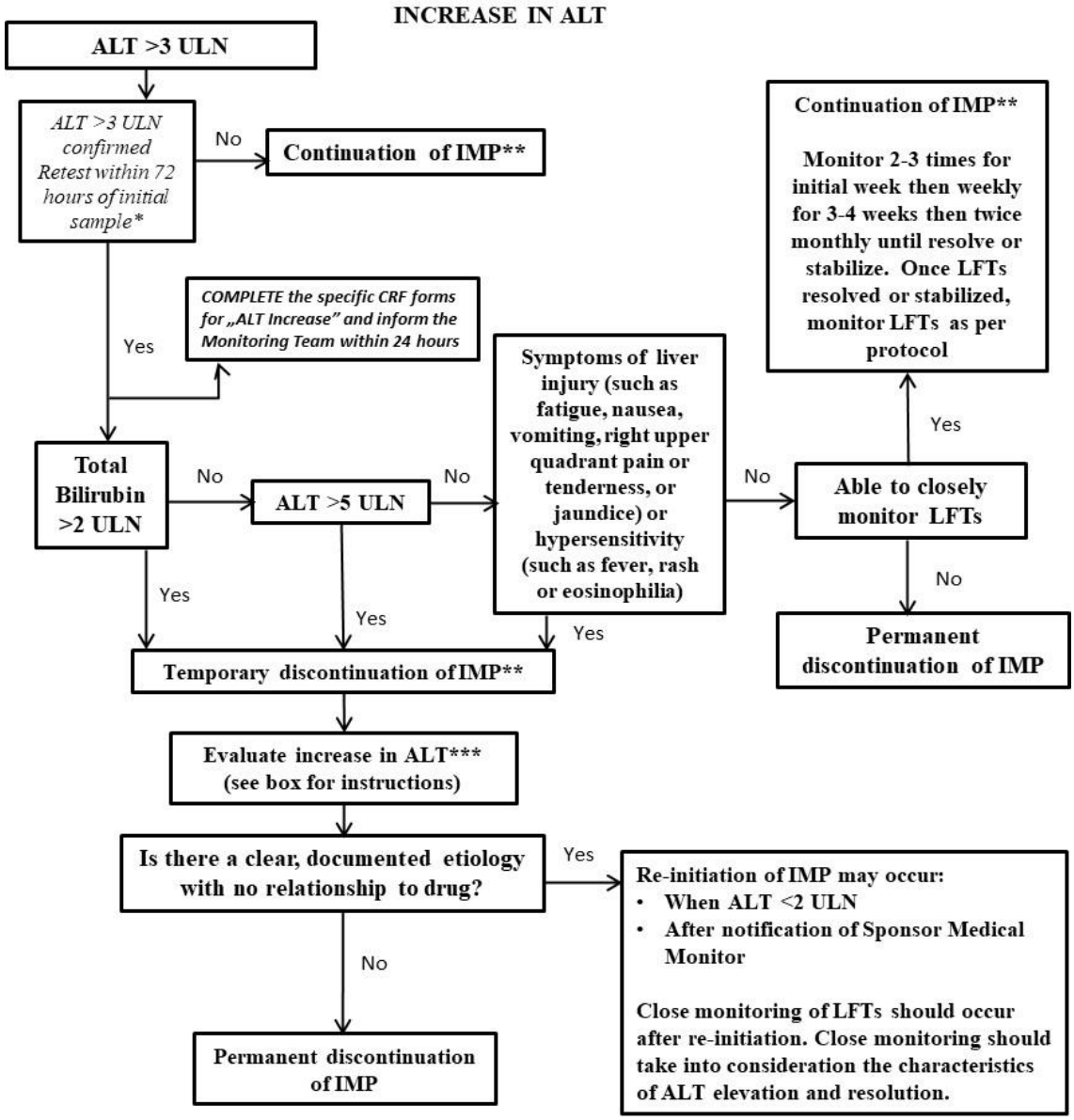
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about alcohol habits, any drug intake including quinine (drinks), heparin administration, aspirin, immunotherapy, etc.
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Locally:
     - Bleeding time and coagulation tests (INR or PT, aPTT, D-Dimers)
     - Infectious serologies to be performed according to clinical symptoms / medical history
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
7. **DECISION** for bone marrow aspiration to be taken in specialized unit
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

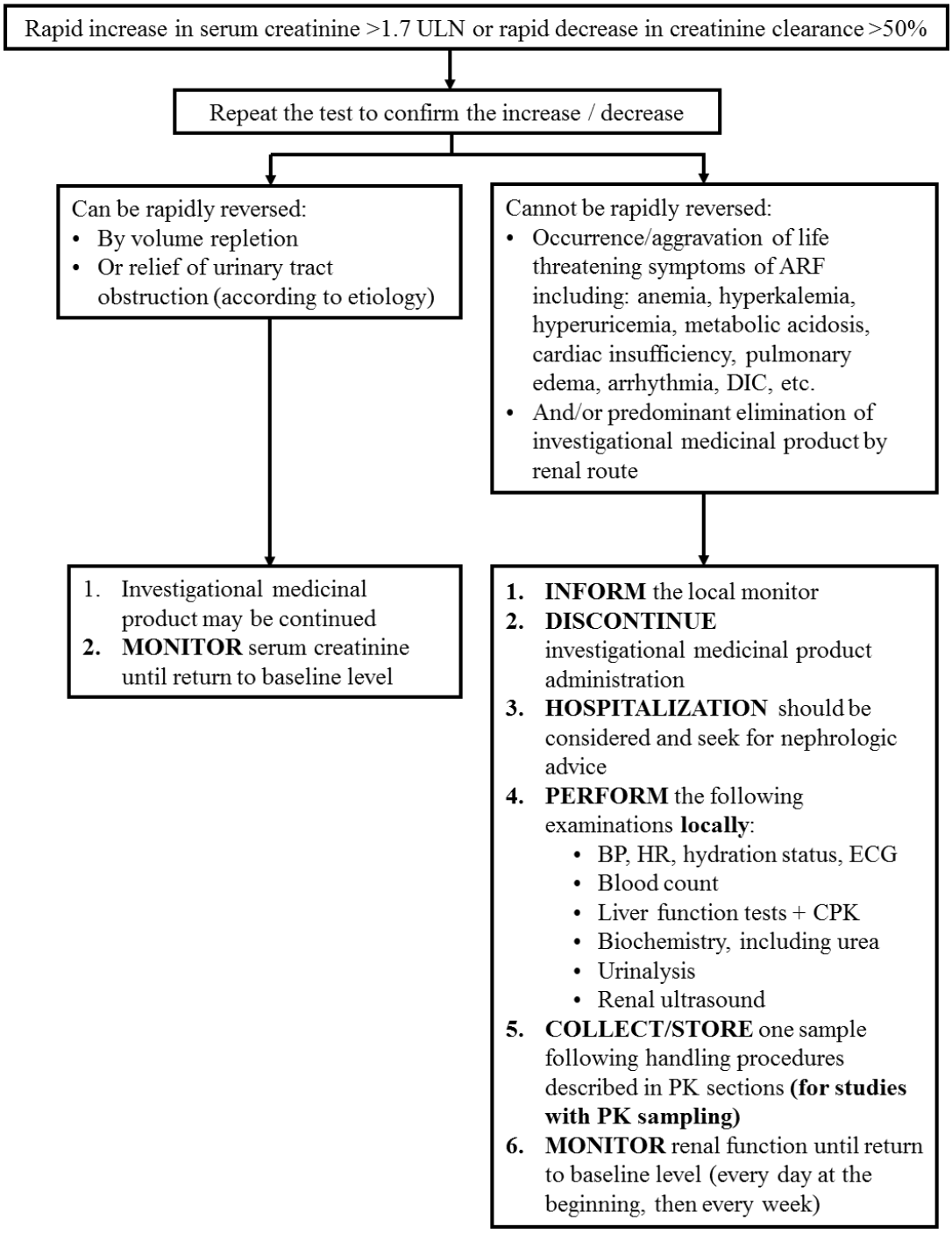


*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
** Unless a protocol-defined criterion for permanent discontinuation is met.
*** See box below.
Note:
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Section 10.3 for guidance on safety reporting.
Normalization is defined as ≤ULN or baseline value if baseline value is >ULN.

Evaluate Increase in ALT***

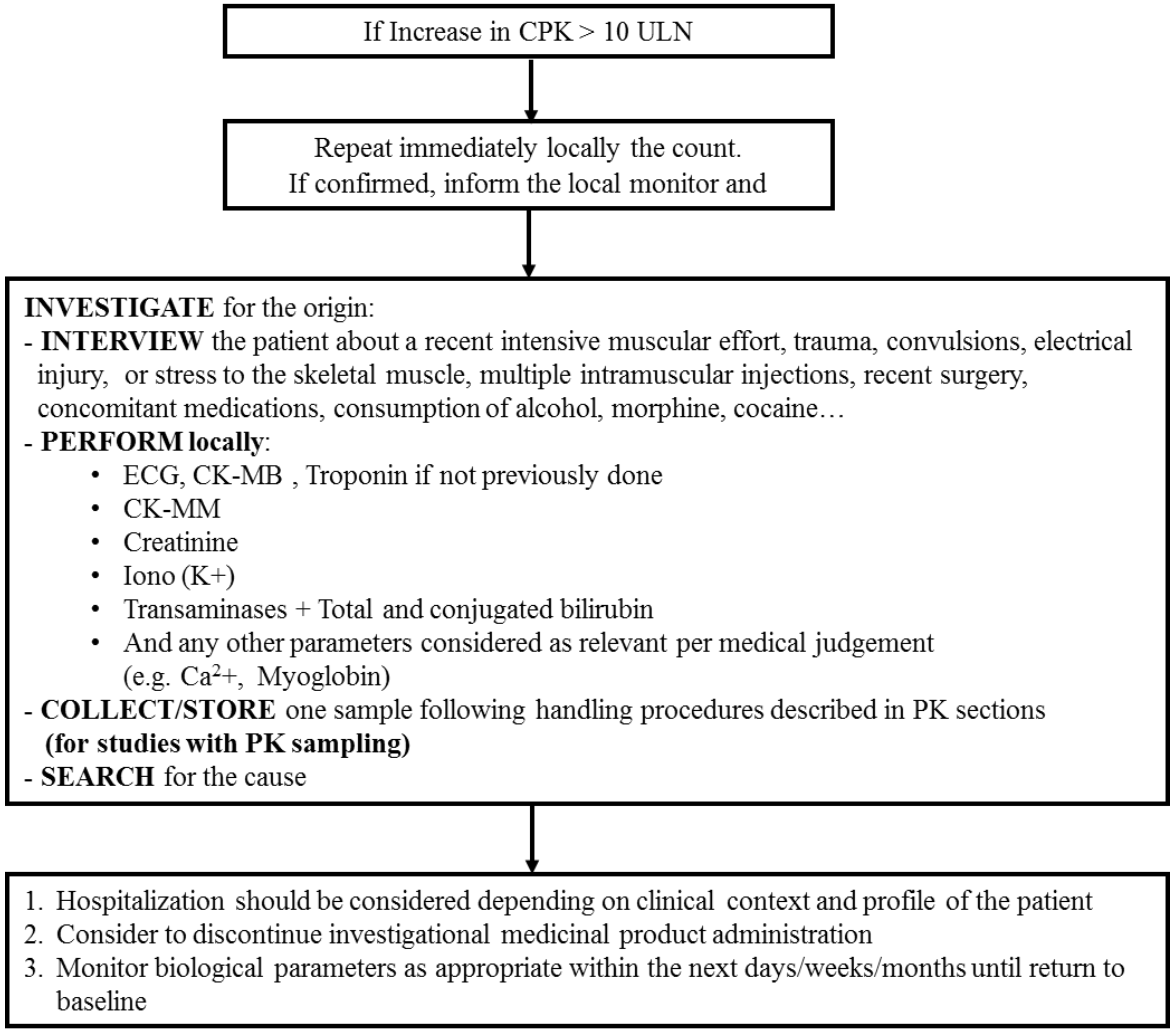
1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any recent alcohol use or travel
4. **INVESTIGATE** if any use of non-prescription medications including herbal or dietary supplements
5. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, GGT, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** iron, ferritin and transferrin
6. **CONSIDER** biomarkers for alcohol use (eg, urine ethyl glucuronide (EtG)]
7. **CONSIDER** consulting with hepatologist
8. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
9. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to ≤ULN, baseline value (if baseline >ULN) or clinical resolution.
10. **FREEZE** serum sample (5ml x 2)
11. **In case of suspicion of GILBERT Syndrome**, a DNA diagnostic test should be done

INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

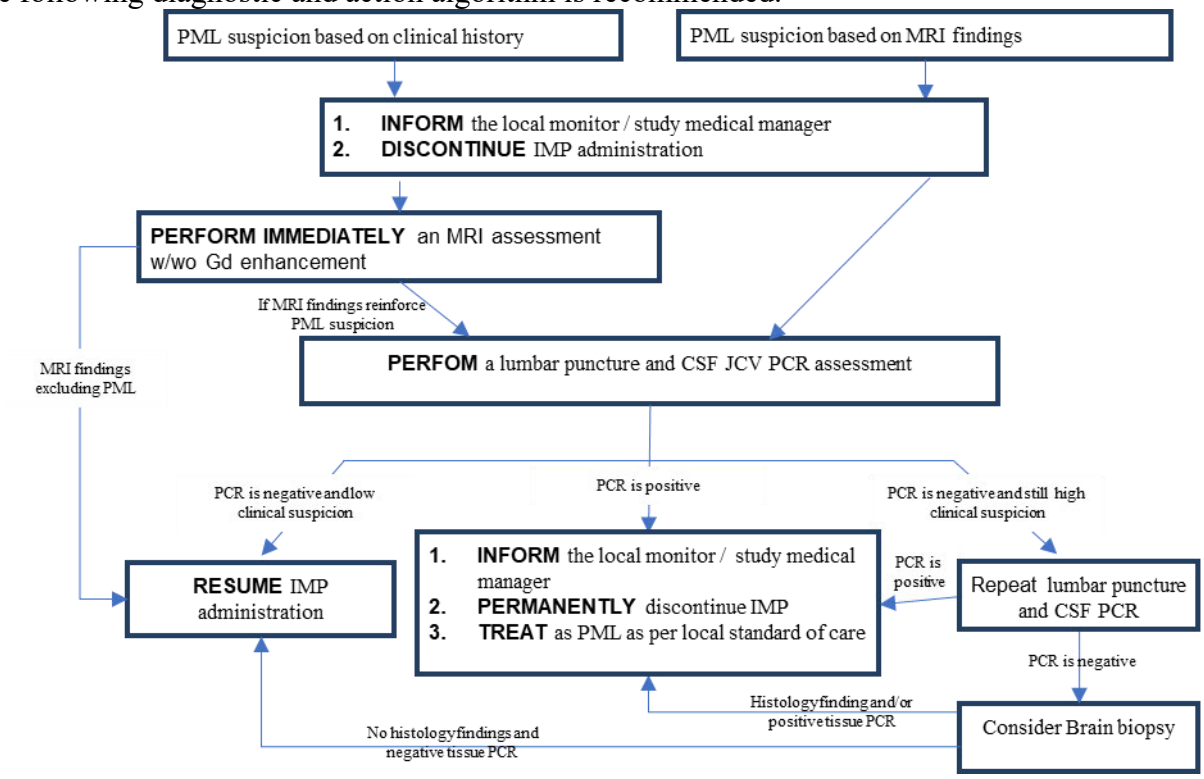
INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.3 is met.

SUSPECTED PML

If either the clinical presentation or MRI features of a participant are suggestive of PML, the following diagnostic and action algorithm is recommended.



Clinical manifestations or MRI lesions features suspicious for PML are proposed in Table 15.

Table 15 - Clinical and MRI features suggestive of PML

Clinical history	Subacute onset of weakness, paresthesias, cognitive or behavioral changes, gait dysfunction, speech/language difficulties or any other signs of cortical dysfunction, retrochiasmal visual defects or seizure
Brain MRI	≥1 T2/FLAIR hyperintense and T1 hypointense lesions involving the subcortical and juxtacortical white matter, sparing the cortex, with no mass effect, with a continuous progression; new lesions with no enhancement (even when large) or with faint rim enhancement

- The detection of JCV DNA in the cerebrospinal fluid of a participant with clinical and MRI features suggestive of PML establishes the diagnosis of PML.
- If JCV DNA is not detected in cerebrospinal fluid and if clinical suspicion of PML remains high, another lumbar puncture should be performed.
- If diagnosis remains uncertain and suspicion of PML remains high, a brain biopsy may be considered to establish a definitive diagnosis.

Clinical or MRI features suggestive of PML should be recorded as an AE/AESI/SAE following the definitions and procedures in Appendix 3 (Section 10.3).

10.7 APPENDIX 7: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.7.1 Germany

For Germany Only: Acceptable forms of effective contraception include:

- Established use of oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Placement of an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Male sterilization (provided that the partner is the sole sexual partner of the WOCBP study participant and that the sterilized partner has received medical assessment of the surgical success).
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulationmethods] and withdrawal are not acceptable methods of contraception).
- All references to "legally authorized representative" are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to "legally authorized representative" are found in Section 5.1, Section 8.3, and Section 10.1.3.

10.7.2 European Union: Safety reporting to the Agency

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.

Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC, irrespective if they are used in accordance with the terms of the marketing authorizations of these products. The Investigator is requested to report any suspected adverse reactions assessed as solely related to an authorized AxMP to the National Competent Authority via the national reporting system.

10.8 APPENDIX 8: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Temporary IMP discontinuation may apply in exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic diseases, terrorist attack) due to which a visit at the clinical study site is no longer feasible. In the case of an exceptional temporary treatment discontinuation, the discontinuation should be approved by the Sponsor.

The Sponsor should also be notified to determine if treatment should be resumed. If deemed safe, the treatment can be resumed at the next scheduled visit. During the discontinuation period, remote checks (eg, telephone calls) will take the place of on-site visits per the SoA (Section 1.3).

- If the above emergency scenario occurs during the follow-up period, one or more follow up visits can be performed remotely (eg, via telephone call), but at least one follow-up visit should be performed on site (EOS visit), even if the visit window needs to be extended (to a maximum of 8 weeks). Remote follow up should be done according to local regulations and approved by the Sponsor.
- If the above emergency scenario leads to site closure or complete regional or national lock-down, the study may be suspended for the affected sites (Section 10.1.9).

For Germany, contingency measures are currently only applicable for the COVID-19 pandemic.

A discontinuation of IMP in Part A of greater than 45 days will be considered definitive and relevant e-CRF sections should be populated. If this occurs in Part B, the Sponsor must be contacted to decide mutually on further treatment continuation.

10.9 APPENDIX 9: LOCAL TOLERABILITY

10.9.1 Assessment of local injection site reaction

Local injection site reactions, if appeared, should be characterized and assessed by the investigator or a trained designee/sub-investigator according to Table 16. If such a local injection site reaction appears, this needs to be recorded in addition as an adverse event.

Table 16 - Assessment of local injection site reactions

Reaction to injectable product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency Room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling[b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Itching	Does not interfere with activity	Interferes with activity or repeated use of topical or systemic treatment	Prevents daily activity or leads to other significant dermatologic conditions (such as infection, scarring, etc)	ER visit or hospitalization

Reaction to injectable product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Other (Please specify)[c]	No modification of daily activities and/or does not require symptomatic treatment	Hinders normal daily activities and/or requires symptomatic treatment	Prevents daily activities and requires symptomatic treatment	ER visit or hospitalization

a In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

b Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

c Please specify the other signs or symptoms (for example, hematoma, discoloration, re activation, etc).

ADAPTED from the toxicity grading scale table from the FDA Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials April 2005.

10.9.2 Local tolerability questionnaire

Participants will be asked to fill out a local tolerability questionnaire before IMP administration, after the completion of the SC or IV administration until 2-hours post administration.

The local tolerability questionnaire is a verbal descriptor scale (VDS) to record pain at the injection site. It is part of the participant booklet with participant questionnaires and is presented below.

Local tolerability questionnaire (participants)

Please rate your pain at the treatment injection site now:

Please tick one box only.

- ☐ No pain = 0
- ☐ Mild pain = 1
- ☐ Moderate pain = 2
- ☐ Severe pain = 3
- ☐ Very severe pain = 4

10.10 APPENDIX 10: PATIENT-REPORTED OUTCOME

10.10.1 Multiple sclerosis impact scale (MSIS)-29

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2)

UK original of MSIS-29 v2

- The following questions ask for your views about the impact of MS on your day-to-day life during **the past two weeks**.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions.

In the past two weeks, how much has your MS limited your ability to …	Not at all	A little	Moderate-ly	Extreme-ly
1. Do physically demanding tasks?	1	2	3	4
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4
3. Carry things?	1	2	3	4

In the past two weeks, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
4. Problems with your balance?	1	2	3	4
5. Difficulties moving about indoors?	1	2	3	4
6. Being clumsy?	1	2	3	4
7. Stiffness?	1	2	3	4
8. Heavy arms and/or legs?	1	2	3	4
9. Tremor of your arms or legs?	1	2	3	4
10. Spasms in your limbs?	1	2	3	4
11. Your body not doing what you want it to do?	1	2	3	4
12. Having to depend on others to do things for you?	1	2	3	4

MSIS-29v2 2005

MSIS-29v2 - United Kingdom/English MSIS-29_AU2.0_eng-GBor.doc

Multiple Sclerosis Impact Scale version 2 (MSIS-29v2) continued

In the past two weeks, how much have you been bothered by …	Not at all	A little	Moderate-ly	Extreme-ly
13. Limitations in your social and leisure activities at home?	1	2	3	4
14. Being stuck at home more than you would like to be?	1	2	3	4
15. Difficulties using your hands in everyday tasks?	1	2	3	4
16. Having to cut down the amount of time you spent on work or other daily activities?	1	2	3	4
17. Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4
18. Taking longer to do things?	1	2	3	4
19. Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4
20. Needing to go to the toilet urgently?	1	2	3	4
21. Feeling unwell?	1	2	3	4
22. Problems sleeping?	1	2	3	4
23. Feeling mentally fatigued?	1	2	3	4
24. Worries related to your MS?	1	2	3	4
25. Feeling anxious or tense?	1	2	3	4
26. Feeling irritable, impatient, or short-tempered?	1	2	3	4
27. Problems concentrating?	1	2	3	4
28. Lack of confidence?	1	2	3	4
29. Feeling depressed?	1	2	3	4

MSIS-29v2 2005

MSIS-29v2 - United Kingdom/English MSIS-29_AU2.0_eng-GBori.doc

2

10.10.2 Patient reported outcome measurement information system (PROMIS)-Fatigue-MS-8

PROMIS® Item Bank v1.0 – Fatigue – Multiple Sclerosis Short Form 8a

Fatigue-Multiple Sclerosis - Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Almost always
FATIMP30	How often were you too tired to think clearly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP20	How often were you too tired to enjoy life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP48	How often did you find yourself getting tired easily?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you feel tired even when you hadn't done anything?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP10	How often did you have trouble finishing things because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP3	How often did you have to push yourself to get things done because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP4	How often did your fatigue interfere with your social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATIMP40	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

29 July 2020

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10.10.3 Patient's qualitative assessment of treatment version 3 (PQATv3)

Patient's Qualitative Assessment of Treatment version 3 (PQATv3)

The following questions ask for your opinion **on the drug you received during this clinical study**.
There are no right or wrong answers; we would like to better understand your own experience of the drug.

1. **During this trial, what were the main benefits you experienced with the drug you received?**

2. **On a scale of 0 to 10, how beneficial was the drug you received during this trial?**

0 1 2 3 4 5 6 7 8 9 10

Not beneficial at all — Extremely beneficial

3. **During this trial, what were the main disadvantages you experienced with the drug you received?**

4. **On a scale of 0 to 10, how disadvantageous was the drug you received during this trial?**

0 1 2 3 4 5 6 7 8 9 10

Not disadvantageous at all — Extremely disadvantageous

PQATv3 © Sanofi, 2020 - 2021

5. **After this trial, would you be willing to continue using the drug you received during this trial?**

Yes ☐ No ☐

Please explain why?

6. **Based on your own experience in this trial, please select a response on the scale below**

☐ -3	☐ -2	☐ -1	☐ 0	☐ 1	☐ 2	☐ 3
The disadvantages of the drug I received significantly outweigh the benefits			There were equal benefits and disadvantages of the drug I received			The benefits of the drug I received significantly outweigh the disadvantages

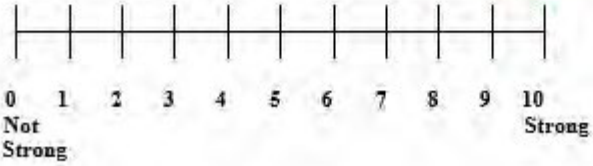
IV versus SC Preferences (below questions are only applicable for subcutaneous arms):

Thinking about the study medication which you received either ***intravenously*** (IV) or ***subcutaneously*** (SC)

7. **Did you prefer one delivery device (IV or SC) for your study medication? (Select ONE)**

☐ Yes, Preferred IV
☐ Yes, Preferred SC
☐ No preference (STOP HERE)

8. **How strong is your preference for IV or SC ? (circle one number)**



9. What is the main reason that you prefer IV or SC? Please check all that apply ; and rank order if more than one reason :

If select > 1 reason below please rank order as follows :

5 = most important reason
4 = next most important
3=next most important
2 = next most important
1 = least important reason

- ☐ **Requires less time in the clinic ____(RANK)**
- ☐ **Feels more comfortable during administration ____(RANK)**
- ☐ **Feels less emotionally distressing ____(RANK)**
- ☐ **Lower level of injection site pain ____(RANK)**
- ☐ **Other, ____(RANK) Please, Specify Reason(s)_____**

_____
_____

10.10.4 Patient global impression of change scale (PGIC-Fatigue)

Patient Global Impression of Change **(PGIC) scale**- Fatigue

Please choose the response below that best describes the overall change in your fatigue symptoms compared to your first study visit

- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse

10.10.5 Patient global impression of severity scale (PGIS-Fatigue)

Patient Global Impression of Severity (PGIS) - Fatigue

Please choose the response below that best describes the overall severity of your fatigue at this time

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

PGIS-Fatigue © Sanofi. 2020 Patient global impression of severity relapsing and Fatigue 08OCT2020_English

10.11 APPENDIX 11: Collection, storage, and future use of data and human biological samples

10.11.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.11.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

10.12 APPENDIX 12: LIST OF ABBREVIATIONS

ADA:	antidrug antibodies
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ARR:	annualized relapse rate
AUC:	area under the curve
AxMP:	auxiliary medicinal product
B-cell:	lymphocyte B
CD40:	cluster of differentiation 40
CD40L:	cluster of differentiation 40 ligand
C_{max}:	maximum concentration
CNS:	central nervous system
COVID-19:	coronavirus disease 2019
CSR:	clinical study report
DMT:	disease-modifying therapy
DNA:	deoxyribonucleic acid
ECG:	electrocardiogram
e-CRF:	electronic case report form
EDSS:	expanded disability status scale
EOS:	end of study
Fc:	fragment crystallizable
FDA:	Food and Drug Administration
FIH:	first-in-human
GCP:	good clinical practice
Gd:	gadolinium
GdE T1:	gadolinium-enhancing T1-hyperintense
GLP:	good laboratory practice
HCG:	human chorionic gonadotropin
HIV:	human immunodeficiency virus
HRT:	hormonal replacement therapy
IB:	investigator’s brochure
ICF:	informed consent form
ICH:	international conference of harmonization
Ig:	immunoglobulin
IMP:	investigational medicinal product
IRT:	interactive response technology
IV:	intravenous
KLH:	keyhole limpet hemocyanin
mAb:	monoclonal antibody
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
MSIS:	multiple sclerosis impact scale
NfL:	neurofilament light chain
NOAEL:	no observed adverse effect level

PGIC:	patient global impression of change
PGIS:	patient global impression of severity
PML:	progressive multifocal leukoencephalopathy
PPMS:	primary progressive multiple sclerosis
PQATv3:	patient's qualitative assessment of treatment version 3
PRO:	patient-reported outcome
PROMIS:	patient reported outcome measurement information system
q2w:	every 2 weeks
q4w:	every 4 weeks
RMS:	relapsing multiple sclerosis
RNA:	ribonucleic acid
SAE:	serious adverse event
SARS-CoV-2:	severe acute respiratory syndrome coronavirus-2
SC:	subcutaneous
SPMS:	secondary progressive multiple sclerosis
SUSAR:	suspected unexpected serious adverse reaction
TB:	tuberculosis
T-cell:	lymphocyte T
TDAR:	T-cell-dependent antibody response
TEAE:	treatment-emergent adverse event
VDS:	verbal descriptor scale

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.13.1 Amended protocol 03 (16 November 2023)

This amended protocol 03 (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to further extend the duration of Part B (open-label period) by approximately 36 months.

This will allow collecting additional long-term safety and exploratory efficacy data.

[redacted]

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout the document	SAR441344 replaced by frexalimab.	INN available.
1.1 Synopsis	Duration of Part B extended up to 280 weeks (study intervention duration extended up to approximately 292 weeks, ie, approximately 73 months).	To collect additional long-term safety and exploratory efficacy data and to make frexalimab available.
	[redacted]	[redacted]
	Addition of possibility of a post trial access option.	To allow participants to continue frexalimab after the study (if applicable).
1.2 Schema	Duration of Part B updated.	To harmonize.
1.3.1 Schedule of activities for Part A	Footnote added for archived bood sample.	To clarify the future use.
1.3.2 Schedule of activities for Part B	Addition of visits up to Week 292/M73.	To harmonize.
	12-lead ECG assessment every 6 months and at follow-up visits modified from mandatory to “if needed”. Hematology and biochemistry assessment and coagulation assessment removed for all follow-up visits.	To decrease the burden for the participants as there is no safety issue for these parameters. These assessments will be done if deemed necessary by the Investigator.
	Antidrug antibodies and frexalimab concentration assessment frequency modified to every 6 months from W168 (at W192, W216, W240, W264, and W288).	To decrease the burden for the participants that were on steady state after the last dose modification per amended protocol 02, [redacted]
	Addition of PROMIS-Fatigue-MS-8 at EOS.	
	IgG/IgM schedule revised from every 6 months to yearly from W120 (ie, W120, W168, W216, and W264). Biomarkers assessment reduced to NfL and CXCL13 after W120 (W144, W240, and early EOT). Immunophenotyping assessment added at W144, W240, and early EOT. Whole blood (PaxGene sample) added at W144, W240, early EOT, and common EOS.	To decrease the burden for the participants and to focus on important biomarkers and timepoints during study intervention.
	Archived blood sample added at W144, W240, and at early EOT and common EOS.	In case of unexpected safety issue, to ensure that a post baseline value is available for previously not assessed parameters and for biomarkers research, if agreed by the participant.
	Footnotes updated or added accordingly.	
	Footnote “n” corrected to -3 days to ±3 days.	Typo correction.

Section # and Name	Description of Change	Brief Rationale
1.3.3 Schedule of activities for the initial 12 weeks in Part B2	Following visits corrected from “as previously planned” to as planned per Part B SoA”	To clarify, since the Part B SoA is being modified by amended protocol 03.
2.3.1 Risk assessment	Updated information, no major change.	Alignment with Investigator’s brochure.
4.1 Overall design	Duration of Part B extended up to 280 weeks (study intervention duration extended up to approximately 292 weeks, ie, approximately 73 months).	To collect additional long-term safety and exploratory efficacy data.
	Addition of the option for [redacted] and for SC arm (Part B2) between 2 quarterly onsite visits.	To decrease the burden for the participants
	Addition of possibility of a post trial access.	To allow participants to continue frexalimab after the study (if applicable)
4.4 End of study definition	Duration of Part B extended up to 292 weeks.	To collect additional long-term safety and exploratory efficacy data
6. Study intervention(s) and concomitant therapy	Addition of the option for [redacted] and for SC arm (Part B2) between 2 quarterly onsite visits.	To decrease the burden for the participants
	Pharmacy manual updated to product management manual also updated throughout the document).	At the time of the implementation of this amended protocol 03, a new version of the pharmacy manual newly named product management manual will be in force
6.1 Study intervention(s) administered 6.1.1 Frexalimab	[redacted]	[redacted]
	[redacted].	[redacted]
6.2.1 Intravenous preparation and handlings	Addition of the option for [redacted] between 2 quarterly onsite visits.	To decrease the burden for the participants.
6.2.2 Subcutaneous preparation and handlings	[redacted]	[redacted].
	Addition of the option for home infusion for Part B1 SC arm between 2 quarterly onsite visits.	To decrease the burden for the participants.
	Harmonization with the Part B SoA for Part B1.	Correction/clarification.
6.6 Continued access to intervention after the end of the study	Addition of possibility of a post trial access option.	To allow participants to continue frexalimab after the study (if applicable).

Section # and Name	Description of Change	Brief Rationale
8 Study assessment and procedures	Maximum amount of blood collected from each participant over the duration of the study updated to approximately 620 mL to approximately 890 mL for the longest participation in the study (updated from 37 months to 73 months).	Extension of duration of the study.
8 Study assessment and procedures 8.4 Pharmacokinetics 10.2 Appendix 2: Clinical laboratory tests	"Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until" updated from "study has been unblinded" to "final database lock"	Although results of Part A were unblinded, the investigative sites and other blinded personnel will remain blinded for study intervention taken during Part A until the final database lock.

10.13.2 Amended protocol 02 (21 February 2023)

This amended protocol 02 (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment is subsequent to the efficacy and safety analysis of Part A (double-blind period). In ACT16877 Part A, frexalimab led to a significant reduction of new T1 gadolinium-enhancing lesions and was well-tolerated; high-dose being most efficacious (see Section 2.3.2).

Consequently, the main purpose of this amendment is to modify the dose regimen of the participants in the SC arm from 300 mg q2w to SC 1800 mg q4w (via syringe infusion material) to increase their exposure, thus achieving similar exposure to that of the most efficacious dose regimen of 1200 mg q4w IV in Part A, while proposing a more convenient dosing schedule.

In addition, the Part B (open-label period) is extended by 15 months to collect additional long-term safety and exploratory efficacy data.

Also, alignment with Part A SAP, minor clarification, template updates, editorial, and document formatting revisions were done.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1 Protocol summary		
1.1 Synopsis	Update of the duration of Part B (extended by 15 months). Increase the dose regimen of SC group to SC 1800 mg q4w via syringe infusion material.	See overall rationale Syringe infusion material is to be used to administer the required volume (12 mL).

Section # and Name	Description of Change	Brief Rationale
	Update process for continuation of treatment and assessment through study extension rather than new long-term study. For the SC group, Part B will be divided in 2 subparts: Part B1 until individual participant switch to the modified dose regimen and Part B2 after this switch.	For this long-term assessment, extending the duration of Part B rather than setting up a separate long-term safety study will simplify operational aspects.
	Objectives and endpoints table splited into Part A and Part B and addition of safety objective and endpoint for the modified SC dose regimen in Part B2.	Clarification, alignment with Part A SAP, assessment of the modified SC dose regimen (Part B2).
1.2 Schema	Updated to reflect the changes in Part B of the study.	
1.3.2 Schedule of activities for Part B	Updated to reflect the changes.	
	Add Inform consent and corresponding footnote	Participants have to be informed of the modified SC dose regimen and the extension of Part B duration.
	Lighten some safety assessments: quarterly physical examination, body temperature and vital signs after W24 in Part B.	No more need for a close safety assessment after 24 weeks in the study.
	Change the periodicity of plasma sample for NfL, CHI3L1, and other biomarkers from every 6 months to yearly from W72 and added a check mark for sample for PBMC substudy and a check mark for MSIS-29 at EOS	No more need for every 6 months plasma sample for NfL, CHI3L1, and other biomarkers. PBMC sample at EOS will allow to have immune profiling to determine chronic treatment effect on immune cells.
1.3.3 Schedule of activities for the initial 12 weeks of Part B2	Subsection added to include additional assessments at the time of switching to 1800 mg q4w SC regimen and up to 12 weeks after the switch.	Participants have to be informed and safety and PK assessment have to be initially reinforced due to the increased dose regimen.
2.2 Background	Update of thromboembolic statement.	Available safety data from frexalimab Phase 2 clinical program: no TEAE of thromboembolism reported.
	Update of predicted exposure for the 1800 mg SC q4w dose regimen in Part B2.	To support the proposed 1800 mg SC q4w regimen.
	Update with Part A results.	Available data from Part A.
2.3.1 Risk assessment	Update of exposure and safety assessment in frexalimab clinical trials.	Available safety data from frexalimab Phase 2 clinical program.
	Update of management of COVID-19 infection.	As different variants of COVID-19 emerge and worldwide vaccination continues the need for systematic permanent IMP discontinuation due to COVID-19 is no longer justified and can be assessed on a case-by-case basis.

Section # and Name	Description of Change	Brief Rationale
	Added that for administration of high SC doses (1800 mg in 12 mL), SC infusions will be administered via syringe infusion material to allow slow delivery.	To support SC infusion of 12 mL.
2.3.2 Benefit assessment	Update with efficacy results from ACT16877 Part A.	Efficacy analysis of ACT16877 Part A available.
2.3.3 Overall benefit:risk conclusion	Update with efficacy and safety results from ACT16877 Part A.	Efficacy and safety analysis of ACT16877 Part A available.
3 Objective and endpoints	Objectives and endpoints splited into Part A and Part B and updated. Addition of safety objectives and endpoints for the modified SC dose regimen (Part B2).	Clarification. Alignment with Part A SAP. Assessment of the modified SC dose regimen.
4.1 Overall design	Update of the duration of Part B (extended by approximately 15 months). Increase the dose regimen of SC group to SC 1800 mg q4w via syringe infusion material.	See overall rationale SC injections are limited to 2 mL volume. Syringe infusion material is to be used to administer the required large volume (12 mL).
	Update process for continuation of treatment and assessment through study extension rather than new long-term study. For the SC group, Part B will be divided in 2 subparts: Part B1 until individual participant switch to the modified dose regimen and Part B2 after this switch.	For this long-term assessment it was decided to extend the duration of Part B rather than setting up a separate long-term safety study to simplify operational aspects.
4.3 Justification for dose	Update to justify the dose of 1800 mg q4w via syringe infusion material.	See overall rationale. SC injections are limited to 2 mL volume. Syringe infusion material is to be used to administer the required large volume (12 mL).
4.4 End of study definition	Added text specifying the criteria for participants not consenting to transition to Part B2 and also updated the total duration of Part B (extended by approximately 15 months)	See overall rationale.
	Update process for continuation of treatment and assessment through study extension rather than new long-term study.	For this long-term assessment, extending the duration of Part B rather than setting up a separate long-term safety study will simplify operational aspects.
	If individual participant does not consent to continue with the modified dose regimen, the individual participation to the study will end.	See overall rationale.
6.1 Study intervention(s) administered	Table 5 and Table 7 updated to include the 1800 mg q4w SC regimen.	See overall rationale.
6.2.2 Subcutaneous preparation and handlings	Add details for syringe infusion material.	SC injections are limited to 2 mL volume. Syringe infusion material is to be used to administer the required large volume (12 mL).

Section # and Name	Description of Change	Brief Rationale
6.6 Continued access to intervention after the end of the study	Update process for continuation of treatment and assessment through study extension rather than new long-term study.	For this long-term assessment, extending the duration of Part B rather than setting up a separate long-term safety study will simplify operational aspects.
7.1.1 Permanent discontinuation	Update process for continuation of treatment and assessment through study extension rather than new long-term study.	For this long-term assessment, extending the duration of Part B rather than setting up a separate long-term safety study will simplify operational aspects.
	Removal of permanent discontinuation in case of COVID-19 infection.	As different variants of COVID-19 emerge and worldwide vaccination continues, the need for systematic permanent IMP discontinuation due to COVID-19 is no longer justified and can be and can be assessed on a case-by-case basis.
7.1.3 Temporary discontinuation	Update of management of discontinuation in case of COVID-19 infection.	As different variants of COVID-19 emerge and worldwide vaccination continues the need for systematic permanent IMP discontinuation due to COVID-19 is no longer justified and can be assessed on a case-by-case basis.
7.2 Participant discontinuation/withdrawal from the study	If individual participant do not consent to continue with the modified dose regimen, the individual's participation in the study will end.	See overall rationale.
8 Study assessments and procedures	Update of approximate maximum amount of blood collected from each participant (620 ml) and approximate total duration of the study (37 months).	See overall rationale.
8.3.7 Adverse event of special interest	Clarification of definition of overdose for IV 1200 mg q4w arm. Add definition of overdose for the SC 1800 mg q4w arm.	Clarification and update for new dose regimen for overdose definition.
9.3.2 Primary endpoint (Part A)	In the primary analysis, baseline score of activation of CD40/CD40L pathway and baseline score of activation of CD40/CD40L pathway by treatment interaction will not be included as covariates. Baseline GdE T1 lesion count by treatment interaction will be deleted as well. They will be included as covariates in a supplementary analysis.	Due to missing data and lack of evidence for the prognostic value of baseline score of activation of CD40/CD40L pathway. Interactions not included in the scope of the primary analysis.
	In the primary analysis and other similar analysis, baseline GdE T1 lesion count will be included as a categorical covariate instead of continuous. A sensitivity analysis based on baseline GdE T1 lesion count as a continuous covariate will be done.	Account for the outliers in the distribution of baseline Gde T1 count.
	A statistical model has been added to include additionally baseline score of activation of CD40/CD40L pathway as covariate.	To assess the prognostic effect of baseline score of activation of CD40/CD40L pathway.

Section # and Name	Description of Change	Brief Rationale
	Frexalimab will be assessed additionally in a subgroup of participants with baseline CD40/CD40L pathway activation score above a pre-defined threshold.	A threshold will be determined based on the baseline activation score distribution (percentile).
	Exploratory subgroup analyses will be done using the same model and population as that utilized for the primary analysis within each subgroup and not in a model including CD40/CD40L pathway activation score entered as an effect (score above threshold Y/N).	To assess the treatment effect within each subgroup separately.
	An additional cut-off of 0.25 will be used for LRV (ie, 75% relative reduction to placebo).	To check the outcome of the decision using a smaller LRV.
9.3.1 General considerations/ 9.3.3 Secondary endpoint(s)/ 9.3.4 Safety analysis/ 9.3.5 Tertiary/exploratory endpoint(s)/ 9.3.6.1 Pharmacokinetics	Add the handling of participants under the new frexalimab 1800mg SC regimen in the descriptive statistics.	See overall rationale.
9.3.6.2 Responder population identification and characterization with biomarker data (Part A)	Update of the responder population analysis.	Analysis based on a negative binomial model which is used for the primary analysis.
10.1.6 Dissemination of clinical study data	Website for requests updated to vivli.org.	Update.
10.1.9 Study and site start and closure	First act of recruitment updated from first site open to first participant screened.	Template update.
10.6 Appendix 6: Liver and other safety: suggested actions and follow-up assessments	Update of algorithm.	Template update to comply with new DILI group recommendation.
10.12 Appendix 12: protocol amendment history	Amended protocol 01 overall rationale and summary of change moved to the history section.	

10.13.3 Amended protocol 01 (20 May 2021)

The amended protocol 01 (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The purpose of the amendment is mainly to extend the follow-up period from 12 weeks to 24 weeks (including contraceptive methods and pregnancy testing requirements) to address comments raised by Health Authorities. In addition, minor clarification of discrepancies, template updates, editorial and document formatting revisions were done.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 Schedule of activities	Follow-up duration after EOT increased from 12 weeks to 24 weeks. Three follow-up visits are planned (4 weeks, 12 weeks, and 24 weeks after EOT, instead of 4 weeks, 8 weeks, and 12 weeks after EOT).	Health authority request.
3 Objectives and Endpoints	Endpoints Soluble CD40L in plasma "at baseline, Week 12, and during 3 months of follow-up after EOT" changed to plasma "at baseline, Week 12, and during 24 weeks of follow-up after EOT "	
4.1 Overall design	Additional follow-up after the stop of study treatment increased from 3 months to 24 weeks.	
7.1.1 Permanent discontinuation	Follow-up visits duration extended from 3 months to 24 weeks.	
8.2.4 Clinical safety laboratory assessment	Follow-up of abnormal laboratory test extended from 12 weeks to 24 weeks.	
9.3.1 General considerations	Treatment-emergent period extended from 90 to 180 days. To better align with the study intervention half-life at the highest doses from results of previous studies.	
1.1 Synopsis 4.1 Overall design 7.1.1 Permanent discontinuation	Clarified that the participants who early stopped intervention can be prescribed disease-modifying therapy for RMS, generally after the 24-week follow-up period. To allow RMS treatment during the extended participation without intervention, generally after the 24 weeks follow-up period.	Health Authority request.
1.1 Synopsis 6.2.1 Intravenous preparation and handling	Clarified that the IV infusion is prepared in a 100 mL pre-filled 0.9% saline bag.	Clarification.
1.3 Schedule of activities	Visit window increased from +/-2 days to +/-5 days after Week 24.	To allow more flexibility for visits after 12 weeks in the open-label Part B.
	ADA and PK samples collection during follow-up was changed from "last" to "2nd and 3rd visit" in Part A and Part B schedules.	To adapt to the new 24 weeks follow-up duration.
	Plasma sample collection for soluble CD40L during follow-up was changed from every months to "2nd and 3rd visit" in Part A and Part B schedules.	To adapt to the new 24 weeks follow-up duration.

Section # and Name	Description of Change	Brief Rationale
	Footnotes “cc” and “r” were added in Part A and Part B schedules, respectively, to specify that the reference to calculate visit windows is Day 1.	Clarification.
	Footnotes “l” of Part A and “h” of Part B schedules were clarified with the applicable local tolerability assessment by Investigator/designee (see Section 10.9.1) and the participant (pain-verbal descriptor scale, see Section 10.9.2).	Clarification.
1.3.1 Schedule of activities for Part A	Footnote “d” referring to all MRI (to be performed before IMP administration) in Part A was modified to be applicable to Week 8 and Week 12. Footnote “w” in Part A schedule was updated to clarify that the MRI should be done not less than 5 days before randomization and that MRI should preferably be performed once all other screening assessments are checked and none of them have excluded the patient.	Clarification.
1.3.2 Schedule of activities for Part B (footnote “a”) 4.1 Overall design 6 Study intervention(s) and concomitant therapy	Possibility for the partner/caregiver/home healthcare professional to manage the subcutaneous injection at home and reference to pharmacy manual were added.	Clarification.
5.1 Inclusion criteria	In Inclusion criteria I05, contraceptive/barrier method and pregnancy testing requirements extended from 12 weeks to 24 weeks. To better align with the study intervention half-life at the highest doses from results of previous studies.	Health Authority request.
5.2 Exclusion criteria 10.2 Clinical laboratory tests	In Exclusion criteria E11, method of calculation of glomerular filtration rate was changed from Cockroft and Gault formula to Modification of Diet in Renal Disease.	Correction.
6.3 Measures to minimize bias: randomization and blinding Unblinding	Statement about unblinding updated in compliance with international guidelines, the Sponsor cannot require or insist on being involved in the decision to unblind, stall or delay in anyway the unblinding of trial participant treatment in emergency situations.	Health Authority request.
6.3 Measures to minimize bias: randomization and blinding Methods of blinding 8.1.1 Magnetic resonance imaging assessments	Availability of MRI report was changed from “once a year starting at Week 48” to “full report of MRI performed from Week 24”. To make MRI results available earlier to Investigators.	Health Authority request.
6.6 Continued access to intervention after the end of the study	Clarification that the entry in the LTS study will occur after the end of the study for participants who completed the study and are still taking the study intervention.	Clarification.

Section # and Name	Description of Change	Brief Rationale
7.1.1 Permanent discontinuation	Clarified that during extended participation in the study without study intervention, the participant can be treated for RMS according to local clinical practices and the best judgment of the investigator, generally after the follow-up period. Addition of reasons for mandatory definitive discontinuation (considered necessary by Investigator and/or participant, need for use of prohibited medication, no longer deriving therapeutic/clinical benefit for the participant in the opinion of the investigator).	Health Authority request.
7.1.1 Permanent discontinuation 7.2 Participant discontinuation/withdrawal from the study	Addition of definition of key visits until Common EOS for participants with early EOT: primarily visits with efficacy assessment.	Clarification.
8.1.3 Expanded disability status scale	Clarified that all Investigators/raters should be qualified to perform neurological assessments as per local requirement and that they must be trained and certified to perform the EDSS in a consistent manner (Neurostatus® training version 04/10.2). Clarification that investigator and rater can be the same person by removing an ambiguous sentence.	Clarification. Correction.
8.2.5 Local tolerability	Clarification of assessment of local tolerability by investigator/designee and participant at site and home visits.	Clarification.
8.3.4 Regulatory reporting requirements for SAEs	Specific rules for SUSARs reporting were replaced by a more general reporting statement to comply with local regulatory requirements and Sponsor policy.	Clarification.
8.3.7 Adverse event of special interest	Specification of exploratory assessments to be performed in case of suspicion of thromboembolic event (eg, D-dimer, venous ultrasound and other radiological investigations) as needed, as per Investigator clinical judgment and/or local regulation.	Health Authority request.
9.3.1 General considerations	The on-treatment period was updated from +18 to +24 days for SC group and from 32 to 38 days for the IV group.	To comply with the updated visit window in the late Part B (from +/-2 days to +/-5 days).
Appendix 2: Clinical laboratory tests	Specification of laboratory assessments to be performed in case of suspicion of thromboembolic event (D-dimer). Addition of CPK, chloride, bicarbonates, phosphorous, and albumin.	Omission in the initial protocol.
Appendix 10 Patient-reported outcome	Correction of PQATv3 (10.10.3) and PGIC-Fatigue (10.10.4).	Correction.

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